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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/384,070	07/23/2021	Kenneth S. Graham		1061

147803	7590	12/17/2024
Schwabe W&W, PC / Regeneron Pharmaceuticals, Inc.		
PacWest Center		
1211 SW Fifth Avenue, Suite 1900		
Portland, OR 97204		

EXAMINER	
LOCKARD, JON MCCLELLAND	

ART UNIT	PAPER NUMBER
1647	

NOTIFICATION DATE	DELIVERY MODE
12/17/2024	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):

LTermes@schwabe.com
ipdocketing@schwabe.com

APPLICATION NO.	ISSUE DATE	PATENT NO.
17/384,070	17-Dec-2024	12168036

Schwabe W&W, PC / Regeneron Pharmaceuticals, Inc.
PacWest Center
Portland, OR 97204

EGRANT NOTIFICATION

Your electronic patent grant (eGrant) is now available, which can be accessed via Patent Center at <https://patentcenter.uspto.gov>

The electronic patent grant is the official patent grant under 35 U.S.C. 153. For more information, please visit <https://www.uspto.gov/electronicgrants>



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APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/384,070	12/17/2024	12168036		1061

147803 7590 11/27/2024
Schwabe W&W, PC / Regeneron Pharmaceuticals, Inc.
PacWest Center
1211 SW Fifth Avenue, Suite 1900
Portland, OR 97204

ISSUE NOTIFICATION

The projected patent number and issue date are specified above. The patent will issue electronically. The electronically issued patent is the official patent grant pursuant to 35 U.S.C. § 153. The patent may be accessed on or after the issue date through Patent Center at <https://patentcenter.uspto.gov/>. The patent will be available in both the public and the private sides of Patent Center. Further assistance in electronically accessing the patent, or about Patent Center, is available by calling the Patent Electronic Business Center at 1-888-217-9197.

The USPTO is implementing electronic patent issuance with a transition period, during which period the USPTO will mail a ceremonial paper copy of the electronic patent grant to the correspondence address of record. Additional copies of the patent (i.e., certified and presentation copies) may be ordered for a fee from the USPTO's Certified Copy Center at <https://certifiedcopycenter.uspto.gov/index.html>. The Certified Copy Center may be reached at (800)972-6382.

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 Center (<https://patentcenter.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 Patents Stakeholder Experience (OPSE), Stakeholder Support Division (SSD) at (571)-272-4200.

INVENTOR(s) (Please see PATENT CENTER site <https://patentcenter.uspto.gov> for additional inventors):

Kenneth S. Graham, Pleasant Valley, NY;
Saurabh WADHWA, Nanuet, NY;

APPLICANT(s) (Please see PATENT CENTER site <https://patentcenter.uspto.gov> for additional applicants):

Regeneron Pharmaceuticals, Inc., Tarrytown, NY;

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.



United States Patent and Trademark Office

Office of the Chief Financial Officer

Document Code:WFEE

User :Hieu Le

Refund Accounting Date:09/12/2024

Effective Date	Sale Item Reference Number	Refund Total
09/12/2024	17384070	\$1,200.00

Document Number	Fee Code	Fee Code Description	Amount Paid	Payment Method	Account Number
I20249BF13448672	1501	UTILITY APPL ISSUE FEE	\$1,200.00	DA	500393



United States Patent and Trademark Office

Office of the Chief Financial Officer

Document Code:WFEE

User :Hieu Le

Sale Adjustment Accounting Date:09/12/2024

Effective Date	Sale Accounting Date	Sale Item Reference Number
09/12/2024	09/12/2024	17384070

Document Number	Fee Code	Fee Code Description	Amount Paid	Payment Method
I20249BF13448672	1501	UTILITY APPL ISSUE FEE	\$1,200.00	DA



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Document Code:WFEE

User :Hieu Le

Sale Accounting Date:09/12/2024

Sale Item Reference Number	Effective Date
17384070	09/11/2024

Document Number	Fee Code	Fee Code Description	Amount Paid	Payment Method
I20249BF15478796	1501	UTILITY APPL ISSUE FEE	\$1,200.00	Deposit Account

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via the USPTO patent electronic filing system.

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 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. **Because electronic patent issuance may occur shortly after issue fee payment, any desired continuing application should preferably be filed prior to payment of this issue fee in order not to jeopardize copendency.**

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

147803 7590 09/11/2024
Schwabe W&W, PC / Regeneron Pharmaceuticals, Inc.
PacWest Center
1211 SW Fifth Avenue, Suite 1900
Portland, OR 97204

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 the USPTO patent electronic filing system or by facsimile to (571) 273-2885, on the date below.

Lance A. Termes	(Typed or printed name)
/Lance A. Termes/	(Signature)
September 11, 2024	(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/384,070	07/23/2021	Kenneth S. Graham		1061

TITLE OF INVENTION: Methods for Treating Angiogenic Eye Disorders with High Doses of VEGF Receptor Fusion Proteins

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	\$1200	\$0.00	\$1200.00	\$0	12/11/2024

EXAMINER	ART UNIT	CLASS-SUBCLASS
LOCKARD, JON MCCLELLAND	1647	424-134100

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

☐ Change of correspondence address for Change of Correspondence Address form PTO/AIA/122 or PTO/SB/122) attached.

☒ "Fee Address" indication (or "Fee Address" Indication form PTO/AIA/47 or 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 Schwabe, Williamson & Wyatt PC

2 Thomas Triolo

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

Regeneron Pharmaceuticals, Inc.

(B) RESIDENCE: (CITY and STATE OR COUNTRY)

Tarrytown, NY

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)

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

☒ Electronic Payment via the USPTO patent electronic filing system ☐ 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. 500393

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 /Lance A. Termes/

Date September 11, 2024

Typed or printed name Lance A. Termes

Registration No. 43,184

"FEE ADDRESS" INDICATION FORM

MAIL STOP M CORRESPONDENCE

Fax to: (571) 273-6500

Commissioner for Patents

P.O. Box 1450

Alexandria, VA 22313-1450

For the following listed patents, please recognize as the "Fee Address" under the provisions of 37 C.F.R. 1.363 the address associated with:

CUSTOMER NO. 26693

PATENT NUMBER (if known)	APPLICATION NUMBER
	17/384,070

Date: September 11, 2024

Signed: /Lance A. Termes/
Lance A. Termes

Attorney for Applicant, Registration No. 43,184

Address of signer:

Schwabe, Williamson & Wyatt PC

PacWest Center

1211 SW Fifth Avenue, Ste. 1900

Portland, OR 97204

Tel: Bend Office (541) 749-4044

Fax: Portland Office (503) 796-2900

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PATENT AND TRADEMARK OFFICE

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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
17/384,070	09/11/2024 05:31:42 PM Z ET	-

Title of Invention

Methods for Treating Angiogenic Eye Disorders with High Doses of VEGF Receptor Fusion Proteins

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	1061	FILED BY	Lance Termes
PATENT CENTER #	67138677	FILING DATE	07/23/2021
CUSTOMER #	147803	FIRST NAMED INVENTOR	Kenneth S. Graham
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	-

Documents

TOTAL DOCUMENTS: 2

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
10430US02_IF_Transmittal.pdf	1	Issue Fee Payment (PTO-85B)	204 KB
10430US02_Fee_Address.pdf	1	Maintenance Fee Address Change	17 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
10430US02_IF_Transmittal.pdf	EC08FEDAB8BC06E83141F6C52F24C12D305ADA3647691883851C5251D61752FE6BA24FB1756A559603A9AEE357C2E13AB89C97C6D1A059D992D3A8ACF20CAD60
10430US02_Fee_Address.pdf	D888885BF9742316EBBD508FE9EEFE3AC4D798496A5E50E88

E1BD615120FFD92ACD2AC7F8D3944480606FF7AC1CDA6454
2D41FDF358398538570F3CA6BFBD986

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 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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NOTICE OF ALLOWANCE AND FEE(S) DUE

147803 7590 09/11/2024
Schwabe W&W, PC / Regeneron Pharmaceuticals, Inc.
PacWest Center
1211 SW Fifth Avenue, Suite 1900
Portland, OR 97204

EXAMINER

LOCKARD, JON MCCLELLAND

ART UNIT PAPER NUMBER

1647

DATE MAILED: 09/11/2024

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/384,070	07/23/2021	Kenneth S. Graham		1061

TITLE OF INVENTION: Methods for Treating Angiogenic Eye Disorders with High Doses of VEGF Receptor Fusion Proteins

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	\$1200	\$0.00	\$1200.00	\$0	12/11/2024

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 40% the amount of undiscounted fees, and micro entity fees are 20% the amount of undiscounted 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. 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 the USPTO patent electronic filing system.

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 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. **Because electronic patent issuance may occur shortly after issue fee payment, any desired continuing application should preferably be filed prior to payment of this issue fee in order not to jeopardize copendency.**

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147803 7590 09/11/2024
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PacWest Center
1211 SW Fifth Avenue, Suite 1900
Portland, OR 97204

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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 the USPTO patent electronic filing system 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.
17/384,070	07/23/2021	Kenneth S. Graham		1061

TITLE OF INVENTION: Methods for Treating Angiogenic Eye Disorders with High Doses of VEGF Receptor Fusion Proteins

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	\$1200	\$0.00	\$1200.00	\$0	12/11/2024

EXAMINER	ART UNIT	CLASS-SUBCLASS
LOCKARD, JON MCCLELLAND	1647	424-134100

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/AIA/122 or PTO/SB/122) attached.

☐ "Fee Address" indication (or "Fee Address" Indication form PTO/AIA/47 or 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 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)

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

☐ Electronic Payment via the USPTO patent electronic filing system ☐ 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.

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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. _____



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/384,070	07/23/2021	Kenneth S. Graham		1061
147803	7590	09/11/2024		
Schwabe W&W, PC / Regeneron Pharmaceuticals, Inc.				
PacWest Center				
1211 SW Fifth Avenue, Suite 1900				
Portland, OR 97204				
				EXAMINER
				LOCKARD, JON MCCLELLAND
			ART UNIT	PAPER NUMBER
			1647	

DATE MAILED: 09/11/2024

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. The United States Patent and Trademark Office (USPTO) collects the information in this record under authority of 35 U.S.C. 2. The USPTO's system of records is used to manage all applicant and owner information including name, citizenship, residence, post office address, and other information with respect to inventors and their legal representatives pertaining to the applicant's/owner's activities in connection with the invention for which a patent is sought or has been granted. The applicable Privacy Act System of Records Notice for the information collected in this form is COMMERCE/PAT-TM-7 Patent Application Files, available in the Federal Register at 78 FR 19243 (March 29, 2013).

<https://www.govinfo.gov/content/pkg/FR-2013-03-29/pdf/2013-07341.pdf>

Routine uses of the information in this record may include disclosure to:

- 1) law enforcement, in the event that the system of records indicates a violation or potential violation of law;
- 2) a federal, state, local, or international agency, in response to its request;
- 3) a contractor of the USPTO having need for the information in order to perform a contract;
- 4) the Department of Justice for determination of whether the Freedom of Information Act (FOIA) requires disclosure of the record;
- 5) a Member of Congress submitting a request involving an individual to whom the record pertains, when the individual has requested the Member's assistance with respect to the subject matter of the record;
- 6) a court, magistrate, or administrative tribunal, in the course of presenting evidence, including disclosures to opposing counsel in the course of settlement negotiations;
- 7) the Administrator, General Services Administration (GSA), or their designee, during an inspection of records conducted by GSA under authority of 44 U.S.C. 2904 and 2906, in accordance with the GSA regulations and any other relevant (i.e., GSA or Commerce) directive, where such disclosure shall not be used to make determinations about individuals;
- 8) 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));
- 9) the Office of Personnel Management (OPM) for personnel research purposes; and
- 10) the Office of Management and Budget (OMB) for legislative coordination and clearance.

If you do not furnish the information requested on this form, the USPTO may not be able to process and/or examine your submission, which may result in termination of proceedings, abandonment of the application, and/or expiration of the patent.

Notice of Allowability	Application No. 17/384,070	Applicant(s) Graham et al.	
	Examiner JON M LOCKARD	Art Unit 1647	AIA (FITF) Status Yes

-- 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 the Request for Continued Examination filed 27 August 2024.
☐ 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 See Continuation Sheet . 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)	5. ☒ Examiner's Amendment/Comment
2. ☒ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____.	6. ☒ Examiner's Statement of Reasons for Allowance
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____.	7. ☐ Other _____.
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____.	

/J.L/ Examiner, Art Unit 1647	/CHRISTINE J SAOUD/ Primary Examiner, Art Unit 1645
----------------------------------	--

Continuation of 3. The allowed claim(s) is/are: 30-32 and 53-87 (renumbered as claims 1-11, 13-14, 16, 18, 20, 22, 24, 12, 26, 15, 17, 19, 21, 23, 25 and 27-38, respectively)

Notice of Pre-AIA or AIA Status

1. The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

Continued Examination Under 37 CFR 1.114

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 allowance or after an Office action under *Ex Parte Quayle*, 25 USPQ 74, 453 O.G. 213 (Comm'r Pat. 1935). 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, prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 27 August 2024 has been entered.

Information Disclosure Statement

3. The information disclosure statement (IDS) submitted on 27 August 2024 has been considered by the examiner.

REASONS FOR ALLOWANCE

4. The following is an examiner's statement of reasons for allowance: The information disclosure statement (IDS) submitted on 27 August 2024 has been considered by the Examiner. After careful consideration, the Examiner has determined that none of the information contained therein raises new issues of patentability.

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."

Summary

6. Claims 30-32 and 53-87 are allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **JON M LOCKARD** whose telephone number is **(571) 272-2717**. The examiner can normally be reached M-F 9-6 EST.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at <http://www.uspto.gov/interviewpractice>. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joanne Hama** can be reached on **(571) 272-2911**. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of published or unpublished applications may be obtained from Patent Center. Unpublished application information in Patent Center is available to registered users. To file and manage patent submissions in Patent Center, visit: <https://patentcenter.uspto.gov>. Visit <https://www.uspto.gov/patents/apply/patent-center> for more information about Patent Center and <https://www.uspto.gov/patents/docx> for information about filing in DOCX format. For additional questions, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/J.L/
Examiner, Art Unit 1647
September 6, 2024

/Christine J Saoud/
Primary Examiner, Art Unit 1645

<i>Search Notes</i> 	Application/Control No. 17/384,070	Applicant(s)/Patent Under Reexamination Graham et al.
	Examiner JON M LOCKARD	Art Unit 1647

CPC - Searched*		
Symbol	Date	Examiner

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner
NONE		03/16/2023	JML

* 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
PE2E Search (USPAT, US-PGPUB, EPO, DERWENT): See attached search history.	03/16/2023	JML
STN (MEDLINE, SCISEARCH, EMBASE, BIOSIS): See attached search history.	03/16/2023	JML
PALM: Inventor search.	03/16/2023	JML
PE2E Search (USPAT, US-PGPUB, EPO, DERWENT): See attached search history.	11/01/2023	JML

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<i>Search Notes</i> 	Application/Control No. 17/384,070	Applicant(s)/Patent Under Reexamination Graham et al.
	Examiner JON M LOCKARD	Art Unit 1647

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner
	PE2E Search (USPAT): See attached search history.	08/24/2023	JML
	DAV: Inventor search.	08/24/2023	JML
	PE2E Search (USPAT): See attached search history.	11/01/2023	JML
	DAV: Inventor search.	11/01/2023	JML
	PE2E Search (USPAT): See attached search history.	11/29/2023	JML
	DAV: Inventor search.	11/29/2023	JML
	PE2E Search (USPAT): See attached search history.	01/11/2024	JML
	DAV: Inventor search.	01/11/2024	JML
	PE2E Search (USPAT): See attached search history.	05/10/2024	JML
	DAV: Inventor search.	05/10/2024	JML
	PE2E Search (USPAT): See attached search history.	06/11/2024	JML
	DAV: Inventor search.	06/11/2024	JML
	PE2E Search (USPAT): See attached search history.	07/25/2024	JML
	DAV: Inventor search.	07/25/2024	JML
	PE2E Search (USPAT): See attached search history.	09/06/2024	JML
	DAV: Inventor search.	09/06/2024	JML

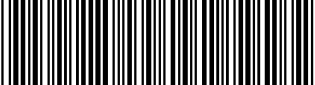
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Issue Classification 	Application/Control No. 17/384,070	Applicant(s)/Patent Under Reexamination Graham et al.
	Examiner JON M LOCKARD	Art Unit 1647

CPC						
Symbol					Type	Version
A61K	/	38	/	179	F	2013-01-01
A61K	/	9	/	0048	I	2013-01-01
A61K	/	47	/	12	I	2013-01-01
A61P	/	27	/	02	I	2018-01-01
A61K	/	47	/	22	I	2013-01-01
A61K	/	47	/	26	I	2013-01-01
A61K	/	47	/	183	I	2013-01-01

CPC Combination Sets					
Symbol				Type	Version
	/		/		

Use images from artifact folder? ☒ Yes ☐ No							
/JON M LOCKARD/ Examiner, Art Unit 1647 (Assistant Examiner)		06 September 2024 (Date)	Total Claims Allowed: 38				
/CHRISTINE J SAOUD/ Primary Examiner, Art Unit 1645 (Primary Examiner)		07 September 2024 (Date)	<table border="1"> <tr> <td>O.G. Print Claim(s)</td> <td>O.G. Print Figure</td> </tr> <tr> <td>1</td> <td>NONE</td> </tr> </table>	O.G. Print Claim(s)	O.G. Print Figure	1	NONE
O.G. Print Claim(s)	O.G. Print Figure						
1	NONE						

Issue Classification 	Application/Control No. 17/384,070	Applicant(s)/Patent Under Reexamination Graham et al.
	Examiner JON M LOCKARD	Art Unit 1647

INTERNATIONAL CLASSIFICATION			
CLAIMED			
A61K	/	38	/ 17
A61K	/	38	/ 18
C07K	/	14	/ 71
NON-CLAIMED			
	/		/

US ORIGINAL CLASSIFICATION	
CLASS	SUBCLASS

CROSS REFERENCES(S)						
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)					

Use images from artifact folder? ☒ Yes ☐ No							
/JON M LOCKARD/ Examiner, Art Unit 1647 (Assistant Examiner)		06 September 2024 (Date)	Total Claims Allowed: 38				
/CHRISTINE J SAOUD/ Primary Examiner, Art Unit 1645 (Primary Examiner)		07 September 2024 (Date)	<table border="1"> <tr> <td>O.G. Print Claim(s)</td> <td>O.G. Print Figure</td> </tr> <tr> <td>1</td> <td>NONE</td> </tr> </table>	O.G. Print Claim(s)	O.G. Print Figure	1	NONE
O.G. Print Claim(s)	O.G. Print Figure						
1	NONE						

Issue Classification 	Application/Control No. 17/384,070	Applicant(s)/Patent Under Reexamination Graham et al.
	Examiner JON M LOCKARD	Art Unit 1647

☐ 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
1	30	10	59	12	68	28	77	37	86						
2	31	11	60	26	69	29	78	38	87						
3	32	13	61	15	70	30	79								
4	53	14	62	17	71	31	80								
5	54	16	63	19	72	32	81								
6	55	18	64	21	73	33	82								
7	56	20	65	23	74	34	83								
8	57	22	66	25	75	35	84								
9	58	24	67	27	76	36	85								

Use images from artifact folder? ☒ Yes ☐ No			
/JON M LOCKARD/ Examiner, Art Unit 1647 (Assistant Examiner)		06 September 2024 (Date)	
		Total Claims Allowed: 38	
/CHRISTINE J SAOUD/ Primary Examiner, Art Unit 1645 (Primary Examiner)		07 September 2024 (Date)	
		O.G. Print Claim(s) 1	O.G. Print Figure NONE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT <small>(not for submission under 37 CFR 1.99)</small>	Application Number	17/384,070
	Filing Date	Jul-23-2021
	First Named Inventor	Kenneth S. Graham
	Art Unit	1647
	Confirmation Number	1061
	Examiner Name	Lockard, Jon McClelland
	Attorney Docket Number	125984-266215

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

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

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

NON-PATENT LITERATURE DOCUMENTS			
Examiner Initial*	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
/J.L./	655	BORWANKAR et al., "Viscosity Reduction of a Concentrated Monoclonal Antibody with Arginine·HCl and Arginine·Glutamate," I&EC Research, American Chemical Society, Volume (No 55): 11225-11234, (2016). [DOI: 10.1021/acs.iecr.6b02042].	

Receipt date: 08/27/2024

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (not for submission under 37 CFR 1.99)	Application Number	17/384,070
	Filing Date	Jul-23-2021
	First Named Inventor	Kenneth S. Graham
	Art Unit	1647
	Confirmation Number	1061
	Examiner Name	Lockard, Jon McClelland
	Attorney Docket Number	125984-266215

EXAMINER SIGNATURE			
Examiner Signature	/JON M LOCKARD/	Date Considered	09/06/2024
*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.			
<p>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.</p>			

PE2E SEARCH - Search History (Prior Art)

J.L./

There are no Prior Art searches to show.

PE2E SEARCH - Search History (Interference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	British Equivalents	Time Stamp
N59	2888	vegf ADJ trap	(USPAT)	OR	ON	ON	2024/09/06 06:31 PM
N60	3056	aflibercept	(USPAT)	OR	ON	ON	2024/09/06 06:31 PM
N61	503	eylea	(USPAT)	OR	ON	ON	2024/09/06 06:31 PM
N62	129	vegf ADJ trap-eye	(USPAT)	OR	ON	ON	2024/09/06 06:31 PM
N63	469	(N41 N42 N43 N44) SAME formulation	(USPAT)	OR	ON	ON	2024/09/06 06:31 PM
N64	12	N45 SAME "high concentration"	(USPAT)	OR	ON	ON	2024/09/06 06:31 PM
N65	1	N45 AND (8mg OR "8 mg").clm.	(USPAT)	OR	ON	ON	2024/09/06 06:31 PM
N66	19	(graham-k\$-s\$ washawa-s\$).in.	(USPAT)	OR	ON	ON	2024/09/06 06:31 PM
N67	1	N46 AND N48	(USPAT)	OR	ON	ON	2024/09/06 06:31 PM

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via the USPTO patent electronic filing system.

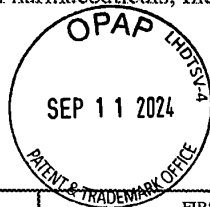
By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

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 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. **Because electronic patent issuance may occur shortly after issue fee payment, any desired continuing application should preferably be filed prior to payment of this issue fee in order not to jeopardize copendency.**

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

147803 7590 09/11/2024
Schwabe W&W, PC / Regeneron Pharmaceuticals, Inc.
PacWest Center
1211 SW Fifth Avenue, Suite 1900
Portland, OR 97204



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 the USPTO patent electronic filing system or by facsimile to (571) 273-2885, on the date below.

Lance A. Termes	(Typed or printed name)
/Lance A. Termes/	(Signature)
September 11, 2024	(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/384,070	07/23/2021	Kenneth S. Graham		1061

TITLE OF INVENTION: Methods for Treating Angiogenic Eye Disorders with High Doses of VEGF Receptor Fusion Proteins

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	\$1200	\$0.00	\$1200.00	\$0	12/11/2024

EXAMINER	ART UNIT	CLASS-SUBCLASS
LOCKARD, JON MCCLELLAND	1647	424-134100

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/AIA/122 or PTO/SB/122) attached.

☒ "Fee Address" indication (or "Fee Address" Indication form PTO/AIA/47 or 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 Schwabe, Williamson & Wyatt PC

2 Thomas Triolo

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

Regeneron Pharmaceuticals, Inc.

(B) RESIDENCE: (CITY AND STATE OR COUNTRY)

Tarrytown, NY

Please check the appropriate assignee category or categories (will not be printed on the patent): ☐ Individual ☒ Corporation or other private group entity ☐ Government4a. Fees submitted: ☒ Issue Fee ☐ Publication Fee (if required)

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

☒ Electronic Payment via the USPTO patent electronic filing system ☐ 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. 500393

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 /Lance A. Termes/

Date September 11, 2024

Typed or printed name Lance A. Termes

Registration No. 43,184



P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

PETITION TO WITHDRAW AN APPLICATION FROM ISSUE AFTER PAYMENT OF THE ISSUE FEE UNDER 37 CFR 1.313(c)(2)

APPLICATION #
17384070

ATTORNEY DOCKET #
—

FILING DATE
07/23/2021

Title of Invention

Methods for Treating Angiogenic Eye Disorders with High Doses of VEGF Receptor Fusion Proteins

Application Information

CONFIRMATION # 1061

FILING DATE 07/23/2021

ART UNIT 1647

FIRST NAMED INVENTOR Kenneth Graham

EXAMINER JON LOCKARD

An application may be withdrawn from issue for further action upon petition by the applicant. To request that the Office withdraw an application from issue, applicant must file a petition under this section including the fee set forth in § 1.17(h) and a showing of good and sufficient reasons why withdrawal of the application from issue is necessary.

APPLICANT HEREBY PETITIONS TO WITHDRAW THIS APPLICATION FROM ISSUE UNDER 37 CFR 1.313(c).

A grantable petition requires the following items:

- (1) Petition fee; and
- (2) One of the following reasons: A grantable petition requires the following items: (a) Unpatentability of one or more claims, which must be accompanied by an unequivocal statement that one or more claims are unpatentable, an amendment to such claim or claims, and an explanation as to how the amendment causes such claim or claims to be patentable;
- (b) Consideration of a request for continued examination in compliance with § 1.114 (for a utility or plant application only); or
- (c) Express abandonment of the application. Such express abandonment may be in favor of a continuing application, but not a CPA under 37 CFR 1.53(d).

Reason for withdrawal

Consideration of a request for continued examination - I certify, in accordance with 37 CFR 1.4(d)(4) that the RCE Request,

Submission, and Fee have already been filed in the above-identified application on 08/27/2024

Applicant claims the following entity status
Regular Undiscounted

Signature

I certify, in accordance with 37 CFR 1.4(d)(4) that I am:
An attorney or agent registered to practice before the Patent and Trademark Office who has been given power of attorney in this application

Signature	Name	Registration #
/Lance A. Termes/	Lance Termes	43184



UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
17/384,070	08/27/2024 06:38:50 PM Z ET	-

Title of Invention

Methods for Treating Angiogenic Eye Disorders with High Doses of VEGF Receptor Fusion Proteins

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	1061	FILED BY	Lance Termes
PATENT CENTER #	66949694	FILING DATE	07/23/2021
CUSTOMER #	147803	FIRST NAMED INVENTOR	Kenneth S. Graham
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	-

Documents

TOTAL DOCUMENTS: 1

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
petition-request.pdf	2	ePetition Request Form	29 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
petition-request.pdf	9001765BF8332CAF06DF19E05AE2627E332ED5AE3B338773F 8AA3D80E7EF1ACF1AEB195AFA3F3853311BEE09DBD9405B1 8E434A71C6D8F81CE672D2D6D3DD83B

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

PGR2026-00039
Biocon Ex.1002
Page 32 of 4945

If a new application is being filed and the application includes the necessary components for 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

P.O. Box 1450
Alexandria, VA 22313 - 1450
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GRANT LETTER

APPLICATION #	DECISION DATE	DECISION ON PETITION #	ATTORNEY DOCKET NUMBER
17/384,070	08/27/2024	37 CFR 1.313(c)(2)	

Title of Invention

Methods for Treating Angiogenic Eye Disorders with High Doses of VEGF Receptor Fusion Proteins

In re Application of Kenneth Graham

This is an electronic decision on the petition under 37 CFR 1.313(c)(2), filed August 27, 2024 to withdraw the above-identified application from issue after payment of the issue fee.

The request is **GRANTED**.

The above-identified application is withdrawn from issue for consideration of a submission under 37 CFR 1.114 (request for continued examination). See 37 CFR 1.313(c)(2).

Petitioner is advised that the issue fee paid in this application cannot be refunded. If, however, this application is again allowed, petitioner may request that it be applied towards the issue fee required by the new Notice of Allowance.

The application is being referred to Technology Center AU for processing of the request for continuing examination under 37 CFR 1.114 .

Telephone inquired concerning this decision should be directed to the Patent Electronic Business Center (EBC) at 866-217-9197.

Office of Petitions



UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

ELECTRONIC PAYMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
17/384,070	08/27/2024 06:38:50 PM Z ET	-

Title of Invention

Methods for Treating Angiogenic Eye Disorders with High Doses of VEGF Receptor Fusion Proteins

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	1061	FILED BY	Lance Termes
PATENT CENTER #	66949694	AUTHORIZED BY	-
CUSTOMER #	147803	FILING DATE	07/23/2021
CORRESPONDENCE ADDRESS	-	FIRST NAMED INVENTOR	Kenneth S. Graham

Payment Information

PAYMENT METHOD	PAYMENT TRANSACTION ID	PAYMENT AUTHORIZED BY
DA / 500393	E20248QI38596413	Lance Termes

FEE CODE	DESCRIPTION	ITEM PRICE(\$)	QUANTITY	ITEM TOTAL(\$)
1464	PETITIONS REQUIRING THE PETITION FEE SET FORTH IN 37 CFR 1.17(H) (GROUP III)	140.00	1	140.00
TOTAL AMOUNT:				\$140.00

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 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

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
17/384,070	08/27/2024 06:31:57 PM Z ET	-

Title of Invention

Methods for Treating Angiogenic Eye Disorders with High Doses of VEGF Receptor Fusion Proteins

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	1061	FILED BY	Lance Termes
PATENT CENTER #	66949608	FILING DATE	07/23/2021
CUSTOMER #	147803	FIRST NAMED INVENTOR	Kenneth S. Graham
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	-

Documents

TOTAL DOCUMENTS: 4

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
10430US02_RCE.pdf	1	Request for Continued Examination (RCE)	210 KB
Warning: This is not a USPTO supplied RCE fillable form. Data in the form cannot be automatically loaded to other USPTO systems.			
10430US02_IDS_Transmittal.pdf	3	Transmittal Letter	24 KB
10430US02_IDS_SB08.pdf	3	Information Disclosure Statement (IDS) Form (SB08)	55 KB
Warning: This is not a USPTO supplied IDS fillable form. Data in the form cannot be automatically loaded to other USPTO systems.			
655_Borwankar_2016.pdf	25	Non Patent Literature	1260 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
10430US02_RCE.pdf	09E7FF05B9DDEDBEBEF93A321052C93A6293F2731D87FD 905DF33015711D38C726F97B4CD673CB14491D1F10B3183FC BA0C4DC0ACDD98B353ABDB78F3608F7
10430US02_IDS_Transmittal.pdf	9D24CFBB44E48AD756580F1AD4DAD06ED588D0D582BB90B A133FE681021F5CC171C8F2427A922F1DFE36A34CDC346372 99BB09D1D71083FFB83ADF0182D83DCB
10430US02_IDS_SB08.pdf	D208259FC31FD7B82C51294F412B74158C1CE847C3FFCD285 6A8D869CAA2C23BB9CFD44E49058E48D4268099BC5325C88 85B2B4B6645E61E34DDEC6F1B59C723
655_Borwankar_2016.pdf	27B7C5DF0A0672BB82A28C3ACE2CD05BE46DD6B362699A93 E76ECBDB16E420CA5DA8E18FFB3289D27D8A1C30C5A37C2 F64C35EC7CDB65D847DA04EA80D438ED1

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 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

In re application of: Kenneth S. Graham, et al. Application No.: 17/384,070 Filed: Jul-23-2021 For: HIGH CONCENTRATION VEGF RECEPTOR FUSION PROTEIN CONTAINING FORMULATIONS Customer No.: 147803	Confirmation No.: 1061 Examiner: Lockard, Jon McClelland Art Unit: 1647 SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR §1.97 and §1.98 <hr/> Date of Transmission: August 27, 2024
---	--

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

Commissioner:

The references cited on the attached IDS are being called to the attention of the Examiner. Copies of the references in compliance with the requirements of 37 CFR §1.98(a)(2) are submitted herewith.

It is respectfully requested that the cited reference be expressly considered during the prosecution of this application, and the reference be made of record therein and appear among the “references cited” on any patent to issue therefrom.

The Examiner is encouraged to review the full prosecution history from related cases. Applicant understands that the prosecution history can be viewed electronically on

PALM. Nevertheless, if the Examiner wishes Applicant to provide copies of any documents from related applications to the extent not already provided, he or she is requested to contact the undersigned.

Applicant cites the following applications, which are directed to related subject matter and are commonly owned or under an assignment obligation to be commonly owned:

Attorney Docket No.	Application No.	Filing Date	Publication No.	Status
125984-248591	62/669,506	05-10-2018	N/A	Expired
125984-248592	62/752,127	10-29-2018	N/A	Expired
125984-248593	62/769,876	11-20-2018	N/A	Expired
125984-248594	62/813,882	03-05-2019	N/A	Expired
125984-248595	16/409,631	05-10-2019	US 11,103,552	Issued
125984-248596	PCT/US2019/031879	05-10-2019	WO 2019/217927	Expired
125984-281135	18/367,444	09-12-2023	US-2024-0058418	Published

As provided for by 37 CFR §1.97(g) and (h), no inference should be made that the information and references cited are prior art merely because they are in this statement and no representation is being made that a search has been conducted or that this statement encompasses all the possible relevant information.

Applicant believes that no fee is required for submission of this statement.

However, if a fee is required in connection with this paper, the Commissioner is authorized to deduct such fee from the undersigned's Deposit Account No. 500393.

Respectfully submitted,

/Lance A. Termes/

Lance A. Termes
Reg. No. 43184

Schwabe Williamson & Wyatt, PC
1211 SW 5th Avenue, Suite 1900
Portland, OR 97204
Tel: 503-222-9981

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.

**Request
for
Continued Examination (RCE)
Transmittal**

Address to:
Mail Stop RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Application Number	17/384,070
Filing Date	July 23, 2021
First Named Inventor	Kenneth S. Graham
Art Unit	1647
Examiner Name	Jon McClelland Lockard
Attorney Docket Number	125984-266215

This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. See Instruction Sheet for RCEs (not to be submitted to the USPTO) on page 2.

1. **Submission required under 37 CFR 1.114** Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).
- a. ☐ Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.
- i. ☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____
- ii. ☐ Other _____
- b. ☒ Enclosed
- i. ☐ Amendment/Reply
- iii. ☒ Information Disclosure Statement (IDS)
- ii. ☐ Affidavit(s)/ Declaration(s)
- iv. ☐ Other _____
2. **Miscellaneous**
- a. ☐ Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a period of _____ months. (Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)
- b. ☐ Other _____
3. **Fees** The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.
- a. ☒ The Director is hereby authorized to charge the following fees, any underpayment of fees, or credit any overpayments, to Deposit Account No. 500393.
- i. ☒ RCE fee required under 37 CFR 1.17(e)
- ii. ☐ Extension of time fee (37 CFR 1.136 and 1.17)
- iii. ☐ Other _____
- b. ☐ Check in the amount of \$ _____ enclosed
- c. ☐ Payment by credit card (Form PTO-2038 enclosed)
- d. ☒ Payment by USPTO patent electronic filing system.

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.

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

Signature	/Lance A. Termes/	Date	August 27, 2024
Name (Print/Type)	Lance A. Termes	Registration No.	43,184

CERTIFICATE OF MAILING OR TRANSMISSION

I hereby certify that this correspondence is transmitted by the USPTO patent electronic filing system, or by facsimile to (571) 273-8300, to the USPTO, or deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop RCE, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on the date shown below.

Signature	/Lance A. Termes/	Date	August 27, 2024
Name (Print/Type)	Lance A. Termes		

A Federal agency may not conduct or sponsor, and a person is not required to respond to, nor shall a person be subject to a penalty for failure to comply with an information collection subject to the requirements of the Paperwork Reduction Act of 1995, unless the information collection has a currently valid OMB Control Number. The OMB Control Number for this information collection is 0651-0031. Public burden for this form is estimated to average 12 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the information collection. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden to the Chief Administrative Officer, United States Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450 or email InformationCollection@uspto.gov. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. If filing this completed form by mail, 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.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (not for submission under 37 CFR 1.99)	Application Number	17/384,070
	Filing Date	Jul-23-2021
	First Named Inventor	Kenneth S. Graham
	Art Unit	1647
	Confirmation Number	1061
	Examiner Name	Lockard, Jon McClelland
	Attorney Docket Number	125984-266215

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

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

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

NON-PATENT LITERATURE DOCUMENTS			
Examiner Initial*	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
	655	BORWANKAR et al., "Viscosity Reduction of a Concentrated Monoclonal Antibody with Arginine·HCl and Arginine·Glutamate," I&EC Research, American Chemical Society, Volume (No 55): 11225-11234, (2016). [DOI: 10.1021/acs.iecr.6b02042].	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (not for submission under 37 CFR 1.99)	Application Number	17/384,070
	Filing Date	Jul-23-2021
	First Named Inventor	Kenneth S. Graham
	Art Unit	1647
	Confirmation Number	1061
	Examiner Name	Lockard, Jon McClelland
	Attorney Docket Number	125984-266215

EXAMINER SIGNATURE			
Examiner Signature		Date Considered	
<p>*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.</p>			
<p>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.</p>			

INFORMATION DISCLOSURE STATEMENT BY APPLICANT <small>(not for submission under 37 CFR 1.99)</small>	Application Number	17/384,070
	Filing Date	Jul-23-2021
	First Named Inventor	Kenneth S. Graham
	Art Unit	1647
	Confirmation Number	1061
	Examiner Name	Lockard, Jon McClelland
	Attorney Docket Number	125984-266215

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.			
☐ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.			
☒ None			
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	/Lance A. Termes/	Date (YYYY-MM-DD)	2024-08-27
Name/Print	Lance A. Termes	Registration Number	43184



UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
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ELECTRONIC PAYMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
17/384,070	08/27/2024 06:31:57 PM Z ET	-

Title of Invention

Methods for Treating Angiogenic Eye Disorders with High Doses of VEGF Receptor Fusion Proteins

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	1061	FILED BY	Lance Termes
PATENT CENTER #	66949608	AUTHORIZED BY	-
CUSTOMER #	147803	FILING DATE	07/23/2021
CORRESPONDENCE ADDRESS	-	FIRST NAMED INVENTOR	Kenneth S. Graham

Payment Information

PAYMENT METHOD	PAYMENT TRANSACTION ID	PAYMENT AUTHORIZED BY
DA / 500393	E20248QI32175901	Lance Termes

FEE CODE	DESCRIPTION	ITEM PRICE(\$)	QUANTITY	ITEM TOTAL(\$)
1820	REQUEST FOR CONTINUED EXAMINATION (RCE)- 2ND AND SUBSEQUENT REQUEST (SEE 37 CFR 1.114)	2000.00	1	2000.00
TOTAL AMOUNT:				\$2,000.00

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 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

Office of the Chief Financial Officer

Document Code:WFEE

User :Sofia Mohammed

Refund Accounting Date:08/27/2024

Effective Date	Sale Item Reference Number	Refund Total
08/26/2024	17384070	\$1,200.00

Document Number	Fee Code	Fee Code Description	Amount Paid	Payment Method	Account Number
I20248PL35449615	1501	UTILITY APPL ISSUE FEE	\$1,200.00	DA	500393



United States Patent and Trademark Office

Office of the Chief Financial Officer

Document Code:WFEE

User :Sofia Mohammed

Sale Adjustment Accounting Date:08/27/2024

Effective Date	Sale Accounting Date	Sale Item Reference Number
08/26/2024	08/27/2024	17384070

Document Number	Fee Code	Fee Code Description	Amount Paid	Payment Method
I20248PL35449615	1501	UTILITY APPL ISSUE FEE	\$1,200.00	DA



United States Patent and Trademark Office

Office of the Chief Financial Officer

Document Code:WFEE

User :Sofia Mohammed

Sale Accounting Date:08/27/2024

Sale Item Reference Number
17384070

Effective Date
08/23/2024

Document Number	Fee Code	Fee Code Description	Amount Paid	Payment Method
I20248PL38079622	1501	UTILITY APPL ISSUE FEE	\$1,200.00	Deposit Account

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via the USPTO patent electronic filing system.

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 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. **Because electronic patent issuance may occur shortly after issue fee payment, any desired continuing application should preferably be filed prior to payment of this issue fee in order not to jeopardize copendency.**

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

147803 7590 08/14/2024
Schwabe W&W, PC / Regeneron Pharmaceuticals, Inc.
PacWest Center
1211 SW Fifth Avenue, Suite 1900
Portland, OR 97204

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 the USPTO patent electronic filing system or by facsimile to (571) 273-2885, on the date below.

Lance A. Termes	(Typed or printed name)
/Lance A. Termes/	(Signature)
August 23, 2024	(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/384,070	07/23/2021	Kenneth S. Graham		1061

TITLE OF INVENTION: Methods for Treating Angiogenic Eye Disorders with High Doses of VEGF Receptor Fusion Proteins

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	\$1200	\$0.00	\$1200.00	\$0	11/14/2024

EXAMINER	ART UNIT	CLASS-SUBCLASS
LOCKARD, JON MCCLELLAND	1647	424-134100

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

☐ Change of correspondence address for Change of Correspondence Address form PTO/AIA/122 or PTO/SB/122) attached.

☒ "Fee Address" indication (or "Fee Address" Indication form PTO/AIA/47 or 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 Schwabe, Williamson & Wyatt PC

2 Thomas Triolo

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

Regeneron Pharmaceuticals, Inc.

(B) RESIDENCE: (CITY and STATE OR COUNTRY)

Tarrytown, NY

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)

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

☒ Electronic Payment via the USPTO patent electronic filing system ☐ 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. 500393

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.

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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 /Lance A. Termes/

Date August 23, 2024

Typed or printed name Lance A. Termes

Registration No. 43,184

"FEE ADDRESS" INDICATION FORM

MAIL STOP M CORRESPONDENCE

Fax to: (571) 273-6500

Commissioner for Patents

P.O. Box 1450

Alexandria, VA 22313-1450

For the following listed patents, please recognize as the "Fee Address" under the provisions of 37 C.F.R. 1.363 the address associated with:

CUSTOMER NO. 26693

PATENT NUMBER (if known)	APPLICATION NUMBER
	17/384,070

Date: August 23, 2024

Signed: /Lance A. Termes/
Lance A. Termes

Attorney for Applicant, Registration No. 43,184

Address of signer:

Schwabe, Williamson & Wyatt PC

PacWest Center

1211 SW Fifth Avenue, Ste. 1900

Portland, OR 97204

Tel: Bend Office (541) 749-4044

Fax: Portland Office (503) 796-2900

125984\266215\LAT\46337845.1



UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
17/384,070	08/23/2024 11:01:22 PM Z ET	-

Title of Invention

Methods for Treating Angiogenic Eye Disorders with High Doses of VEGF Receptor Fusion Proteins

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	1061	FILED BY	Lance Termes
PATENT CENTER #	66912813	FILING DATE	07/23/2021
CUSTOMER #	147803	FIRST NAMED INVENTOR	Kenneth S. Graham
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	-

Documents

TOTAL DOCUMENTS: 2

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
10430US02_IF_Transmittal.pdf	1	Issue Fee Payment (PTO-85B)	204 KB
10430US02_Fee_Address.pdf	1	Maintenance Fee Address Change	17 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
10430US02_IF_Transmittal.pdf	C7392591E81EB33BCFD82739D4E3DD2F8367F46454F3BE681780AC4F54900FE510E928B48F1968E0F284F0756828C262473B270BE48C5419897349E3CE24ED7F
10430US02_Fee_Address.pdf	AE77A7D9F7811B21881FFFE17650D41FADFA794B72CD83F13

50617C88DCF18217746A17D1905363D669D8CC0BC982A7728
8BD3794914F2DB5E475E06CDFFB6C1

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 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

LAW

Complete and send this form, together with applicable fee(s), by mail or fax, or via the USPTO patent electronic filing system.

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 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. **Because electronic patent issuance may occur shortly after issue fee payment, any desired continuing application should preferably be filed prior to payment of this issue fee in order not to jeopardize expediency.**

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

147803 7590 08/14/2024
Schwabe W&W, PC / Regeneron Pharmaceuticals
PacWest Center
1211 SW Fifth Avenue, Suite 1900
Portland, OR 97204



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 the USPTO patent electronic filing system or by facsimile to (571) 273-2885, on the date below.

Lance A. Termes	(Typed or printed name)
/Lance A. Termes/	(Signature)
August 23, 2024	(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/384,070	07/23/2021	Kenneth S. Graham		1061

TITLE OF INVENTION: Methods for Treating Angiogenic Eye Disorders with High Doses of VEGF Receptor Fusion Proteins

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	\$1200	\$0.00	\$1200.00	\$0	11/14/2024

EXAMINER	ART UNIT	CLASS-SUBCLASS
LOCKARD, JON MCCLELLAND	1647	424-134100

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/AIA/122 or PTO/SB/122) attached.

☒ "Fee Address" indication (or "Fee Address" Indication form PTO/AIA/47 or 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 Schwabe, Williamson & Wyatt PC
2 Thomas Triolo
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

Regeneron Pharmaceuticals, Inc.

(B) RESIDENCE: (CITY and STATE OR COUNTRY)

Tarrytown, NY

Please check the appropriate assignee category or categories (will not be printed on the patent): ☐ Individual ☒ Corporation or other private group entity ☐ Government4a. Fees submitted: ☒ Issue Fee ☐ Publication Fee (if required)

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

☒ Electronic Payment via the USPTO patent electronic filing system ☐ 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. 500393

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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 /Lance A. Termes/

Date August 23, 2024

Typed or printed name Lance A. Termes

Registration No. 43,184



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

147803 7590 08/14/2024
Schwabe W&W, PC / Regeneron Pharmaceuticals, Inc.
PacWest Center
1211 SW Fifth Avenue, Suite 1900
Portland, OR 97204

EXAMINER

LOCKARD, JON MCCLELLAND

ART UNIT PAPER NUMBER

1647

DATE MAILED: 08/14/2024

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/384,070	07/23/2021	Kenneth S. Graham		1061

TITLE OF INVENTION: Methods for Treating Angiogenic Eye Disorders with High Doses of VEGF Receptor Fusion Proteins

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nonprovisional	UNDISCOUNTED	\$1200	\$0.00	\$1200.00	\$0	11/14/2024

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 40% the amount of undiscounted fees, and micro entity fees are 20% the amount of undiscounted 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. 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 the USPTO patent electronic filing system.

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

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147803 7590 08/14/2024
Schwabe W&W, PC / Regeneron Pharmaceuticals, Inc.
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Certificate of Mailing or Transmission

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

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/384,070	07/23/2021	Kenneth S. Graham		1061

TITLE OF INVENTION: Methods for Treating Angiogenic Eye Disorders with High Doses of VEGF Receptor Fusion Proteins

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
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EXAMINER	ART UNIT	CLASS-SUBCLASS
LOCKARD, JON MCCLELLAND	1647	424-134100

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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 _____

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(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)

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

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

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Authorized Signature _____

Date _____

Typed or printed name _____

Registration No. _____



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
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.
17/384,070	07/23/2021	Kenneth S. Graham		1061
147803	7590	08/14/2024		
Schwabe W&W, PC / Regeneron Pharmaceuticals, Inc.				
PacWest Center				
1211 SW Fifth Avenue, Suite 1900				
Portland, OR 97204				
			EXAMINER	
			LOCKARD, JON MCCLELLAND	
			ART UNIT	PAPER NUMBER
			1647	

DATE MAILED: 08/14/2024

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. The United States Patent and Trademark Office (USPTO) collects the information in this record under authority of 35 U.S.C. 2. The USPTO's system of records is used to manage all applicant and owner information including name, citizenship, residence, post office address, and other information with respect to inventors and their legal representatives pertaining to the applicant's/owner's activities in connection with the invention for which a patent is sought or has been granted. The applicable Privacy Act System of Records Notice for the information collected in this form is COMMERCE/PAT-TM-7 Patent Application Files, available in the Federal Register at 78 FR 19243 (March 29, 2013).

<https://www.govinfo.gov/content/pkg/FR-2013-03-29/pdf/2013-07341.pdf>

Routine uses of the information in this record may include disclosure to:

- 1) law enforcement, in the event that the system of records indicates a violation or potential violation of law;
- 2) a federal, state, local, or international agency, in response to its request;
- 3) a contractor of the USPTO having need for the information in order to perform a contract;
- 4) the Department of Justice for determination of whether the Freedom of Information Act (FOIA) requires disclosure of the record;
- 5) a Member of Congress submitting a request involving an individual to whom the record pertains, when the individual has requested the Member's assistance with respect to the subject matter of the record;
- 6) a court, magistrate, or administrative tribunal, in the course of presenting evidence, including disclosures to opposing counsel in the course of settlement negotiations;
- 7) the Administrator, General Services Administration (GSA), or their designee, during an inspection of records conducted by GSA under authority of 44 U.S.C. 2904 and 2906, in accordance with the GSA regulations and any other relevant (i.e., GSA or Commerce) directive, where such disclosure shall not be used to make determinations about individuals;
- 8) 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));
- 9) the Office of Personnel Management (OPM) for personnel research purposes; and
- 10) the Office of Management and Budget (OMB) for legislative coordination and clearance.

If you do not furnish the information requested on this form, the USPTO may not be able to process and/or examine your submission, which may result in termination of proceedings, abandonment of the application, and/or expiration of the patent.

Notice of Allowability	Application No. 17/384,070	Applicant(s) Graham et al.	
	Examiner JON M LOCKARD	Art Unit 1647	AIA (FITF) Status Yes

-- 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 the Request for Continued Examination filed 15 July 2024.
☐ 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 See Continuation Sheet . 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)	5. ☒ Examiner's Amendment/Comment
2. ☒ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date ____.	6. ☒ Examiner's Statement of Reasons for Allowance
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material ____.	7. ☐ Other ____.
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date ____.	

/J.L/ Examiner, Art Unit 1647	/CHRISTINE J SAOUD/ Primary Examiner, Art Unit 1645
----------------------------------	--

Continuation of 3. The allowed claim(s) is/are: 30-32 and 53-87 (renumbered as claims 1-11, 13-14, 16, 18, 20, 22, 24, 12, 26, 15, 17, 19, 21, 23, 25 and 27-38, respectively)

Notice of Pre-AIA or AIA Status

1. The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

Continued Examination Under 37 CFR 1.114

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 allowance or after an Office action under *Ex Parte Quayle*, 25 USPQ 74, 453 O.G. 213 (Comm'r Pat. 1935). 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, prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 15 July 2024 has been entered.

Information Disclosure Statement

3. The information disclosure statements (IDS) submitted on 18 June 2024, 15 July 2024 and 23 July 2024 have been considered by the examiner.

REASONS FOR ALLOWANCE

4. The following is an examiner's statement of reasons for allowance: The information disclosure statements (IDS) submitted on 18 June 2024, 15 July 2024 and 23 July 2024 have been considered by the Examiner. After careful consideration, the Examiner has determined that none of the information contained therein raises new issues of patentability.
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."

Summary

6. Claims 30-32 and 53-87 are allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **JON M LOCKARD** whose telephone number is **(571) 272-2717**. The examiner can normally be reached M-F 9-6 EST.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at <http://www.uspto.gov/interviewpractice>. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joanne Hama** can be reached on **(571) 272-2911**. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of published or unpublished applications may be obtained from Patent Center. Unpublished application information in Patent Center is available to registered users. To file and manage patent submissions in Patent Center, visit: <https://patentcenter.uspto.gov>. Visit <https://www.uspto.gov/patents/apply/patent-center> for more information about Patent Center and <https://www.uspto.gov/patents/docx> for information about filing in DOCX format. For additional questions, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/J.L/
Examiner, Art Unit 1647
July 25, 2024

/Christine J Saoud/
Primary Examiner, Art Unit 1645

<i>Search Notes</i> 	Application/Control No. 17/384,070	Applicant(s)/Patent Under Reexamination Graham et al.
	Examiner JON M LOCKARD	Art Unit 1647

CPC - Searched*		
Symbol	Date	Examiner

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner
NONE		03/16/2023	JML

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

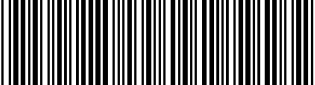
Search Notes		
Search Notes	Date	Examiner
PE2E Search (USPAT, US-PGPUB, EPO, DERWENT): See attached search history.	03/16/2023	JML
STN (MEDLINE, SCISEARCH, EMBASE, BIOSIS): See attached search history.	03/16/2023	JML
PALM: Inventor search.	03/16/2023	JML
PE2E Search (USPAT, US-PGPUB, EPO, DERWENT): See attached search history.	11/01/2023	JML

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<i>Search Notes</i> 	Application/Control No. 17/384,070	Applicant(s)/Patent Under Reexamination Graham et al.
	Examiner JON M LOCKARD	Art Unit 1647

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner
	PE2E Search (USPAT): See attached search history.	08/24/2023	JML
	DAV: Inventor search.	08/24/2023	JML
	PE2E Search (USPAT): See attached search history.	11/01/2023	JML
	DAV: Inventor search.	11/01/2023	JML
	PE2E Search (USPAT): See attached search history.	11/29/2023	JML
	DAV: Inventor search.	11/29/2023	JML
	PE2E Search (USPAT): See attached search history.	01/11/2024	JML
	DAV: Inventor search.	01/11/2024	JML
	PE2E Search (USPAT): See attached search history.	05/10/2024	JML
	DAV: Inventor search.	05/10/2024	JML
	PE2E Search (USPAT): See attached search history.	06/11/2024	JML
	DAV: Inventor search.	06/11/2024	JML
	PE2E Search (USPAT): See attached search history.	07/25/2024	JML
	DAV: Inventor search.	07/25/2024	JML

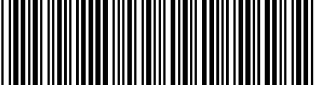
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Issue Classification 	Application/Control No. 17/384,070	Applicant(s)/Patent Under Reexamination Graham et al.
	Examiner JON M LOCKARD	Art Unit 1647

CPC						
Symbol					Type	Version
A61K	/	38	/	179	F	2013-01-01
A61K	/	9	/	0048	I	2013-01-01
A61K	/	47	/	12	I	2013-01-01
A61P	/	27	/	02	I	2018-01-01
A61K	/	47	/	22	I	2013-01-01
A61K	/	47	/	26	I	2013-01-01
A61K	/	47	/	183	I	2013-01-01

CPC Combination Sets					
Symbol				Type	Version
	/		/		

/JON M LOCKARD/ Examiner, Art Unit 1647 (Assistant Examiner)	25 July 2024 (Date)	Total Claims Allowed: 38	
/CHRISTINE J SAUD/ Primary Examiner, Art Unit 1645 (Primary Examiner)	26 July 2024 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure NONE

Issue Classification 	Application/Control No. 17/384,070	Applicant(s)/Patent Under Reexamination Graham et al.
	Examiner JON M LOCKARD	Art Unit 1647

INTERNATIONAL CLASSIFICATION			
CLAIMED			
A61K	/	38	/ 17
A61K	/	38	/ 18
C07K	/	14	/ 71
NON-CLAIMED			
	/		/

US ORIGINAL CLASSIFICATION	
CLASS	SUBCLASS

CROSS REFERENCES(S)						
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)					

/JON M LOCKARD/ Examiner, Art Unit 1647 (Assistant Examiner)	25 July 2024 (Date)	Total Claims Allowed: 38	
/CHRISTINE J SAUD/ Primary Examiner, Art Unit 1645 (Primary Examiner)	26 July 2024 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure NONE

Issue Classification 	Application/Control No. 17/384,070	Applicant(s)/Patent Under Reexamination Graham et al.
	Examiner JON M LOCKARD	Art Unit 1647

☐ 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
1	30	10	59	12	68	28	77	37	86						
2	31	11	60	26	69	29	78	38	87						
3	32	13	61	15	70	30	79								
4	53	14	62	17	71	31	80								
5	54	16	63	19	72	32	81								
6	55	18	64	21	73	33	82								
7	56	20	65	23	74	34	83								
8	57	22	66	25	75	35	84								
9	58	24	67	27	76	36	85								

/JON M LOCKARD/ Examiner, Art Unit 1647 (Assistant Examiner)	25 July 2024 (Date)	Total Claims Allowed: 38	
/CHRISTINE J SAOUD/ Primary Examiner, Art Unit 1645 (Primary Examiner)	26 July 2024 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure NONE

U.S. Patent and Trademark Office

Part of Paper No.: 20240725

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (not for submission under 37 CFR 1.99)	Application Number	17/384,070
	Filing Date	Jul-23-2021
	First Named Inventor	Kenneth S. Graham
	Art Unit	1647
	Confirmation Number	1061
	Examiner Name	Lockard, Jon McClelland
	Attorney Docket Number	125984-266215

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
	646	11,958,894		04-16-2024	Wang et al.	
	647	12,005,097		06-11-2024	Kerwin et al.	

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
	644	2024-0029897		01-25-2024	Perlee et al.	
	645	2024-0189402		06-13-2024	Borodic	

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

NON-PATENT LITERATURE DOCUMENTS			
Examiner Initial*	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
	641	Anonymous: "Product information EYLA aflibercept (rch)", 15 April 2015 (2015-04-15), XP093174268, [Retrieved from the Internet: URL:https://www.tga.gov.au/sites/default/files/auspar-aflibercept-150721-pi.pdf]	
	642	Australian Public Assessment Report for Aflibercept, Australian Government, Department of Health & Aging, Therapeutic Goods Administration, Proprietary Product Name: Eylea sponsored by Bayer Australia Ltd (publication date 07-21-2015).	
	643	Clinical Trials for "Phase 1 Study of VEGF Trap in Patients With Diabetic Macular Edema," sponsored by Regeneron Pharmaceuticals, NCT00320814 (publication date 06-10-2011).	

Receipt date: 07/15/2024

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (not for submission under 37 CFR 1.99)	Application Number	17/384,070
	Filing Date	Jul-23-2021
	First Named Inventor	Kenneth S. Graham
	Art Unit	1647
	Confirmation Number	1061
	Examiner Name	Lockard, Jon McClelland
	Attorney Docket Number	125984-266215

EXAMINER SIGNATURE			
Examiner Signature	/JON M LOCKARD/	Date Considered	07/25/2024
*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.			
<p>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.</p>			

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (not for submission under 37 CFR 1.99)	Application Number	17/384,070
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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

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

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

NON-PATENT LITERATURE DOCUMENTS			
Examiner Initial*	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
	648	AVASTIN label (revised December 2017)	
	649	HERCEPTIN label (September 1998)	
	650	LUCENTIS label (revised October 2014)	
	651	REMICADE label (revised November 2013)	
	652	SIMULECT label (May 1998)	
	653	XOLAIR label (2003)	

Receipt date: 07/23/2024

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	Filing Date	Jul-23-2021
	First Named Inventor	Kenneth S. Graham
	Art Unit	1647
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	Examiner Name	Lockard, Jon McClelland
	Attorney Docket Number	125984-266215

EXAMINER SIGNATURE			
Examiner Signature	/JON M LOCKARD/	Date Considered	07/25/2024
*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.			
<p>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.</p>			

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	Examiner Name	Lockard, Jon McClelland
	Attorney Docket Number	125984-266215

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
	639	11,986,511		05-21-2024	Yancopoulos et al.	

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

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

NON-PATENT LITERATURE DOCUMENTS			
Examiner Initial*	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

Receipt date: 06/18/2024

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (not for submission under 37 CFR 1.99)	Application Number	17/384,070
	Filing Date	Jul-23-2021
	First Named Inventor	Kenneth S. Graham
	Art Unit	1647
	Confirmation Number	1061
	Examiner Name	Lockard, Jon McClelland
	Attorney Docket Number	125984-266215

EXAMINER SIGNATURE			
Examiner Signature	/JON M LOCKARD/	Date Considered	07/25/2024
*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.			
<p>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.</p>			

PE2E SEARCH - Search History (Prior Art)

/J.L./

There are no Prior Art searches to show.
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PE2E SEARCH - Search History (Interference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	British Equivalents	Time Stamp
N50	2831	vegf ADJ trap	(USPAT)	OR	ON	ON	2024/07/25 09:43 PM
N51	2990	aflibercept	(USPAT)	OR	ON	ON	2024/07/25 09:43 PM
N52	462	eylea	(USPAT)	OR	ON	ON	2024/07/25 09:43 PM
N53	125	vegf ADJ trap-eye	(USPAT)	OR	ON	ON	2024/07/25 09:43 PM
N54	456	(N41 N42 N43 N44) SAME formulation	(USPAT)	OR	ON	ON	2024/07/25 09:43 PM
N55	12	N45 SAME "high concentration"	(USPAT)	OR	ON	ON	2024/07/25 09:43 PM
N56	1	N45 AND (8mg OR "8 mg").clm.	(USPAT)	OR	ON	ON	2024/07/25 09:43 PM
N57	18	(graham-k\$-s\$ washawa-s\$).in.	(USPAT)	OR	ON	ON	2024/07/25 09:43 PM
N58	1	N46 AND N48	(USPAT)	OR	ON	ON	2024/07/25 09:43 PM

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (not for submission under 37 CFR 1.99)	Application Number	17/384,070
	Filing Date	Jul-23-2021
	First Named Inventor	Kenneth S. Graham
	Art Unit	1647
	Confirmation Number	1061
	Examiner Name	Lockard, Jon McClelland
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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

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

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

NON-PATENT LITERATURE DOCUMENTS			
Examiner Initial*	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
	648	AVASTIN label (revised December 2017)	
	649	HERCEPTIN label (September 1998)	
	650	LUCENTIS label (revised October 2014)	
	651	REMICADE label (revised November 2013)	
	652	SIMULECT label (May 1998)	
	653	XOLAIR label (2003)	

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	Art Unit	1647
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	Examiner Name	Lockard, Jon McClelland
	Attorney Docket Number	125984-266215

EXAMINER SIGNATURE			
Examiner Signature		Date Considered	
<p>*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.</p>			
<p>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.</p>			

INFORMATION DISCLOSURE STATEMENT BY APPLICANT <small>(not for submission under 37 CFR 1.99)</small>	Application Number	17/384,070
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	First Named Inventor	Kenneth S. Graham
	Art Unit	1647
	Confirmation Number	1061
	Examiner Name	Lockard, Jon McClelland
	Attorney Docket Number	125984-266215

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.			
☐ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.			
☒ None			
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	/Lance A. Termes/	Date (YYYY-MM-DD)	2024-07-23
Name/Print	Lance A. Termes	Registration Number	43184



ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #
17/384,070

RECEIPT DATE / TIME
07/23/2024 08:28:49 PM Z ET

ATTORNEY DOCKET #
-

Title of Invention

Methods for Treating Angiogenic Eye Disorders with High Doses of VEGF Receptor Fusion Proteins

Application Information

APPLICATION TYPE Utility - Nonprovisional Application
under 35 USC 111(a)

PATENT # -

CONFIRMATION # 1061

FILED BY Brandi Henley

PATENT CENTER # 66491121

FILING DATE 07/23/2021

CUSTOMER # 147803

FIRST NAMED
INVENTOR Kenneth S. Graham

CORRESPONDENCE
ADDRESS -

AUTHORIZED BY Lance Termes

Documents

TOTAL DOCUMENTS: 8

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
649_NPL_HerceptinLabel_Se pt1998.pdf	2	Non Patent Literature	156 KB
650_NPL_LucentisLabel_201 4.pdf	14	Non Patent Literature	282 KB
653_NPL_XolairLabel_2003. pdf	17	Non Patent Literature	417 KB
648_NPL_AvastinLabel_Dec 2017.pdf	37	Non Patent Literature	1068 KB
652_NPL_SimulectLabel_Ma y1998.pdf	7	Non Patent Literature	837 KB

651_NPL_RemicadeLabel_Nov2013.pdf	58	Non Patent Literature	2564 KB
10430US02_IDS-Transmittal.pdf	3	Transmittal Letter	20 KB
10430US02_IDS-SB08.pdf	3	Information Disclosure Statement (IDS) Form (SB08)	52 KB

Warning: This is not a USPTO supplied IDS fillable form. Data in the form cannot be automatically loaded to other USPTO systems.

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
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10430US02_IDS-
Transmittal.pdf

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10430US02_IDS-SB08.pdf

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4992E1DD49FAE8916B148EF7B338A339504D8C0C5FD6D7D52
496D2D2DBF2A87BAE970F42ED118BA8

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 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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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Kenneth S. Graham, et al. Application No.: 17/384,070 Filed: Jul-23-2021 For: HIGH CONCENTRATION VEGF RECEPTOR FUSION PROTEIN CONTAINING FORMULATIONS Customer No.: 147803	Confirmation No.: 1061 Examiner: Lockard, Jon McClelland Art Unit: 1647 SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR §1.97 and §1.98 Date of Transmission: July 23, 2024
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Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

The references cited on the attached IDS are being called to the attention of the Examiner. Copies of the references in compliance with the requirements of 37 CFR §1.98(a)(2) are submitted herewith.

It is respectfully requested that the cited reference be expressly considered during the prosecution of this application, and the reference be made of record therein and appear among the “references cited” on any patent to issue therefrom.

The Examiner is encouraged to review the full prosecution history from related cases. Applicant understands that the prosecution history can be viewed electronically on

PALM. Nevertheless, if the Examiner wishes Applicant to provide copies of any documents from related applications to the extent not already provided, he or she is requested to contact the undersigned.

Applicant cites the following applications, which are directed to related subject matter and are commonly owned or under an assignment obligation to be commonly owned:

Attorney Docket No.	Application No.	Filing Date	Publication No.	Status
125984-248591	62/669,506	05-10-2018	N/A	Expired
125984-248592	62/752,127	10-29-2018	N/A	Expired
125984-248593	62/769,876	11-20-2018	N/A	Expired
125984-248594	62/813,882	03-05-2019	N/A	Expired
125984-248595	16/409,631	05-10-2019	US 11,103,552	Issued
125984-248596	PCT/US2019/031879	05-10-2019	WO 2019/217927	Expired
125984-281135	18/367,444	09-12-2023	US-2024-0058418	Published

As provided for by 37 CFR §1.97(g) and (h), no inference should be made that the information and references cited are prior art merely because they are in this statement and no representation is being made that a search has been conducted or that this statement encompasses all the possible relevant information.

Applicant believes that no fee is required for submission of this statement.

However, if a fee is required in connection with this paper, the Commissioner is authorized to deduct such fee from the undersigned's Deposit Account No. 500393.

Respectfully submitted,

/Lance A. Termes/

Lance A. Termes
Reg. No. 43184

Schwabe Williamson & Wyatt, PC
1211 SW 5th Avenue, Suite 1900
Portland, OR 97204
Tel: 503-222-9981



UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #
17/384,070

RECEIPT DATE / TIME
07/15/2024 05:47:47 PM Z ET

ATTORNEY DOCKET #
-

Title of Invention

Methods for Treating Angiogenic Eye Disorders with High Doses of VEGF Receptor Fusion Proteins

Application Information

APPLICATION TYPE Utility - Nonprovisional Application
under 35 USC 111(a)

PATENT # -

CONFIRMATION # 1061

FILED BY Brandi Henley

PATENT CENTER # 66375347

FILING DATE 07/23/2021

CUSTOMER # 147803

FIRST NAMED
INVENTOR Kenneth S. Graham

CORRESPONDENCE
ADDRESS -

AUTHORIZED BY Lance Termes

Documents

TOTAL DOCUMENTS: 5

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
10430US02_IDS- Transmittal.pdf	3	Transmittal Letter	20 KB
10430US02_IDS-SB08.pdf	3	Information Disclosure Statement (IDS) Form (SB08)	54 KB
Warning: This is not a USPTO supplied IDS fillable form. Data in the form cannot be automatically loaded to other USPTO systems.			
643_NPL_NCT00320814- 06102011.pdf	8	Non Patent Literature	479 KB
642_NPL_AustralianPublicAs sessmentReportAflibercept.p	32	Non Patent Literature	19572 KB

df

641_NPL_Anonymous_Product-information.pdf	34	Non Patent Literature	22780 KB
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Digest

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642_NPL_AustralianPublicAssessmentReportAffibercept.pdf	828F6F0775118CCEC61AE032134F4CB1D96D341AC068DA1E0021D85F9EBA174359C924102D62435E59243A0BAAEDE40B2CF96090986B3D6E9E258DF347A37E94
641_NPL_Anonymous_Product-information.pdf	6BD39AA277F5FDBCA7D7A792E8EA45F7D4E90557D51384D63F82072A7758D57375C89C4F9088DA494775E15138028A7F5E8176FA37BE8EFBB4935829F7CB689F

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (not for submission under 37 CFR 1.99)	Application Number	17/384,070
	Filing Date	Jul-23-2021
	First Named Inventor	Kenneth S. Graham
	Art Unit	1647
	Confirmation Number	1061
	Examiner Name	Lockard, Jon McClelland
	Attorney Docket Number	125984-266215

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
	646	11,958,894		04-16-2024	Wang et al.	
	647	12,005,097		06-11-2024	Kerwin et al.	

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
	644	2024-0029897		01-25-2024	Perlee et al.	
	645	2024-0189402		06-13-2024	Borodic	

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

NON-PATENT LITERATURE DOCUMENTS			
Examiner Initial*	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
	641	Anonymous: "Product information EYLA aflibercept (rch)", 15 April 2015 (2015-04-15), XP093174268, [Retrieved from the Internet: URL:https://www.tga.gov.au/sites/default/files/auspar-aflibercept-150721-pi.pdf]	
	642	Australian Public Assessment Report for Aflibercept, Australian Government, Department of Health & Aging, Therapeutic Goods Administration, Proprietary Product Name: Eylea sponsored by Bayer Australia Ltd (publication date 07-21-2015).	
	643	Clinical Trials for "Phase 1 Study of VEGF Trap in Patients With Diabetic Macular Edema," sponsored by Regeneron Pharmaceuticals, NCT00320814 (publication date 06-10-2011).	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (not for submission under 37 CFR 1.99)	Application Number	17/384,070
	Filing Date	Jul-23-2021
	First Named Inventor	Kenneth S. Graham
	Art Unit	1647
	Confirmation Number	1061
	Examiner Name	Lockard, Jon McClelland
	Attorney Docket Number	125984-266215

EXAMINER SIGNATURE			
Examiner Signature		Date Considered	
<p>*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.</p>			
<p>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.</p>			

INFORMATION DISCLOSURE STATEMENT BY APPLICANT <small>(not for submission under 37 CFR 1.99)</small>	Application Number	17/384,070
	Filing Date	Jul-23-2021
	First Named Inventor	Kenneth S. Graham
	Art Unit	1647
	Confirmation Number	1061
	Examiner Name	Lockard, Jon McClelland
	Attorney Docket Number	125984-266215

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.			
☐ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.			
☒ None			
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	/Lance A. Termes/	Date (YYYY-MM-DD)	2024-07-15
Name/Print	Lance A. Termes	Registration Number	43184

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Kenneth S. Graham, et al.

Application No.: 17/384,070

Filed: Jul-23-2021

For: HIGH CONCENTRATION VEGF
RECEPTOR FUSION PROTEIN
CONTAINING FORMULATIONS

Customer No.: 147803

Confirmation No.: 1061

Examiner: Lockard, Jon McClelland

Art Unit: 1647

**SUPPLEMENTAL INFORMATION
DISCLOSURE STATEMENT UNDER
37 CFR §1.97 and §1.98**

Date of Transmission: July 15, 2024

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

Commissioner:

The references cited on the attached IDS are being called to the attention of the Examiner. Copies of the references in compliance with the requirements of 37 CFR §1.98(a)(2) are submitted herewith.

It is respectfully requested that the cited reference be expressly considered during the prosecution of this application, and the reference be made of record therein and appear among the “references cited” on any patent to issue therefrom.

The Examiner is encouraged to review the full prosecution history from related cases. Applicant understands that the prosecution history can be viewed electronically on

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125984-248592	62/752,127	10-29-2018	N/A	Expired
125984-248593	62/769,876	11-20-2018	N/A	Expired
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125984-248596	PCT/US2019/031879	05-10-2019	WO 2019/217927	Expired
125984-281135	18/367,444	09-12-2023	US-2024-0058418	Published

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Applicant believes that no fee is required for submission of this statement.

However, if a fee is required in connection with this paper, the Commissioner is authorized to deduct such fee from the undersigned's Deposit Account No. 500393.

Respectfully submitted,

/Lance A. Termes/

Lance A. Termes
Reg. No. 43184

Schwabe Williamson & Wyatt, PC
1211 SW 5th Avenue, Suite 1900
Portland, OR 97204
Tel: 503-222-9981



UNITED STATES
PATENT AND TRADEMARK OFFICE

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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #
17/384,070

RECEIPT DATE / TIME
07/15/2024 05:15:24 PM Z ET

ATTORNEY DOCKET #
-

Title of Invention

Methods for Treating Angiogenic Eye Disorders with High Doses of VEGF Receptor Fusion Proteins

Application Information

APPLICATION TYPE Utility - Nonprovisional Application
under 35 USC 111(a)

PATENT # -

CONFIRMATION # 1061

FILED BY Lance Termes

PATENT CENTER # 66374458

FILING DATE 07/23/2021

CUSTOMER # 147803

FIRST NAMED
INVENTOR Kenneth S. Graham

CORRESPONDENCE
ADDRESS -

AUTHORIZED BY -

Documents

TOTAL DOCUMENTS: 1

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
10430US02__RCE.pdf	1	Request for Continued Examination (RCE)	209 KB

Warning: This is not a USPTO supplied RCE fillable form. Data in the form cannot be automatically loaded to other USPTO systems.

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
10430US02__RCE.pdf	22226FA298DA7AC7B148186739342815F9EF1D2EB333D81121 9225F6E68199ADB2E9113B5BC1A2A1C0FD213A4BCB66221B5

CEC3EC3ECA3F810D7EB31173F9F8B

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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.

**Request
for
Continued Examination (RCE)
Transmittal**

Address to:
Mail Stop RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Application Number	17/384,070
Filing Date	July 23, 2021
First Named Inventor	Kenneth S. Graham
Art Unit	1647
Examiner Name	Jon McClelland Lockard
Attorney Docket Number	125984-266215

This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. See Instruction Sheet for RCEs (not to be submitted to the USPTO) on page 2.

1. **Submission required under 37 CFR 1.114** Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).
- a. ☐ Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.
- i. ☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____
- ii. ☐ Other _____
- b. ☒ Enclosed
- i. ☐ Amendment/Reply
- ii. ☐ Affidavit(s)/ Declaration(s)
- iii. ☒ Information Disclosure Statement (IDS)
- iv. ☐ Other _____
2. **Miscellaneous**
- a. ☐ Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a period of _____ months. (Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)
- b. ☐ Other _____
3. **Fees** The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.
- a. ☒ The Director is hereby authorized to charge the following fees, any underpayment of fees, or credit any overpayments, to Deposit Account No. 500393.
- i. ☒ RCE fee required under 37 CFR 1.17(e)
- ii. ☐ Extension of time fee (37 CFR 1.136 and 1.17)
- iii. ☐ Other _____
- b. ☐ Check in the amount of \$ _____ enclosed
- c. ☐ Payment by credit card (Form PTO-2038 enclosed)
- d. ☒ Payment by USPTO patent electronic filing system.

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.

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

Signature	/Lance A. Termes/	Date	July 15, 2024
Name (Print/Type)	Lance A. Termes	Registration No.	43,184

CERTIFICATE OF MAILING OR TRANSMISSION

I hereby certify that this correspondence is transmitted by the USPTO patent electronic filing system, or by facsimile to (571) 273-8300, to the USPTO, or deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop RCE, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on the date shown below.

Signature	/Lance A. Termes/	Date	July 15, 2024
Name (Print/Type)	Lance A. Termes		

A Federal agency may not conduct or sponsor, and a person is not required to respond to, nor shall a person be subject to a penalty for failure to comply with an information collection subject to the requirements of the Paperwork Reduction Act of 1995, unless the information collection has a currently valid OMB Control Number. The OMB Control Number for this information collection is 0651-0031. Public burden for this form is estimated to average 12 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the information collection. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden to the Chief Administrative Officer, United States Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450 or email InformationCollection@uspto.gov. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. If filing this completed form by mail, 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.



UNITED STATES
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ELECTRONIC PAYMENT RECEIPT

APPLICATION # 17/384,070	RECEIPT DATE / TIME 07/15/2024 05:15:24 PM Z ET	ATTORNEY DOCKET # -
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Title of Invention

Methods for Treating Angiogenic Eye Disorders with High Doses of VEGF Receptor Fusion Proteins

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	1061	FILED BY	Lance Termes
PATENT CENTER #	66374458	AUTHORIZED BY	-
CUSTOMER #	147803	FILING DATE	07/23/2021
CORRESPONDENCE ADDRESS	-	FIRST NAMED INVENTOR	Kenneth S. Graham

Payment Information

PAYMENT METHOD DA / 500393	PAYMENT TRANSACTION ID E20247EH15539616	PAYMENT AUTHORIZED BY Lance Termes
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FEE CODE	DESCRIPTION	ITEM PRICE(\$)	QUANTITY	ITEM TOTAL(\$)
1820	REQUEST FOR CONTINUED EXAMINATION (RCE)- 2ND AND SUBSEQUENT REQUEST (SEE 37 CFR 1.114)	2000.00	1	2000.00
TOTAL AMOUNT:				\$2,000.00

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UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
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NOTICE OF ALLOWANCE AND FEE(S) DUE

147803 7590 07/01/2024
Schwabe W&W, PC / Regeneron Pharmaceuticals, Inc.
PacWest Center
1211 SW Fifth Avenue, Suite 1900
Portland, OR 97204

EXAMINER

LOCKARD, JON MCCLELLAND

ART UNIT PAPER NUMBER

1647

DATE MAILED: 07/01/2024

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/384,070	07/23/2021	Kenneth S. Graham		1061

TITLE OF INVENTION: Methods for Treating Angiogenic Eye Disorders with High Doses of VEGF Receptor Fusion Proteins

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	\$1200	\$0.00	\$1200.00	\$0	10/01/2024

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 40% the amount of undiscounted fees, and micro entity fees are 20% the amount of undiscounted 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. 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 the USPTO patent electronic filing system.

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 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. **Because electronic patent issuance may occur shortly after issue fee payment, any desired continuing application should preferably be filed prior to payment of this issue fee in order not to jeopardize copendency.**

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

147803 7590 07/01/2024
Schwabe W&W, PC / Regeneron Pharmaceuticals, Inc.
PacWest Center
1211 SW Fifth Avenue, Suite 1900
Portland, OR 97204

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 the USPTO patent electronic filing system 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.
17/384,070	07/23/2021	Kenneth S. Graham		1061

TITLE OF INVENTION: Methods for Treating Angiogenic Eye Disorders with High Doses of VEGF Receptor Fusion Proteins

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	\$1200	\$0.00	\$1200.00	\$0	10/01/2024

EXAMINER	ART UNIT	CLASS-SUBCLASS
LOCKARD, JON MCCLELLAND	1647	424-134100

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/AIA/122 or PTO/SB/122) attached.

☐ "Fee Address" indication (or "Fee Address" Indication form PTO/AIA/47 or 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 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)

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

☐ Electronic Payment via the USPTO patent electronic filing system ☐ 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. _____



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.
17/384,070	07/23/2021	Kenneth S. Graham		1061
147803	7590	07/01/2024		
Schwabe W&W, PC / Regeneron Pharmaceuticals, Inc.				
PacWest Center				
1211 SW Fifth Avenue, Suite 1900				
Portland, OR 97204				
			EXAMINER	
			LOCKARD, JON MCCLELLAND	
			ART UNIT	PAPER NUMBER
			1647	

DATE MAILED: 07/01/2024

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. The United States Patent and Trademark Office (USPTO) collects the information in this record under authority of 35 U.S.C. 2. The USPTO's system of records is used to manage all applicant and owner information including name, citizenship, residence, post office address, and other information with respect to inventors and their legal representatives pertaining to the applicant's/owner's activities in connection with the invention for which a patent is sought or has been granted. The applicable Privacy Act System of Records Notice for the information collected in this form is COMMERCE/PAT-TM-7 Patent Application Files, available in the Federal Register at 78 FR 19243 (March 29, 2013).

<https://www.govinfo.gov/content/pkg/FR-2013-03-29/pdf/2013-07341.pdf>

Routine uses of the information in this record may include disclosure to:

- 1) law enforcement, in the event that the system of records indicates a violation or potential violation of law;
- 2) a federal, state, local, or international agency, in response to its request;
- 3) a contractor of the USPTO having need for the information in order to perform a contract;
- 4) the Department of Justice for determination of whether the Freedom of Information Act (FOIA) requires disclosure of the record;
- 5) a Member of Congress submitting a request involving an individual to whom the record pertains, when the individual has requested the Member's assistance with respect to the subject matter of the record;
- 6) a court, magistrate, or administrative tribunal, in the course of presenting evidence, including disclosures to opposing counsel in the course of settlement negotiations;
- 7) the Administrator, General Services Administration (GSA), or their designee, during an inspection of records conducted by GSA under authority of 44 U.S.C. 2904 and 2906, in accordance with the GSA regulations and any other relevant (i.e., GSA or Commerce) directive, where such disclosure shall not be used to make determinations about individuals;
- 8) 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));
- 9) the Office of Personnel Management (OPM) for personnel research purposes; and
- 10) the Office of Management and Budget (OMB) for legislative coordination and clearance.

If you do not furnish the information requested on this form, the USPTO may not be able to process and/or examine your submission, which may result in termination of proceedings, abandonment of the application, and/or expiration of the patent.

Notice of Allowability	Application No. 17/384,070	Applicant(s) Graham et al.	
	Examiner JON M LOCKARD	Art Unit 1647	AIA (FITF) Status Yes

-- 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 the Request for Continued Examination filed 07 June 2024.
☐ 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 See Continuation Sheet . 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)	5. ☒ Examiner's Amendment/Comment
2. ☒ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date ____.	6. ☒ Examiner's Statement of Reasons for Allowance
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material ____.	7. ☐ Other ____.
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date ____.	

/J.L/ Examiner, Art Unit 1647	/CHRISTINE J SAOUD/ Primary Examiner, Art Unit 1645
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Continuation of 3. The allowed claim(s) is/are: 30-32 and 53-87 (renumbered as claims 1-11, 13-14, 16, 18, 20, 22, 24, 12, 26, 15, 17, 19, 21, 23, 25 and 27-38, respectively)

Notice of Pre-AIA or AIA Status

1. The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

Continued Examination Under 37 CFR 1.114

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 allowance or after an Office action under *Ex Parte Quayle*, 25 USPQ 74, 453 O.G. 213 (Comm'r Pat. 1935). 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, prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 07 June 2024 has been entered.

Information Disclosure Statement

3. The information disclosure statement (IDS) submitted on 07 June 2024 has been considered by the examiner.

REASONS FOR ALLOWANCE

4. The following is an examiner's statement of reasons for allowance: The information disclosure statement (IDS) submitted on 07 June 2024 has been considered by the Examiner. After careful consideration, the Examiner has determined that none of the information contained therein raises new issues of patentability.
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."

Summary

6. Claims 30-32 and 53-87 are allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **JON M LOCKARD** whose telephone number is **(571) 272-2717**. The examiner can normally be reached M-F 9-6 EST.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at <http://www.uspto.gov/interviewpractice>. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joanne Hama** can be reached on **(571) 272-2911**. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of published or unpublished applications may be obtained from Patent Center. Unpublished application information in Patent Center is available to registered users. To file and manage patent submissions in Patent Center, visit: <https://patentcenter.uspto.gov>. Visit <https://www.uspto.gov/patents/apply/patent-center> for more information about Patent Center and <https://www.uspto.gov/patents/docx> for information about filing in DOCX format. For additional questions, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/J.L/
Examiner, Art Unit 1647
June 11, 2024

/Christine J Saoud/
Primary Examiner, Art Unit 1645

<i>Search Notes</i> 	Application/Control No. 17/384,070	Applicant(s)/Patent Under Reexamination Graham et al.
	Examiner JON M LOCKARD	Art Unit 1647

CPC - Searched*		
Symbol	Date	Examiner

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner
NONE		03/16/2023	JML

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

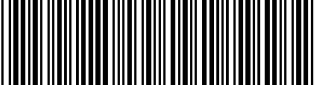
Search Notes		
Search Notes	Date	Examiner
PE2E Search (USPAT, US-PGPUB, EPO, DERWENT): See attached search history.	03/16/2023	JML
STN (MEDLINE, SCISEARCH, EMBASE, BIOSIS): See attached search history.	03/16/2023	JML
PALM: Inventor search.	03/16/2023	JML
PE2E Search (USPAT, US-PGPUB, EPO, DERWENT): See attached search history.	11/01/2023	JML

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<i>Search Notes</i> 	Application/Control No. 17/384,070	Applicant(s)/Patent Under Reexamination Graham et al.
	Examiner JON M LOCKARD	Art Unit 1647

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner
	PE2E Search (USPAT): See attached search history.	08/24/2023	JML
	DAV: Inventor search.	08/24/2023	JML
	PE2E Search (USPAT): See attached search history.	11/01/2023	JML
	DAV: Inventor search.	11/01/2023	JML
	PE2E Search (USPAT): See attached search history.	11/29/2023	JML
	DAV: Inventor search.	11/29/2023	JML
	PE2E Search (USPAT): See attached search history.	01/11/2024	JML
	DAV: Inventor search.	01/11/2024	JML
	PE2E Search (USPAT): See attached search history.	05/10/2024	JML
	DAV: Inventor search.	05/10/2024	JML
	PE2E Search (USPAT): See attached search history.	06/11/2024	JML
	DAV: Inventor search.	06/11/2024	JML

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Issue Classification 	Application/Control No. 17/384,070	Applicant(s)/Patent Under Reexamination Graham et al.
	Examiner JON M LOCKARD	Art Unit 1647

CPC						
Symbol					Type	Version
A61K	/	38	/	179	F	2013-01-01
A61K	/	9	/	0048	I	2013-01-01
A61K	/	47	/	12	I	2013-01-01
A61P	/	27	/	02	I	2018-01-01
A61K	/	47	/	22	I	2013-01-01
A61K	/	47	/	26	I	2013-01-01
A61K	/	47	/	183	I	2013-01-01

CPC Combination Sets					
Symbol				Type	Set
	/		/		

/JON M LOCKARD/ Examiner, Art Unit 1647 (Assistant Examiner)	11 June 2024 (Date)	Total Claims Allowed: 38	
/CHRISTINE J SAOUD/ Primary Examiner, Art Unit 1645 (Primary Examiner)	14 June 2024 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure NONE

U.S. Patent and Trademark Office

Part of Paper No.: 20240611

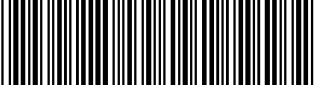
Issue Classification 	Application/Control No. 17/384,070	Applicant(s)/Patent Under Reexamination Graham et al.
	Examiner JON M LOCKARD	Art Unit 1647

INTERNATIONAL CLASSIFICATION			
CLAIMED			
A61K	/	38	/ 17
A61K	/	38	/ 18
C07K	/	14	/ 71
NON-CLAIMED			
	/		/

US ORIGINAL CLASSIFICATION	
CLASS	SUBCLASS

CROSS REFERENCES(S)						
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)					

/JON M LOCKARD/ Examiner, Art Unit 1647 (Assistant Examiner)	11 June 2024 (Date)	Total Claims Allowed: 38	
/CHRISTINE J SAUD/ Primary Examiner, Art Unit 1645 (Primary Examiner)	14 June 2024 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure NONE

Issue Classification 	Application/Control No. 17/384,070	Applicant(s)/Patent Under Reexamination Graham et al.
	Examiner JON M LOCKARD	Art Unit 1647

☐ 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
1	30	10	59	12	68	28	77	37	86						
2	31	11	60	26	69	29	78	38	87						
3	32	13	61	15	70	30	79								
4	53	14	62	17	71	31	80								
5	54	16	63	19	72	32	81								
6	55	18	64	21	73	33	82								
7	56	20	65	23	74	34	83								
8	57	22	66	25	75	35	84								
9	58	24	67	27	76	36	85								

/JON M LOCKARD/ Examiner, Art Unit 1647 (Assistant Examiner)	11 June 2024 (Date)	Total Claims Allowed: 38	
/CHRISTINE J SAOUD/ Primary Examiner, Art Unit 1645 (Primary Examiner)	14 June 2024 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure NONE

U.S. Patent and Trademark Office

Part of Paper No.: 20240611

PE2E SEARCH - Search History (Prior Art)

/J.L./

There are no Prior Art searches to show.

PE2E SEARCH - Search History (Interference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	British Equivalents	Time Stamp
N41	2795	vegf ADJ trap	(USPAT)	OR	ON	ON	2024/06/11 08:22 PM
N42	2941	aflibercept	(USPAT)	OR	ON	ON	2024/06/11 08:22 PM
N43	393	eylea	(USPAT)	OR	ON	ON	2024/06/11 08:22 PM
N44	121	vegf ADJ trap-eye	(USPAT)	OR	ON	ON	2024/06/11 08:22 PM
N45	449	(N41 N42 N43 N44) SAME formulation	(USPAT)	OR	ON	ON	2024/06/11 08:22 PM
N46	12	N45 SAME "high concentration"	(USPAT)	OR	ON	ON	2024/06/11 08:23 PM
N47	1	N45 AND (8mg OR "8 mg").clm.	(USPAT)	OR	ON	ON	2024/06/11 08:23 PM
N48	17	(graham-k\$-s\$ washawa-s\$).in.	(USPAT)	OR	ON	ON	2024/06/11 08:24 PM
N49	1	N46 AND N48	(USPAT)	OR	ON	ON	2024/06/11 08:24 PM

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (not for submission under 37 CFR 1.99)	Application Number	17/384,070
	Filing Date	Jul-23-2021
	First Named Inventor	Kenneth S. Graham
	Art Unit	1647
	Confirmation Number	1061
	Examiner Name	Lockard, Jon McClelland
	Attorney Docket Number	125984-266215

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

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

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

NON-PATENT LITERATURE DOCUMENTS			
Examiner Initial*	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
	585	clinicaltrials.gov posting-NCT02305238-11282014 to 12202018, December 20, 2018.	
	586	clinicaltrials.gov posting-NCT02581891-10202015 to 05122020, May 12, 2020.	
	601	clinicaltrials.gov posting NCT00036946, June 1, 2016.	
	602	clinicaltrials.gov posting NCT00527423, June 10, 2013.	
	611	clinicaltrials.gov posting NCT01331681, March 20, 2016.	
	636	GAUDREAU et al., "PHARMACOKINETICS AND RETINAL DISTRIBUTION OF RANIBIZUMAB, A HUMANIZED ANTIBODY FRAGMENT DIRECTED AGAINST VEGF-A, FOLLOWING INTRAVITREAL ADMINISTRATION IN RABBITS," RETINA, THE JOURNAL OF RETINAL AND VITREOUS DISEASES, Volume 27 (No 9): 1260-1266, (2007).	
	637	GAUDREAU et al., "Preclinical Pharmacokinetics of Ranibizumab (rhuFabV2) after a Single Intravitreal Administration," Publication, Volume 46 (No 2): 726-733, (2005). [downloaded from lovs.arvojournals.org on 10/03/2023].	

Receipt date: 06/07/2024

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (not for submission under 37 CFR 1.99)	Application Number	17/384,070
	Filing Date	Jul-23-2021
	First Named Inventor	Kenneth S. Graham
	Art Unit	1647
	Confirmation Number	1061
	Examiner Name	Lockard, Jon McClelland
	Attorney Docket Number	125984-266215

NON-PATENT LITERATURE DOCUMENTS			
Examiner Initial*	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
	638	Assessment report; International non-proprietary name: faricimab; Procedure No. EMEA/H/C/005642/0000. Committee for Medicinal Products for Human Use (CHMP) 319 pages (21 July 2022). [EMA/687844/2022]	
	634	U.S. Application No. 18/367,444, Non-Final Office Action mailed 05-21-2024.	

EXAMINER SIGNATURE			
Examiner Signature	/JON M LOCKARD/		Date Considered 06/11/2024
*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.			
<p>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.</p>			

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Kenneth S. Graham, et al. Application No.: 17/384,070 Filed: Jul-23-2021 For: HIGH CONCENTRATION VEGF RECEPTOR FUSION PROTEIN CONTAINING FORMULATIONS Customer No.: 147803	Confirmation No.: 1061 Examiner: Lockard, Jon McClelland Art Unit: 1647 SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR §1.97 and §1.98 Date of Transmission: June 18, 2024
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Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

The reference cited on the attached IDS is being called to the attention of the Examiner. A copy of the reference does not need to be submitted herewith pursuant to the requirements of 37 CFR §1.98(a)(2).

It is respectfully requested that the cited reference be expressly considered during the prosecution of this application, and the reference be made of record therein and appear among the “references cited” on any patent to issue therefrom.

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Attorney Docket No.	Application No.	Filing Date	Publication No.	Status
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125984-248592	62/752,127	10-29-2018	N/A	Expired
125984-248593	62/769,876	11-20-2018	N/A	Expired
125984-248594	62/813,882	03-05-2019	N/A	Expired
125984-248595	16/409,631	05-10-2019	US 11,103,552	Issued
125984-248596	PCT/US2019/031879	05-10-2019	WO 2019/217927	Expired
125984-281135	18/367,444	09-12-2023	US-2024-0058418	Published

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Applicant believes that no fee is required for submission of this statement.

However, if a fee is required in connection with this paper, the Commissioner is authorized to deduct such fee from the undersigned's Deposit Account No. 500393.

Respectfully submitted,

/Lance A. Termes/

Lance A. Termes
Reg. No. 43184

Schwabe Williamson & Wyatt, PC
1211 SW 5th Avenue, Suite 1900
Portland, OR 97204
Tel: 503-222-9981

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (not for submission under 37 CFR 1.99)	Application Number	17/384,070
	Filing Date	Jul-23-2021
	First Named Inventor	Kenneth S. Graham
	Art Unit	1647
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	Examiner Name	Lockard, Jon McClelland
	Attorney Docket Number	125984-266215

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
	639	11,986,511		05-21-2024	Yancopoulos et al.	

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

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

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	Art Unit	1647
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EXAMINER SIGNATURE			
Examiner Signature		Date Considered	
<p>*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.</p>			
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	Art Unit	1647
	Confirmation Number	1061
	Examiner Name	Lockard, Jon McClelland
	Attorney Docket Number	125984-266215

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.			
☐ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.			
☒ None			
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	/Lance A. Termes/	Date (YYYY-MM-DD)	2024-06-18
Name/Print	Lance A. Termes	Registration Number	43184



UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #
17/384,070

RECEIPT DATE / TIME
06/18/2024 06:16:27 PM Z ET

ATTORNEY DOCKET #
-

Title of Invention

Methods for Treating Angiogenic Eye Disorders with High Doses of VEGF Receptor Fusion Proteins

Application Information

APPLICATION TYPE Utility - Nonprovisional Application
under 35 USC 111(a)

PATENT # -

CONFIRMATION # 1061

FILED BY Brandi Henley

PATENT CENTER # 66023475

FILING DATE 07/23/2021

CUSTOMER # 147803

FIRST NAMED
INVENTOR Kenneth S. Graham

CORRESPONDENCE
ADDRESS -

AUTHORIZED BY Lance Termes

Documents

TOTAL DOCUMENTS: 2

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
10430US02_IDS- Transmittal.pdf	3	Transmittal Letter	20 KB
10430US02_IDS-SB08.pdf	3	Information Disclosure Statement (IDS) Form (SB08)	51 KB

Warning: This is not a USPTO supplied IDS fillable form. Data in the form cannot be automatically loaded to other USPTO systems.

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DOCUMENT	MESSAGE DIGEST(SHA-512)
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10430US02_IDS- Transmittal.pdf	9816F041F8E5AB8C1B5DC331E0728CC5BB37752E0764DB89E 4F0AA5B537D53A66965FB02419E29369D838D325DA36F2E974 943050C6FBC05AFAB47A9E77B6E25
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10430US02_IDS-SB08.pdf	1FA324A17EC57821A345B11D5820E18D5A94B7362F09C246B8 D5927B15580C47B4D9578FD29F665F7F5BA0CF19F9754DBEB FA5536DDFC06681E43BF9D55C88A7
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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 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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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #
17/384,070

RECEIPT DATE / TIME
06/07/2024 05:48:11 PM Z ET

ATTORNEY DOCKET #
-

Title of Invention

Methods for Treating Angiogenic Eye Disorders with High Doses of VEGF Receptor Fusion Proteins

Application Information

APPLICATION TYPE Utility - Nonprovisional Application
under 35 USC 111(a)

PATENT # -

CONFIRMATION # 1061

FILED BY Brandi Henley

PATENT CENTER # 65882963

FILING DATE 07/23/2021

CUSTOMER # 147803

FIRST NAMED
INVENTOR Kenneth S. Graham

CORRESPONDENCE
ADDRESS -

AUTHORIZED BY Lance Termes

Documents

TOTAL DOCUMENTS: 0

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
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Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
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APPLICATION #
17/384,070

RECEIPT DATE / TIME
06/07/2024 05:48:11 PM Z ET

ATTORNEY DOCKET #
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Title of Invention

Methods for Treating Angiogenic Eye Disorders with High Doses of VEGF Receptor Fusion Proteins

Application Information

APPLICATION TYPE Utility - Nonprovisional Application
under 35 USC 111(a)

PATENT # -

CONFIRMATION # 1061

FILED BY Brandi Henley

PATENT CENTER # 65882963

AUTHORIZED BY Lance Termes

CUSTOMER # 147803

FILING DATE 07/23/2021

CORRESPONDENCE ADDRESS -

FIRST NAMED INVENTOR Kenneth S. Graham

Payment Information

PAYMENT METHOD
DA / 500393

PAYMENT TRANSACTION ID
E202467H49087078

PAYMENT AUTHORIZED BY
Brandi Henley

PRE-AUTHORIZED ACCOUNT
500393

PRE-AUTHORIZED CATEGORY

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 1.21 (Miscellaneous fees and charges)

FEE CODE	DESCRIPTION	ITEM PRICE(\$)	QUANTITY	ITEM TOTAL(\$)
1820	REQUEST FOR CONTINUED EXAMINATION (RCE)- 2ND AND SUBSEQUENT REQUEST (SEE 37 CFR 1.114)	2000.00	1	2000.00
TOTAL AMOUNT:				\$2,000.00

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (not for submission under 37 CFR 1.99)	Application Number	17/384,070
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	First Named Inventor	Kenneth S. Graham
	Art Unit	1647
	Confirmation Number	1061
	Examiner Name	Lockard, Jon McClelland
	Attorney Docket Number	125984-266215

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

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

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

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	Art Unit	1647
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	Examiner Name	Lockard, Jon McClelland
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CERTIFICATION STATEMENT			
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☐ See attached certification statement.			
☐ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.			
☒ None			
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	/Lance A. Termes/	Date (YYYY-MM-DD)	2024-06-07
Name/Print	Lance A. Termes	Registration Number	43184

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Kenneth S. Graham, et al. Application No.: 17/384,070 Filed: Jul-23-2021 For: HIGH CONCENTRATION VEGF RECEPTOR FUSION PROTEIN CONTAINING FORMULATIONS Customer No.: 147803	Confirmation No.: 1061 Examiner: Lockard, Jon McClelland Art Unit: 1647 SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR §1.97 and §1.98 Date of Transmission: June 7, 2024
---	---

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

Commissioner:

The references cited on the attached IDS are being called to the attention of the Examiner. Copies of the references in compliance with the requirements of 37 CFR §1.98(a)(2) are submitted herewith along with reciting Cite Nos. 585, 586, 601, 602 and 611 to include dates.

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125984-248593	62/769,876	11-20-2018	N/A	Expired
125984-248594	62/813,882	03-05-2019	N/A	Expired
125984-248595	16/409,631	05-10-2019	US 11,103,552	Issued
125984-248596	PCT/US2019/031879	05-10-2019	WO 2019/217927	Expired
125984-281135	18/367,444	09-12-2023	US-2024-0058418	Published

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Applicant believes that no fee is required for submission of this statement.

However, if a fee is required in connection with this paper, the Commissioner is authorized to deduct such fee from the undersigned's Deposit Account No. 500393.

Respectfully submitted,

/Lance A. Termes/

Lance A. Termes
Reg. No. 43184

Schwabe Williamson & Wyatt, PC
1211 SW 5th Avenue, Suite 1900
Portland, OR 97204
Tel: 503-222-9981

UNITED STATES
PATENT AND TRADEMARK OFFICEP.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #
17/384,070RECEIPT DATE / TIME
06/07/2024 05:35:39 PM Z ETATTORNEY DOCKET #
-

Title of Invention

Methods for Treating Angiogenic Eye Disorders with High Doses of VEGF Receptor Fusion Proteins

Application Information

APPLICATION TYPE Utility - Nonprovisional Application
under 35 USC 111(a)

PATENT # -

CONFIRMATION # 1061

FILED BY Brandi Henley

PATENT CENTER # 65882689

FILING DATE 07/23/2021

CUSTOMER # 147803

FIRST NAMED
INVENTOR Kenneth S. GrahamCORRESPONDENCE
ADDRESS -

AUTHORIZED BY Lance Termes

Documents

TOTAL DOCUMENTS: 11

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
10430US02_IDS- Transmittal.pdf	3	Transmittal Letter	20 KB
10430US02_IDS-SB08.pdf	3	Information Disclosure Statement (IDS) Form (SB08)	56 KB
Warning: This is not a USPTO supplied IDS fillable form. Data in the form cannot be automatically loaded to other USPTO systems.			
602_NPL_NCT00527423.pdf	22	Non Patent Literature	315 KB
611_NPL_VIVIDNCT0133168 1.pdf	47	Non Patent Literature	587 KB

636_NPL_Gaudreault2007.pdf	7	Non Patent Literature	815 KB
637_NPL_Gaudreault2005.pdf	8	Non Patent Literature	974 KB
601_NPL_NCT00036946-06012016_57440.1_63131.1.pdf	10	Non Patent Literature	267 KB
634_NPL_18367444-NFOA.pdf	41	Non Patent Literature	4775 KB
586_NPL_clinicaltrials.govpostingNCT025818911-41.pdf	274	Non Patent Literature	6531 KB
585_NPL_clinicaltrials.govpostingNCT02305238_1-24.pdf	150	Non Patent Literature	9101 KB
638_NPL_vabysmo-epar-public-assessment-report.pdf	319	Non Patent Literature	11367 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
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601_NPL_NCT00036946-06012016_57440.1_63131.1.pdf	BAFA2B60195355819007979EB7FCC46D25F02026561BFE47F1 CC43F811FC45D3F656D3DD4DC0C0C374DEFDA9F7EE7B907 D86E1DEC2EAB889F4476B919EFB48A9
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638_NPL_vabysmo-epar-public-assessment-report.pdf	9E429DFF647B8EC0ACCEABC2D25EA7EA8E1F589D7DB1C93 900D0AE1EAF4B65287A2568A2A6B8171C9D7E524610236C3F4 65287650FC3FF3CC4793DFADC441B2C

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 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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P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #
17/384,070

RECEIPT DATE / TIME
06/07/2024 05:23:01 PM Z ET

ATTORNEY DOCKET #
-

Title of Invention

Methods for Treating Angiogenic Eye Disorders with High Doses of VEGF Receptor Fusion Proteins

Application Information

APPLICATION TYPE Utility - Nonprovisional Application
under 35 USC 111(a)

PATENT # -

CONFIRMATION # 1061

FILED BY Lance Termes

PATENT CENTER # 65882449

FILING DATE 07/23/2021

CUSTOMER # 147803

FIRST NAMED INVENTOR Kenneth S. Graham

CORRESPONDENCE ADDRESS -

AUTHORIZED BY -

Documents

TOTAL DOCUMENTS: 0

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
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Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
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New Applications Under 35 U.S.C. 111

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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #
17/384,070

RECEIPT DATE / TIME
06/07/2024 05:21:36 PM Z ET

ATTORNEY DOCKET #
-

Title of Invention

Methods for Treating Angiogenic Eye Disorders with High Doses of VEGF Receptor Fusion Proteins

Application Information

APPLICATION TYPE Utility - Nonprovisional Application
under 35 USC 111(a)

PATENT # -

CONFIRMATION # 1061

FILED BY Lance Termes

PATENT CENTER # 65882339

FILING DATE 07/23/2021

CUSTOMER # 147803

FIRST NAMED
INVENTOR Kenneth S. Graham

CORRESPONDENCE
ADDRESS -

AUTHORIZED BY -

Documents

TOTAL DOCUMENTS: 1

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
10430US02__RCE.pdf	1	Request for Continued Examination (RCE)	209 KB

Warning: This is not a USPTO supplied RCE fillable form. Data in the form cannot be automatically loaded to other USPTO systems.

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
10430US02__RCE.pdf	0BB4B0C21A430C850D57152C426A4E90EB0674862204BA7B09 2F58AEFD592D9367394EE7632ACD3B29FDBA9D09822FDEDB

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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

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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.

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.

**Request
for
Continued Examination (RCE)
Transmittal**

Address to:
Mail Stop RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Application Number	17/384,070
Filing Date	July 23, 2021
First Named Inventor	Kenneth S. Graham
Art Unit	1647
Examiner Name	Jon McClelland Lockard
Attorney Docket Number	125984-266215

This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. See Instruction Sheet for RCEs (not to be submitted to the USPTO) on page 2.

1. **Submission required under 37 CFR 1.114** Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).
- a. ☐ Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.
- i. ☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____
- ii. ☐ Other _____
- b. ☒ Enclosed
- i. ☐ Amendment/Reply
- iii. ☒ Information Disclosure Statement (IDS)
- ii. ☐ Affidavit(s)/ Declaration(s)
- iv. ☐ Other _____
2. **Miscellaneous**
- a. ☐ Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a period of _____ months. (Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)
- b. ☐ Other _____
3. **Fees** The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.
- a. ☒ The Director is hereby authorized to charge the following fees, any underpayment of fees, or credit any overpayments, to Deposit Account No. 500393.
- i. ☒ RCE fee required under 37 CFR 1.17(e)
- ii. ☐ Extension of time fee (37 CFR 1.136 and 1.17)
- iii. ☐ Other _____
- b. ☐ Check in the amount of \$ _____ enclosed
- c. ☐ Payment by credit card (Form PTO-2038 enclosed)
- d. ☒ Payment by USPTO patent electronic filing system.

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.

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

Signature	/Lance A. Termes/	Date	June 7, 2024
Name (Print/Type)	Lance A. Termes	Registration No.	43,184

CERTIFICATE OF MAILING OR TRANSMISSION

I hereby certify that this correspondence is transmitted by the USPTO patent electronic filing system, or by facsimile to (571) 273-8300, to the USPTO, or deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop RCE, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on the date shown below.

Signature	/Lance A. Termes/	Date	June 7, 2024
Name (Print/Type)	Lance A. Termes		

A Federal agency may not conduct or sponsor, and a person is not required to respond to, nor shall a person be subject to a penalty for failure to comply with an information collection subject to the requirements of the Paperwork Reduction Act of 1995, unless the information collection has a currently valid OMB Control Number. The OMB Control Number for this information collection is 0651-0031. Public burden for this form is estimated to average 12 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the information collection. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden to the Chief Administrative Officer, United States Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450 or email InformationCollection@uspto.gov. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. If filing this completed form by mail, 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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UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

147803 7590 05/28/2024
Schwabe W&W, PC / Regeneron Pharmaceuticals, Inc.
PacWest Center
1211 SW Fifth Avenue, Suite 1900
Portland, OR 97204

EXAMINER

LOCKARD, JON MCCLELLAND

ART UNIT PAPER NUMBER

1647

DATE MAILED: 05/28/2024

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/384,070	07/23/2021	Kenneth S. Graham		1061

TITLE OF INVENTION: Methods for Treating Angiogenic Eye Disorders with High Doses of VEGF Receptor Fusion Proteins

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	\$1200	\$0.00	\$1200.00	\$0	08/28/2024

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 40% the amount of undiscounted fees, and micro entity fees are 20% the amount of undiscounted 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. 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 the USPTO patent electronic filing system.

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 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. **Because electronic patent issuance may occur shortly after issue fee payment, any desired continuing application should preferably be filed prior to payment of this issue fee in order not to jeopardize copendency.**

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

147803 7590 05/28/2024
Schwabe W&W, PC / Regeneron Pharmaceuticals, Inc.
PacWest Center
1211 SW Fifth Avenue, Suite 1900
Portland, OR 97204

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 the USPTO patent electronic filing system 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.
17/384,070	07/23/2021	Kenneth S. Graham		1061

TITLE OF INVENTION: Methods for Treating Angiogenic Eye Disorders with High Doses of VEGF Receptor Fusion Proteins

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	\$1200	\$0.00	\$1200.00	\$0	08/28/2024

EXAMINER	ART UNIT	CLASS-SUBCLASS
LOCKARD, JON MCCLELLAND	1647	424-134100

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/AIA/122 or PTO/SB/122) attached.

☐ "Fee Address" indication (or "Fee Address" Indication form PTO/AIA/47 or 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 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)

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

☐ Electronic Payment via the USPTO patent electronic filing system ☐ 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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UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
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Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/384,070	07/23/2021	Kenneth S. Graham		1061
147803	7590	05/28/2024		
Schwabe W&W, PC / Regeneron Pharmaceuticals, Inc.				
PacWest Center				
1211 SW Fifth Avenue, Suite 1900				
Portland, OR 97204				
				EXAMINER
				LOCKARD, JON MCCLELLAND
			ART UNIT	PAPER NUMBER
			1647	

DATE MAILED: 05/28/2024

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. The United States Patent and Trademark Office (USPTO) collects the information in this record under authority of 35 U.S.C. 2. The USPTO's system of records is used to manage all applicant and owner information including name, citizenship, residence, post office address, and other information with respect to inventors and their legal representatives pertaining to the applicant's/owner's activities in connection with the invention for which a patent is sought or has been granted. The applicable Privacy Act System of Records Notice for the information collected in this form is COMMERCE/PAT-TM-7 Patent Application Files, available in the Federal Register at 78 FR 19243 (March 29, 2013).

<https://www.govinfo.gov/content/pkg/FR-2013-03-29/pdf/2013-07341.pdf>

Routine uses of the information in this record may include disclosure to:

- 1) law enforcement, in the event that the system of records indicates a violation or potential violation of law;
- 2) a federal, state, local, or international agency, in response to its request;
- 3) a contractor of the USPTO having need for the information in order to perform a contract;
- 4) the Department of Justice for determination of whether the Freedom of Information Act (FOIA) requires disclosure of the record;
- 5) a Member of Congress submitting a request involving an individual to whom the record pertains, when the individual has requested the Member's assistance with respect to the subject matter of the record;
- 6) a court, magistrate, or administrative tribunal, in the course of presenting evidence, including disclosures to opposing counsel in the course of settlement negotiations;
- 7) the Administrator, General Services Administration (GSA), or their designee, during an inspection of records conducted by GSA under authority of 44 U.S.C. 2904 and 2906, in accordance with the GSA regulations and any other relevant (i.e., GSA or Commerce) directive, where such disclosure shall not be used to make determinations about individuals;
- 8) 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));
- 9) the Office of Personnel Management (OPM) for personnel research purposes; and
- 10) the Office of Management and Budget (OMB) for legislative coordination and clearance.

If you do not furnish the information requested on this form, the USPTO may not be able to process and/or examine your submission, which may result in termination of proceedings, abandonment of the application, and/or expiration of the patent.

Notice of Allowability	Application No. 17/384,070	Applicant(s) Graham et al.	
	Examiner JON M LOCKARD	Art Unit 1647	AIA (FITF) Status Yes

-- 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 the Request for Continued Examination filed 29 April 2024.
☐ 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 See Continuation Sheet . 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)	5. ☒ Examiner's Amendment/Comment
2. ☒ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date ____.	6. ☒ Examiner's Statement of Reasons for Allowance
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material ____.	7. ☐ Other ____.
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date ____.	

/J.L/ Examiner, Art Unit 1647	/CHRISTINE J SAOUD/ Primary Examiner, Art Unit 1645
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Continuation of 3. The allowed claim(s) is/are: 30-32 and 53-87)renumbered as claims 1-11,13-14,16,18,20,22,24,12,26,15,17,19,21,23,25 and 27-38, respectively)

Notice of Pre-AIA or AIA Status

1. The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

Continued Examination Under 37 CFR 1.114

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 allowance or after an Office action under *Ex Parte Quayle*, 25 USPQ 74, 453 O.G. 213 (Comm'r Pat. 1935). 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, prosecution in this application has been reopened pursuant to 37 CFR 1.114.

Applicant's submission filed on 29 April 2024 has been entered.

Information Disclosure Statement

3. The information disclosure statements (IDS) submitted on 29 April 2024, 08 May 2024 and 10 May 2024 have been considered by the examiner. NPL references 585, 586, 601, 602 and 611 (filed 29 April 2024) have been lined through. The references have been considered, but will not appear on the cover of the issued patent as they do not provide a date.

REASONS FOR ALLOWANCE

4. The following is an examiner's statement of reasons for allowance: The information disclosure statements (IDS) submitted on 29 April 2024, 08 May 2024 and 10 May 2024 have been considered by the Examiner. After careful consideration, the Examiner has determined that none of the information contained therein raises new issues of patentability.

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."

Summary

6. Claims 30-32 and 53-87 are allowed.

Advisory Information

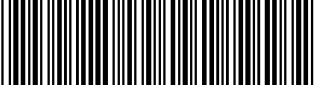
Any inquiry concerning this communication or earlier communications from the examiner should be directed to **JON M LOCKARD** whose telephone number is **(571) 272-2717**. The examiner can normally be reached M-F 9-6 EST.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at <http://www.uspto.gov/interviewpractice>. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joanne Hama** can be reached on **(571) 272-2911**. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of published or unpublished applications may be obtained from Patent Center. Unpublished application information in Patent Center is available to registered users. To file and manage patent submissions in Patent Center, visit: <https://patentcenter.uspto.gov>. Visit <https://www.uspto.gov/patents/apply/patent-center> for more information about Patent Center and <https://www.uspto.gov/patents/docx> for information about filing in DOCX format. For additional questions, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/J.L/
Examiner, Art Unit 1647
May 10, 2024

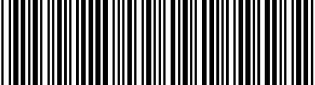
/Christine J Saoud/
Primary Examiner, Art Unit 1645

Issue Classification 	Application/Control No. 17/384,070	Applicant(s)/Patent Under Reexamination Graham et al.
	Examiner JON M LOCKARD	Art Unit 1647

CPC						
Symbol					Type	Version
A61K	/	38	/	179	F	2013-01-01
A61K	/	9	/	0048	I	2013-01-01
A61K	/	47	/	12	I	2013-01-01
A61P	/	27	/	02	I	2018-01-01
A61K	/	47	/	22	I	2013-01-01
A61K	/	47	/	26	I	2013-01-01
A61K	/	47	/	183	I	2013-01-01

CPC Combination Sets					
Symbol				Type	Version
	/		/		

/JON M LOCKARD/ Examiner, Art Unit 1647 (Assistant Examiner)	10 May 2024 (Date)	Total Claims Allowed: 38	
/CHRISTINE J SAOUD/ Primary Examiner, Art Unit 1645 (Primary Examiner)	15 May 2024 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure NONE

Issue Classification 	Application/Control No. 17/384,070	Applicant(s)/Patent Under Reexamination Graham et al.
	Examiner JON M LOCKARD	Art Unit 1647

INTERNATIONAL CLASSIFICATION			
CLAIMED			
A61K	/	38	/ 17
A61K	/	38	/ 18
C07K	/	14	/ 71
NON-CLAIMED			
	/		/

US ORIGINAL CLASSIFICATION	
CLASS	SUBCLASS

CROSS REFERENCES(S)						
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)					

/JON M LOCKARD/ Examiner, Art Unit 1647 (Assistant Examiner)	10 May 2024 (Date)	Total Claims Allowed: 38	
/CHRISTINE J SAOUD/ Primary Examiner, Art Unit 1645 (Primary Examiner)	15 May 2024 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure NONE

Issue Classification 	Application/Control No. 17/384,070	Applicant(s)/Patent Under Reexamination Graham et al.
	Examiner JON M LOCKARD	Art Unit 1647

☐ 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
1	30	10	59	12	68	28	77	37	86						
2	31	11	60	26	69	29	78	38	87						
3	32	13	61	15	70	30	79								
4	53	14	62	17	71	31	80								
5	54	16	63	19	72	32	81								
6	55	18	64	21	73	33	82								
7	56	20	65	23	74	34	83								
8	57	22	66	25	75	35	84								
9	58	24	67	27	76	36	85								

/JON M LOCKARD/ Examiner, Art Unit 1647 (Assistant Examiner)	10 May 2024 (Date)	Total Claims Allowed: 38	
/CHRISTINE J SAUD/ Primary Examiner, Art Unit 1645 (Primary Examiner)	15 May 2024 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure NONE

U.S. Patent and Trademark Office

Part of Paper No.: 20240510

<i>Search Notes</i> 	Application/Control No. 17/384,070	Applicant(s)/Patent Under Reexamination Graham et al.
	Examiner JON M LOCKARD	Art Unit 1647

CPC - Searched*		
Symbol	Date	Examiner

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner
NONE		03/16/2023	JML

* 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
PE2E Search (USPAT, US-PGPUB, EPO, DERWENT): See attached search history.	03/16/2023	JML
STN (MEDLINE, SCISEARCH, EMBASE, BIOSIS): See attached search history.	03/16/2023	JML
PALM: Inventor search.	03/16/2023	JML
PE2E Search (USPAT, US-PGPUB, EPO, DERWENT): See attached search history.	11/01/2023	JML

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<i>Search Notes</i> 	Application/Control No. 17/384,070	Applicant(s)/Patent Under Reexamination Graham et al.
	Examiner JON M LOCKARD	Art Unit 1647

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner
	PE2E Search (USPAT): See attached search history.	08/24/2023	JML
	DAV: Inventor search.	08/24/2023	JML
	PE2E Search (USPAT): See attached search history.	11/01/2023	JML
	DAV: Inventor search.	11/01/2023	JML
	PE2E Search (USPAT): See attached search history.	11/29/2023	JML
	DAV: Inventor search.	11/29/2023	JML
	PE2E Search (USPAT): See attached search history.	01/11/2024	JML
	DAV: Inventor search.	01/11/2024	JML
	PE2E Search (USPAT): See attached search history.	05/10/2024	JML
	DAV: Inventor search.	05/10/2024	JML

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (not for submission under 37 CFR 1.99)	Application Number	17/384,070
	Filing Date	Jul-23-2021
	First Named Inventor	Kenneth S. Graham
	Art Unit	1647
	Confirmation Number	1061
	Examiner Name	Lockard, Jon McClelland
	Attorney Docket Number	125984-266215

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
/J.L./	615	10,392,430		08-27-2019	Papadopoulos et al.	
/J.L./	616	11,975,045		05-07-2024	Yancopoulos	

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

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

NON-PATENT LITERATURE DOCUMENTS			
Examiner Initial*	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
/J.L./	614	Regeneron Pharmaceuticals, Inc., "Safety and Efficacy of Repeated Intravitreal Administration of Vascular Endothelial Growth Factor (VEGF) Trap in Patients With Wet Age-Related Macular Degeneration (AMD)," ClinicalTrials.gov ID NCT00320788, March 1, 2012. [https://www.clinicaltrials.gov/study/NCT00320788?term=NC00320788&rank=1].	

Receipt date: 05/08/2024

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (not for submission under 37 CFR 1.99)	Application Number	17/384,070
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	Art Unit	1647
	Confirmation Number	1061
	Examiner Name	Lockard, Jon McClelland
	Attorney Docket Number	125984-266215

EXAMINER SIGNATURE			
Examiner Signature	/JON M LOCKARD/	Date Considered	05/10/2024
*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.			
<p>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.</p>			

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (not for submission under 37 CFR 1.99)	Application Number	17/384,070
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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

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
	572	2021-0393738		12-23-2021	Ke	
	273	2022-0162296		05-26-2022	Lin et al.	

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
	568	2981145	CA	A1	10-06-2016	Seong Beom Kim et al.	
	567	103816115	CN	A	05-28-2014	Ke Xiao et al.	X
	569	17/075252	WO	A1	05-04-2017	GENENTECH, INC.	
	571	19/108770	WO	A1	06-06-2019	Regeneron Pharmaceuticals, Inc.	

NON-PATENT LITERATURE DOCUMENTS			
Examiner Initial*	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
	574	Arevalo et al., Retinal Detachment after Bevacizumab, Ophthalmology 18(11):2304.e3 (Nov. 2011).	
	575	Australian Public Assessment Report for Aflibercept, Australian Government, Department of Health & Aging, Therapeutic Goods Administration, July 2012	
	140	AVASTIN label (revised January 2021).	
	576	Boulanger-Scemama E, Querques G, About F, et al. Ranibizumab for exudative age-related macular degeneration: A five year study of adherence to follow-up in a real-life setting. J Fr Ophtalmol 2015; 38(7): 620-7.	

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Examiner Initial*	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
	577	Bressler et al., NM, Beaulieu WT, Glassman AR, Blinder KJ, Bressler SB, Jampol LM, Melia M, Wells JA 3rd, for the Diabetic Retinopathy Clinical Research Network. Persistent Macular Thickening Following Intravitreal Aflibercept, Bevacizumab, or Ranibizumab for Central-Involved Diabetic Macular Edema With Vision Impairment: A Secondary Analysis of a Randomized Clinical Trial. JAMA Ophthalmol. 2018 Mar 1;136(3):257-269 & Erratum in: JAMA Ophthalmol. 2018 May 1;136(5):601.	
	578	Brown et al., Primary Endpoint Results of a Phase II Study of Vascular Endothelial Growth Factor Trap-Eye in Wet Age-related Macular Degeneration, Ophthalmology 2011;118:1089-1097 (2011).	
	579	Brown DM, Schmidt-Erfurth U, Do DV, et al. Intravitreal aflibercept for diabetic macular edema: 100-week results from the VISTA and VIVID studies. Ophthalmology 2015; 122(10): 2044-52.	
	580	Busbee BG, Ho AC, Brown DM, et al. Twelve-month efficacy and safety of 0.5 mg or 2.0 mg ranibizumab in patients with subfoveal neovascular age-related macular degeneration. Ophthalmology 2013; 120(5): 1046-56.	
	581	Center For Drug Evaluation and Research Application Number: 125418orig1s000, Clinical Pharmacology And Biopharmaceutics Review(s), Feb. 2012.	
	582	Center for Drug Evaluation and Research, FDA, Approval Package for Application No. 125387Orig1s048, Eylea, March 25, 2015.	
	583	Cho NH, Shaw JE, Karuranga S, et al. IDF Diabetes Atlas: Global estimates of diabetes prevalence for 2017 and projections for 2045. Diabetes Res Clin Pract 2018; 138: 271-81.	
	584	Ciulla TA, Bracha P, Pollack J, Williams DF. Real-world outcomes of anti-vascular endothelial growth factor therapy in diabetic macular edema in the United States. Ophthalmol Retina 2018; 2(12): 1179-87.	
	585	clinicaltrials.gov posting NCT02305238-11282014 to 12202018	
	586	clinicaltrials.gov posting NCT02581891-10202015 to 05122020	
	601	clinicaltrials.gov posting NCT00036946-06012016	
	602	clinicaltrials.gov posting NCT00527423-06102013	
	611	clinicaltrials.gov posting NCT01331681-03202016	
	603	Da Vinci, clinicaltrials.gov posting NCT00789477, latest version, August 28, 2014.	
	587	Do DV, Nguyen QD, Boyer D, Schmidt-Erfurth U, Brown DM, Vitti R, Berliner AJ, Gao B, Zeitz O, Ruckert R, Schmelter T, Sandbrink R, Heier JS; da Vinci Study Group. One-year outcomes of the da Vinci Study of VEGF Trap-Eye in eyes with diabetic macular edema. Ophthalmology. 2012 Aug;119(8):1658-65- Epub 2012 Apr 24.	
	588	Do et al., Month-6 primary outcomes of the READ-3 study (Ranibizumab for Edema of the mAcula in Diabetes-Protocol 3 with high dose). Eye (Lond). 2015 Dec;29(12):1538-44.	
	589	Dugel et al., Brolucizumab Versus Aflibercept in Participants with Neovascular Age-Related Macular Degeneration: A Randomized Trial. Ophthalmology. 2017 Sep;124(9):1296-1304 - Epub 2017 May 24.	
	590	Ehlsen C, Helms M, Bohringer D, Agostini HT, Stahl A. Association of treatment adherence with real-life VA outcomes in AMD, DME, and BRVO patients. Clin Ophthalmol 2018; 12: 13-20.	

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	Attorney Docket Number	125984-266215

NON-PATENT LITERATURE DOCUMENTS			
Examiner Initial*	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
	570	EU Clinical Trials Register, EudraCT Number 2007-000583-25, UK, December 7, 2007.	
	591	European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP), EMA/430291/2014, Assessment Report, Eylea, June 26, 2014.	
	592	Heier JS, Brown DM, Chong V, et al. Intravitreal aflibercept (VEGF trap-eye) in wet age-related macular degeneration. Ophthalmology 2012; 119(12): 2537-48.	
	162	HERCEPTIN label (revised February 2021).	
	593	Ho AC, Busbee BG, Regillo CD, et al. Twenty-four-month efficacy and safety of 0.5 mg or 2.0 mg ranibizumab in patients with subfoveal neovascular age-related macular degeneration. Ophthalmology 2014; 121(11): 2181-92.	
	594	Jaffe GJ, Ying GS, Toth CA, et al. Macular Morphology and Visual Acuity in Year Five of the Comparison of Age-related Macular Degeneration Treatments Trials. Ophthalmology 2019- Epub 2018 Sep 3; 126(2): 252-60.	
	595	Kim JH. Re: Nguyen et al.: Characterization of poor visual outcomes of neovascular age-related macular degeneration treated with anti-vascular endothelial growth factor agents (Ophthalmology. 2019;126:735-742). Ophthalmology. 2020 Apr;127(4):e21.	
	596	Korobelnik JF, Do DV, Schmidt-Erfurth U, et al. Intravitreal aflibercept for diabetic macular edema. Ophthalmology 2014; 121(11): 2247-54.	
	597	Lally DR, Shah CP, Heier JS. Vascular endothelial growth factor and diabetic macular edema. Surv Ophthalmol 2016; 61(6): 759-68.	
	598	Lanzetta P, Loewenstein A; Vision Academy Steering Committee. Fundamental principles of an anti-VEGF treatment regimen: optimal application of intravitreal anti-vascular endothelial growth factor therapy of macular diseases. Graefes Arch Clin Exp Ophthalmol. 2017 Jul;255(7):1259-1273-Epub 2017 May 19.	
	167	LUCENTIS label (revised March 2018).	
	566	LIANG, Fang, "Cataloguing In Publication (CI P) Data," Pharmaceuticals/Editor-in-Chief Fang Liang. -- Third Edition. --Beijing: China Medical Science Press, March, 2016. [ISBN 978-7-5067-7405-5; www.cmstp.com].	
	599	Mitchell P, Liew G, Gopinath B, Wong TY. Age-related macular degeneration. Lancet (London, England) 2018; 392(10153): 1147-59.	
	600	Modarres et al., Intravitreal Injection of 2.5 mg versus 1.25 mg Bevacizumab (Avastin) for Treatment of CNV Associated with AMD, Retina 29:319 –324, 2009.	
	604	Nguyen CL, Gillies MC, Nguyen V, et al. Characterization of Poor Visual Outcomes of Neovascular Age-related Macular Degeneration Treated with Anti-Vascular Endothelial Growth Factor Agents. Ophthalmology 2019- Epub 2018 Dec 6.; 126(5): 735-42.	
	605	Nguyen QD, Brown DM, Marcus DM, et al. Ranibizumab for diabetic macular edema: results from 2 phase III randomized trials: RISE and RIDE. Ophthalmology 2012; 119(4): 789-801.	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (not for submission under 37 CFR 1.99)	Application Number	17/384,070
	Filing Date	Jul-23-2021
	First Named Inventor	Kenneth S. Graham
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	Attorney Docket Number	125984-266215

NON-PATENT LITERATURE DOCUMENTS			
Examiner Initial*	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
	606	Papadopoulos N, Martin J, Ruan Q, Rafique A, Rosconi MP, Shi E, Pyles EA, Yancopoulos GD, Stahl N, Wiegand SJ. Binding and neutralization of vascular endothelial growth factor (VEGF) and related ligands by VEGF Trap, ranibizumab and bevacizumab. Angiogenesis. 2012 Jun;15(2):171-85.	
	180	RAPTIVA label (revised March 2009).	
	607	Regeneron Reports Fourth Quarter and Full Year 2018 Financial and Operating Results, Plus Company Updates(PCU), February 7, 2019.	
	193	REMICADE label (Revised May 2020).	
	608	Regula JT, et al. Targeting key angiogenic pathways with a bispecific CrossMAb optimized for neovascular eye diseases, EMBO Mol Med. 2016;8(11):1265-1288.	
	609	Schmidt-Erfurth U, Kaiser PK, Korobelnik JF, et al. Intravitreal aflibercept injection for neovascular age-related macular degeneration: ninety-six-week results of the VIEW studies. Ophthalmology 2014; 121(1): 193-201.	
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	218	XOLAIR label (revised December 2020).	

EXAMINER SIGNATURE			
Examiner Signature	/JON M LOCKARD/	Date Considered	05/10/2024
*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	17/384,070
	Filing Date	Jul-23-2021
	First Named Inventor	Kenneth S. Graham
	Art Unit	1647
	Confirmation Number	1061
	Examiner Name	Lockard, Jon McClelland
	Attorney Docket Number	125984-266215

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

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

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

NON-PATENT LITERATURE DOCUMENTS			
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	617	clinicaltrials.gov posting NCT00090623, A Study of rhuFab V2 (Ranibizumab) in Subjects With Subfoveal Choroidal Neovascularization Secondary to Age-Related Macular Degeneration (AMD), PIER, 06212013	
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	623	clinicaltrials.gov posting NCT00473382, A Study of Ranibizumab Injection in Subjects With Clinically Significant Macular Edema (ME) With Center Involvement Secondary to Diabetes Mellitus (RIDE), 04172017	
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Examiner Signature	/JON M LOCKARD/	Date Considered	05/16/2024
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PE2E SEARCH - Search History (Prior Art)

/J.L./

There are no Prior Art searches to show.

PE2E SEARCH - Search History (Interference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	British Equivalents	Time Stamp
N32	2771	vegf ADJ trap	(USPAT)	OR	ON	ON	2024/05/10 02:08 PM
N33	2897	aflibercept	(USPAT)	OR	ON	ON	2024/05/10 02:08 PM
N34	363	eylea	(USPAT)	OR	ON	ON	2024/05/10 02:08 PM
N35	118	vegf ADJ trap-eye	(USPAT)	OR	ON	ON	2024/05/10 02:08 PM
N36	443	(N32 N33 N34 N35) SAME formulation	(USPAT)	OR	ON	ON	2024/05/10 02:08 PM
N37	12	N36 SAME "high concentration"	(USPAT)	OR	ON	ON	2024/05/10 02:09 PM
N38	1	N36 AND (8mg OR "8 mg").clm.	(USPAT)	OR	ON	ON	2024/05/10 02:10 PM
N39	17	(graham-k\$-s\$ washawa-s\$).in.	(USPAT)	OR	ON	ON	2024/05/10 02:10 PM
N40	1	N37 AND N39	(USPAT)	OR	ON	ON	2024/05/10 02:11 PM



ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #
17/384,070

RECEIPT DATE / TIME
05/10/2024 05:27:06 PM Z ET

ATTORNEY DOCKET #
-

Title of Invention

Methods for Treating Angiogenic Eye Disorders with High Doses of VEGF Receptor Fusion Proteins

Application Information

APPLICATION TYPE Utility - Nonprovisional Application
under 35 USC 111(a)

PATENT # -

CONFIRMATION # 1061

FILED BY Brandi Henley

PATENT CENTER # 65478309

FILING DATE 07/23/2021

CUSTOMER # 147803

FIRST NAMED
INVENTOR Kenneth S. Graham

CORRESPONDENCE
ADDRESS -

AUTHORIZED BY Lance Termes

Documents

TOTAL DOCUMENTS: 19

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
10430US02_IDS- Transmittal.pdf	3	Transmittal Letter	20 KB
10430US02_IDS-SB08.pdf	4	Information Disclosure Statement (IDS) Form (SB08)	61 KB
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620_NPL_NCT00486018- BRAVO-05102017.pdf	15	Non Patent Literature	756 KB
621_NPL_NCT00485836- CRUISE-07282017.pdf	15	Non Patent Literature	765 KB

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627_NPL_NCT00891735-HARBOR-01182013.pdf	15	Non Patent Literature	786 KB
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735 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
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New Applications Under 35 U.S.C. 111

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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

In re application of:

Kenneth S. Graham, et al.

Application No.: 17/384,070

Filed: Jul-23-2021

For: HIGH CONCENTRATION VEGF
RECEPTOR FUSION PROTEIN
CONTAINING FORMULATIONS

Customer No.: 147803

Confirmation No.: 1061

Examiner: Lockard, Jon McClelland

Art Unit: 1647

**SUPPLEMENTAL INFORMATION
DISCLOSURE STATEMENT UNDER
37 CFR §1.97 and §1.98**

Date of Transmission: May 10, 2024

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

Commissioner:

The references cited on the attached IDS are being called to the attention of the Examiner. Copies of the references in compliance with the requirements of 37 CFR §1.98(a)(2) are submitted herewith.

It is respectfully requested that the cited references be expressly considered during the prosecution of this application, and the references be made of record therein and appear among the “references cited” on any patent to issue therefrom.

The Examiner is encouraged to review the full prosecution history from related cases. Applicant understands that the prosecution history can be viewed electronically on

PALM. Nevertheless, if the Examiner wishes Applicant to provide copies of any documents from related applications to the extent not already provided, he or she is requested to contact the undersigned.

Applicant cites the following applications, which are directed to related subject matter and are commonly owned or under an assignment obligation to be commonly owned:

Attorney Docket No.	Application No.	Filing Date	Publication No.	Status
125984-248591	62/669,506	05-10-2018	N/A	Expired
125984-248592	62/752,127	10-29-2018	N/A	Expired
125984-248593	62/769,876	11-20-2018	N/A	Expired
125984-248594	62/813,882	03-05-2019	N/A	Expired
125984-248595	16/409,631	05-10-2019	US 11,103,552	Issued
125984-248596	PCT/US2019/031879	05-10-2019	WO 2019/217927	Expired
125984-281135	18/367,444	09-12-2023	US-2024-0058418	Published

As provided for by 37 CFR §1.97(g) and (h), no inference should be made that the information and references cited are prior art merely because they are in this statement and no representation is being made that a search has been conducted or that this statement encompasses all the possible relevant information.

Applicant believes that no fee is required for submission of this statement.

However, if a fee is required in connection with this paper, the Commissioner is authorized to deduct such fee from the undersigned's Deposit Account No. 500393.

Respectfully submitted,

/Lance A. Termes/

Lance A. Termes
Reg. No. 43184

Schwabe Williamson & Wyatt, PC
1211 SW 5th Avenue, Suite 1900
Portland, OR 97204
Tel: 503-222-9981

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	623	clinicaltrials.gov posting NCT00473382, A Study of Ranibizumab Injection in Subjects With Clinically Significant Macular Edema (ME) With Center Involvement Secondary to Diabetes Mellitus (RIDE), 04172017	
	624	clinicaltrials.gov posting NCT00473330, A Study of Ranibizumab Injection in Subjects With Clinically Significant Macular Edema (ME) With Center Involvement Secondary to Diabetes Mellitus (RISE), 04172017	
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	630	clinicaltrials.gov posting NCT00383370, Safety and Tolerability of Intravitreal VEGF Trap Formulations in Subjects With Neovascular AMD, VGFT-OD-0603, 04212011	
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (not for submission under 37 CFR 1.99)	Application Number	17/384,070
	Filing Date	Jul-23-2021
	First Named Inventor	Kenneth S. Graham
	Art Unit	1647
	Confirmation Number	1061
	Examiner Name	Lockard, Jon McClelland
	Attorney Docket Number	125984-266215

EXAMINER SIGNATURE			
Examiner Signature		Date Considered	
<p>*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.</p>			
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CERTIFICATION STATEMENT			
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☐ See attached certification statement.			
☐ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.			
☒ None			
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	/Lance A. Termes/	Date (YYYY-MM-DD)	2024-05-10
Name/Print	Lance A. Termes	Registration Number	43184



UNITED STATES
PATENT AND TRADEMARK OFFICE

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APPLICATION #
17/384,070

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Title of Invention

Methods for Treating Angiogenic Eye Disorders with High Doses of VEGF Receptor Fusion Proteins

Application Information

APPLICATION TYPE Utility - Nonprovisional Application
under 35 USC 111(a)

PATENT # -

CONFIRMATION # 1061

FILED BY Brandi Henley

PATENT CENTER # 65433287

FILING DATE 07/23/2021

CUSTOMER # 147803

FIRST NAMED
INVENTOR Kenneth S. Graham

CORRESPONDENCE
ADDRESS -

AUTHORIZED BY Lance Termes

Documents

TOTAL DOCUMENTS: 3

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
10430US02_IDS- Transmittal.pdf	3	Transmittal Letter	20 KB
10430US02_IDS-SB08.pdf	3	Information Disclosure Statement (IDS) Form (SB08)	53 KB
Warning: This is not a USPTO supplied IDS fillable form. Data in the form cannot be automatically loaded to other USPTO systems.			
614_NPL_NCT00320788- latestversion03012012.pdf	13	Non Patent Literature	796 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
10430US02_IDS-Transmittal.pdf	156F54A0C379AEA91FD5FAAE1D13C3C8BAED7F706D76D192 EC81AA3E4A34DE405764F6CB5F79B808F78CBF49C1F10AE9F 98CF9BE6D71D56CC2E2D65740199C26
10430US02_IDS-SB08.pdf	C9F36F3179E47B5BC8D533CCF3C6D881A5E20C9766026B7D3 2927A057430B2A7A030E7AD7F70A5958B60FD0B8232384673A 9B037862F4DF4AD0F6AAD26F2D047
614_NPL_NCT00320788-latestversion03012012.pdf	DF92779F90ED30FC3AE9A5A5FF64B153E0A59046D87C9351D 0A911A774B8B9FCBAB794FEC29ED77D55EC0A8DD97621A53 5D5868A9C881B3AC1F3AA1B915522A1

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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 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

In re application of: Kenneth S. Graham, et al. Application No.: 17/384,070 Filed: Jul-23-2021 For: HIGH CONCENTRATION VEGF RECEPTOR FUSION PROTEIN CONTAINING FORMULATIONS Customer No.: 147803	Confirmation No.: 1061 Examiner: Lockard, Jon McClelland Art Unit: 1647 SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR §1.97 and §1.98 Date of Transmission: May 8, 2024
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Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

The references cited on the attached IDS are being called to the attention of the Examiner. Copies of the references in compliance with the requirements of 37 CFR §1.98(a)(2) are submitted herewith.

It is respectfully requested that the cited references be expressly considered during the prosecution of this application, and the references be made of record therein and appear among the “references cited” on any patent to issue therefrom.

The Examiner is encouraged to review the full prosecution history from related cases. Applicant understands that the prosecution history can be viewed electronically on

PALM. Nevertheless, if the Examiner wishes Applicant to provide copies of any documents from related applications to the extent not already provided, he or she is requested to contact the undersigned.

Applicant cites the following applications, which are directed to related subject matter and are commonly owned or under an assignment obligation to be commonly owned:

Attorney Docket No.	Application No.	Filing Date	Publication No.	Status
125984-248591	62/669,506	05-10-2018	N/A	Expired
125984-248592	62/752,127	10-29-2018	N/A	Expired
125984-248593	62/769,876	11-20-2018	N/A	Expired
125984-248594	62/813,882	03-05-2019	N/A	Expired
125984-248595	16/409,631	05-10-2019	US 11,103,552	Issued
125984-248596	PCT/US2019/031879	05-10-2019	WO 2019/217927	Expired
125984-281135	18/367,444	09-12-2023	US-2024-0058418	Published

As provided for by 37 CFR §1.97(g) and (h), no inference should be made that the information and references cited are prior art merely because they are in this statement and no representation is being made that a search has been conducted or that this statement encompasses all the possible relevant information.

Applicant believes that no fee is required for submission of this statement.

However, if a fee is required in connection with this paper, the Commissioner is authorized to deduct such fee from the undersigned's Deposit Account No. 500393.

Respectfully submitted,

/Lance A. Termes/

Lance A. Termes
Reg. No. 43184

Schwabe Williamson & Wyatt, PC
1211 SW 5th Avenue, Suite 1900
Portland, OR 97204
Tel: 503-222-9981

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	Examiner Name	Lockard, Jon McClelland
	Attorney Docket Number	125984-266215

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
	615	10,392,430		08-27-2019	Papadopoulos et al.	
	616	11,975,045		05-07-2024	Yancopoulos	

U.S. PATENT APPLICATION PUBLICATIONS						
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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

NON-PATENT LITERATURE DOCUMENTS			
Examiner Initial*	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
	614	Regeneron Pharmaceuticals, Inc., "Safety and Efficacy of Repeated Intravitreal Administration of Vascular Endothelial Growth Factor (VEGF) Trap in Patients With Wet Age-Related Macular Degeneration (AMD)," ClinicalTrials.gov ID NCT00320788, March 1, 2012. [https://www.clinicaltrials.gov/study/NCT00320788?term=NC00320788&rank=1].	

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☐ See attached certification statement.			
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☒ None			
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	/Lance A. Termes/	Date (YYYY-MM-DD)	2024-05-08
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(71) Applicant Chengdu Kanghong Biotechnology Co., Ltd.

Address 610036 No. 36 Shuxi Road, Jinniu
District, Chengdu City, Sichuan Province

(72) Inventor Ke Xiao Zheng Qiang

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A61K 47/36 (2006.01)

A61K 47/26 (2006.01)

A61K 47/18 (2006.01)

A61K 47/04 (2006.01)

Claims 2 pages Specification 14
pages Sequence Table 2 pages

(54) Name of invention

A pharmaceutical composition containing a fusion
protein that inhibits angiogenesis and its use

(57) Abstract

The invention discloses a pharmaceutical composition
containing a fusion protein that inhibits angiogenesis and its
use, specifically involving a pharmaceutical composition
containing a fusion protein of an extracellular domain 2
(Flt-2) of vascular endothelial cell growth factor (VEGF)
receptor 1 and extracellular domains 3 and 4 (KDR-3, 4) of
VEGF receptor 2 and a human immunoglobulin 1 (Ig1) Fc,
which pharmaceutical composition can stabilize the fusion
protein, and effectively inhibit the purity decline caused by
production of fusion protein polymer, thereby maintaining
biological activity of effective components.

CN 103816115 A

1. A pharmaceutical composition containing a fusion protein that inhibits angiogenesis and its use, characterized in that it comprises

(a) 0.1-100 mg/ml of fusion protein containing extracellular domain 2 of VEGF receptor 1 and extracellular domains 3 and 4 of VEGF receptor 2 and human immunoglobulin Fc, comprising amino acid sequence with SEQ ID No: 1;

(b) 5-100 mM buffer, wherein the acid is selected from one or more of Tris-HCL citric acid, sodium hydrogen phosphate, sodium dihydrogen phosphate, acetic acid, succinic acid, and hydrochloric acid thereof;

(c) 5-500 mM basic amino acids, selected from one or a combination of lysine, arginine, and histidine thereof;

(d) 0.1-30% salt osmotic pressure modulator, wherein the sugar is selected from one or more of sucrose, trehalose, mannitol, glycerin, propylene glycol, sorbitol thereof, and the salt is selected from one or a combination of sodium chloride or other pharmaceutically acceptable salts thereof;

(e) 0.01-0.1% of one or more surfactants or cosolvents, selected from one or more of polyethylene glycol, Tween 20, Tween 80, propylene glycol, dimethyl sulfoxide, or other pharmaceutically acceptable surfactants thereof;

(f) Adjust pH to 7.5~8.3.

2. The pharmaceutical composition of Claim 1, characterized in that it comprises

(a) 10-40mg/ml of fusion protein as shown in SEQ ID No: 1;

(b) One or both of 5-100mM citrate buffer or sodium dihydrogen phosphate buffer;

(c) One or both of 5-500mM arginine or histidine;

(d) One or both of 5-30% sucrose or trehalose;

(e) One or both of 0.01-0.1% Tween-20 or polyethylene glycol;

(f) Adjust pH to 7.5~8.3.

3. The pharmaceutical composition of Claim 3, characterized in that it comprises

(a) 10 mg/ml of fusion protein as shown in SEQ ID No: 1;

(b) 10-100mM citrate buffer;

(c) 5-250 mM arginine;

(d) 5-20% sucrose;

(e) 0.05-0.1% Tween-20;

(f) Adjust pH to 7.5~8.3.

The said pharmaceutical composition preferably consists of the following components: 10 mg/ml of fusion protein as shown in SEQ ID No : 1, 10 mM citrate buffer, 8% sucrose, 5 mM arginine, 0.05% Tween 20, pH 7.5 ~8.3;

The said pharmaceutical composition preferably consists of the following components: 10 mg/ml of fusion protein as shown in SEQ ID No : 1, 100 mM citrate buffer, 20% sucrose, 250 mM arginine, 0.1% Tween 20, pH 7.5~8.3.

4. The pharmaceutical composition of Claim 3, characterized in that it comprises

(a) 20 mg/ml of fusion protein as shown in SEQ ID No: 1;

(b) 10-55 mM citrate buffer;

(c) 250-500 mM arginine;

(d) 12.5-30% sucrose;

(e) 0.05-0.1% Tween-20;

(f) Adjust pH to 7.5~8.3.

The said pharmaceutical composition preferably consists of the following components: 20 mg/ml of fusion protein as shown in SEQ ID No : 1, 10 mM citrate buffer, 30% sucrose, 500 mM arginine, 0.1% Tween 20, pH 7.5~8.3.

5. The pharmaceutical composition of Claim 3, characterized in that it comprises

- (a) 40 mg/ml of fusion protein as shown in SEQ ID No: 1;
- (b) 10-250 mM citrate buffer;
- (c) 100 mM arginine;
- (d) 8-12.5 % sucrose;
- (e) 0.05-0.1% Tween-20;
- (f) Adjust pH to 7.5~8.3.

The said pharmaceutical composition preferably consists of the following components: 40 mg/ml of fusion protein as shown in SEQ ID No : 1, 250 mM citrate buffer, 8% sucrose, 100 mM arginine, 0.1% Tween 20, pH 7.5~8.3.

6. The said pharmaceutical composition of Claims 1-5, characterized in that it may also comprise sodium chloride.

7. The said pharmaceutical composition of Claim 6, characterized in that it consists of the following components: 10 mg/ml of fusion protein as shown in SEQ ID No: 1, 5 mM citrate buffer, 4% sucrose, 4% sodium chloride, 100 mM arginine, 100mM histidine, 0.05% Tween 20, 0.05% PEG400, pH 7.5~8.3.

8. The said pharmaceutical composition of Claim 2, characterized in that it consists of the following components: 10 mg/ml of fusion protein as shown in SEQ ID No: 1, 5 mM sodium dihydrogen phosphate buffer, 10.0% trehalose, 100 mM arginine, 0.01 % PEG400, pH 7.5~8.3.

9. The said pharmaceutical composition according to any one of Claims 1 to 8, characterized in liquid formulation or lyophilized formulation, the said liquid formulation is preferably an ophthalmic formulation, more preferably an eye drop or a pre-filled injection.

10. The said pharmaceutical composition according to any one of Claims 1-9, characterized in its use in preparing drug for treatment of disease caused by angiogenesis or growth, in particular age-related macular degeneration.

A pharmaceutical composition containing a fusion protein that inhibits angiogenesis and its use

[0001] This application is a subcase application for invention with application dated August 31, 2010, application number 201010267503.7, and invention name "A pharmaceutical composition containing a fusion protein that inhibits angiogenesis and its use".

Field of technology

[0002] The present invention relates to the field of pharmaceutical preparations, to pharmaceutical compositions containing protein formed by the fusion of VEGF receptor fragments and immunoglobulin Fc, and to its medical application.

Background technology

[0003] With the development of modern cell molecular biology, the role of cytokines and cell surface-related molecules in ophthalmic diseases has been widely concerned and studied. VEGF is vascular endothelial cell mitogenic hormone that has the biological characteristic of increasing vascular permeability. VEGF is extremely important for the development of blood vessels during fetal period, and its level declines after birth. VEGF is expressed at low level in physiological conditions, and is necessary to maintain vascular function. The latest study results suggest that it plays a broad and important role in angiogenesis-related diseases, such as age-related macular degeneration (AMD) and diabetic retinopathy (DR). AMD mostly occurs over the age of 45, and its prevalence increases with age. It is currently an important disease causing blindness in the middle-aged and elderly. Wet AMD is mainly destruction of the vitreous membrane. The invasion of choroidal blood vessels under the retina forms choroidal neovascularization, the serous or hemorrhagic disciform macular detachment under the retinal pigment epithelium or under the neuroepithelium in the macular region occurs, and finally it becomes mechanical scar. It effectively inhibits VEGF, the vascular endothelial cell growth factor that causes wet macular disease, and blocks VEGF or VEGF receptors to achieve the goal of inhibiting angiogenesis, which has important therapeutic effects. In DR, VEGF levels are higher than normal in cells and body fluids. Increased VEGF causes changes in capillary permeability, retinal exudation, bleeding, and retinal macular edema, induces increased Angiogenin production, and synergistically promotes the formation of retinal neovascularization, causing visual damage.

[0004] Salt bond, hydrogen bond, disulfide bond and hydrophobic action are the forces that maintain conformational stability of proteins. The interaction of metal ions, substrates, cofactors and other relatively low molecular weight ligands makes the protein conformationally stable. The interaction of proteins with other biomacromolecules, especially proteins and lipids. In organisms, proteins often interact with lipids or polysaccharides to form complexes, shielding hydrophobic regions on the surface of the protein, thereby significantly increasing protein stability. Protein instability is mainly caused by the following factors: (1) Physical action: contact of the polar water molecules regulated by Brown motion with the hydrophobic nuclei of the protein leads to protein instability. (2) Chemical action: oxidation of amino acid residues at the active site is one of the most common mechanisms of enzyme inactivation. For example, sulfhydryl group of cysteine and indole ring of tryptophan are particularly sensitive to oxidation. (3) Biological action: proteolytic enzyme action. Microbiological and exogenous proteolytic enzymes act to catalyze the hydrolysis of peptide bonds. Low yield when eukaryotic polypeptides are purified by genetically engineered bacteria, is due to proteolysis in vitro.

[0005] Polymerization first exposes the embedded hydrophobic amino acid residues to aqueous solvent, resulting in reversible protein denaturation; second, protein molecules associate with each other to reduce unfavorable exposure of hydrophobic amino acids; and finally, if the protein molecules contain cysteine and cystine residues, an intermolecular disulfide bond exchange reaction occurs. Polymerization sometimes regenerates natural disulfide bonds through reduction and reoxidation, to reactivate proteins. Polymerization and simple precipitation are distinct, and the latter does not cause significant conformational changes in the protein.

[0006] The inventor also observed an obvious problem that the solution preparation tended to form soluble polymers and insoluble particles after long-term storage. How to solve this problem is to find a pharmaceutical composition that is both physically and chemically stable, capable of inhibiting polymer

formation and capable of forming fewer soluble polymers and insoluble particles after long-term storage. In addition, since its components are pharmaceutically acceptable components, it can be used for the treatment of eye diseases, including intravitreal injection and external administration. Furthermore, the inventor finds that the obtained formulation is more stable in the syringe than in the vial.

[0007] The invention adopts a protein (FP3 protein) that can inhibit angiogenesis and is derived from the fusion of extracellular domain 2 (Fit-2) of vascular endothelial growth factor (VEGF) receptor 1 and extracellular domains 3 and 4 (KDR-3, 4) of VEGF receptor 2 with human immunoglobulin 1 (Ig1) Fc. It is expressed by working cells of the recombinant technology, and purified to achieve medicinal purity. The appropriate pharmaceutical preparation is prepared through displacement and preparation packaging. These formulations are preferably liquid or lyophilized, and are suitable for the treatment of eye diseases, in particular for vitreous injection.

[0008] FP3 protein, as a protein drug, is much less stable than ordinary small molecule chemical drugs, and less stable than naturally occurring immunoglobulins. The fusion protein described in the Chinese patent is the Chinese patent "The Application of VEGF Receptor Fusion Protein in the Treatment of Eye Disease" with Patent No. ZL200610066257.2. The prescription described needs to be stored at -20°C, which puts forward higher requirements for production, transportation, preservation and application of the drug. It is well known that generally recombinant fusion proteins have poor stability, and are affected by a variety of environmental factors during storage, for example, temperature, humidity, oxygen, ultraviolet light. They can make the fusion protein undergo a variety of physical or chemical changes, resulting in protein polymerization, decomposition, oxidation or denaturation, etc.. All these changes can reduce activity of the protein, reduce the therapeutic effect, and cause serious toxic side effects. Therefore, the development of fusion protein preparations that are stable and easy to transport and store is of great clinical significance.

Content of invention

[0009] One of the objects of the present invention is to provide a pharmaceutical composition of fusion protein containing extracellular domain 2 (Fit-2) of vascular endothelial growth factor (VEGF) receptor 1 and extracellular domains 3 and 4 (KDR-3, 4) of VEGF receptor 2 and human immunoglobulin 1 (Ig1) Fc, more specifically, liquid preparation that can be used for vitreous injection, which can stabilize the fusion protein, and its most prominent feature is that it can effectively inhibit the purity decline caused by production of fusion protein polymer, thereby maintaining biological activity of the active component.

[0010] On the one hand, the present invention provides a pharmaceutical composition containing a fusion protein that inhibits angiogenesis, characterized in that it comprises

[0011] (a) 0.1-100mg/ml of fusion protein containing extracellular domain 2 of VEGF receptor 1 and extracellular domains 3 and 4 of VEGF receptor 2 and human immunoglobulin Fc, including the amino acid sequence shown in SEQ ID No:1;

[0012] (b) 5-100 mM buffer, wherein the acid is selected from one or more of Tris-HCL citric acid, sodium hydrogen phosphate, sodium dihydrogen phosphate, acetic acid, and succinic acid, and hydrochloric acid thereof;

[0013] (c) 5-500 mM basic amino acids, selected from one or a combination of lysine, arginine, and histidine thereof;

[0014] (d) 0.1-30% salt osmotic pressure modulator, wherein the sugar is selected from one or more of sucrose, trehalose, mannitol, glycerin, propylene glycol, sorbitol thereof, and the salt is selected from one or a combination of sodium chloride or other pharmaceutically acceptable salts thereof;

[0015] (e) 0.01-0.1% of one or more surfactants or cosolvents, selected from one or more of polyethylene glycol, Tween 20, Tween 80, propylene glycol, dimethyl sulfoxide or other pharmaceutically acceptable surfactants thereof;

[0016] (f) Adjust pH to 7.5~8.3.

[0017] Wherein the pharmaceutical composition is preferably a pharmaceutical composition comprising the following components:

[0018] (a) 10-40 mg/ml fusion protein as shown in SEQ ID No:1;

- [0019] (b) 5-100mM of one or both of citric acid or sodium dihydrogen phosphate;
- [0020] (c) 5-500mM of one or both of arginine or histidine;
- [0021] (d) 8-30% of one or both of sucrose or trehalose;
- [0022] (e) 0.01-0.1% of one or both of Tween-20 or polyethylene glycol;
- [0023] (f) Adjust pH to 7.5~8.3.
- [0024] The pharmaceutical composition of the invention is further a pharmaceutical composition comprising the following components:
- [0025] (a) 10 mg/ml of fusion protein as shown in SEQ ID No: 1;
- [0026] (b) 10-100mM citric acid buffer;
- [0027] (c) 5-250mM arginine;
- [0028] (d) 5-20% sucrose;
- [0029] (e) 0.05-0.1% Tween-20;
- [0030] (f) Adjust pH to 7.5~8.3.
- [0031] The aforementioned pharmaceutical composition is further preferably composed of the following components: 10mg/ml of fusion protein as shown in SEQ ID No: 1, 10 mM citric acid buffer, 8% sucrose, 5 mM arginine, 0.05% Tween 20, pH 7.5~8.3;
- [0032] The said pharmaceutical composition of the invention is further preferably composed of the following components: 10 mg/ml of fusion protein as shown in SEQ ID No: 1, 100 mM citric acid buffer, 20% sucrose, 250 mM arginine, 0.1% Tween 20, pH 7.5~8.3.
- [0033] The said pharmaceutical composition of the invention is further a pharmaceutical composition comprising the following components:
- [0034] (a) 20 mg/ml of fusion protein as shown in SEQ ID No: 1; b) 10-55 mM citric acid buffer; 250-500mM arginine; d) 12.5-30% sucrose; e) 0.05-0.1% Tween-20; (f) Adjustment pH to 7.5~8.3.
- [0035] The pharmaceutical composition of the present invention is further preferably composed of the following components: 20mg/ml of fusion protein as shown in SEQ ID No: 1, 10 mM citric acid buffer, 30% sucrose, 500 mM arginine, 0.1% Tween 20, pH 7.5~8.3.
- [0036] The aforementioned pharmaceutical composition is a pharmaceutical composition further preferably composed of the following components: (a) 40 mg/ml of fusion protein as shown in SEQ ID No: 1; b) 10-250 mM citric acid buffer; (c) 100 mM arginine; 8-12.5% sucrose; (e) 0.05-0.1% Tween-20; (f) adjusts pH to 7.5~8.3.
- [0037] The aforementioned pharmaceutical composition is further preferably composed of the following components: 40 mg/ml of fusion protein as shown in SEQ ID No: 1, 250 mM citric acid buffer, 8% sucrose, 100 mM arginine, 0.1% Tween 20, pH 7.5~8.3.
- [0038] The aforementioned pharmaceutical composition may also contain sodium chloride.
- [0039] The said pharmaceutical composition of the invention is further preferably composed of the following components: 10 mg/ml of fusion protein as shown in SEQ ID No: 1, 5 mM citric acid buffer, 4% sucrose, 4% sodium chloride, 100 mM arginine, 100mM histidine, 0.05% Tween 20, 0.05% PEG400, pH 7.5~8.3.
- [0040] The said pharmaceutical composition of the invention is further preferably composed of the following components: 10 mg/ml of fusion protein as shown in SEQ ID No:1, 5 mM sodium dihydrogen phosphate buffer, 10.0% trehalose, 100 mM arginine, 0.01% PEG400, pH 7.5~8.3.
- [0041] The form of preparation made from the aforementioned pharmaceutical composition may be liquid preparation or lyophilized preparation, of which the liquid preparation is preferably ophthalmic preparation, especially eye drops; also available for pre-filled injections.

[0042] The aforementioned pharmaceutical composition may be used to treat diseases caused by angiogenesis or growth, preferably age-related macular degeneration.

[0043] In the present invention, the said fusion protein is the fusion protein described in the Chinese patent "The Application of VEGF Receptor Fusion Protein in the Treatment of Eye Disease" with Patent No. ZL200610066257.2, specifically the FP3 fusion protein, so the content of ZL200610066257.2 can be used to further explain the Invention.

Specific embodiments

[0044] Embodiment 1 Stability study of 10 mg/ml FP3 fusion protein original prescription in 3 ml glass ampoules at 4°C

[0045] The prescription is as follows:

[0046]

FP3 fusion protein 10 mg/ml

Sodium succinate 10 mM

Trehalose 9.0%

Tween 20 0.05 %

[0047] Adjust the system pH to 6.0~6.5 with hydrochloric acid

[0048] After the stock protein solution is displaced, it is aseptically packaged to 3 ml glass ampoules, retention sample at 4°C, and test samples at months 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12. Stability is determined by SEC-HPLC. The results showed that this prescription could not effectively inhibit the production of polymers, resulting in decrease in purity of the product, and decrease in affinity with VEGF. After entering the body, it may induce immune response

[0049] Table 1. Stability of 10 mg/ml FP3 fusion protein at 4°C

[0050]

Time (month)	Appearance	pH value	Concentration (mg/ml)	Polymers (%)	Affinity (p M)
0	Qualified	6.0	10.0	0.3	10.6
1	Qualified	6.0	9.4	1.9	9.5
2	Qualified	6.0	10.2	2.8	9.1
3	Qualified	6.0	10.2	3.6	8.7
6	Qualified	6.0	10.0	9.1	8.4
9	Qualified	6.0	10.0	18.2	7.7
12	Qualified	6.1	10.3	31.8	7.0

[0051] Embodiment 2 Stability study of 10 mg/ml FP3 fusion protein in 3 ml glass ampoules at 4°C

[0052]

FP3 fusion protein 10 mg/ml

Disodium hydrogen phosphate 10 mM

Sucrose 10 %

Sodium chloride 0.5 %

Tween 20 0.05 %

pH 7.5~8.3

[0053] After the stock protein solution is displaced, it is aseptically packaged to 3 ml glass ampoules, retention sample at 4°C, and test samples at months 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12. Stability is determined by SEC-HPLC. The results showed that this prescription could not effectively inhibit the production of polymers, resulting in decrease in purity of the product, and decrease in affinity with VEGF. After entering the body, it may induce immune response

[0054] Table 2. Stability of 10 mg/ml FP3 fusion protein at 4°C

[0055]

Time (month)	Appearance	pH value	Concentration (mg/ml)	Polymers (%)	Affinity (p M)
0	Qualified	7.7	10.1	0.2	10.7

[0056]

1	Qualified	7.9	10.1	2.0	9.9
2	Qualified	7.7	10.7	3.2	9.3
3	Qualified	7.8	10.6	5.4	8.4
6	Qualified	7.7	10.3	9.9	8.1
9	Qualified	7.5	10.1	13.1	8.5
12	Qualified	7.9	10.3	23.3	7.3

[0057] Embodiment 3 Stability study of 10 mg/ml FP3 fusion protein in 3 ml glass ampoules at 4°C

[0058]

FP3 fusion protein 10 mg/ml

Disodium hydrogen phosphate 5 mM

Sucrose 8.0 %

Tween 20 0.05 %

pH 7.5~8.3

[0059] After the stock protein solution is displaced, it is aseptically packaged to 3 ml glass ampoules, retention sample at 4°C, and test samples at months 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12. Stability is determined by SEC-HPLC. The results showed that this prescription could not effectively inhibit the

production of polymers, resulting in decrease in purity of the product, and decrease in affinity with VEGF. After entering the body, it may induce immune response

[0060] Table 3. Stability of 10 mg/ml FP3 fusion protein at 4°C

[0061]

Time (month)	Appearance	pH value	Concentration (mg/ml)	Polymers (%)	Affinity (p M)
0	Qualified	7.9	10.2	0.3	10.4
1	Qualified	7.9	10.2	1.4	10.0
2	Qualified	7.8	10.6	2.6	9.7
3	Qualified	7.8	10.7	3.6	8.1
6	Qualified	8.1	10.5	9.4	7.9
9	Qualified	8.3	10.1	18.5	9.7
12	Qualified	8.0	10.4	19.1	9.6

[0062] Embodiment 4 Stability study of 10 mg/ml FP3 fusion protein in 3 ml glass ampoules at 4°C

[0063]

FP3 fusion protein 10 mg/ml

Citric acid 10 mM

[0064]

Sucrose 8.0 %

Arginine 5 %

Tween 20 0.05 %

pH 7.5~8.3

[0065] After the stock protein solution is displaced, it is aseptically packaged to 3 ml glass ampoules, retention sample at 4°C, and test samples at months 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12. Stability is determined by SEC-HPLC. The results showed that this prescription could effectively inhibit the production of polymers, the purity of the product decreased slowly, and the affinity between the fusion protein and VEGF was almost unchanged.

[0066] Table 4. Stability of 10 mg/ml FP3 fusion protein at 4°C

[0067]

Time (month)	Appearance	pH value	Concentration (mg/ml)	Polymers (%)	Affinity (p M)
0	Qualified	7.7	10.1	0.4	10.5
1	Qualified	7.9	10.1	0.5	10.4
2	Qualified	7.5	10.7	0.7	10.1

3	Qualified	7.8	10.6	0.8	10.0
6	Qualified	7.7	10.3	0.9	9.9
9	Qualified	7.9	10.1	1.8	9.7
12	Qualified	7.9	10.3	1.9	9.6

[0068] Embodiment 5 Stability study of 10 mg/ml FP3 fusion protein in 3 ml glass ampoules at 4°C

[0069]

FP3 fusion protein 10 mg/ml

Citric acid 100 mM

Sucrose 20.0 %

Arginine 250 %

Tween 20 0.10 %

pH 7.5~8.3

[0070] After the stock protein solution is displaced, it is aseptically packaged to 3 ml glass ampoules, retention sample at 4°C, and test samples at months 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12. Stability is determined by SEC-HPLC. The results showed that this prescription could effectively inhibit the production of polymers, the purity of the product decreased slowly, and the affinity between the fusion protein and VEGF was almost unchanged.

[0071] Table 5. Stability of 10 mg/ml FP3 fusion protein at 4°C

[0072]

Time (month)	Appearance	pH value	Concentration (mg/ml)	Polymers (%)	Affinity (p M)
0	Qualified	7.9	10.0	0.3	10.4
1	Qualified	7.9	10.1	0.3	10.3
2	Qualified	7.9	10.0	0.4	10.4
3	Qualified	7.9	10.1	0.5	10.2
6	Qualified	7.9	10.2	0.7	10.1
9	Qualified	7.9	10.0	0.8	10.2
12	Qualified	7.9	10.1	0.9	10.0

[0073] Embodiment 6 Stability study of 10 mg/ml FP3 fusion protein in 3 ml glass ampoules at 4°C

[0074]

FP3 fusion protein 10 mg/ml

Sodium dihydrogen phosphate 5 mM

Trehalose 10.0 %

Arginine 100 %

PEG400 0.01 %

pH 7.5~8.3

[0075] After the stock protein solution is displaced, it is aseptically packaged to 3 ml glass ampoules, retention sample at 4°C, and test samples at months 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12. Stability is determined by SEC-HPLC.

[0076] Table 6. Stability of 10 mg/ml FP3 fusion protein at 4°C

[0077]

Time (month)	Appearance	pH value	Concentration (mg/ml)	Polymer (%)	Affinity (pM)
0	Qualified	8.3	10.4	0.3	10.1
1	Qualified	8.3	10.3	0.3	10.2
2	Qualified	8.2	10.2	0.5	10.0
3	Qualified	8.3	10.1	0.5	10.1
6	Qualified	8.1	10.2	0.9	9.9
9	Qualified	8.3	10.2	1.4	10.0
12	Qualified	8.2	10.1	4.2	9.8

[0078] Embodiment 7 Stability study of 20 mg/ml FP3 fusion protein in 3 ml glass ampoules at 4°C

[0079]

FP3 fusion protein 20 mg/ml

[0080]

Citric acid 5 mM

Sucrose 4.0%

Sodium chloride 4.0%

Arginine 100 mM

Histidine 100 mM

Tween 20 0.05%

PEG400 0.05%

pH 7.5 ~ 8.3

[0081] After the stock protein solution is displaced, it is aseptically packaged to 3 ml glass ampoules, retention sample at 4°C, and test samples at months 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12. Stability is determined by SEC-HPLC.

[0082] Table 7. Stability of 20 mg/ml FP3 fusion protein at 4°C

[0083]

Time (month)	Appearance	pH value	Concentration (mg/ml)	Polymers (%)	Affinity (p M)
0	Qualified	8.0	19.8	1	14.3
1	Qualified	7.8	20.7	1.5	10.2
2	Qualified	7.9	19.8	1.3	12.6
3	Qualified	7.9	20.6	2	10.5
4	Qualified	7.8	N/D	1.7	N/D
5	Qualified	7.8	N/D	2.2	N/D
6	Qualified	8.0	N/D	2.7	N/D
7	Qualified	7.8	N/D	2.7	N/D
8	Qualified	7.9	N/D	2.7	N/D
9	Qualified	7.9	19.5	2.7	12.5
10	Qualified	7.8	N/D	3.1	N/D
11	Qualified	7.8	N/D	3.5	N/D
12	Qualified	7.9	20.3	3.6	14.3

[0084] N/D indicates not detected.

[0085] Embodiment 8 Stability study of 20 mg/ml FP3 fusion protein in 3 ml glass ampoules at 4°C

[0086]

FP3 fusion protein 20 mg/ml

[0087]

Citric acid	10 mM
Sucrose	30%
Arginine	500 mM
Tween 20	0.1%
pH	7.5 ~ 8.3

[0088] After the stock protein solution is displaced, it is aseptically packaged to 3 ml glass ampoules,

retention sample at 4°C, and test samples at months 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12. Stability is determined by SEC-HPLC.

[0089] Table 8. Stability of 20 mg/ml FP3 fusion protein at 4°C

[0090]

Time (month)	Appearance	pH value	Concentration (mg/ml)	Polymers (%)	Affinity (p M)
0	Qualified	7.7	20.0	0.1	10.2
1	Qualified	7.9	20.0	0.1	10.2
2	Qualified	7.7	20.2	0.1	10.3
3	Qualified	7.8	20.2	0.2	10.3
6	Qualified	7.7	20.1	0.2	9.9
9	Qualified	7.9	20.3	0.3	10.0
12	Qualified	7.9	20.0	0.5	10.3

[0091] Embodiment 9 Stability study of 10 mg/ml FP3 fusion protein in 3 ml glass ampoules at 4°C

[0092]

FP3 fusion protein 10 mg/ml

Citric acid 10 mM

Sucrose 5 %

Arginine 100 mM

Tween 20 0.05%

pH 7.5 ~ 8.3

[0093] After the stock protein solution is displaced, it is aseptically packaged to 3 ml glass ampoules, retention sample at 4°C, and test samples at months 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12. Stability is determined by SEC-HPLC.

[0094] Table 9. Stability of 10 mg/ml FP3 fusion protein at 4°C

[0095]

Time (month)	Appearance	pH value	Concentration (mg/ml)	Polymers (%)	Affinity (p M)
0	Qualified	7.7	10.1	0.4	10.5
1	Qualified	7.9	10.1	0.5	10.4
2	Qualified	7.7	10.7	0.7	10.1
3	Qualified	7.8	10.6	0.8	10.0
6	Qualified	7.7	10.3	0.9	9.9

9	Qualified	7.9	10.1	1.8	7.7
12	Qualified	7.9	10.3	1.9	6.3

[0096] Embodiment 10 Stability study of 10 mg/ml FP3 fusion protein in 3 ml glass ampoules at 4°C

[0097] The stock solution of FP3 fusion protein was concentrated with Vivaflow and displaced, then it was subpackaged aseptically to obtain the semi-finished product, which was placed in 55 mM citric acid, 12.5% sucrose, 250 mM arginine, 0.05% Tween 20, and pH7.9 buffer; adjusted the FP3 fusion protein to 10 mg/ml; it was aseptically packaged to 3 ml glass ampoules, retention sample at 4°C, and tested samples at months 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12. Stability was determined by SEC-HPLC.

[0098] Table 10. Stability of 10 mg/ml FP3 fusion protein at 4°C

[0099]

Time (month)	Appearance	pH value	Concentration (mg/ml)	Polymers (%)	Affinity (p M)
0	Qualified	8.3	10.0	0.2	9.7
1	Qualified	8.3	10.1	0.2	9.6
2	Qualified	8.2	10.2	0.3	9.6
3	Qualified	7.9	10.0	0.4	9.3
6	Qualified	8.0	10.1	0.5	9.3
9	Qualified	7.9	10.1	0.6	9.1
12	Qualified	7.9	10.3	1.0	9.4

[0100] Embodiment 11 Stability study of 20 mg/ml FP3 fusion protein in 3 ml glass ampoules at 4°C

[0101] The stock solution of FP3 fusion protein was concentrated with Vivaflow and displaced, then it was subpackaged aseptically to obtain the semi-finished product, which was placed in 55 mM citric acid, 12.5% sucrose, 250 mM arginine, 0.05% Tween 20, and pH7.5~8.3 buffer; adjusted the FP3 fusion protein to 20 mg/ml; it was aseptically packaged to 3 ml glass ampoules, retention sample at 4°C, and tested samples at months 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12. Stability was determined by SEC-HPLC.

[0102] Table 11. Stability of 20 mg/ml FP3 fusion protein at 4°C

[0103]

Time (month)	Appearance	pH value	Concentration (mg/ml)	Polymers (%)	Affinity (p M)
0	Qualified	7.9	19.9	0.7	10.7
1	Qualified	7.9	20.1	1.2	10.2
2	Qualified	7.7	20.1	1.3	10.3
3	Qualified	7.8	21.6	1.4	10.4

6	Qualified	8.0	21.6	1.4	10.4
9	Qualified	7.9	21.1	2.6	9.6
12	Qualified	7.9	21.3	3.6	9.4

[0104] Embodiment 12 Stability study of 40 mg/ml FP3 fusion protein lyophilized preparation at 4°C

[0105]

FP3 fusion protein 40 mg/ml

Citric acid 250 mM

Sucrose 8.0 %

Arginine 100 mM

Tween 20 0.10 %

pH 7.5 ~ 8.3

[0106] Adjusted the FP3 fusion protein solution to 40 mg/ml, adjusted the pH to 7.5~8.3, and then subpackaged to 3 ml glass ampoules. The conditions of the optimized lyophilization curve were: quickly pre-froze at -50°C for 4 hours, controlled it to sublimate at -20°C to remove most of the moisture, then gradually increased temperature of the separator to further remove the residual moisture, and applied 25°C and reached the limit vacuum in the last step, reducing the moisture while keeping the sample temperature from rising too high. After the lyophilization was completed, drying under reduced pressure, removed from the lyophilization box, rolled the aluminum cap, and analyzed water and purity, etc., retained samples at 4°C. In months 0, 1, 6, 12, redissolved by adding equal volume of water for injection, tested samples, and stability was determined by SEC-HPLC.

[0107] Table 12. Stability of 40 mg/ml FP3 fusion protein at 4°C

[0108]

Time (month)	Appearance after	pH value	Concentration (mg/ml)	Polymers (%)	Affinity (pM)
0	Qualified	7.9	39.9	0.1	11.2
1	Qualified	7.9	40.1	0.2	10.6
6	Qualified	7.9	40.7	0.3	10.1
12	Qualified	8.3	40.6	0.4	10.0

[0109] Embodiment 13 Stability study of 40 mg/ml FP3 fusion protein lyophilized preparation at 4°C

[0110]

FP3 fusion protein	40 mg/ml
Citric acid	10 mM
Sucrose	5 %
Arginine	100 mM
Tween 20	0.05 %
pH	7.5 ~ 8.3

[0111] Adjusted the FP3 fusion protein solution to 20 mg/ml, adjusted the pH to 7.5~8.3, and then subpackaged to 3 ml glass ampoules. The conditions of the optimized lyophilization curve were: quickly pre-froze at -50°C for 4 hours, controlled it to sublimate at -20°C to remove most of the moisture, then gradually increased temperature of the separator to further remove the residual moisture, and applied 25°C and reached the limit vacuum in the last step, reducing the moisture while keeping the sample temperature from rising too high. After the lyophilization was completed, drying under reduced pressure, removed from the lyophilization box, rolled the aluminum cap, and analyzed water and purity, etc., retained samples at 4°C. In months 0, 1, 6, 12, redissolved by adding equal volume of water for injection, tested samples, and stability was determined by SEC-HPLC.

[0112] Table 13. Stability of 40 mg/ml FP3 fusion protein at 4°C

[0113]

Time (month)	Appearance after	pH value	Concentration (mg/ml)	Polymers (%)	Affinity (pM)
0	Qualified	8.0	40	0.1	10. 2
1	Qualified	8. 3	40	0.1	10. 5
6	Qualified	7.9	40	0.2	10. 2
12	Qualified	8. 2	40. 1	0. 3	10. 3

[0114] Embodiment 14 Stability study of 20 mg/ml FP3 fusion protein in glass pre-filled syringe at 4°C

[0115]

FP3 fusion protein	20 mg/ml
Citric acid	55 mM
Sucrose	12.5 %
Arginine	250 mM
Tween 20	0.05 %
pH	7.5 ~ 8.3

[0116] The stock solution of FP3 fusion protein was concentrated and displaced, then aseptically subpackaged to obtain the semi-finished product. Adjusted the FP3 fusion protein to 20 mg/ml, and aseptically subpackaged it to 1 ml glass pre-filled syringe with FluroTec coating, retained samples at 4°C, tested samples in months 0, 1, 6, 12, and the stability was determined by SEC-HPLC.

[0117] Table 14. Stability study of 20 mg/ml FP3 fusion protein in glass pre-filled syringe at 4°C

[0118]

Time (month)	Appearance	pH value	Concentration (mg/ml)	Polymers (%)	Affinity (pM)
0	Qualified	7.9	20.0	0.1	11.2
1	Qualified	7.9	20.1	0.1	11.6
6	Qualified	7.9	20.1	0.1	11.1
12	Qualified	8.2	20.1	0.1	11.0

[0119] Embodiment 15 Gel Size Exclusion Chromatography of Polymers (SEC-HPLC)

[0120] Porous silica gel column has high stability, heat and pressure resistance, long life, and enables rapid separation of biomacromolecules. TSK G3000SWx1 is a porous silica gel column with particle size of 5 μm , pore size of 250 Angstroms, and a range of 10-500 kD for globulin separation, sample separation time of 30 min. It is a chromatographic column commonly used in analysis of biological macromolecules internationally. In the present invention, we selected the porous silica column TSK G3000SWx1 chromatographic column. The instrument was Waters 2695 high performance liquid chromatograph, with phosphate buffer pH to 7.20 as the mobile phase, the flow rate of 0.5 ml/ml, the column temperature of 25°C, and the detection wavelength of 280 nm. The purity of the recombinant human vascular endothelial growth factor receptor-antibody FP3 fusion protein was tested.

[0121] Embodiment 16 Repeat-Dose Trial of Vitreous Injection in Rabbits

[0122] Twelve Japanese white rabbits were randomly divided into two groups, namely the test article group and the solvent control group, with six rabbits in each group, half male and half female. In the right eye of each group of animals, a single vitreous injection of the test article (0.5 mg/50 μL /eye) or an equal volume of solvent reference standard was given, and a sham injection control or a blank control was given on the other side. Visual observation was performed daily after drug administration, and indirect ophthalmoscopes and slit lamps were regularly used for examination. Animals were sacrificed 14 days after dosing, and the eyeballs were taken for histopathological examination. The local toxicity of the test article was investigated through observation results and histopathological examination results. Findings: Intravitreal injection was given to Japanese white rabbits. Among the six eyes given the test article, one eye had slight congestion, and one eye had a small amount of secretions observed by the naked eye; one eye had lens opacity observed by the slit lamp. At the same time, the same phenomenon was observed in the eyes of the solvent control side, the sham injection side and the blank control side, respectively, and the incidence and occurrence time were basically consistent with those of the eyes of the test article side. Therefore, it can be ruled out that these phenomena were stimulus response caused by the test article. Histopathological examination showed that all ocular tissue structures were normal. Therefore, under the conditions of this trial, a single vitreous injection of recombinant human vascular endothelial growth factor receptor-antibody fusion protein injection into the rabbit eye did not cause local irritation or tissue damage reaction.

[0001]

<110> Chengdu Kanghong Biotechnology Co., Ltd.

<120> A pharmaceutical composition containing a fusion protein that inhibits angiogenesis and its use

<130> ZL200610066257.2

<160> 1

<170> PatentIn version 3.3

<210> 1

<211> 552

<212> PRT

<213> Manual sequence

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85           90           95
Ile Gly Leu Leu Thr Cys Glu Ala Thr Val Asn Gly His Leu Tyr Lys
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[0002]

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Glu Ser Asp His Thr Ile Lys Ala Gly His Val Leu Thr Ile Met Glu			
275	280	285	
Val Ser Glu Arg Asp Thr Gly Asn Tyr Thr Val Ile Leu Thr Asn Pro			
290	295	300	
Ile Ser Lys Glu Lys Gln Ser His Val Val Ser Leu Val Val Tyr Val			
305	310	315	320
Pro Pro Gly Pro Gly Asp Lys Thr His Thr Cys Pro Leu Cys Pro Ala			
325	330	335	
Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro			
340	345	350	
Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val			
355	360	365	
Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val			
370	375	380	
Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln			
385	390	395	400
Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln			
405	410	415	
Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala			
420	425	430	
Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro			
435	440	445	
Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr			
450	455	460	
Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser			
465	470	475	480
Asp Ile Ala Val Glu Trp Gln Ser Asn Gly Gln Pro Gln Asn Asn Tyr			
485	490	495	
Lys Ala Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr			
500	505	510	
Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe			
515	520	525	
Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys			
530	535	540	
Ser Leu Ser Leu Ser Pro Gly Lys			
545	550		



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(71) 申请人 成都康弘生物科技有限公司

地址 610036 四川省成都市金牛区蜀西路
36 号

(72) 发明人 柯潇 郑强

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(54) 发明名称

一种含有抑制血管增生的融合蛋白的药物组
合物及用途

(57) 摘要

本发明公开了一种含有抑制血管增生的融合蛋白的药物组合物及用途,具体涉及一种含有的血管内皮细胞生长因子(VEGF)受体1的细胞外结构域2(Flt-2)和VEGF受体2的细胞外结构域3和4(KDR-3,4)与人免疫球蛋白1(IG1)Fc的融合蛋白的药物组合物,该药物组合物能使融合蛋白保持稳定,能有效抑制融合蛋白聚合物的产生而造成的纯度下降,从而保持有效组分的生物活性。

CN 103816115 A

1. 一种含有抑制血管增生的融合蛋白的药物组合物,其特征在于包含
 - (a) 0.1-100mg/ml 的 VEGF 受体 1 的细胞外结构域 2 和 VEGF 受体 2 的细胞外结构域 3 和 4 与人免疫球蛋白 Fc 的融合蛋白,包含 SEQ ID No:1 的氨基酸序列;
 - (b) 5-100mM 缓冲液,其中的酸选自 Tris-HCl,柠檬酸,磷酸氢钠,磷酸二氢钠,醋酸,丁二酸,盐酸中的一种或多种;
 - (c) 5-500mM 碱性氨基酸选自赖氨酸,精氨酸,和组氨酸中的一种或其组合;
 - (d) 0.1-30% 盐渗透压剂调节剂,其中的糖选自蔗糖,海藻糖,甘露醇,甘油,丙二醇,山梨酯醇中的一种或多种,盐选自氯化钠或其它药理学上可以接受的盐中的一种或其组合;
 - (e) 0.01-0.1% 的一种或多种表面活性剂或助溶剂,选自聚乙二醇,吐温 20,吐温 80,丙二醇,二甲基亚砷或其它药理学上可以接受的表面活性剂中的一种或多种;
 - (f) 调节 pH 为 7.5 ~ 8.3。
2. 根据权利要求 1 所述的药物组合物,其特征在于包含
 - (a) 10-40mg/ml 的如 SEQ ID No:1 所示的融合蛋白;
 - (b) 5-100mM 的柠檬酸缓冲液或磷酸二氢钠缓冲液的一种或两种;
 - (c) 5-500mM 的精氨酸或组氨酸的一种或两种;
 - (d) 5-30% 的蔗糖或海藻糖的一种或两种;
 - (e) 0.01-0.1% 的吐温 -20 或聚乙二醇的一种或两种;
 - (f) 调节 pH 为 7.5 ~ 8.3。
3. 根据权利要求 3 所述的药物组合物,其特征在于包含
 - (a) 10mg/ml 的如 SEQ ID No:1 所示的融合蛋白;
 - (b) 10-100mM 的柠檬酸缓冲液;
 - (c) 5-250mM 的精氨酸;
 - (d) 5-20% 的蔗糖;
 - (e) 0.05-0.1% 的吐温 -20;
 - (f) 调节 pH 为 7.5 ~ 8.3。

所述药物组合物,优选由以下组分组成:10mg/ml 的如 SEQ ID No:1 所示的融合蛋白、10mM 的柠檬酸缓冲液,8% 的蔗糖,5mM 的精氨酸,0.05% 的吐温 20, pH7.5 ~ 8.3;

所述药物组合物,优选由以下组分组成:10mg/ml 的如 SEQ ID No:1 所示的融合蛋白、100mM 的柠檬酸缓冲液,20% 的蔗糖,250mM 的精氨酸,0.1% 的吐温 20, pH7.5 ~ 8.3。
4. 根据权利要求 3 所述的药物组合物,其特征在于包含
 - (a) 20mg/ml 的如 SEQ ID No:1 所示的融合蛋白;
 - (b) 10-55mM 的柠檬酸缓冲液;
 - (c) 250-500mM 的精氨酸;
 - (d) 12.5-30% 的蔗糖;
 - (e) 0.05-0.1% 的吐温 -20;
 - (f) 调节 pH 为 7.5 ~ 8.3。

所述药物组合物,优选由以下组分组成:20mg/ml 的如 SEQ ID No:1 所示的融合蛋白、10mM 的柠檬酸缓冲液,30% 的蔗糖,500mM 的精氨酸,0.1% 的吐温 20, pH7.5 ~ 8.3。
5. 根据权利要求 3 所述的药物组合物,其特征在于包含

(a) 40mg/ml 的如 SEQ ID No:1 所示的融合蛋白；

(b) 10-250mM 的柠檬酸缓冲液；

(c) 100mM 的精氨酸；

(d) 8-12.5% 的蔗糖；

(e) 0.05-0.1% 的吐温-20；

(f) 调节 pH 为 7.5 ~ 8.3。

所述药物组合物, 优选由以下组分组成: 40mg/ml 的如 SEQ ID No:1 所示的融合蛋白、250mM 的柠檬酸缓冲液, 8% 的蔗糖, 100mM 的精氨酸, 0.1% 的吐温 20, pH7.5 ~ 8.3。

6. 根据权利要求 1-5 所述的药物组合物, 其特征在于还可以含有氯化钠。

7. 根据权利要求 6 所述的药物组合物, 其特征在于由以下组分组成: 10mg/ml 的如 SEQ ID No:1 所示的融合蛋白、5mM 的柠檬酸缓冲液, 4% 的蔗糖, 4% 的氯化钠, 100mM 的精氨酸, 100mM 的组氨酸, 0.05% 的吐温 20, 0.05% 的 PEG400, pH7.5 ~ 8.3。

8. 根据权利要求 2 所述的药物组合物, 其特征在于由以下组分组成: 10mg/ml 的如 SEQ ID No:1 所示的融合蛋白、5mM 的磷酸二氢钠缓冲液, 10.0% 的海藻糖, 100mM 的精氨酸, 0.01% 的 PEG400, pH7.5 ~ 8.3。

9. 根据权利要求 1-8 中任一项所述的药物组合物, 其特征在于制成液体制剂或冻干制剂, 所述液体制剂优选为眼用制剂, 更优选为滴眼液或预填充注射剂。

10. 根据权利要求 1-9 中任一项所述的药物组合物, 其特征在于在制备治疗由血管新生或生长引起的疾病的药物中的用途, 尤其是年龄相关性黄斑变性。

一种含有抑制血管增生的融合蛋白的药物组合物及用途

[0001] 本申请是申请日为2010年08月31日,申请号为201010267503.7,发明名称为“一种含有抑制血管增生的融合蛋白的药物组合物及用途”的分案申请。

技术领域

[0002] 本发明涉及药物制剂领域,涉及包含 VEGF 受体片段和免疫球蛋白 Fc 融合而成的蛋白的药物组合物,以及其在医疗上的应用。

背景技术

[0003] 随着现代细胞分子生物学的发展,细胞因子和细胞表面相关分子在眼科疾病中的作用已经被广泛的关注和研究,VEGF 是血管内皮细胞促有丝分裂素具有增加血管通透性的生物特性,在胎儿时期 VEGF 对血管的发生极为重要,出生后水平下降。生理状态下 VEGF 呈低水平表达状态,对于维持血管的功能是必要的。最新的研究结果提示,对于老年性视网膜血管病变(Age-related macular degeneration,简称为 AMD)、糖尿病视网膜病变(Diabetic retinopathy, DR)等血管新生相关的疾病都起着广泛和重要的作用。AMD 多发生于 45 岁以上,其患病率随年龄的增长而增高,是当前中老年人致盲的重要疾病。湿性 AMD 主要为玻璃膜的破坏,脉络膜血管侵入视网膜下构成脉络膜新生血管,发生黄斑区视网膜色素上皮下或神经上皮浆液性或出血性的盘状脱离,最终成为机化瘢痕,有效抑制导致湿性黄斑病变的血管内皮细胞生长因子 VEGF,阻断 VEGF 或 VEGF 受体从而达到抑制血管新生具有重要的有着重要的治疗作用。在 DR 中,细胞和体液中 VEGF 的含量高于正常水平。VEGF 增高,引起毛细血管通透性改变,引起视网膜渗出,出血及视网膜黄斑水肿,诱导血管生成素(Angiogenin)生成增加,协同促进视网膜新生血管的形成,造成视力损害。

[0004] 盐键、氢键、二硫键和疏水作用是维持蛋白质构象稳定作用力。金属离子、底物、辅助因子和其他低相对分子量配体的相互作用使蛋白构象稳定。蛋白质与其它的生物大分子尤其是蛋白质与脂的作用。在生物体内,蛋白质常与脂类或多糖相互作用形成复合物,屏蔽了蛋白质表面的疏水区域,从而显著增加蛋白质的稳定性。蛋白不稳定主要由以下因素引起:(1)物理作用:由布朗运动调节的极性水分子与蛋白质疏水核的接触会导致蛋白质不稳定。(2)化学作用:活性部位的氨基酸残基的氧化作用是酶失活的最常见机理之一。如半胱氨酸的巯基和色氨酸的吲哚环,对氧化特别敏感。(3)生物学作用:蛋白质水解酶作用。微生物和外源蛋白水解酶作用催化肽键水解。由基因工程菌纯化真核细胞多肽时收率低,是由于体外蛋白水解造成的。

[0005] 聚合作用首先使包埋的疏水性氨基酸残基暴露于水溶剂,导致蛋白质可逆变性;其次,蛋白质分子彼此缔合,以减少疏水氨基酸的不利裸露;最后,如果蛋白质分子含有半胱氨酸和胱氨酸残基,则会发生分子间二硫键交换反应。聚合作用有时可通过还原和再氧化再生天然二硫键,使蛋白质再活化。聚合和简单沉淀是有区别的,后者并未使蛋白质发生显著的构象变化。

[0006] 本发明人还观察到一个明显的问题是溶液制剂在长期储存后容易形成可溶聚合

物和不可溶颗粒,如何解决这个问题,找到一种在物理和化学上都稳定的药物组合物,能够抑制聚合物生成,并能够在长期储存后形成较少的可溶聚合物和不溶颗粒。另外,由于其组分是药理学上可接受的组分,可以用于治疗眼部疾病,包括玻璃体内注射和外部给药。此外,本发明人发现得到的制剂处方在注射器中比在小瓶中更加稳定。

[0007] 本发明中采用能够抑制血管新生,由血管内皮细胞生长因子(VEGF)受体1的细胞外结构域2(Flt-2)和VEGF受体2的细胞外结构域3和4(KDR-3,4)与人免疫球蛋白1(IG1)Fc的融合而成的蛋白(FP3蛋白)是通过重组技术的工作细胞表达并经过纯化后达到药用纯度,经过换液制剂分装制得合适的药物制剂。这些制剂优选液体制剂或冻干制剂,适用于眼睛疾病的治疗,尤其是用于玻璃体注射。

[0008] FP3蛋白作为蛋白药物,其稳定性比普通小分子化学药物差很多,相比于天然存在的免疫球蛋白,其稳定性也更差。中国专利所述的融合蛋白是中国专利“VEGF受体融合蛋白在治疗眼睛疾病中的应用”(专利号ZL200610066257.2)中描述的处方需要在-20℃保存,对药物的生产,运输保存和应用都提出了较高的要求。众所周知,一般重组的融合蛋白的稳定性都比较差,在保存过程中会受到多种环境因素的影响,如温度,湿度,氧,紫外线等都可以是融合蛋白发生多种物理或化学变化,造成蛋白质的聚合,分解,氧化或变性等。这些变化都可以使蛋白的活性降低,治疗效果下降并引起严重的毒副作用。因此,开发出稳定且易于运输和贮藏的融合蛋白制剂是具有十分重要的临床意义的。

发明内容

[0009] 本发明的目的之一在于提供一种含有的血管内皮细胞生长因子(VEGF)受体1的细胞外结构域2(Flt-2)和VEGF受体2的细胞外结构域3和4(KDR-3,4)与人免疫球蛋白1(IG1)Fc的融合蛋白的药物组合物,更具体的是能用于玻璃体注射的液体制剂,该液体制剂能使融合蛋白保持稳定,其最突出的特征是能有效抑制融合蛋白聚合物的产生而造成的纯度下降,从而保持有效组分的生物活性。

[0010] 本发明一方面提供了一种含有抑制血管增生的融合蛋白的药物组合物,其特征在于包含

[0011] (a)0.1-100mg/ml的VEGF受体1的细胞外结构域2和VEGF受体2的细胞外结构域3和4与人免疫球蛋白Fc的融合蛋白,包含SEQ ID No:1的氨基酸序列;

[0012] (b)5-100mM缓冲液,其中的酸选自Tris-HCl,柠檬酸,磷酸氢钠,磷酸二氢钠,醋酸,丁二酸,盐酸中的一种或多种;

[0013] (c)5-500mM碱性氨基酸选自赖氨酸,精氨酸,和组氨酸中的一种或其组合;

[0014] (d)0.1-30%盐渗透压剂调节剂,其中的糖选自蔗糖,海藻糖,甘露醇,甘油,丙二醇,山梨醇中的一种或多种,盐选自氯化钠或其它药理学上可以接受的盐中的一种或其组合;

[0015] (e)0.01-0.1%的一种或多种表面活性剂或助溶剂,选自聚乙二醇,吐温20,吐温80,丙二醇,二甲基亚砜或其它药理学上可以接受的表面活性剂中的一种或多种;

[0016] (f)调节pH为7.5~8.3。

[0017] 其中药物组合物优选为包含下列组分的药物组合物:

[0018] (a)10-40mg/ml的如SEQ ID No:1的融合蛋白;

- [0019] (b) 5-100mM 的柠檬酸或磷酸二氢钠的一种或两种；
- [0020] (c) 5-500mM 的精氨酸或组氨酸的一种或两种；
- [0021] (d) 8-30% 的蔗糖或海藻糖的一种或两种；
- [0022] (e) 0.01-0.1% 的吐温-20 或聚乙二醇的一种或两种；
- [0023] (f) 调节 pH 为 7.5 ~ 8.3。
- [0024] 本发明所述的药物组合物, 进一步为包含下列组分的药物组合物：
- [0025] (a) 10mg/ml 的如 SEQ ID No :1 所示的融合蛋白；
- [0026] (b) 10-100mM 的柠檬酸缓冲液；
- [0027] (c) 5-250mM 的精氨酸；
- [0028] (d) 5-20% 的蔗糖；
- [0029] (e) 0.05-0.1% 的吐温-20；
- [0030] (f) 调节 pH 为 7.5 ~ 8.3。
- [0031] 上述药物组合物, 进一步优选为由以下组分组成：10mg/ml 的如 SEQ ID No :1 所示的融合蛋白、10mM 的柠檬酸缓冲液, 8% 的蔗糖, 5mM 的精氨酸, 0.05% 的吐温 20, pH7.5 ~ 8.3；
- [0032] 本发明所述的所述药物组合物, 进一步优选由以下组分组成：10mg/ml 的如 SEQ ID No :1 所示的融合蛋白、100mM 的柠檬酸缓冲液, 20% 的蔗糖, 250mM 的精氨酸, 0.1% 的吐温 20, pH7.5 ~ 8.3。
- [0033] 本发明所述的药物组合物, 进一步为包含下列组分的药物组合物：
- [0034] (a) 20mg/ml 的如 SEQ ID No :1 所示的融合蛋白；(b) 10-55mM 的柠檬酸缓冲液；(c) 250-500mM 的精氨酸；(d) 12.5-30% 的蔗糖；(e) 0.05-0.1% 的吐温-20；(f) 调节 pH 为 7.5 ~ 8.3。
- [0035] 本发明所述的药物组合物, 进一步优选为由以下组分组成：20mg/ml 的如 SEQ ID No :1 所示的融合蛋白、10mM 的柠檬酸缓冲液, 30% 的蔗糖, 500mM 的精氨酸, 0.1% 的吐温 20, pH7.5 ~ 8.3。
- [0036] 上述的药物组合物, 进一步优选为包含下列组分的药物组合物：(a) 40mg/ml 的如 SEQ ID No :1 所示的融合蛋白；(b) 10-250mM 的柠檬酸缓冲液；(c) 100mM 的精氨酸；(d) 8-12.5% 的蔗糖；(e) 0.05-0.1% 的吐温-20；(f) 调节 pH 为 7.5 ~ 8.3。
- [0037] 上述的药物组合物, 进一步优选为由以下组分组成：40mg/ml 的如 SEQ ID No :1 所示的融合蛋白、250mM 的柠檬酸缓冲液, 8% 的蔗糖, 100mM 的精氨酸, 0.1% 的吐温 20, pH7.5 ~ 8.3。
- [0038] 上述的药物组合物中还可以含有氯化钠。
- [0039] 本发明所述的药物组合物, 进一步优选为由以下组分组成：10mg/ml 的如 SEQ ID No :1 所示的融合蛋白、5mM 的柠檬酸缓冲液, 4% 的蔗糖, 4% 的氯化钠, 100mM 的精氨酸, 100mM 的组氨酸, 0.05% 的吐温 20, 0.05% 的 PEG400, pH7.5 ~ 8.3。
- [0040] 本发明所述的药物组合物, 进一步优选为由以下组分组成：10mg/ml 的如 SEQ ID No :1 所示的融合蛋白、5mM 的磷酸二氢钠缓冲液, 10.0% 的海藻糖, 100mM 的精氨酸, 0.01% 的 PEG400, pH7.5 ~ 8.3。
- [0041] 上述药物组合物制成的制剂形式可为液体制剂或冻干制剂, 其中液体制剂优选为

眼用制剂,尤其是滴眼液;还可以为预填充注射剂。

[0042] 上述药物组合物可以用于治疗血管新生或生长引起的疾病,优选为年龄相关性黄斑变性。

[0043] 在本发明中,所述的融合蛋白是中国专利“VEGF 受体融合蛋白在治疗眼睛疾病中的应用”(专利号 ZL200610066257.2)中描述的融合蛋白,具体而言是 FP3 融合蛋白,因此 ZL200610066257.2 的内容可用于进一步阐述本发明。

具体实施方式

[0044] 实施例 110mg/ml FP3 融合蛋白原处方在 4℃ 下 3ml 玻璃安瓿中的稳定性研究

[0045] 处方如下:

[0046]

FP3 融合蛋白 10 mg/ml

丁二酸钠 10 mM

海藻糖 9.0%

吐温 20 0.05 %

[0047] 用盐酸调节系统 pH 到 6.0 ~ 6.5

[0048] 将蛋白原液换液后, 无菌分装得到 3ml 玻璃安瓿中, 4℃ 留样, 在 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 月测定样品, 通过 SEC-HPLC 确定稳定性。结果显示, 该处方不能有效抑制聚合物的生成, 造成产品纯度下降, 与 VEGF 的亲合力降低, 进入体内以后可能诱发免疫反应。

[0049] 表 1. 10mg/ml FP3 融合蛋白在 4℃ 的稳定性

[0050]

时间(月)	外观	pH 值	浓度(mg/ml)	聚合物(%)	亲合力(pM)
0	合格	6.0	10.0	0.3	10.6
1	合格	6.0	9.4	1.9	9.5
2	合格	6.0	10.2	2.8	9.1
3	合格	6.0	10.2	3.6	8.7
6	合格	6.0	10.0	9.1	8.4
9	合格	6.0	10.0	18.2	7.7
12	合格	6.1	10.3	31.8	7.0

[0051] 实施例 210mg/ml FP3 融合蛋白在 4℃ 下 3ml 玻璃安瓿中的稳定性研究

[0052]

FP3 融合蛋白 10 mg/ml

磷酸氢二钠 10 mM

蔗糖 10 %

氯化钠 0.5%

吐温 20 0.05 %

pH 7.5~8.3

[0053] 将蛋白原液换液后, 无菌分装得到 3ml 玻璃安瓿中, 4℃留样, 在 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 月测定样品, 通过 SEC-HPLC 确定稳定性。结果显示, 该处方不能有效抑制聚合物的生成, 造成产品纯度下降, 与 VEGF 的亲合力降低, 进入体内以后可能诱发免疫反应。

[0054] 表 2. 10mg/ml FP3 融合蛋白在 4℃的稳定性

[0055]

时间(月)	外观	pH 值	浓度 (mg/ml)	聚合物 (%)	亲和力 (pM)
0	合格	7.7	10.1	0.2	10.7

[0056]

1	合格	7.9	10.1	2.0	9.9
2	合格	7.7	10.7	3.2	9.3
3	合格	7.8	10.6	5.4	8.4
6	合格	7.7	10.3	9.9	8.1
9	合格	7.5	10.1	13.1	8.5
12	合格	7.9	10.3	23.3	7.3

[0057] 实施例 3 10mg/ml FP3 融合蛋白在 4℃下 3ml 玻璃安瓿中的稳定性研究

[0058]

FP3 融合蛋白 10 mg/ml

柠檬酸 5 mM

蔗糖 8.0 %

吐温 20 0.05 %

pH 7.5~8.3

[0059] 将蛋白原液换液后, 无菌分装得到 3ml 玻璃安瓿中, 4℃留样, 在 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 月测定样品, 通过 SEC-HPLC 确定稳定性。结果显示, 该处方不能有效抑制

聚合物的生成,造成产品纯度下降,与 VEGF 的亲合力降低,进入体内以后可能诱发免疫反应。

[0060] 表 3. 10mg/ml FP3 融合蛋白在 4℃ 的稳定性

[0061]

时间(月)	外观	pH 值	浓度(mg/ml)	聚合物(%)	亲和力(pM)
0	合格	7.9	10.2	0.3	10.4
1	合格	7.9	10.2	1.4	10.0
2	合格	7.8	10.6	2.6	9.7
3	合格	7.8	10.7	3.6	8.1
6	合格	8.1	10.5	9.4	7.9
9	合格	8.3	10.1	18.5	9.7
12	合格	8.0	10.4	19.1	9.6

[0062] 实施例 410mg/ml FP3 融合蛋白在 4℃ 下 3ml 玻璃安瓿中的稳定性研究

[0063]

FP3 融合蛋白 10 mg/ml

柠檬酸 10 mM

[0064]

蔗糖 8.0 %

精氨酸 5 mM

吐温 20 0.05 %

pH 7.5~8.3

[0065] 将蛋白原液换液后, 无菌分装得到 3ml 玻璃安瓿中, 4℃ 留样, 在 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 月测定样品, 通过 SEC-HPLC 确定稳定性。结果显示, 该处方能有效抑制聚合物的生成, 产品纯度下降很慢, 融合蛋白与 VEGF 的亲合力几乎不变。

[0066] 表 4. 10mg/ml FP3 融合蛋白在 4℃ 的稳定性

[0067]

时间(月)	外观	pH 值	浓度(mg/ml)	聚合物(%)	亲和力(pM)
0	合格	7.7	10.1	0.4	10.5
1	合格	7.9	10.1	0.5	10.4
2	合格	7.5	10.7	0.7	10.1

3	合格	7.8	10.6	0.8	10.0
6	合格	7.7	10.3	0.9	9.9
9	合格	7.9	10.1	1.8	9.7
12	合格	7.9	10.3	1.9	9.6

[0068] 实施例 510mg/ml FP3 融合蛋白在 4℃ 下 3ml 玻璃安瓿中的稳定性研究

[0069]

FP3 融合蛋白 10 mg/ml

柠檬酸 100 mM

蔗糖 20.0 %

精氨酸 250 mM

吐温 20 0.10 %

pH 7.5~8.3

[0070] 将蛋白原液换液后，无菌分装得到 3ml 玻璃安瓿中，4℃ 留样，在 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 月测定样品，通过 SEC-HPLC 确定稳定性。结果显示，该处方能有效抑制聚合物的生成，产品纯度下降很慢，融合蛋白与 VEGF 的亲合力几乎不变。

[0071] 表 5. 10mg/ml FP3 融合蛋白在 4℃ 的稳定性

[0072]

时间(月)	外观	pH 值	浓度 (mg/ml)	聚合物 (%)	亲和力 (pM)
0	合格	7.9	10.0	0.3	10.4
1	合格	7.9	10.1	0.3	10.3
2	合格	7.9	10.0	0.4	10.4
3	合格	7.9	10.1	0.5	10.2
6	合格	7.9	10.2	0.7	10.1
9	合格	7.9	10.0	0.8	10.2
12	合格	7.9	10.1	0.9	10.0

[0073] 实施例 610mg/ml FP3 融合蛋白在 4℃ 下 3ml 玻璃安瓿中的稳定性研究

[0074]

FP3 融合蛋白 10 mg/ml
 磷酸二氢钠 5 mM
 海藻糖 10.0 %
 精氨酸 100 mM
 PEG400 0.01 %
 pH 7.5~8.3

[0075] 将蛋白原液换液后, 无菌分装得到 3ml 玻璃安瓿中, 4℃留样, 在 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 月测定样品, 通过 SEC-HPLC 确定稳定性。

[0076] 表 6. 10mg/ml FP3 融合蛋白在 4℃的稳定性

[0077]

时间 (月)	外观	pH 值	浓度 (mg/ml)	聚合物 (%)	亲和力 (pM)
0	合格	8.3	10.4	0.3	10.1
1	合格	8.3	10.3	0.3	10.2
2	合格	8.2	10.2	0.5	10.0
3	合格	8.3	10.1	0.5	10.1
6	合格	8.1	10.2	0.9	9.9
9	合格	8.3	10.2	1.4	10.0
12	合格	8.2	10.1	4.2	9.8

[0078] 实施例 7 20mg/ml FP3 融合蛋白在 4℃下 3ml 玻璃安瓿中的稳定性研究

[0079]

FP3 融合蛋白 20 mg/ml

[0080]

柠檬酸 5 mM
 蔗糖 4.0 %
 氯化钠 4.0%
 精氨酸 100 mM
 组氨酸 100 mM
 吐温 20 0.05 %
 PEG400 0.05%
 pH 7.5~8.3

[0081] 将蛋白原液换液后, 无菌分装得到 3ml 玻璃安瓿中, 4℃留样, 在 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 月测定样品, 通过 SEC-HPLC 确定稳定性。

[0082] 表 7. 20mg/ml FP3 融合蛋白在 4℃的稳定性

[0083]

时间(月)	外观	pH 值	浓度(mg/ml)	聚合物(%)	亲和力(pM)
0	合格	8.0	19.8	1	14.3
1	合格	7.8	20.7	1.5	10.2
2	合格	7.9	19.8	1.3	12.6
3	合格	7.9	20.6	2	10.5
4	合格	7.8	N/D	1.7	N/D
5	合格	7.8	N/D	2.2	N/D
6	合格	8.0	N/D	2.7	N/D
7	合格	7.8	N/D	2.7	N/D
8	合格	7.9	N/D	2.7	N/D
9	合格	7.9	19.5	2.7	12.5
10	合格	7.8	N/D	3.1	N/D
11	合格	7.8	N/D	3.5	N/D
12	合格	7.9	20.3	3.6	14.3

[0084] N/D 表示未检测。

[0085] 实施例 8 20mg/ml FP3 融合蛋白在 4℃下 3ml 玻璃安瓿中的稳定性研究

[0086]

FP3 融合蛋白 20 mg/ml

[0087]

柠檬酸 10 mM

蔗糖 30 %

精氨酸 500 M

吐温 20 0.1 %

pH 7.5~8.3

[0088] 将蛋白原液换液后, 无菌分装得到 3ml 玻璃安瓿中, 4℃留样, 在 0, 1, 2, 3, 4, 5, 6,

7,8,9,10,11,12 月测定样品,通过 SEC-HPLC 确定稳定性。

[0039] 表 8. 20mg/ml FP3 融合蛋白在 4℃ 的稳定性

[0090]

时间(月)	外观	pH 值	浓度 (mg/ml)	聚合物 (%)	亲和力 (pM)
0	合格	7.7	20.0	0.1	10.2
1	合格	7.9	20.0	0.1	10.2
2	合格	7.7	20.2	0.1	10.3
3	合格	7.8	20.2	0.2	10.3
6	合格	7.7	20.1	0.2	9.9
9	合格	7.9	20.3	0.3	10.0
12	合格	7.9	20.0	0.5	10.3

[0091] 实施例 9 10mg/ml FP3 融合蛋白在 4℃ 下 3ml 玻璃安瓿中的稳定性研究

[0092]

FP3 融合蛋白 10 mg/ml

柠檬酸 10 mM

蔗糖 5 %

精氨酸 100 M

吐温 20 0.05 %

pH 7.5~8.3

[0093] 将蛋白原液换液后, 无菌分装得到 3ml 玻璃安瓿中, 4℃ 留样, 在 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 月测定样品, 通过 SEC-HPLC 确定稳定性。

[0094] 表 9. 10mg/ml FP3 融合蛋白在 4℃ 的稳定性

[0095]

时间(月)	外观	pH 值	浓度 (mg/ml)	聚合物 (%)	亲和力 (pM)
0	合格	7.7	10.1	0.4	10.5
1	合格	7.9	10.1	0.5	10.4
2	合格	7.7	10.7	0.7	10.1
3	合格	7.8	10.6	0.8	10.0
6	合格	7.7	10.3	0.9	9.9

9	合格	7.9	10.1	1.8	7.7
12	合格	7.9	10.3	1.9	6.3

[0096] 实施例 10 10mg/ml FP3 融合蛋白在 4℃ 下 3ml 玻璃安瓿中的稳定性研究

[0097] 将 FP3 融合蛋白原液经 Vivaflow 浓缩换液后无菌分装后分装得到半成品, 置 55mM 的柠檬酸, 12.5% 的蔗糖, 250mM 的精氨酸, 0.05% 的吐温 20, pH7.9 缓冲液, 调节 FP3 融合蛋白至 10mg/ml 的, 无菌分装得到 3ml 玻璃安瓿中, 4℃ 留样, 在 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 月测定样品, 通过 SEC-HPLC 确定稳定性。

[0098] 表 10. 10mg/ml FP3 融合蛋白在 4℃ 的稳定性

[0099]

时间(月)	外观	pH 值	浓度(mg/ml)	聚合物(%)	亲和力(pM)
0	合格	8.3	10.0	0.2	9.7
1	合格	8.3	10.1	0.2	9.6
2	合格	8.2	10.2	0.3	9.6
3	合格	7.9	10.0	0.4	9.3
6	合格	8.0	10.1	0.5	9.3
9	合格	7.9	10.1	0.6	9.1
12	合格	7.9	10.3	1.0	9.4

[0100] 实施例 11 20mg/ml FP3 融合蛋白在 4℃ 下 3ml 玻璃安瓿中的稳定性研究

[0101] 将 FP3 融合蛋白原液经 Vivaflow 浓缩换液后无菌分装后分装得到半成品, 置 55mM 的柠檬酸, 12.5% 的蔗糖, 250mM 的精氨酸, 0.05% 的吐温 20, pH7.5 ~ 8.3 缓冲液, 调节 FP3 融合蛋白至 20mg/ml 的, 无菌分装得到 3ml 玻璃安瓿中, 4℃ 留样, 在 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 月测定样品, 通过 SEC-HPLC 确定稳定性。

[0102] 表 11. 20mg/ml FP3 融合蛋白在 4℃ 的稳定性

[0103]

时间(月)	外观	pH 值	浓度(mg/ml)	聚合物(%)	亲和力(pM)
0	合格	7.9	19.9	0.7	10.7
1	合格	7.9	20.1	1.2	10.2
2	合格	7.7	20.7	1.3	10.3
3	合格	7.8	21.6	1.4	10.4

6	合格	8.0	21.6	1.4	10.4
9	合格	7.9	21.1	2.6	9.6
12	合格	7.9	21.3	3.6	9.4

[0104] 实施例 124℃下 40mg/ml FP3 融合蛋白冻干制剂的稳定性研究

[0105]

FP3 融合蛋白 40 mg/ml

柠檬酸 250 mM

蔗糖 8.0 %

组氨酸 100 mM

吐温 20 0.10 %

pH 7.5~8.3

[0106] 将 FP3 融合蛋白溶液调节到 40mg/ml, pH 调节到 7.5 ~ 8.3 后分装后分装到 3ml 玻璃安瓿中, 优化的冻干曲线的条件为: -50℃迅速预冻 4 个小时, 控制在 -20℃升华除去大部分水分, 然后逐步升高隔板的温度进一步去除残留的水分, 最后一步应用 25 度并达到极限真空, 使水分降低, 同时使样品温度升得不会太高。冻干结束后, 亚塞, 出冻干箱, 轧铝盖, 进行水分和纯度等分析, 4℃留样, 在 0, 1, 6, 12 月加入等体积注射用水复溶, 测定样品, 通过 SEC-HPLC 确定稳定性。

[0107] 表 12. 40mg/ml FP3 融合蛋白在 4℃的稳定性

[0108]

时间(月)	复溶后外观	pH 值	浓度(mg/ml)	聚合物(%)	亲和力(pM)
0	合格	7.9	39.9	0.1	11.2
1	合格	7.9	40.1	0.2	10.6
6	合格	7.9	40.7	0.3	10.1
12	合格	8.3	40.6	0.4	10.0

[0109] 实施例 134℃下 40mg/ml FP3 融合蛋白冻干制剂的稳定性研究

[0110]

FP3 融合蛋白 40 mg/ml

柠檬酸 10 mM

蔗糖 5 %

精氨酸 100 mM

吐温 20 0.05 %

pH 7.5~8.3

[0111] 将 FP3 融合蛋白溶液调节到 20mg/ml, pH 调节到 7.5 ~ 8.3 后分装后分装到 3ml 玻璃安瓿中, 优化的冻干曲线的条件为: -50℃ 迅速预冻 4 个小时, 控制在 -20℃ 升华除去大部分水分, 然后逐步升高隔板的温度进一步去除残留的水分, 最后一步应用 25 度并达到极限真空, 使水分降低, 同时使样品温度升得不会太高。冻干结束后, 亚塞, 出冻干箱, 轧铝盖, 进行水分和纯度等分析, 4℃ 留样, 在 0, 1, 6, 12 月加入等体积注射用水复溶, 测定样品, 通过 SEC-HPLC 确定稳定性。

[0112] 表 13. 40mg/ml FP3 融合蛋白在 4℃ 的稳定性

[0113]

时间(月)	复溶后外观	pH 值	浓度(mg/ml)	聚合物(%)	亲和力(pM)
0	合格	8.0	40	0.1	10.2
1	合格	8.3	40	0.1	10.5
6	合格	7.9	40	0.2	10.2
12	合格	8.2	40.1	0.3	10.3

[0114] 实施例 144℃ 下 20mg/ml FP3 融合蛋白在玻璃预填充注射器中的稳定性研究

[0115]

FP3 融合蛋白 20 mg/ml

柠檬酸 55 mM

蔗糖 12.5 %

精氨酸 250 mM

吐温 20 0.05 %

pH 7.5~8.3

[0116] 将 FP3 融合蛋白原液经浓缩换液后无菌分装后分装得到半成品, 调节 FP3 融合蛋白至 20mg/ml 的, 无菌分装到具有 FluroTec 涂层的 1ml 玻璃玻璃预填充注射器中, 4℃ 留样, 在 0, 1, 6, 12 月测定样品, 通过 SEC-HPLC 确定稳定性。

[0117] 表 14. 4℃ 下 20mg/ml FP3 融合蛋白在玻璃预填充注射器中的稳定性研究

[0118]

时间(月)	外观	pH 值	浓度(mg/ml)	聚合物(%)	亲和力(pM)
0	合格	7.9	20.0	0.1	11.2
1	合格	7.9	20.1	0.1	11.6
6	合格	7.9	20.1	0.1	11.1
12	合格	8.2	20.1	0.1	11.0

[0119] 实施例 15 聚合物的凝胶排阻色谱分析(SEC-HPLC)

[0120] 多孔硅胶柱稳定性高、耐热耐压、寿命长、能实现生物大分子的快速分离。TSK G3000SWxl 为多孔硅胶柱,粒径 5 μ m、孔径 250 埃、分离球蛋白的范围 10-500kD,分离样品时间 30min,是国际上分析生物大分子普遍使用的色谱柱。本发明中,我们选用多孔硅胶柱 TSK G3000SWxl 色谱柱,仪器为 Waters 的 2695 高效液相色谱仪,以 pH 至 7.20 的磷酸盐缓冲液为流动相,流速为 0.5ml/ml,柱温为 25℃,检测波长为 280nm,对重组人血管内皮生长因子受体-抗体 FP3 融合蛋白的纯度进行检测。

[0121] 实施例 16 兔玻璃体注射重复给药试验

[0122] 12 只日本大耳白兔,随机分为 2 组,分别是供试品组和溶剂对照组,每组 6 只,雌雄各半。在各组动物的右眼,分别单次玻璃体注射给予供试品(0.5mg/50 μ L/眼)或等体积溶剂对照品,另一侧做假注射对照或空白对照。给药后每日进行肉眼观察,定期使用间接检眼镜及裂隙灯进行检查。给药后 14 天处死动物,取眼球进行组织病理学检查。通过观察结果及组织病理学检查结果,考察供试品的局部毒性。结果发现:日本大耳白兔眼玻璃体内注射给药,6 只给予供试品的眼睛中,有 1 只肉眼观察见有轻微充血,1 只见少量分泌物;裂隙灯观察见 1 只出现晶状体混浊。同时,分别在给予溶剂对照侧、假注射侧及空白对照侧眼睛观察到相同现象,且发生率及发生时间与给予供试品侧眼睛基本一致。由此可排除这些现象是由供试品引起的刺激反应。组织病理学检查见所有眼球组织结构均正常。故在本次试验条件下,兔眼单次玻璃体注射给予重组人血管内皮生长因子受体-抗体融合蛋白注射液,未引起局部刺激性或组织损伤反应。

[0001]

<110> 成都康弘生物科技有限公司
<120> 一种含有抑制血管增生的融合蛋白的药物组合物及用途
<130> ZL200610066257.2
<160> 1
<170> PatentIn version 3.3
<210> 1
<211> 552
<212> PRT
<213> 人工序列
<400> 1

```
Met Val Ser Tyr Trp Asp Thr Gly Val Leu Leu Cys Ala Leu Leu Ser
1           5           10           15
Cys Leu Leu Leu Thr Gly Ser Ser Ser Gly Gly Arg Pro Phe Val Glu
                20           25           30
Met Tyr Ser Glu Ile Pro Glu Ile Ile His Met Thr Glu Gly Arg Glu
        35           40           45
Leu Val Ile Pro Cys Arg Val Thr Ser Pro Asn Ile Thr Val Thr Leu
        50           55           60
Lys Lys Phe Pro Leu Asp Thr Leu Ile Pro Asp Gly Lys Arg Ile Ile
65           70           75           80
Trp Asp Ser Arg Lys Gly Phe Ile Ile Ser Asn Ala Thr Tyr Lys Glu
        85           90           95
Ile Gly Leu Leu Thr Cys Glu Ala Thr Val Asn Gly His Leu Tyr Lys
        100          105          110
Thr Asn Tyr Leu Thr His Arg Gln Thr Asn Thr Ile Ile Asp Val Val
        115          120          125
Leu Ser Pro Ser His Gly Ile Glu Leu Ser Val Gly Glu Lys Leu Val
        130          135          140
Leu Asn Cys Thr Ala Arg Thr Glu Leu Asn Val Gly Ile Asp Phe Asn
145          150          155          160
Trp Glu Tyr Pro Ser Ser Lys His Gln His Lys Lys Leu Val Asn Arg
        165          170          175
Asp Leu Lys Thr Gln Ser Gly Ser Glu Met Lys Lys Phe Leu Ser Thr
        180          185          190
Leu Thr Ile Asp Gly Val Thr Arg Ser Asp Gln Gly Leu Tyr Thr Cys
        195          200          205
Ala Ala Ser Ser Gly Leu Met Thr Lys Lys Asn Ser Thr Phe Val Arg
```

[0002]

210	215	220
Val His Glu Lys Pro Phe Val Ala Phe Gly Ser Gly Met Glu Ser Leu		
225	230	235
Val Glu Ala Thr Val Gly Glu Arg Val Arg Ile Pro Ala Lys Tyr Leu		
	245	250
Gly Tyr Pro Pro Pro Glu Ile Lys Trp Tyr Lys Asn Gly Ile Pro Leu		
	260	265
Glu Ser Asn His Thr Ile Lys Ala Gly His Val Leu Thr Ile Met Glu		
	275	280
Val Ser Glu Arg Asp Thr Gly Asn Tyr Thr Val Ile Leu Thr Asn Pro		
	290	295
Ile Ser Lys Glu Lys Gln Ser His Val Val Ser Leu Val Val Tyr Val		
305	310	315
Pro Pro Gly Pro Gly Asp Lys Thr His Thr Cys Pro Leu Cys Pro Ala		
	325	330
Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro		
	340	345
Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val		
	355	360
Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val		
	370	375
Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln		
385	390	395
Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln		
	405	410
Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala		
	420	425
Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro		
	435	440
Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr		
	450	455
Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser		
465	470	475
Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr		
	485	490
Lys Ala Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr		
	500	505
Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe		
	515	520
Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys		
	530	535
Ser Leu Ser Leu Ser Pro Gly Lys		
545	550	

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(71) Applicant (for all designated States except AL, AT, BE, BG, CH, CN, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IN, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR): **GENENTECH, INC.** [US/US]; 1 DNA Way, South San Francisco, California 94080 (US).

(71) Applicant (for AL, AT, BE, BG, CH, CN, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IN, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR only): **F. HOFFMANN-LA ROCHE AG** [CH/CH]; Grenzacherstrasse 124, 4070 Basel (CH).

(72) Inventors: **HASS, Philip E.**; Genentech, Inc., 1 DNA Way, South San Francisco, California 94080 (US). **KELLEY, Robert F.**; Genentech, Inc., 1 DNA Way, South San Francisco, California 94080 (US). **SCHEER, Justin M.**; Genentech, Inc., 1 DNA Way, South San Francisco, California 94080 (US). **SHATZ, Whitney**; Genentech, Inc., 1 DNA Way, South San Francisco, California 94080 (US). **TESAR, Devin**; Genentech, Inc., 1 DNA Way, South San

Francisco, California 94080 (US). **VAN LOOKEREN CAMPAGNE, Menno**; Genentech, Inc., 1 DNA Way, South San Francisco, California 94080 (US).

(74) Agents: **ALLEN, Derick E.** et al.; Armstrong Teasdale LLP, 7700 Forsyth Boulevard, Suite 1800, St. Louis, Missouri 63105 (US).

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(54) Title: ANTI-FACTOR D ANTIBODY VARIANT CONJUGATES AND USES THEREOF

(57) Abstract: The disclosure relates to antibody-polymer conjugates comprising one or more anti-Factor D antibody variants, their production and their use in the preparation of compositions and medicaments for treatment of diseases and disorders associated with excessive or uncontrolled complement activation.



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PGR2026-00039

Biocon Ex.1002

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ANTI-FACTOR D ANTIBODY VARIANT CONJUGATES AND USES THEREOF**Cross-Reference to Related Applications**

[0001] The instant application claims the benefit of priority to U.S. Provisional Application No. 62/249,020, which was filed on October 30, 2015, and to U.S. Provisional Application No. 62/250,965, which was filed on November 4, 2015, both of which are herein incorporated by reference in their entirety.

Sequence Listing

[0002] 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 October 27, 2016, is named P33044-WO.txt and is 172,164 bytes in size.

Background of the Disclosure

[0003] The development of therapeutic antibodies represents a revolutionary era in the long history of human medicine. More than 30 antibodies have been approved for human therapy, and over 250 antibodies are in clinical development worldwide for a wide range of major diseases, including cancer, autoimmunity, inflammation, cardiovascular disease, infectious diseases and ocular disease. Over the past decade, the market for monoclonal antibody products has grown exponentially, propelled by the success of such blockbuster drugs as trastuzumab, bevacizumab, rituximab, infliximab and adalimumab. While these first-generation antibody therapeutics have benefited numerous patients, advances in antibody technology and a deeper understanding of the mechanism of action have paved the way for improved versions of antibodies with even better efficacy and fewer side effects.

[0004] Successful development and viable use of antibody therapeutics pose many unique challenges compared to traditional medicines that are small organic and inorganic molecules. The biophysical properties of antibodies, like all proteins, are important determinants of their behavior and have significant impacts for development of therapeutics relating to expression, purification, formulation, storage, delivery, pharmacokinetics, immunogenicity and dosing regimens. Among the many characteristics, protein stability is a main feature defining the quality of a candidate antibody and its desirability as a successful therapeutic.

[0005] Protein therapy often requires delivering high dose of the protein to patients in order to achieve the desired efficacy. Meanwhile, certain routes of administration are associated

with limitations such as delivery time, volume and physical force that require the high dose protein to be in a high-concentration formulation (e.g., at least 100 mg/ml). However, highly concentrated protein formulations pose particular challenges with respect to stability, solubility, viscosity and other protein properties.

[0006] Proteins can be unstable and become degraded via multiple physical and chemical degradation pathways. Physical instability occurs mainly via two pathways – denaturation and aggregation, whereas chemical instability can occur via many pathways, such as deamidation, isomerization, cross-linking, oxidation, and fragmentation. Antibody instability is undesirable for drug development, as it can lead to decreased amount of active drug and lower *in vivo* efficacy, increased variability among batches of the therapeutics, and perhaps most importantly, immunogenicity in patients against aggregates and degradants. Wang et al (2007) *J. Pharm. Sci.* 96:1-26; Moore et al (1980) *J Clin Endocrinology & Metabolism* 51: 691-697; Rosenberg et al (2006) *AAPSJ* 8:E501-7; Joubert et al (2011) *J Biol Chem* 286: 25118-25133; Joubert et al (2012) *J Biol Chem*(2012) 286:25266-79).

[0007] Antibodies are large multidomain proteins, and factors contributing to their stability and propensity to aggregate are complex, including many extrinsic conditions such as temperature, pH, concentration, ionic strength and physical stress. Equally critical is the protein's own primary sequence. Although by nature the Fc region is largely identical between antibodies of a particular isotype, the Fab region differs greatly. Thus, there are significant variations in stability and aggregation propensity between antibodies, largely due to Fab sequence differences and the particular antigen specificity of the antibody. Lowe et al. (2011) *Adv. Protein Chem. Struct Biol.* 84:41-61.

[0008] The complement system plays a central role in the clearance of immune complexes and the immune response to infectious agents, foreign antigens, virus-infected cells and tumor cells. However, complement is also involved in pathological inflammation and in autoimmune diseases. Therefore, inhibition of excessive or uncontrolled activation of the complement cascade could provide clinical benefit to patients with such diseases and conditions.

[0009] The complement system encompasses three distinct activation pathways, designated the classical, mannose-binding lectin, and the alternative pathways. V.M. Holers In *Clinical Immunology: Principles and Practice*, ed. R.R. Rich, Mosby Press; 1996, 363-391. The classical pathway is a calcium/magnesium-dependent cascade which is normally activated by the formation of antigen-antibody complexes. The mannose-binding lectin (MBL) pathway is initiated by the binding of MBL to carbohydrate structures on pathogens, resulting in the activation of MBL protease (MASP) that cleaves C2 and C4 to form active C2a, C2b, C4a and

C4b. The alternative pathway is a magnesium-dependent cascade which is activated by deposition and activation of C3 on certain susceptible surfaces (*e.g.*, cell wall polysaccharides of yeast and bacteria, and certain biopolymer materials). Activation of the complement pathway generates biologically active fragments of complement proteins, *e.g.*, C3a, C4a and C5a anaphylatoxins and C5b-9 membrane attack complexes (MAC), which mediate inflammatory activities involving leukocyte chemotaxis, activation of macrophages, neutrophils, platelets, mast cells and endothelial cells, vascular permeability, cytolysis, and tissue injury.

[0010] Factor D is a highly specific serine protease essential for activation of the alternative complement pathway. It cleaves factor B bound to C3b, generating the C3b/Bb enzyme which is the active component of the alternative pathway C3/C5 convertases. Factor D may be a suitable target for inhibition, since its plasma concentration in humans is very low (1.8 µg/ml), and it has been shown to be the limiting enzyme for activation of the alternative complement pathway. P.H. Lesavre and H.J. Müller-Eberhard. (1978) *J. Exp. Med.* 148: 1498-1510; J.E. Volanakis et al. (1985) *New Eng. J. Med.* 312: 395-401.

[0011] The down-regulation of complement activation has been demonstrated to be effective in treating several disease indications in animal models and in *ex vivo* studies, *e.g.*, systemic lupus erythematosus and glomerulonephritis, rheumatoid arthritis, cardiopulmonary bypass and hemodialysis, hyperacute rejection in organ transplantation, myocardial infarction, reperfusion injury, and adult respiratory distress syndrome. In addition, other inflammatory conditions and autoimmune/immune complex diseases are also closely associated with complement activation, including thermal injury, severe asthma, anaphylactic shock, bowel inflammation, urticaria, angioedema, vasculitis, multiple sclerosis, myasthenia gravis, membranoproliferative glomerulonephritis, and Sjögren's syndrome.

[0012] Age-related macular degeneration (AMD) is a progressive chronic disease of the central retina with significant consequences for visual acuity. Lim et al. (2012) *Lancet* 379:1728. Late forms of the disease are the leading cause of vision loss in industrialized countries. For the Caucasian population ≥ 40 years of age the prevalence of early AMD is estimated at 6.8% and advanced AMD at 1.5%. de Jong (2006) *N. Engl. J. Med.* 355: 1474. The prevalence of late AMD increases dramatically with age rising to 11.8% after 80 years of age. Two types of AMD exist, non-exudative (dry) and exudative (wet) AMD. The more common dry form AMD involves atrophic and hypertrophic changes in the retinal pigment epithelium (RPE) underlying the central retina (macula) as well as deposits (drusen) on the RPE. Advanced dry AMD can result in significant retinal damage, including geographic atrophy (GA), with irreversible vision loss. Moreover, patients with dry AMD can progress to the wet form, in

which abnormal blood vessels called choroidal neovascular membranes (CNVMs) develop under the retina, leak fluid and blood, and ultimately cause a blinding disciform scar in and under the retina.

[0013] Drugs targeting new blood vessel formation (neovascularization) have been the mainstay for treating wet AMD. Ranibizumab, which is an anti-VEGFA antibody fragment, has proven to be highly effective in improving vision for patients afflicted with wet AMD. Recent studies have implicated an association between AMD and key proteins in the complement cascade and a number of therapies targeting specific complement components are being developed to treat dry AMD. A humanized anti-Factor D Fab fragment (aFD, lampalizumab; FCFD4514S) that potently inhibits Factor D and the alternative complement pathway, through binding to an exosite on factor D is currently in clinical development for the treatment of GA associated with dry AMD. Katschke et al. (2012) *J. Biol. Chem.* 287:12886. A recent phase II clinical trial has shown that monthly intravitreal injection of lampalizumab effectively slowed the progression of GA lesions in patients with advanced dry AMD.

[0014] Eyes have many unique biophysical and anatomic features that make the ocular drug delivery more challenging. For example, blood-ocular barriers are defense mechanisms to protect the eye from infection, but at the same time make it hard for drug to penetrate, especially for diseases in the posterior segments of the eye. Consequently, high-dose administration is often desired to achieve and maintain drug's onsite bioavailability (e.g., ocular residence time) in order to improve efficacy. Meanwhile, the limited space in the back of the eye restrains the drug volume to be delivered, which in turn demands drugs to be delivered in a high concentration formulation.

[0015] Patients with ocular diseases can also benefit from long acting/slow released delivery of therapeutics. Less frequent dosing would provide improved convenience to the patient, have potential benefits of decreased infection rate and increased clinical efficacy. Controlled release of high dose drugs could also minimize drug side effects. Two promising systems for long-acting delivery are PLGA-based solid implants and an implantable port delivery system (PDS). Both systems have the potential to provide near zero-order release kinetics for an extended period of time. For PLGA implants the protein drug is encapsulated in a hydrophobic polymer matrix and drug release is accomplished via slow hydrolysis of the polymer. The rate of release can be controlled by changing the drug loading, polymer hydrophobicity, or polymer molecular weight. The PDS is a refillable device where release into the vitreous is controlled by a porous metal membrane comprising a titanium frit. Since the

reservoir has a low volume, a high protein concentration is required for effective delivery with the PDS.

[0016] The conditions that a drug is exposed to vary depending on the delivery system used. For incorporation into solid PLGA implants, lyophilized or spray-dried drug is used. Implants are produced using a hot-melt extrusion process such that the drug is briefly exposed to temperatures approaching 90°C. Although the drug remains in solid state for the duration of release, degradation of PLGA may expose the drug to a low pH environment. In contrast, drug delivered with the PDS is maintained at high concentration in liquid state and exposed to vitreous which is characterized as a reducing environment at physiological ionic strength and pH.

[0017] In addition to or in lieu of high concentration and long acting delivery, increased bioavailability (e.g., ocular residence time) of the drug can be achieved, or facilitated, by post-translational modifications, wherein the protein drug is covalently conjugated with natural or synthetic polymers such as polysialylation, HESylation (conjugation with hydroxyethyl starch) and PEGylation. Chen et al (2011) *Expert. Opin. Drug Deliv.* 8:1221-36; Kontermann (2009) *BioDrugs* 23:93-109. PEGylation, the covalent attachment of polymer polyethylene glycol (PEG) to a protein, is a well-established technology especially useful for extending the half-life of antibody fragment therapeutics. Jevsevar et al. (2010) *Biotech. J.* 5:113-128.

[0018] Thus, there exists a great need for anti-factor D antibodies, as well as conjugates thereof, having improved stabilities, and that in some embodiments, are suitable for high concentration formulation and/or long acting delivery.

Summary of the Invention

[0019] The present disclosure is based in part on the discovery that targeted amino acid substitutions of identified hot spots in an antibody can effectively improve the antibody's stability and overall potency as a therapeutic. Conjugation of such antibodies to multi-armed polymers, such as multi-armed polyols, can improve the vitreous humour half-life, the aqueous humour half-life, and/or the retinal half-life, as compared to the unconjugated antibodies.

[0020] In some aspects, the present disclosure relates to conjugates comprising one or more anti-Factor D antibodies or anti-Factor D antibody variants covalently linked to one or more multi-armed polyols. In certain embodiments, the polyol is an eight-armed polyol (i.e., an octamer). In some embodiments, the polyol is a polyethylene glycol (PEG). In certain embodiments, the PEG may have the structure of any of general formulas (Ia), (Ib), (IIa), (IIIa), or (IVa), as set forth hereinafter.

[0021] The anti-factor D antibody variants used in the conjugates of the present disclosure have improved stability. The anti-factor D antibody variants comprise substitution of at least one target aspartic acid (D or Asp) residue within a hypervariable region (HVR) of a reference anti-Factor D antibody, wherein the target Asp residue is identified as prone to isomerization and the substitution is Asp to Glutamic acid (E or Glu), and wherein the anti-Factor D antibody variant exhibits improved stability without significant loss of Factor D binding affinity when compared to the reference anti-Factor D antibody. In some aspects, the target Asp residue subject to substitution is within an Asp-Xaa motif, wherein Xaa is Asp, Gly, His, Ser or Thr. In some aspects, the target Asp residue is the first Asp of an Asp-Asp (DD) motif. In some aspects, the anti-factor D antibody variants comprise one or more substitutions at additional Asp sites within a HVR of a reference anti-Factor D antibody, wherein the substitution is Asp to Serine (S or Ser) in order to reduce the overall charges of the antibody, thereby improving the solubility of the antibody. In some aspects, the anti-factor D antibody variants comprise one or more substitutions at asparagine (N or Asn) sites identified as prone to deamidation, wherein the substitution is Asn to Ser in order to reduce or eliminate the antibody's deamidation.

[0022] In some embodiments, the anti-Factor D antibody variant is a Fab fragment, wherein the C-terminus of the heavy chain of the Fab fragment ends in the amino acids "CDKTHT," "CDKTHL," "CDKTH," "CDKT," "CDK," or "CD." In some embodiments, the C-terminus of the heavy chain of the Fab fragment ends in the sequence "CDKTHX," wherein X is any amino acid except T. Truncations and/or mutations at the C terminus may be able to reduce or eliminate AHA-reactivity against the Fab, without compromising thermostability or expression. In some embodiments, the C-terminus of the heavy chain of a Fab fragment ends in the amino acids "CDKTHTC," "CDKTHTCPPC," "CDKTHTCPPS," "CDKTHTSPPC," "CDKTHTAPPC," "CDKTHTSGGC" or "CYGPPC". In some such embodiments, a free cysteine in the C-terminal amino acids may be amenable to conjugation, for example, to a polymer such as PEG. In some embodiments, a Fab fragment comprises a heavy chain constant domain amino acid sequence selected from the group consisting of SEQ ID NOs: 54 (ending in "CDKTHT"), 55-66 (ending in "CDKTHL," "CDKTHTC," "CPPC," "CPPS," "SPPC," "APPC," "SGGC," "CYGPPC," "CDKTH," "CDKT," "CDK," or "CD"), and 116 (ending in "CDKTHX"). In some embodiments, a Fab is an IgG2 Fab fragment comprising a heavy chain constant domain amino acid sequence of SEQ ID NOs: 67 (ending in "VERK") or an IgG2 Fab-C fragment comprising a heavy chain constant domain amino acid sequence of SEQ ID NO: 68 (ending in "VERKC"). In some embodiments, a Fab is an IgG4 Fab fragment comprising a

heavy chain constant domain amino acid sequence selected from the group consisting of SEQ ID NOs: 69-73 (ending in “KYGPP”, “KYGP”, “KYG”, “KY”, or “K”) or an IgG4 Fab-C fragment comprising a heavy chain constant domain amino acid sequence of SEQ ID NO: 74 (ending in “KYGPPC”). As an alternative to truncating and/or mutation at the C terminus, to avoid pre-existing anti-hinge antibody (PE-AHA) responses, IgG2 or IgG4 Fab fragments may be used, since these do not show PE-AHA response.

[0023] In some aspects, the reference anti-factor D antibody used to generate the antibody variants used in the conjugates of the disclosure comprises the light chain variable domain sequence of SEQ ID NO:3, the heavy chain variable domain sequence of SEQ ID NO:4, or both. Subsequently, the resulting antibody variants may comprise a light chain HVR1 (HVR-L1) sequence of SEQ ID NO:11 and a heavy chain HVR2 (HVR-H2) sequence of SEQ ID NO:12, or may comprise a light chain HVR3 (HVR-L3) sequence of SEQ ID NO:13, or may comprise a light chain HVR1 (HVR-L1) sequence of SEQ ID NO:14 and a heavy chain HVR2 (HVR-H2) sequence of SEQ ID NO:12, or may comprise a heavy chain HVR3 (HVR-H3) sequence of SEQ ID NO:15.

[0024] In some aspects, the anti-factor D antibody variant used in the conjugates of the disclosure is a variant of a reference anti-factor D antibody, wherein the reference anti-factor D antibody comprises the light chain sequence of SEQ ID NO:1 and the heavy chain sequence of SEQ ID NO:2, and wherein the variant comprises the following sequence modifications over the reference anti-factor D antibody: a light chain HVR1 (HVR-L1) sequence of SEQ ID NO:11 and a heavy chain HVR2 (HVR-H2) sequence of SEQ ID NO:12. Such variant is referred to as the “TM” variant (AFD.v6) in the Examples herein below (see, e.g., Table 1).

[0025] In some aspects, the anti-factor D antibody variant used in the conjugates of the disclosure is a variant of a reference anti-factor D antibody, wherein the reference anti-factor D antibody comprises the light chain sequence of SEQ ID NO:1 and a heavy chain sequence selected from the group consisting of SEQ ID NOs: 34-53 and 115, and wherein the variant comprises the following sequence modifications over the reference anti-factor D antibody: a light chain HVR1 (HVR-L1) sequence of SEQ ID NO:11 and a heavy chain HVR2 (HVR-H2) sequence of SEQ ID NO:12. Such variants are referred to as “modified TM” variants. These modified TM variants comprise a heavy chain constant domain that differs from that of the TM variant, and which is selected from the group consisting of SEQ ID NOs: 55-74 and 116.

[0026] In some aspects, the anti-factor D antibody variant used in the conjugates of the disclosure is a variant of a reference anti-factor D antibody, wherein the reference anti-factor D antibody comprises the light chain sequence of SEQ ID NO:1 and the heavy chain sequence of

SEQ ID NO:2, and wherein the variant comprises the following sequence modifications over the reference anti-factor D antibody: a light chain HVR1 (HVR-L1) sequence of SEQ ID NO:11, a heavy chain HVR2 (HVR-H2) sequence of SEQ ID NO:12 and a light chain HVR3 (HVR-L3) sequence of SEQ ID NO:13. Such variant is referred to as the “TM.D92E” variant (AFD.v7) in Examples herein below (see, e.g., Table 1).

[0027] In some aspects, the anti-factor D antibody variant used in the conjugates of the disclosure is a variant of a reference anti-factor D antibody, wherein the reference anti-factor D antibody comprises the light chain sequence of SEQ ID NO:1 and a heavy chain sequence selected from the group consisting of SEQ ID NOs: 34-53 and 115, and wherein the variant comprises the following sequence modifications over the reference anti-factor D antibody: a light chain HVR1 (HVR-L1) sequence of SEQ ID NO:11, a heavy chain HVR2 (HVR-H2) sequence of SEQ ID NO:12 and a light chain HVR3 (HVR-L3) sequence of SEQ ID NO:13. Such variants are referred to as “modified TM.D92E” variants. These modified TM.D92E variants comprise a heavy chain constant domain that differs from that of the TM.D92E variant, and which is selected from the group consisting of SEQ ID NOs: 55-74 and 116.

[0028] In some aspects, the anti-factor D antibody variant used in the conjugates of the disclosure is a variant of a reference anti-factor D antibody, wherein the reference anti-factor D antibody comprises the light chain sequence of SEQ ID NO:1 and the heavy chain sequence of SEQ ID NO:2, and wherein the variant comprises the following sequence modifications over the reference anti-factor D antibody: a light chain HVR1 (HVR-L1) sequence of SEQ ID NO:14 and a heavy chain HVR2 (HVR-H2) sequence of SEQ ID NO:12. Such variant is referred to as the “SIESD” variant (AFD.v8) in Examples herein below (see, e.g., Table 1). In some embodiments, the “SIESD” variant (AFD.v8) comprises the light chain sequence of SEQ ID NO: 26 and the heavy chain sequence of SEQ ID NO: 27. In some embodiments, a Cys-modified version of the “SIESD” variant comprises the light chain sequence of SEQ ID NO: 26 and the heavy chain sequence of SEQ ID NO: 30. In some embodiments, a Cys-Pro-Pro-Cys-modified version of the “SIESD” variant comprises the light chain sequence of SEQ ID NO: 26 and the heavy chain sequence of SEQ ID NO: 31. In some embodiments, a modified version of the “SIESD” variant comprises the light chain sequence of SEQ ID NO: 26 and the heavy chain sequence selected from the group consisting of SEQ ID NOs: 75-92 and 117.

[0029] In some aspects, the anti-factor D antibody variant used in the conjugates of the disclosure is a variant of a reference anti-factor D antibody, wherein the reference anti-factor D antibody comprises the light chain sequence of SEQ ID NO:1 and a heavy chain sequence selected from the group consisting of SEQ ID NOs: 34-53 and 115, and wherein the variant

comprises the following sequence modifications over the reference anti-factor D antibody: a light chain HVR1 (HVR-L1) sequence of SEQ ID NO:14 and a heavy chain HVR2 (HVR-H2) sequence of SEQ ID NO:12. Such variants are referred to as “modified SIESD” variants. These modified SIESD variants comprise a heavy chain constant domain that differs from that of the SIESD variant, and which is selected from the group consisting of SEQ ID NOs: 55-74 and 116.

[0030] In some aspects, the anti-factor D antibody variant used in the conjugates of the disclosure is a variant of a reference anti-factor D antibody, wherein the reference anti-factor D antibody comprises the light chain sequence of SEQ ID NO:1 and the heavy chain sequence of SEQ ID NO:2, and wherein the variant comprises the following sequence modifications over the reference anti-factor D antibody: a light chain HVR1 (HVR-L1) sequence of SEQ ID NO:14, a heavy chain HVR2 (HVR-H2) sequence of SEQ ID NO:12 and a heavy chain HVR3 (HVR-H3) sequence of SEQ ID NO:15. Such variant is referred to as the “SIESD.N103S” variant (AFD.v14) in Examples herein below (see, e.g., Table 1). In some embodiments, the “SIESD.N103S” variant (AFD.v14) comprises the light chain sequence of SEQ ID NO: 28 and the heavy chain sequence of SEQ ID NO: 29. In some embodiments, a Cys-modified version of the “SIESD.N103S” variant comprises the light chain sequence of SEQ ID NO: 28 and the heavy chain sequence of SEQ ID NO: 32. In some embodiments, a Cys-Pro-Pro-Cys-modified version of the “SIESD.N103S” variant comprises the light chain sequence of SEQ ID NO: 28 and the heavy chain sequence of SEQ ID NO: 33. In some embodiments, a modified version of the “SIESD.N103S” variant comprises the light chain sequence of SEQ ID NO: 28 and a heavy chain sequence selected from the group consisting of SEQ ID NOs: 93-110 and 118.

[0031] In some aspects, the anti-factor D antibody variant used in the conjugates of the disclosure is a variant of a reference anti-factor D antibody, wherein the reference anti-factor D antibody comprises the light chain sequence of SEQ ID NO:1 and a heavy chain sequence selected from the group consisting of SEQ ID NOs: 34-53 and 115, and wherein the variant comprises the following sequence modifications over the reference anti-factor D antibody: a light chain HVR1 (HVR-L1) sequence of SEQ ID NO:14, a heavy chain HVR2 (HVR-H2) sequence of SEQ ID NO:12 and a heavy chain HVR3 (HVR-H3) sequence of SEQ ID NO:15. Such variants are referred to as “modified SIESD.N103S” variants. These modified SIESD.N103S variants comprise a heavy chain constant domain that differs from that of the SIESD.N103S variant, and which is selected from the group consisting of SEQ ID NOs: 55-74 and 116.

[0032] In some aspects, the present disclosure relates to conjugates comprising one or more anti-Factor D antibody variants comprising one or more substitutions within the HVRs of

a reference anti-Factor D antibody. In some aspects, the reference anti-Factor D antibody comprises the following HVR sequences:

HVR-L1: ITSTDIDDDMN (SEQ ID NO: 5);
HVR-L2: GGNTLRP (SEQ ID NO: 6);
HVR-L3: LQSDSLPYT (SEQ ID NO: 7);
HVR-H1: GYTFTNYGMN (SEQ ID NO: 8);
HVR-H2: WINTYTGETTYADDFKG (SEQ ID NO: 9); and
HVR-H3: EGGVNN (SEQ ID NO: 10).

The corresponding variants comprise one or more of the following substitutions:

- (a) D5S in SEQ ID NO: 5;
- (b) D7E in SEQ ID NO: 5;
- (c) D8S in SEQ ID NO: 5 (a, b, and c disclosed in SEQ ID NO: 22);
- (d) D13E in SEQ ID NO: 9 (SEQ ID NO: 23);
- (e) D4E in SEQ ID NO: 7 (SEQ ID NO: 24); or
- (f) N5S in SEQ ID NO: 10 (SEQ ID NO: 25).

In some embodiments, the reference anti-Factor D antibody comprises a heavy chain constant domain amino acid sequence selected from the group consisting of SEQ ID NOs: 54-74 and 116.

[0033] In some aspects, the variant combines the substitutions (b)-(d) above. In another aspect, the variant combines the substitutions (b)-(e) above. In another aspect, the variant combines the substitutions (a)-(d) above. In another aspect, the variant combines the substitutions (a)-(d) and (f) above. In another aspect, the variant comprises one or more of substitution (a), (b), (c), (d), (e), or (f) above, and further comprises a heavy chain constant domain amino acid sequence selected from the group consisting of SEQ ID NOs: 54-74 and 116. In another aspect the variant comprises substitutions selected from the group consisting of: the substitutions (b)-(d) above, the substitutions (b)-(e) above, the substitutions (a)-(d) above, and the substitutions (a)-(d) and (f) above, wherein the variant further comprises a heavy chain constant domain amino acid sequence selected from the group consisting of SEQ ID NOs: 54-74 and 116.

[0034] In some aspects, the present disclosure relates to a conjugate comprising one or more anti-Factor D antibody comprising a light chain variable domain amino acid sequence of SEQ ID NO:16, 18 or 19. In another aspect, the present disclosure relates to a conjugate comprising an anti-Factor D antibody comprising a heavy chain variable domain amino acid sequence of SEQ ID NO:17 or 20. In another aspect, the anti-Factor D antibody may comprise a

heavy chain constant domain amino acid sequence selected from the group consisting of SEQ ID NOs: 54-74 and 116. In another aspect, the anti-Factor D antibody comprises a light chain variable domain amino acid sequence of SEQ ID NO:16, 18 or 19 and a heavy chain variable domain amino acid sequence of SEQ ID NO:17 or 20. For example, the anti-Factor D antibody can be the “TM” variant (AFD.v6) that comprises the light chain variable domain amino acid sequence of SEQ ID NO:16 and the heavy chain variable domain amino acid sequence of SEQ ID NO:17; the “TM.D92E” variant (AFD.v7) that comprises the light chain variable domain amino acid sequence of SEQ ID NO:18 and the heavy chain variable domain amino acid sequence of SEQ ID NO:17; the “SIESD” variant (AFD.v8) that comprises the light chain variable domain amino acid sequence of SEQ ID NO:19 and the heavy chain variable domain amino acid sequence of SEQ ID NO:17; or the “SIESD.N103S” variant (AFD.v14) that comprises the light chain variable domain amino acid sequence of SEQ ID NO:19 and the heavy chain variable domain amino acid sequence of SEQ ID NO:20.

[0035] In another aspect, the anti-Factor D antibody comprises a light chain variable domain amino acid sequence of SEQ ID NO:16, 18 or 19, a heavy chain variable domain amino acid sequence of SEQ ID NO:17 or 20, and a heavy chain constant domain amino acid sequence selected from the group consisting of SEQ ID NOs: 54-74 and 116. For example, the anti-Factor D antibody can be a modified version of the “TM” variant (AFD.v6) that comprises the light chain variable domain amino acid sequence of SEQ ID NO:16, the heavy chain variable domain amino acid sequence of SEQ ID NO:17, and a heavy chain constant domain amino acid sequence selected from the group consisting of SEQ ID NOs: 55-74 and 116; a modified version of the “TM.D92E” variant (AFD.v7) that comprises the light chain variable domain amino acid sequence of SEQ ID NO:18, the heavy chain variable domain amino acid sequence of SEQ ID NO:17, and a heavy chain constant domain amino acid sequence selected from the group consisting of SEQ ID NOs: 55-74 and 116; a modified version of the “SIESD” variant (AFD.v8) that comprises the light chain variable domain amino acid sequence of SEQ ID NO:19, the heavy chain variable domain amino acid sequence of SEQ ID NO:17, and a heavy chain constant domain amino acid sequence selected from the group consisting of SEQ ID NOs: 55-74 and 116; or a modified version of the “SIESD.N103S” variant (AFD.v14) that comprises the light chain variable domain amino acid sequence of SEQ ID NO:19, the heavy chain variable domain amino acid sequence of SEQ ID NO:20, and a heavy chain constant domain amino acid sequence selected from the group consisting of SEQ ID NOs: 55-74 and 116.

[0036] In some embodiments, the anti-Factor D antibody is a modified version of the “SIESD” variant (AFD.v8) that comprises the light chain variable domain amino acid sequence

of SEQ ID NO:19, and a heavy chain sequence selected from the group consisting of SEQ ID NOs: 30, 31, 75-92, and 117. In some embodiments, the anti-Factor D antibody is a modified version of the “SIESD” variant (AFD.v8) that comprises the light chain sequence of SEQ ID NO: 26, and a heavy chain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 30, 31, 75-92, and 117. In another embodiment, the anti-Factor D antibody is a modified version of the “SIESD.N103S” variant (AFD.v14) that comprises the light chain variable domain amino acid sequence of SEQ ID NO:19 and a heavy chain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 32, 33, 93-110, and 118. In some embodiments, the anti-Factor D antibody is a modified version of the “SIESD.N103S” variant (AFD.v14) that comprises the light chain sequence of SEQ ID NO: 28, and a heavy chain sequence selected from the group consisting of SEQ ID NOs: 32, 33, 93-110, and 118.

[0037] In some aspects, the present disclosure relates to conjugates comprising one or more anti-Factor D antibody having a variable light chain comprising a HVR-L1 having the sequence of SEQ ID NO:11 or 14, a HVR-L2 having the sequence of SEQ ID NO:6, and a HVR-L3 having the sequence of SEQ ID NO:7 or 13; and a variable heavy chain comprising a HVR-H1 having the sequence of SEQ ID NO:8, a HVR-H2 having the sequence of SEQ ID NO:9 or 12, and a HVR-H3 having the sequence of SEQ ID NO:10 or 15. In another embodiment, the anti-Factor D antibody may further comprise a heavy chain constant domain amino acid sequence selected from the group consisting of SEQ ID NOs: 54-74 and 116. For example, the anti-Factor D antibody can be the “SIESD” variant (AFD.v8) comprising the following six HVR sequences: HVR-L1 (SEQ ID NO:14), HVR-L2 (SEQ ID NO:6), HVR-L3 (SEQ ID NO:7), HVR-H1 (SEQ ID NO:8), HVR-H2 (SEQ ID NO:12), and HVR-H3 (SEQ ID NO:10); or the “SIESD.N103S” variant (AFD.v14) comprising the following six HVR sequences: HVR-L1 (SEQ ID NO:14), HVR-L2 (SEQ ID NO:6), HVR-L3 (SEQ ID NO:7), HVR-H1 (SEQ ID NO:8), HVR-H2 (SEQ ID NO:12), and HVR-H3 (SEQ ID NO:15). In some embodiments, the anti-Factor D antibody can be a modified version of the “SIESD” variant (AFD.v8) comprising the following six HVR sequences: HVR-L1 (SEQ ID NO:14), HVR-L2 (SEQ ID NO:6), HVR-L3 (SEQ ID NO:7), HVR-H1 (SEQ ID NO:8), HVR-H2 (SEQ ID NO:12), and HVR-H3 (SEQ ID NO:10), and further comprising a heavy chain constant domain amino acid sequence selected from the group consisting of SEQ ID NOs: 55-74 and 116. In another embodiment, the anti-Factor D antibody can be a modified version of the “SIESD.N103S” variant (AFD.v14) comprising the following six HVR sequences: HVR-L1 (SEQ ID NO:14), HVR-L2 (SEQ ID NO:6), HVR-L3 (SEQ ID NO:7), HVR-H1 (SEQ ID NO:8), HVR-H2 (SEQ ID NO:12), and HVR-H3 (SEQ ID NO:15), and further comprising a

heavy chain constant domain amino acid sequence selected from the group consisting of SEQ ID NOs: 55-74 and 116.

[0038] In some aspects, the present disclosure relates to conjugates comprising one or more anti-Factor D antibody variants with no detectable Asp isomerization, wherein the variants are made by a method for removing or reducing isomerization, comprising: (a) identifying one or more Asp residues prone to Asp isomerization within HVRs of a reference anti-Factor D antibody; (b) substituting Glu for the Asp residue identified in step (a); (c) screening the resulting candidate variants for Asp isomerization; and (d) selecting those variants that have no detectable Asp isomerization. In some aspects, the method above is combined with a method for removing or reducing deamidation, comprising (a) identifying one or more Asn residues prone to deamidation within HVRs of the reference anti-Factor D antibody; (b) substituting Ser for the Asn residue identified in step (a); (c) screening the resulting candidate variants for deamidation; and (d) selecting those variants having reduced or eliminated deamidation. In another aspect, the method for removing or reducing isomerization is combined with a method for reducing overall charge of the antibody by: (a) selecting one or more negatively charged amino acid residues D or E within HVRs of the reference anti-Factor D antibody; (b) substituting Ser for the residue selected in step (a); (c) screening the resulting candidate variants for solubility; and (d) selecting those variants having improved solubility when compared to the reference anti-Factor D antibody.

[0039] In some aspects, the present disclosure is directed to a conjugate comprising one or more anti-Factor D antibody or antibody variant disclosed herein and one or more multi-armed polyol, wherein the conjugate is prepared by covalently linking at least one of the anti-Factor D antibodies or antibody variants disclosed herein to the polyol. In some embodiments, the multi-armed polyol is a PEG. In some embodiments, the PEG is an octamer. In some embodiments, the PEG has the structure of general formula (Ia), (Ib), (IIa), (IIIa), or (IVa), as set forth herein.

[0040] In some aspects, the conjugates of the present disclosure comprise anti-factor D antibody variants that have improved stability while maintaining the factor D binding affinity when compared to the reference anti-factor D antibody. In some aspects, the antibodies bind to Factor D with a binding affinity of at least about 10^{-9} to 10^{-12} M. In some aspects, the antibodies used in the conjugates of the present disclosure include human, humanized or chimeric antibodies.

[0041] In some aspects, the antibodies used in the conjugates of the present disclosure are antibody fragments (e.g., antigen-binding fragments). The antibody fragments may, for

example, be Fab, Fab', F(ab')₂, scFv, (scFv)₂, dAb, complementarity determining region (CDR) fragments, linear antibodies, single-chain antibody molecules, minibodies, diabodies, or multispecific antibodies formed from antibody fragments.

[0042] In other aspects of the disclosure, the present disclosure includes compositions comprising a conjugate of the disclosure. In another aspect, the disclosure concerns a composition of matter comprising a conjugate of the disclosure, as described herein, in combination with a carrier. Optionally, the carrier is a pharmaceutically acceptable carrier.

[0043] In some aspects, the present disclosure includes pharmaceutical formulations comprising the conjugates described herein, at therapeutically effective concentrations. In some aspects, the pharmaceutical formulation comprises the antibody or antibody variant at a concentration of at least about 100 mg/mL, from about 100 to about 150 mg/mL, from about 100 to about 200 mg/mL, from about 100 to about 300 mg/mL, from about 100 to about 400 mg/mL, from about 100 to about 500 mg/mL; at least about 200 mg/mL, at least about 300 mg/mL, at least about 400 mg/mL or at least about 500 mg/mL. In some aspects, the concentration of the antibody or antibody variant in the formulation is about 200, 250, 300, 350, 400, 450 or 500 mg/mL. In some aspects, the concentration of the antibody or antibody variant in the formulation is less than about 450 mg/mL.

[0044] Another aspect of the present disclosure is the use of the conjugate or pharmaceutical formulation of the disclosure for treatment of disorders associated with excessive or uncontrolled complement activation. In one embodiment, the disclosure is directed to a method of treating a complement-associated disorder in a subject, the method comprising administering to the subject a conjugate or pharmaceutical formulation of the disclosure. The disorders include complement activation during cardiopulmonary bypass operations; complement activation due to ischemia-reperfusion following acute myocardial infarction, aneurysm, stroke, hemorrhagic shock, crush injury, multiple organ failure, hypobolemic shock, intestinal ischemia or other events causing ischemia. Complement activation has also been shown to be associated with inflammatory conditions such as severe burns, endotoxemia, septic shock, adult respiratory distress syndrome, hemodialysis; anaphylactic shock, severe asthma, angioedema, Crohn's disease, sickle cell anemia, poststreptococcal glomerulonephritis and pancreatitis. The disorder may be the result of an adverse drug reaction, drug allergy, IL-2 induced vascular leakage syndrome or radiographic contrast media allergy. In one embodiment, the complement-associated disorder is systemic. It may also include autoimmune disease such as systemic lupus erythematosus, myasthenia gravis, rheumatoid arthritis, Alzheimer's disease and multiple sclerosis. In another embodiment, complement activation is also associated with

transplant rejection. In another embodiment, complement activation is also associated with ocular diseases (all ocular conditions and diseases the pathology of which involve complement, including the classical and the alternative pathway of complement) or complement-associated eye conditions, such as, for example, without limitation, macular degenerative disease, such as all stages of age-related macular degeneration (AMD), including dry and wet (non-exudative and exudative) forms, diabetic retinopathy and other ischemia-related retinopathies, choroidal neovascularization (CNV), uveitis, diabetic macular edema, pathological myopia, von Hippel-Lindau disease, histoplasmosis of the eye, Central Retinal Vein Occlusion (CRVO), corneal neovascularization, and retinal neovascularization. In one example, complement-associated eye conditions include age-related macular degeneration (AMD), including non-exudative (e.g. intermediate dry AMD or geographic atrophy (GA)) and exudative (e.g., wet AMD (choroidal neovascularization (CNV)) AMD, diabetic retinopathy (DR), endophthalmitis and uveitis. In a further example, nonexudative AMD may include the presence of hard drusen, soft drusen, geographic atrophy and/or pigment clumping. In another example, complement-associated eye conditions include age-related macular degeneration (AMD), including early AMD (e.g., includes multiple small to one or more non-extensive medium sized drusen), intermediate AMD (e.g., includes extensive medium drusen to one or more large drusen) and advanced AMD (e.g., includes geographic atrophy or advanced wet AMD (CNV)). In a further example, intermediate dry AMD may include large confluent drusen. In a further example, geographic atrophy may include photoreceptor and/or Retinal Pigmented Epithelial (RPE) loss. In a further example, the area of geographic atrophy may be small or large and/or may be in the macula area or in the peripheral retina. In one example, the complement-associated eye condition is intermediate dry AMD. In one example, the complement-associated eye condition is geographic atrophy. In one example, the complement-associated eye condition is wet AMD (choroidal neovascularization (CNV)). In one embodiment, the conjugate or pharmaceutical formulation is administered using an implantable port-delivery system. In one embodiment, the conjugate or pharmaceutical formulation is administered by intravitreal administration. In one embodiment, the method or use further comprises administering to the subject an additional therapeutic agent, such as a HTRA1 antagonist, an ANG2 antagonist, a TIE2 antagonist, a VEGF antagonist, or an antagonist of one or more of the C1, C2, C3, C4, C5, C6, C7, C8, or C9 complement components.

[0045] In another aspect, the disclosure provides a kit, comprising a conjugate of the disclosure. In some embodiments, the disclosure provides a kit, comprising a conjugate of the disclosure and instructions for use. In some embodiments, the disclosure concerns a kit

comprising a conjugate of the disclosure and instructions for administering said conjugate, to treat a complement-associated disorder. In some embodiments, the disclosure provides a kit comprising a first container comprising a composition comprising one or more one or more conjugate of the disclosure; and a second container comprising a buffer. In some embodiments, the buffer is pharmaceutically acceptable. In some embodiments, a composition comprising a conjugate of the disclosure further comprises a carrier, which in some embodiments is pharmaceutically acceptable. In some embodiments, a kit further comprises instructions for administering the composition (e.g., the conjugate comprising one or more antibody, or antibody fragment thereof (e.g., antigen-binding fragment) to a subject. In some embodiments, a kit further comprises instructions for use of the kit.

[0046] In some aspects, the disclosure concerns an article of manufacture containing materials useful for the treatment, prevention and/or diagnosis of complement-associated disorders. In some embodiments, the disclosure concerns an article of manufacture, comprising: (a) a container; (b) a label on the container; and (c) a composition of matter comprising a conjugate of the present disclosure, contained with the container, wherein the label on said container indicates that the composition can be used for treatment, prevention and/or diagnosis of complement-associated disorders.

[0047] In some aspects, the disclosure provides use of a conjugate of the disclosure in the preparation of a medicament for the therapeutic and/or prophylactic treatment of a disease, such as a complement-associated eye condition. In one embodiment, the disclosure is directed to a method of treating a complement-associated disorder, such as a complement-associated eye condition, in a subject, the method comprising administering to the subject a conjugate or pharmaceutical formulation of the disclosure. In some embodiments, the complement-associated eye condition is selected from age-related macular degeneration (AMD), including non-exudative (e.g intermediate dry AMD or geographic atrophy (GA)) and exudative (e.g., wet AMD (choroidal neovascularization (CNV)) AMD, diabetic retinopathy (DR), endophthalmitis and uveitis. In one example, the complement-associated eye condition is intermediate dry AMD. In one example, the complement-associated eye condition is geographic atrophy. In one example, the complement-associated eye condition is wet AMD (choroidal neovascularization (CNV)).

[0048] In some aspects, the disclosure provides use of an article of manufacture of the disclosure in the preparation of a medicament for the therapeutic and/or prophylactic treatment of a disease, such as a complement-associated eye condition. In some embodiments, the complement-associated eye condition is selected from age-related macular degeneration (AMD),

including non-exudative (e.g intermediate dry AMD or geographic atrophy (GA)) and exudative (e.g., wet AMD (choroidal neovascularization (CNV)) AMD, diabetic retinopathy (DR), endophthalmitis and uveitis. In one example, the complement-associated eye condition is intermediate dry AMD. In one example, the complement-associated eye condition is geographic atrophy. In one example, the complement-associated eye condition is wet AMD (choroidal neovascularization (CNV)).

[0049] In some aspects, the disclosure provides use of a kit of the disclosure in the preparation of a medicament for the therapeutic and/or prophylactic treatment of a disease, such as a complement-associated eye condition. In some embodiments, the complement-associated eye condition is selected from age-related macular degeneration (AMD), including non-exudative (e.g intermediate dry AMD or geographic atrophy (GA)) and exudative (e.g., wet AMD (choroidal neovascularization (CNV)) AMD, diabetic retinopathy (DR), endophthalmitis and uveitis. In one example, the complement-associated eye condition is intermediate dry AMD. In one example, the complement-associated eye condition is geographic atrophy. In one example, the complement-associated eye condition is wet AMD (choroidal neovascularization (CNV)).

[0050] In some aspects, the disclosure provides a formulation comprising a conjugate comprising one or more Factor D antagonist, and further comprises a HTRA1 antagonist, an ANG2 antagonist, a TIE2 antagonist, a VEGF antagonist, or an antagonist of one or more of the C1, C2, C3, C4, C5, C6, C7, C8, and C9 complement components. In some embodiments, the Factor D antagonist is an anti-Factor D antibody. In a further embodiment, the anti-Factor D antibody is an anti-Factor D antibody variant described herein. In some embodiments the HTRA1 antagonist is an anti-HTRA1 antibody. In another embodiment the ANG2 antagonist is an anti-ANG2 antibody. In another embodiment, the TIE2 antagonist is an anti-TIE2 antibody. In another embodiment, the VEGF antagonist is an anti-VEGF antibody. In another embodiment, the antagonist of the C2 and/or C4 and/or C5 complement components is an anti-C2 and/or anti-C4 and/or anti-C5 antibody.

[0051] In some aspects, the treatment of disorders associated with excessive or uncontrolled complement activation in a human subject with a disorder associated with excessive or uncontrolled complement activation comprises administering to the subject an effective amount of a therapeutic compound, such as conjugate comprising one or more Factor D antagonist, and further comprises administering to the subject an effective amount of a second therapeutic compound, such as a HTRA1 antagonist, an ANG2 antagonist, a TIE2 antagonist, a VEGF antagonist, or an antagonist of one or more of the C1, C2, C3, C4, C5, C6, C7, C8, and

C9 complement components. In some embodiments, the Factor D antagonist is an anti-Factor D antibody. In some embodiments, the anti-Factor D antibody is an anti-Factor D antibody variant described herein. In some embodiments, the HTRA1 antagonist is an anti-HTRA1 antibody. In another embodiment the ANG2 antagonist is an anti-ANG2 antibody. In another embodiment, the TIE2 antagonist is an anti-TIE2 antibody. In another embodiment, the VEGF antagonist is an anti-VEGF antibody. In another embodiment, the antagonist of the C2 and/or C4 and/or C5 complement components is an anti-C2 and/or anti-C4 and/or anti-C5 antibody.

[0052] In some aspects, the administration of the conjugate comprising the Factor D antagonist and any second therapeutic compound can be done simultaneously, e.g., as a single composition or as two or more distinct compositions using the same or different administration routes. Alternatively, or additionally the administration can be done sequentially, in any order.

Brief Description of the Figures

[0053] Figures 1A-1D shows amino acid sequences of a reference anti-factor D antibody WT (aFD.WT) and its select variants (1A: light and heavy chain sequences of WT; 1B: alignment of light and heavy chain variable domains; 1C: light and heavy chain sequences of SIESD (AFD.v8) and heavy chain sequences of Cys-modified SIESD (AFD.v8) and Cys-Pro-Pro-Cys-modified SIESD (AFD.v8); 1D: light and heavy chain sequences of SIESD.N103S (AFD.v14) and heavy chain sequences of Cys-modified SIESD.N103S (AFD.v14) and Cys-Pro-Pro-Cys-modified SIESD.N103S (AFD.v14)). HVRs within the variable domains are underlined. Residue substitutions in the variants are shown in bold. Cys and Cys-Pro-Pro-Cys (SEQ ID NO: 21) modifications are shown in italics in Figure 1C and 1D.

[0054] Figures 2A-2C illustrates antigen binding capacity of various antibody Fab fragments over prolonged time under defined conditions (2A: Fab protein concentration of 10 mg/mL in pH 5.5 buffer; 2B: Fab protein concentration of 100 mg/ml in PBS; 2C: Fab protein concentration of 100 mg/ml in PBS).

[0055] Figures 3A-3B illustrates degradations of various antibody Fab fragments over time under defined conditions whereby main peak is determined by ion-exchange chromatography (IEC) (3A: Fab protein concentration of 10 mg/mL in pH 5.5 buffer; 3B: Fab protein concentration of 100 mg/ml in PBS).

[0056] Figures 4A-4B illustrates isomerization and deamidation of various antibody Fab fragments over time under defined conditions (4A: Fab protein concentration of 10 mg/mL in pH 5.5 buffer; 4B: Fab protein concentration of 100 mg/ml in PBS).

[0057] Figure 5 illustrates aggregation of various antibody Fab fragments over prolonged time under defined condition (Fab protein concentration of 100 mg/ml in PBS) as determined by measurements of monomer peak by size-exclusion chromatography (SEC).

[0058] Figure 6 illustrates solubility of aFD.WT, AFD.v2, AFD.v6 and AFD.v8 at pH 6 and low ionic strength (~100 mg/ml in 20 mM His-HCl, pH 6).

[0059] Figure 7 illustrates solubility of antibody Fab fragments at pH 6 and low ionic strength (~ 100 mg/ml in 20 mM His-HCl, pH 6). The insolubility of aFD.WT is reversed by the exchange into PBS, a salt (NaCl) containing buffer, via dialysis.

[0060] Figure 8 illustrates solubility of antibody Fab fragments in PBS (pH 7.3) at 227 mg/ml for aFD.WT, 269 mg/ml for AFD.v8 and 344 mg/ml for AFD.v14.

[0061] Figure 9 illustrates % aggregate as measured by size-exclusion chromatography (SEC) of SIESD.N103S (AFD.v14) in PBS prior to 3 week incubation at 2-8°C.

[0062] Figure 10A illustrates the antigen binding capacity for a high concentration (272 mg/mL) AFD.v8 formulation (20 mM His-HCl, pH 5.5) over prolonged time under thermal stress at 37°C. The hatched area denotes the $\pm 10\%$ standard error in the measurements.

[0063] Figure 10B illustrates the chemical and physical stability for a high concentration (272 mg/mL) AFD.v8 formulation (20 mM His-HCl, pH 5.5) over prolonged time under thermal stress at 37°C. The N101 and E95 are according to Kabat numbering.

[0064] Figure 11 illustrates pharmacokinetics of antibody Fab fragments upon intravitreal injection in rabbits.

[0065] Figure 12 illustrates protein concentration dependence of viscosity for antibody Fab fragments in pH 5.5 buffer.

[0066] Figures 13A and 13B show the MALDI analysis of a multi-armed PEG comprising a hexaglycerol (HGEO) core (Sunbright® HGEO-400MA, NOF America, Corp.) and a tripentaerythritol (TP) core (8ARM (TP)-PEG-MAL, JenKem Technology, USA) (13A: HGEO core; 13B: TP core).

[0067] Figures 14A – 14C show the results of a purification of the AFD.v14.C + TP octamer by Size Exclusion Chromatography (SEC) on a Sephacryl S-300 HR (GE Healthcare) column in 20 mM His-acetate, pH 5.5, 50 mM NaCl (isocratic gradient) (14A: initial chromatogram of the SEC column; 14B: an expansion of the peak from 600 mL to 1100 mL; 14C: MALS profile of the chromatogram fractions collected during the purification shown in 14B).

[0068] Figures 15A – 15C show the results of a purification of the AFD.v14.C + HG octamer by SEC on a Sephacryl S-300 HR (GE Healthcare) column in 20 mM His-acetate, pH

5.5, 50 mM NaCl (isocratic gradient) (15A: initial chromatogram of the SEC column; 15B: enlargement of the chromatogram of 15A from 2900-3600 mL; 15C: MALS profile of the chromatogram fractions collected during the purification shown in Figure 15B).

[0069] Figures 16A – 16B show the results of an analysis of the AFD.v14.C + HG octamer using a Sephacryl S-400 HR (GE Healthcare) column in PBS, pH 7.4 (16A: initial chromatogram of the column; 16B: MALS profile of the chromatogram in Figure 16A).

[0070] Figures 17A – 17B show the results of a purification of the AFD.v14.C + HGEO octamer by SEC on a Sephacryl S-300 HR (GE Healthcare) column in 20 mM His-acetate, pH 5.5, 50 mM NaCl (isocratic gradient), followed by SEC-MALS characterization on Sephacryl S-400 HR at 0.25 mL/minute in PBS, pH 7.4 (17A: initial chromatogram of the SEC S-400 column; 17B: MALS profile of the chromatogram fractions in Figure 17A).

[0071] Figures 18A – 18B show the results of a purification of the AFD.v14.C + HGEO octamer by SEC on a Sephacryl S-300 HR (GE Healthcare) column in 20 mM His-acetate, pH 5.5, 50 mM NaCl (isocratic gradient), followed by SEC-MALS characterization on a Tosoh G3000PW column (18A: initial chromatogram of the SEC S-300 column; 18B: overlay of laser intensity for S-300 fractions from 18A using SEC-MALS with G3000PW column).

[0072] Figures 19A – 19C show further purification of select fractions in Example 9a (shown in Figure 14) by cation exchange chromatography (CEX) in Triton wash, 10-20% 1M NaCl gradient over 50CV (19A: initial chromatogram of the CEX column; 19B: SEC gel of the fractions from the CEX column; 19C: MALS profile of the chromatogram fractions in Figure 19A).

[0073] Figure 20 shows the final analytical run of the AFD.v14.C + TP octamer after CEX purification.

[0074] Figures 21A – 21B compare the results of the purification methods for the AFD.v14.C + TP octamer after cation exchange chromatography (CEX), SEC chromatography on the SEC S-400 HR column, or SEC chromatography on the SEC S-300 HR column (21A: stacked display of the chromatograms of the three different purification columns; 21B: SEC gel comparing the samples from the three different purification columns).

[0075] Figures 22A – 22B compare PEG-Fab conjugates prepared with PEGs having different cores (22A: SEC gel comparing the purified samples of the conjugates with the different cores; 22B: MALS profile of the conjugates prepared with the different cores).

[0076] Figure 23 shows the viscosity of the AFD.v14.C + HG octamer and a PEG-Fab conjugate prepared from Sunbright® PTE-400MA from NOF America Corp. (a tetramer) as a function of AFD.v14 concentration.

[0077] Figure 24 shows the viscosity of the AFD.v14.C + TP octamer and the AFD.v14.C + HGEO octamer as a function of AFD.v14 concentration in 20mL His-Ace, pH 6.5 and 50 mM NaCl at 20°C.

[0078] Figures 25A and 25B show the thermal stability of the AFD.v14.C + TP octamer in 10 mg/mL, PBS (25A) and 10 mg/mL of 20 mM histidine HCl, 50 mM NaCl, at pH 6.5 (25B) as a function of time.

[0079] Figures 26 and 27 show the slow release of the Fab fragment and dimerization during the course of the thermal stability study (26: SEC-MALS analysis of the conjugate over time; 27: CE-SDS analysis of the conjugate over time).

[0080] Figure 28 shows the maintenance of binding capacity of the AFD.v14.C + TP octamer to Factor D during the thermal stability study as measured by surface plasmon resonance.

[0081] Figures 29A and 29B show the concentration versus time of AFD.v14 in cynomolgus monkey vitreous humor following administration of AFD.v14 or AFD.v14.C + TP octamer in a pharmacokinetic study (29A: vitreous humor concentration; 29B: vitreous humor concentration data normalized for dosing strength).

[0082] Figures 30A and 30B show the concentration versus time of AFD.v14 in cynomolgus monkey eye aqueous humor following administration of AFD.v14 or AFD.v14.C + TP octamer in a pharmacokinetic study (30A: eye aqueous humor concentration; 30B: eye aqueous humor concentration data normalize for dosing strength).

[0083] Figures 31A and 31B show the concentration versus time of AFD.v14 in cynomolgus monkey retinal homogenate following administration of AFD.v14 or AFD.v14.C + TP octamer in a pharmacokinetic study (31A: retinal concentration; 31B: retinal concentration data normalize for dosing strength).

[0084] Figures 32A – 32C show the concentration versus time of AFD.v14 in cynomolgus monkey serum following administration of AFD.v14 or AFD.v14.C + TP octamer in a pharmacokinetic study for both intravitreal and intravenous injection administration (32A: serum concentration for intravitreal injection; 32B: serum concentration for intravitreal injection normalize for dosing strength; 32C: serum concentration for intravenous administration).

[0085] Figures 33A – 33B shows a comparison of the Factor D concentration and AFD.v14.C + TP octamer in a pharmacokinetic study following the administration of the AFD.v14.C + TP octamer by either an intravenous or intravitreal injection (33A: serum concentrations; 33B: ocular concentrations).

[0086] Figures 34A – 34B show inhibition curves for a time-resolved fluorescence energy transfer (TR-FRET) assay of Factor D-dependent factor B activation (34A: Fab-tetramer conjugates as compared to unconjugated Fab; 34B: AFD.v14.C + TP octamer as compared to unconjugated Fab).

[0087] Figures 35A – 35E show the systemic AP complement activity as compared to total Factor D and therapeutic agent concentration in cynomolgus monkey serum following intravitreal injection administration (35A: 10 mg/eye lampalizumab (comparative data); 35B: 25 mg/eye AFD.v14; 35C: 3.9 mg/eye AFD.v14.C + TP octamer; 35D: 7.1 mg/eye AFD.v14.C + HG octamer; 35E: 11.8 mg/eye AFD.v14.C + HG octamer).

Detailed Description of the Invention

Definitions

[0088] Terms used throughout this application are to be construed with ordinary and typical meaning to those of ordinary skill in the art. However, Applicants desire that the following terms be given the particular definition as defined below.

[0089] The term "antibody" is used in the broadest sense, and specifically covers full length monoclonal antibodies, polyclonal antibodies, multispecific antibodies (e.g., bispecific antibodies) and antibody fragments so long as they exhibit the desired biological activity such as antigen-binding activity. Antibodies (Abs) and immunoglobulins (Igs) are glycoproteins having the same structural characteristics. While antibodies exhibit binding specificity to a specific target, immunoglobulins include both antibodies and other antibody-like molecules which lack target specificity. Native antibodies and immunoglobulins are usually heterotetrameric glycoproteins of about 150,000 daltons, composed of two identical light (L) chains and two identical heavy (H) chains. Each heavy chain has at one end a variable domain (V_H) followed by a number of constant domains. Each light chain has a variable domain at one end (V_L) and a constant domain at its other end. The term "Antibody" as used herein expressly encompasses antibody fragments retaining antigen-binding activity.

[0090] An "antibody fragment" refers to a molecule other than an intact antibody that comprises a portion of an intact antibody that binds the antigen to which the intact antibody binds. Examples of antibody fragments include but are not limited to Fv, Fab, Fab-SH, Fab'-SH, Fab', Fab-C, Fab'-C, Fab'-C-SH, Fab-C-SH, scFv, diabody, or $F(ab')_2$; diabodies; linear antibodies; single-chain antibody molecules (e.g., scFv); and multispecific antibodies formed from antibody fragments.

[0091] As used herein, an “anti-factor D antibody” means an antibody which specifically binds to Factor D in such a manner so as to inhibit or substantially reduce complement activation.

[0092] The term “Factor D” is used herein to refer to native sequence and variant Factor D polypeptides.

[0093] As used herein, the term “AFD.Ab” refers to any anti-Factor D antibody.

[0094] As used herein, a “Fab” refers to an antibody that comprises a heavy chain constant region that comprises the CH1 domain, or a sufficient portion of the CH1 domain to form a disulfide bond with the light chain constant region, but does not contain a CH2 domain or a CH3 domain. As used herein, a Fab may comprise one or more amino acids of the hinge region. Thus, as used herein, the term “Fab” encompasses Fab’ antibodies. A Fab may comprise additional non-native amino acids, such as a C-terminal cysteine, in which case it may be referred to as a Fab-C. As discussed below, the term Fab-C also encompasses Fabs comprising native amino acids of the hinge region, including a native cysteine at the C-terminus. In some embodiments, a Fab comprises an engineered cysteine (i.e., a Fab may be a THIOMAB).

[0095] A “Fab-C” refers to a Fab with a C-terminal cysteine, which may be a native cysteine that occurs at that residue position (such as a cysteine from the hinge region), or may be a cysteine added to the C-terminus that does not correspond to a native cysteine. The anti-Factor D antibodies include without limitation AFD.C antibodies, with “C” indicating that the antibody is a Fab with a C-terminal cysteine. Nonlimiting exemplary Fab-C heavy chain constant regions include the sequences of SEQ ID NOs: 56, 57, 59, 60, 61, 62, 68, and 74.

[0096] A “Fab-SH” refers to a Fab with a free thiol group. In some embodiments, the free thiol group is located in the last 10 amino acids of the C-terminus of the Fab. Fab-C antibodies are typically also Fab-SH antibodies. A further nonlimiting exemplary Fab-SH heavy chain constant region having the amino acid sequence of SEQ ID NO: 58. Typically, a Fab comprising an engineered cysteine (i.e., a Fab that is a THIOMAB) is a Fab-SH.

[0097] The term “variable region” or “variable domain” refers to the domain of an antibody heavy or light chain that is involved in binding the antibody to antigen. The variable domains of the heavy chain and light chain (VH and VL, respectively) of a native antibody generally have similar structures, with each domain comprising four conserved framework regions (FRs) and three hypervariable regions (HVRs). (See, e.g., Kindt et al. Kuby Immunology, 6th ed., W.H. Freeman and Co., page 91 (2007).) A single VH or VL domain may be sufficient to confer antigen-binding specificity. Furthermore, antibodies that bind a

particular antigen may be isolated using a VH or VL domain from an antibody that binds the antigen to screen a library of complementary VL or VH domains, respectively. See, e.g., Portolano et al., *J. Immunol.* 150:880-887 (1993); Clarkson et al., *Nature* 352:624-628 (1991).

[0098] The term “variable” refers to the fact that certain portions of the variable domains differ extensively in sequence among antibodies and are used in the binding and specificity of each particular antibody for its particular antigen. However, the variability is not evenly distributed throughout the variable domains of antibodies. It is concentrated in three segments called hypervariable regions both in the light chain and the heavy chain variable domains. The more highly conserved portions of variable domains are called the framework regions (FRs). The variable domains of native heavy and light chains each comprise four FRs, largely adopting a β -sheet configuration, connected by three hypervariable regions, which form loops connecting, and in some cases forming part of, the β -sheet structure. The hypervariable regions in each chain are held together in close proximity by the FRs and, with the hypervariable regions from the other chain, contribute to the formation of the antigen-binding site of antibodies (see Kabat et al., *Sequences of Proteins of Immunological Interest*, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, Md. (1991)). The constant domains are not involved directly in binding an antibody to an antigen, but exhibit various effector functions, such as participation of the antibody in antibody dependent cellular cytotoxicity (ADCC).

[0099] 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 yields an F(ab')₂ fragment that has two antigen-binding sites and is still capable of cross-linking antigen.

[00100] The Fab fragment also contains the constant domain of the light chain and the first constant domain (CH1) of the heavy chain. Fab' fragments (including Fab-C) 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. Antibody fragments with free thiol groups may be indicated with an “-SH.” Fab'-SH (including Fab-C-SH) is the designation for Fab' in which at least one cysteine residue of the constant domains bears a free thiol group. F(ab')₂ antibody fragments originally were produced as pairs of Fab' fragments which have hinge cysteines between them. Other chemical couplings of antibody fragments are also known.

[00101] “Fv” is the minimum antibody fragment which contains a complete antigen-recognition and antigen-binding site. This region consists of a dimer of one heavy chain and one light chain variable domain in tight, non-covalent association. It is in this configuration that the

three hypervariable regions of each variable domain interact to define an antigen-binding site on the surface of the VH-VL dimer. Collectively, the six hypervariable regions confer antigen-binding specificity to the antibody. However, even a single variable domain (or half of an Fv comprising only three hypervariable regions specific for an antigen) has the ability to recognize and bind antigen, although at a lower affinity than the entire binding site.

[00102] The term “hypervariable region” or “HVR,” as used herein, refers to each of the regions of an antibody variable domain which are hypervariable in sequence and/or form structurally defined loops (“hypervariable loops”). Generally, native four-chain antibodies comprise six HVRs; three in the VH (H1, H2, H3), and three in the VL (L1, L2, L3). HVRs generally comprise amino acid residues from the hypervariable loops and/or from the “complementarity determining regions” (CDRs), the latter being of highest sequence variability and/or involved in antigen recognition. HVR-H3 is believed to play a unique role in conferring fine specificity to antibodies. See, e.g., Xu et al. (2000) *Immunity* 13:37-45; Johnson and Wu (2003) in *Methods in Molecular Biology* 248:1-25 (Lo, ed., Human Press, Totowa, N.J.). “Framework Region” or “FR” residues are those variable domain residues other than the hypervariable region residues as herein defined. An HVR region as used herein comprise any number of residues located within positions 24-36 (for L1), 46-56 (for L2), 89-97 (for L3), 26-35B (for H1), 47-65 (for H2), and 93-102 (for H3). Therefore, an HVR includes residues in positions described previously:

A) 24-34 (L1), 50-52 (L2), 91-96 (L3), 26-32 (H1), 53-55 (H2), and 96-101 (H3) (Chothia and Lesk, *J. Mol. Biol.* 196:901-917 (1987);

B) 24-34 of L1, 50-56 of L2, 89-97 of L3, 31-35B of H1, 50-65 of H2, and 95-102 of H3 (Kabat et al., *Sequences of Proteins of Immunological Interest*, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD (1991).

C) 30-36 (L1), 46-55 (L2), 89-96 (L3), 30-35 (H1), 47-58 (H2), 93-100a-j (H3) (MacCallum et al. *J. Mol. Biol.* 262:732-745 (1996).

[00103] Hypervariable regions may comprise “extended hypervariable regions” as follows: 24-36 or 24-34 (L1), 46-56 or 50-56 (L2) and 89-97 (L3) in the VL and 26-35B (H1), 50-65, 47-65 or 49-65 (H2) and 93-102, 94-102 or 95-102 (H3) in the VH. The variable domain residues are numbered according to Kabat *et al.*, *supra* for each of these definitions.

[00104] With the exception of CDR1 in VH, CDRs generally comprise the amino acid residues that form the hypervariable loops. CDRs also comprise “specificity determining residues,” or “SDRs,” which are residues that contact antigen. SDRs are contained within regions of the CDRs called abbreviated-CDRs, or a-CDRs. Exemplary a-CDRs (a-CDR-L1, a-

CDR-L2, a-CDR-L3, a-CDR-H1, a-CDR-H2, and a-CDR-H3) occur at amino acid residues 31-34 of L1, 50-55 of L2, 89-96 of L3, 31-35B of H1, 50-58 of H2, and 95-102 of H3. (See Almagro and Fransson, *Front. Biosci.* 13:1619-1633 (2008).)

[00105] An “antibody variant” or “modified antibody” of a reference antibody (also referred to as “starting antibody” or “parent antibody”) is an antibody that comprises an amino acid sequence different from that of the reference/starting antibody, wherein one or more of the amino acid residues of the reference antibody have been modified. Generally, an antibody variant will possess at least 80% sequence identity, preferably at least 90% sequence identity, more preferably at least 95% sequence identity, and most preferably at least 98% sequence identity with the reference antibody. Percentage sequence identity is determined for example, by the Fitch et al., *Proc. Natl. Acad. Sci. USA*, 80: 1382-1386 (1983), version of the algorithm described by Needleman et al., *J. Mol. Biol.*, 48: 443-453 (1970), after aligning the sequences of the reference antibody and the candidate antibody variant to provide for maximum homology. Identity or similarity is defined herein as the percentage of amino acid residues in the candidate variant sequence that are identical (i.e., same residue) or similar (i.e., amino acid residue from the same group based on common side-chain properties, see below) with the parent antibody residues, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity. Amino acid sequence variants of an antibody may be prepared by introducing appropriate nucleotide changes into DNA encoding the antibody, or by peptide synthesis. Such variants include, for example, deletions from, and/or insertions into and/or substitutions of, residues within the amino acid sequence of the antibody of interest. Any combination of deletion, insertion, and substitution is made to arrive at the final construct, provided that the final construct possesses the desired characteristics. The amino acid changes also may alter post-translational processes of the antibody, such as changing the number or position of glycosylation sites. Methods for generating antibody sequence variants of antibodies are similar to those for generating amino acid sequence variants of polypeptides described in U.S. Pat. No. 5,534,615, expressly incorporated herein by reference, for example.

[00106] A protein including an antibody is said to be “stable” if it essentially retains the intact conformational structure and biological activity. Various analytical techniques for measuring protein stability are available in the art and are reviewed in, e.g., *Peptide and Protein Drug Delivery*, 247-301, Vincent Lee Ed., Marcel Dekker, Inc., New York, N.Y., Pubs. (1991) and Jones (1993) *Adv. Drug Delivery Rev.* 10: 29-90. An antibody variant with “improved stability” refers to an antibody variant that is more stable comparing to the starting reference antibody. Preferably, antibody variants with improved stability are variants of the native (wild-

type) antibodies in which specific amino acid residues are altered for the purpose of improving physical stability, and/or chemical stability, and/or biological activity, and/or reducing immunogenicity of the native antibodies. Walsh (2000) *Nat. Biotech.* 18:831-3.

[00107] The term “isomerization” refers generally to a chemical process by which a chemical compound is transformed into any of its isomeric forms, i.e., forms with the same chemical composition but with different structure or configuration and, hence, generally with different physical and chemical properties. Specifically used herein is aspartate isomerization, a process wherein one or more aspartic acid (D or Asp) residue(s) of a polypeptide have been transformed to isoaspartic acid residue(s). Geiger and Clarke (1987) *J. Biol. Chem.* 262:785-94.

[00108] The term “deamidation” refers generally to a chemical reaction wherein an amide functional group is removed from an organic compound. Specifically used herein is asparagine deamidation, a process wherein one or more asparagine (N or Asn) residue(s) of a polypeptide have been converted to aspartic acid (D or Asp), i.e., the neutral amide side chain has been converted to a residue with an overall acidic property. Xie and Schowen (1999) *J. Pharm. Sci.* 88:8-13.

[00109] Amino acid residues “prone” to certain identified physical or chemical processes (e.g., isomerization or deamidation) refer to those residues within a specific protein molecule that have been identified to have the propensity to undergo the identified processes such as isomerization or deamidation. Their propensities are often determined by their relative positions within the primary and/or conformational structure of the protein. For example, it has been shown that the first Asp in an Asp-XXX motif (wherein XXX can be Asp, Gly, His, Ser or Thr) is prone to Asp isomerization due to the involvement of its adjacent residue, where some other Asp within the same protein may not possess such propensity. Assays for identifying residues to certain process within a specific protein molecule are known in the art. See, e.g., Cacia et al (1996) *Biochem.* 35:1897-1903.

[00110] “Active” or “activity” or “biological activity” in the context of an anti-factor D antibody of the present disclosure is the ability to antagonize (partially or fully inhibit) a biological activity of Factor D. One example of a biological activity of a Factor D antagonist is the ability to achieve a measurable improvement in the state, e.g., pathology, of a Factor D-associated disease or condition, such as, for example, a complement-associated eye condition. The activity can be determined in *in vitro* or *in vivo* tests, including binding assays, alternative pathway hemolysis assays (e.g., assays measuring inhibition of the alternative pathway complement activity or activation), using a relevant animal model, or human clinical trials.

[00111] The term “complement-associated disorder” is used in the broadest sense and includes disorders associated with excessive or uncontrolled complement activation. They include complement activation during cardiopulmonary bypass operations; complement activation due to ischemia-reperfusion following acute myocardial infarction, aneurysm, stroke, hemorrhagic shock, crush injury, multiple organ failure, hypobolemic shock, intestinal ischemia or other events causing ischemia. Complement activation has also been shown to be associated with inflammatory conditions such as severe burns, endotoxemia, septic shock, adult respiratory distress syndrome, hemodialysis; anaphylactic shock, severe asthma, angioedema, Crohn’s disease, sickle cell anemia, poststreptococcal glomerulonephritis and pancreatitis. The disorder may be the result of an adverse drug reaction, drug allergy, IL-2 induced vascular leakage syndrome or radiographic contrast media allergy. It also includes autoimmune disease such as systemic lupus erythematosus, myasthenia gravis, rheumatoid arthritis, Alzheimer’s disease and multiple sclerosis. Complement activation is also associated with transplant rejection. Complement activation is also associated with ocular diseases such as age-related macular degeneration, diabetic retinopathy and other ischemia-related retinopathies, choroidal neovascularization (CNV), uveitis, diabetic macular edema, pathological myopia, von Hippel-Lindau disease, histoplasmosis of the eye, Central Retinal Vein Occlusion (CRVO), corneal neovascularization, and retinal neovascularization.

[00112] The term “complement-associated eye condition” is used in the broadest sense and includes all eye conditions the pathology of which involves complement, including the classical and the alternative pathways, and in particular the alternative pathway of complement. Complement-associated eye conditions include, without limitation, macular degenerative diseases, such as all stages of age-related macular degeneration (AMD), including dry and wet (non-exudative and exudative) forms, choroidal neovascularization (CNV), uveitis, diabetic and other ischemia-related retinopathies, and other intraocular neovascular diseases, such as diabetic macular edema, pathological myopia, von Hippel-Lindau disease, histoplasmosis of the eye, Central Retinal Vein Occlusion (CRVO), corneal neovascularization, and retinal neovascularization. In one example, complement-associated eye conditions includes age-related macular degeneration (AMD), including non-exudative (e.g., intermediate dry AMD or geographic atrophy (GA)) and exudative (e.g., wet AMD (choroidal neovascularization (CNV)) AMD, diabetic retinopathy (DR), endophthalmitis and uveitis. In a further example, nonexudative AMD may include the presence of hard drusen, soft drusen, geographic atrophy and/or pigment clumping. In one example, complement-associated eye conditions include age-related macular degeneration (AMD), including early AMD (e.g., includes multiple small to one

or more non-extensive medium sized drusen), intermediate AMD (e.g., includes extensive medium drusen to one or more large drusen) and advanced AMD (e.g., includes geographic atrophy or advanced wet AMD (CNV). (Ferris et al., AREDS Report No. 18; Sallo et al., *Eye Res.*, 34(3): 238-40 (2009); Jager et al., *New Engl. J. Med.*, 359(1): 1735 (2008)). In a further example, intermediate dry AMD may include large confluent drusen. In a further example, geographic atrophy may include photoreceptor and/or Retinal Pigmented Epithelial (RPE) loss. In a further example, the area of geographic atrophy may be small or large and/or may be in the macula area or in the peripheral retina. In one example, complement-associated eye condition is intermediate dry AMD. In one example, complement-associated eye condition is geographic atrophy. In one example, complement-associated eye condition is wet AMD (choroidal neovascularization (CNV)).

[00113] “Treatment” (and grammatical variations thereof such as “treat” or “treating”) is an intervention performed with the intention of preventing the development or altering the pathology of a disorder. Accordingly, “treatment” refers to both therapeutic treatment and prophylactic or preventative measures. Those in need of treatment include those already with the disorder as well as those in which the disorder is to be prevented. Desirable effects of treatment include, but are not limited to, preventing occurrence or recurrence of disease, alleviation of symptoms, diminishment of any direct or indirect pathological consequences of the disease, decreasing the rate of disease progression, amelioration or palliation of the disease state, and remission or improved prognosis. In some embodiments, conjugates of the invention are used to delay development of a disease or to slow the progression of a disease. In treatment of an immune related disease, a therapeutic agent may directly alter the magnitude of response of a component of the immune response, or render the disease more susceptible to treatment by other therapeutic agents, *e.g.*, antibiotics, antifungals, anti-inflammatory agents, chemotherapeutics, etc.

[00114] The “pathology” of a disease, such as a complement-associated eye condition, includes all phenomena that compromise the well-being of the patient. This includes, without limitation, abnormal or uncontrollable cell growth (neutrophilic, eosinophilic, monocytic, lymphocytic cells), antibody production, auto-antibody production, complement production, interference with the normal functioning of neighboring cells, release of cytokines or other secretory products at abnormal levels, suppression or aggravation of any inflammatory or immunological response, infiltration of inflammatory cells (neutrophilic, eosinophilic, monocytic, lymphocytic) into cellular spaces, *etc.*

[00115] The term “mammal” as used herein refers to any animal classified as a mammal, including, without limitation, humans, higher primates, domestic and farm animals, and zoo, sports or pet animals such as horses, pigs, cattle, dogs, cats and ferrets, *etc.* In some embodiments of the disclosure, the mammal is a human.

[00116] Administration “in combination with” one or more further therapeutic agents includes simultaneous (concurrent) and consecutive administration in any order.

[00117] “Therapeutically effective amount” is the amount of a “Factor D antagonist” which is required to achieve a measurable improvement in the state, e.g., pathology, of the target disease or condition, such as, for example, a complement-associated eye condition.

[00118] An “amino acid substitution” refers to the replacement of at least one existing amino acid residue in a predetermined amino acid sequence with another different “replacement” amino acid residue. The replacement residue or residues may be “naturally occurring amino acid residues” (*i.e.*, encoded by the genetic code) and selected from the group consisting of: alanine (ala); arginine (Arg); asparagine (Asn); aspartic acid (Asp); cysteine (Cys); glutamine (Gln); glutamic acid (Glu); glycine (Gly); histidine (His); isoleucine (Ile); leucine (Leu); lysine (Lys); methionine (Met); phenylalanine (Phe); proline (Pro); serine (Ser); threonine (Thr); tryptophan (Trp); tyrosine (Tyr); and valine (Val). Substitution with one or more non-naturally occurring amino acid residues is also encompassed by the definition of an amino acid substitution herein. A “non-naturally occurring amino acid residue” refers to a residue, other than those naturally occurring amino acid residues listed above, which is able to covalently bind adjacent amino acid residue(s) in a polypeptide chain. Examples of non-naturally occurring amino acid residues include norleucine, ornithine, norvaline, homoserine and other amino acid residue analogues such as those described in Ellman et al., *Meth. Enzym.* 202: 301-336 (1991). To generate such non-naturally occurring amino acid residues, the procedures of Noren et al., *Science*, 244: 182 (1989) and Ellman et al., *supra*, can be used. Briefly, these procedures involve chemically activating a suppressor tRNA with a non-naturally occurring amino acid residue followed by *in vitro* transcription and translation of the RNA.

[00119] An “amino acid insertion” refers to the incorporation of at least one amino acid into a predetermined amino acid sequence. While the insertion will usually consist of the insertion of one or two amino acid residues, the present application contemplates larger “peptide insertions”, e.g., insertion of about three to about five or even up to about ten amino acid residues. The inserted residue(s) may be naturally occurring or non-naturally occurring as disclosed above.

[00120] An "amino acid deletion" refers to the removal of at least one amino acid residue from a predetermined amino acid sequence.

[00121] The terms "long-acting delivery", "sustained-release" and "controlled release" are used generally to describe a delivery mechanism using formulation, dosage form, device or other types of technologies to achieve the prolonged or extended release or bioavailability of a therapeutic drug. It may refer to technologies that provide prolonged or extended release or bioavailability of the drug to the general systemic circulation or a subject or to local sites of action in a subject including (but not limited to) cells, tissues, organs, joints, regions, and the like. Furthermore, these terms may refer to a technology that is used to prolong or extend the release of the drug from a formulation or dosage form or they may refer to a technology used to extend or prolong the bioavailability or the pharmacokinetics or the duration of action of the drug to a subject or they may refer to a technology that is used to extend or prolong the pharmacodynamic effect elicited by a formulation. A "long-acting formulation," a "sustained release formulation," or a "controlled release formulation" is a pharmaceutical formulation, dosage form, or other technology that is used to provide long-acting delivery. In some aspects, the controlled release is used to improve drug's local bioavailability, specifically ocular residence time in the context of ocular delivery. "Increased ocular residence time" refers to the post-delivery period during which the delivered ocular drug remains effective both in terms of quality (activity) and in terms of quantity (effective amount). In addition to or in lieu of high dose and controlled release, the drug can be modified post-translationally, such as via PEGylation, to achieve increased *in vivo* half-life.

[00122] The term "port delivery system" refers to an implantable device for the eye with a refillable reservoir that allows delivery of a therapeutic agent over an extended period of time. Exemplary port delivery systems are described, e.g., in U.S. Patent Application Serial No. 2010/0174272, and U.S. Patent Nos. 8,277,830; 8,399,006; 8,795,712; and 8,808,727, all of which are herein incorporated by reference.

[00123] The term "polyol" when used herein refers broadly to polyhydric alcohol compounds. Polyols can be any water-soluble poly(alkylene oxide) polymer for example, and can have a linear or branched chain. Preferred polyols include those substituted at one or more hydroxyl positions with a chemical group, such as an alkyl group having between one and four carbons. Typically, the polyol is a poly(alkylene glycol), preferably polyethylene glycol (PEG). However, those skilled in the art recognize that other polyols, such as, for example, poly(propylene glycol) and polyethylene-polypropylene glycol copolymers, can be employed using the techniques for conjugation described herein for PEG. The polyols of the disclosure include

those well known in the art and those publicly available, such as from commercially available sources.

[00124] The term "conjugate" is used herein according to its broadest definition to mean joined or linked together. Molecules are "conjugated" when they act or operate as if joined. In particular embodiments, "conjugate" refers to an antibody (e.g., an antibody fragment, as detailed herein) covalently bound to a multi-armed polyol.

[00125] A "small-bore needle" or a "narrow-bore needle" refers to a needle for injection of fluid composition of about 30, 29, 28, 27, 26, 25, 24, 23, or 22 gauge or higher, such as a 30 gauge needle. In some embodiments, the small-bore needle has standard sized walls. In another embodiment, the small-bore needle has thin walls, which may be preferred for viscous solutions.

[00126] "Percent (%) amino acid sequence identity" with respect to a reference polypeptide sequence is defined as the percentage of amino acid residues in a candidate sequence that are identical with the amino acid residues in the reference polypeptide sequence, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity, and not considering any conservative substitutions as part of the sequence identity. Alignment for purposes of determining percent amino acid sequence identity can be achieved in various ways that are within the skill in the art, for instance, using publicly available computer software such as BLAST, BLAST-2, ALIGN or Megalign (DNASTAR) software. Those skilled in the art can determine appropriate parameters for aligning sequences, including any algorithms needed to achieve maximal alignment over the full length of the sequences being compared. For purposes herein, however, % amino acid sequence identity values are generated using the sequence comparison computer program ALIGN-2. The ALIGN-2 sequence comparison computer program was authored by Genentech, Inc., and the source code has been filed with user documentation in the U.S. Copyright Office, Washington D.C., 20559, where it is registered under U.S. Copyright Registration No. TXU510087. The ALIGN-2 program is publicly available from Genentech, Inc., South San Francisco, California, or may be compiled from the source code. The ALIGN-2 program should be compiled for use on a UNIX operating system, including digital UNIX V4.0D. All sequence comparison parameters are set by the ALIGN-2 program and do not vary.

[00127] In situations where ALIGN-2 is employed for amino acid sequence comparisons, the % amino acid sequence identity of a given amino acid sequence A to, with, or against a given amino acid sequence B (which can alternatively be phrased as a given amino acid sequence A that has or comprises a certain % amino acid sequence identity to, with, or against a given amino acid sequence B) is calculated as follows:

$$100 \text{ times the fraction } X/Y$$

where X is the number of amino acid residues scored as identical matches by the sequence alignment program ALIGN-2 in that program's alignment of A and B, and where Y is the total number of amino acid residues in B. It will be appreciated that where the length of amino acid sequence A is not equal to the length of amino acid sequence B, the % amino acid sequence identity of A to B will not equal the % amino acid sequence identity of B to A. Unless specifically stated otherwise, all % amino acid sequence identity values used herein are obtained as described in the immediately preceding paragraph using the ALIGN-2 computer program.

[00128] The term “pharmaceutical formulation” refers to a preparation which is in such form as to permit the biological activity of an active ingredient contained therein to be effective, and which contains no additional components which are unacceptably toxic to a subject to which the formulation would be administered.

[00129] A “pharmaceutically acceptable carrier” refers to an ingredient in a pharmaceutical formulation, other than an active ingredient, which is nontoxic to a subject. A pharmaceutically acceptable carrier includes, but is not limited to, a buffer, excipient, stabilizer, or preservative.

[00130] A drug that is administered “simultaneously” with one or more other drugs is administered during the same treatment cycle, on the same day of treatment as the one or more other drugs, and, optionally, at the same time as the one or more other drugs.

Anti-Factor D Antibodies and Variants thereof

[00131] In some aspects, the present disclosure is directed to the production and use of conjugates comprising one or more anti-Factor D antibodies or variants thereof. Anti-Factor D antibodies and variants thereof that are suitable for use in forming the conjugates of the disclosure are described in U.S. Patent Application Serial No. 14/700853 (filed April 30, 2015), which is herein incorporated by reference in its entirety.

[00132] In some aspects, the parent reference anti-Factor D antibody forming the base for creating the variants used in the conjugates of the disclosure is a humanized anti-Factor D antibody. Methods for humanizing non-human antibodies are well known in the art. Generally,

a humanized antibody has one or more amino acid residues introduced into it from a source which is non-human. These non-human amino acid residues are often referred to as "import" residues, which are typically taken from an "import" variable domain. Humanization can be essentially performed following the method of Winter and co-workers (Jones et al. (1986) *Nature* 321:522-525; Riechmann et al. (1988) *Nature* 332:323-327; Verhoeyen et al. (1988) *Science* 239:1534-1536), by substituting rodent CDRs or CDR sequences for the corresponding sequences of a human antibody. Accordingly, such "humanized" antibodies are chimeric antibodies (U.S. Patent No. 4,816,567), wherein substantially less than an intact human variable domain has been substituted by the corresponding sequence from a non-human species. In practice, humanized antibodies are typically human antibodies in which some CDR residues and possibly some FR residues are substituted by residues from analogous sites in rodent antibodies.

[00133] The choice of human variable domains, both light and heavy, to be used in making the humanized antibodies can in some instances be important to reduce antigenicity and/or HAMA response (human anti-mouse antibody) when the antibody is intended for human therapeutic use. Reduction or elimination of a HAMA response is generally a significant aspect of clinical development of suitable therapeutic agents. See, e.g., Khazzaeli et al. (1988) *J. Natl. Cancer Inst* 80:937; Jaffers et al. (1986) *Transplantation* 41:572; Shawler et al. (1985) *J. Immunol.* 135:1530; Sears et al. (1984) *J. Biol. Response Mod.* 3:138; Miller et al. (1983) *Blood* 62:988; Hakimi et al. (1991) *J. Immunol.* 147:1352; Reichmann et al. (1988) *Nature* 332:323; Junghans et al. (1990) *Cancer Res.* 50:1495. As described herein, in some aspects, the present disclosure provides conjugates comprising antibodies that are humanized such that HAMA response is reduced or eliminated. Variants of these antibodies can further be obtained using routine methods known in the art, some of which are further described below. According to the so-called "best-fit" method, the sequence of the variable domain of a rodent antibody is screened against the entire library of known human variable domain sequences. The human V domain sequence which is closest to that of the rodent is identified and the human framework region (FR) within it accepted for the humanized antibody (Sims et al. (1993) *J. Immunol.* 151:2296; Chothia et al. (1987) *J. Mol. Biol.* 196:901). Another method uses a particular framework region derived from the consensus sequence of all human antibodies of a particular subgroup of light or heavy chains. The same framework may be used for several different humanized antibodies (Carter et al. (1992) *Proc. Natl. Acad. Sci. USA* 89:4285; Presta et al. (1993) *J. Immunol.* 151:2623).

[00134] For example, an amino acid sequence from an antibody as described herein can serve as a starting (parent) sequence for diversification of the framework and/or hypervariable

sequence(s). A selected framework sequence to which a starting hypervariable sequence is linked is referred to herein as an acceptor human framework. While the acceptor human frameworks may be from, or derived from, a human immunoglobulin (the VL and/or VH regions thereof), the acceptor human frameworks may be from, or derived from, a human consensus framework sequence as such frameworks have been demonstrated to have minimal, or no, immunogenicity in human patients. An “acceptor human framework” for the purposes herein is a framework comprising the amino acid sequence of a VL or VH framework derived from a human immunoglobulin framework, or from a human consensus framework. An acceptor human framework “derived from” a human immunoglobulin framework or human consensus framework may comprise the same amino acid sequence thereof, or may contain pre-existing amino acid sequence changes. Where pre-existing amino acid changes are present, preferably no more than 5 and preferably 4 or less, or 3 or less, pre-existing amino acid changes are present. In some embodiments, the VH acceptor human framework is identical in sequence to the VH human immunoglobulin framework sequence or human consensus framework sequence. In some embodiments, the VL acceptor human framework is identical in sequence to the VL human immunoglobulin framework sequence or human consensus framework sequence. A “human consensus framework” is a framework which represents the most commonly occurring amino acid residue in a selection of human immunoglobulin VL or VH framework sequences. Generally, the selection of human immunoglobulin VL or VH sequences is from a subgroup of variable domain sequences. Generally, the subgroup of sequences is a subgroup as in Kabat *et al.* In some embodiments, for the VL, the subgroup is subgroup kappa I as in Kabat *et al.* In some embodiments, for the VH, the subgroup is subgroup III as in Kabat *et al.*

[00135] Where the acceptor is derived from a human immunoglobulin, one may optionally select a human framework sequence that is selected based on its homology to the donor framework sequence by aligning the donor framework sequence with various human framework sequences in a collection of human framework sequences, and select the most homologous framework sequence as the acceptor. The acceptor human framework may be from or derived from human antibody germline sequences available in the public databases.

[00136] In some embodiments, human consensus frameworks herein are from, or derived from, VH subgroup VII and/or VL kappa subgroup I consensus framework sequences.

[00137] In some embodiments, the human framework template used for generation of an anti-Factor D antibody may comprise framework sequences from a template comprising a combination of VI-4.1b+ (VH7 family) and JH4d for VH chain and/or a combination of DPK4 (VkI family) and JK2 for VL chain.

[00138] While the acceptor may be identical in sequence to the human framework sequence selected, whether that be from a human immunoglobulin or a human consensus framework, the present disclosure contemplates that the acceptor sequence may comprise pre-existing amino acid substitutions relative to the human immunoglobulin sequence or human consensus framework sequence. These pre-existing substitutions are preferably minimal; usually four, three, two or one amino acid differences only relative to the human immunoglobulin sequence or consensus framework sequence.

[00139] Hypervariable region residues of the non-human antibody are incorporated into the VL and/or VH acceptor human frameworks. For example, one may incorporate residues corresponding to the Kabat CDR residues, the Chothia hypervariable loop residues, the Abm residues, and/or contact residues. Optionally, the extended hypervariable region residues as follows are incorporated: 24-36 or 24-34 (L1), 46-56 or 50-56 (L2) and 89-97 (L3), 26-35B (H1), 50-65, 47-65 or 49-65 (H2) and 93-102, 94-102, or 95-102 (H3).

[00140] In some aspects, the anti-Factor D antibody or antibody variants used in the conjugates comprise a light chain domain and a heavy chain variable domain. In some aspects, the reference anti-Factor D antibody comprises a light chain variable domain of SEQ ID NO:3. In some aspects, the reference anti-Factor D antibody comprises a heavy chain variable domain of SEQ ID NO:4.

[00141] Further, an anti-Factor D antibody may comprise any suitable constant domain sequence, provided that the antibody retains the ability to bind Factor D. For example, in some embodiments, anti-Factor D antibodies used in the conjugates of the disclosure comprise at least a portion of a heavy chain constant domain. In some embodiments, anti-Factor D antibodies comprise a heavy chain constant domain of either one or a combination of an α , δ , ϵ , γ , or μ heavy chain. Depending on the amino acid sequence of the constant domain of their heavy chains (C_H), immunoglobulins can be assigned to different classes or isotypes. There are five classes of immunoglobulins: IgA, IgD, IgE, IgG, and IgM, having heavy chains designated α , δ , ϵ , γ , and μ , respectively. The γ and α classes are further divided into subclasses on the basis of relatively minor differences in C_H sequence and function, e.g., humans express the following subclasses: IgG1, IgG2, IgG3, IgG4, IgA1, and IgA2. In some embodiments, anti-Factor D antibodies used in the conjugates of the disclosure comprise a heavy chain constant domain comprising substitutions at amino acid positions that results in a desired effect on effector function (e.g., binding affinity). In some embodiments, anti-Factor D antibodies used in the conjugates of the disclosure comprise a heavy chain constant domain comprising substitutions at amino acid positions that do not result in an effect on effector function (e.g., binding affinity).

In some embodiments, the anti-Factor D antibodies comprise a heavy chain constant domain of the IgG type (e.g., IgG1, IgG2, IgG3 or IgG4) and further comprise a substitution at position 114 (Kabat numbering; equivalent to 118 in EU numbering), 168 (Kabat numbering; equivalent to 172 in EU numbering), 172 (Kabat numbering; equivalent to 176 in EU numbering) and/or 228 (EU numbering). In some embodiments, the anti-Factor D antibodies comprise a heavy chain constant domain of the IgG (e.g., IgG1, IgG2, IgG3 or IgG4) type and further comprise a substitution at position 114 wherein position 114 is a cysteine (C) or alanine (A), position 168 is cysteine (C) or alanine (A), position 172 is a cysteine (C) or alanine (A) and/or position 228 is a proline (P), arginine (R) or serine (S).

[00142] Further, for example, in some embodiments, anti-Factor D antibodies used in the conjugates of the disclosure comprise at least a portion of a light chain constant domain. In some embodiments, the anti-Factor D antibodies comprise a light chain constant domain of either one or a combination of a kappa or a lambda light chain, as the light chain from any vertebrate species can be assigned to one of two clearly distinct types, called kappa and lambda, based on the amino acid sequences of their constant domains. In some embodiments, anti-Factor D antibodies used in the conjugates of the disclosure comprise a light chain constant domain comprising substitutions at amino acid positions that results in a desired effect on effector function (e.g., binding affinity). In some embodiments, anti-Factor D antibodies used in the conjugates of the disclosure comprise a light chain constant domain comprising substitutions at amino acid positions that do not result in an effect on effector function (e.g., binding affinity). In some embodiments, anti-Factor D antibodies used in the conjugates of the disclosure comprise a light chain constant domain of the kappa type and further comprise a substitution at position 110, 144, 146 and/or 168 (Kabat numbering). In some embodiments, anti-Factor D antibodies used in the conjugates of the disclosure comprise a light chain constant domain of the kappa type and further comprise a substitution at position 110 wherein 110 is a cysteine (C) or valine (V), at position 144 wherein 144 is a cysteine (C) or alanine (A), at position 146 wherein 146 is a isoleucine (I) or valine (V) and/or at position 168 wherein 168 is a cysteine (C) or serine (S).

[00143] A parent or reference anti-Factor D antibody, including a humanized anti-Factor D antibody, can be modified to generate modified anti-Factor D antibodies, or anti-Factor D antibody variants. In some embodiments, the modified anti-Factor D antibodies, and variants thereof, may have improved physical, chemical, biological or homogeneity properties over the parent antibody.

[00144] In some embodiments, an antibody used in the conjugates of the disclosure comprises one or more amino acid alterations (e.g., substitutions) into one or more of the hypervariable regions of the parent antibody. Alternatively, or in addition, one or more alterations (e.g., substitutions) of framework region residues may be introduced in the parent antibody. Examples of framework region residues to modify include those which non-covalently bind antigen directly (Amit et al., (1986) *Science*, 233: 747-753); interact with/effect the conformation of a CDR (Chothia et al. (1987) *J. Mol. Biol.*, 196: 901-917), and/or participate in the V_L-V_H interface (EP 239 400B1). In certain embodiments, modification of one or more of such framework region residues results in an enhancement of the binding affinity of the antibody for the antigen. For example, from about one to about 5 framework residues may be altered in this embodiment of the disclosure. Examples of framework or HVR region residues to modify include sites, wherein modifications at such sites result in the generation of deamidated variants (for example, asparagine (N or Asn) residue(s) modified to aspartate (D or Asp), oxidation variants (for example, methionine (M or Met) residue(s) and/or tryptophan (W or Trp) residue(s) modified to sulfone or sulfoxide) or pyroglutamate variants (for example, glutamine (Q or Gln) residue(s) modified to pyroglutamate). Examples of framework region residues or HVR region residues to modify include possible deamidation sites (i.e., asparagine (N or Asn)), oxidation sites (i.e., methionine (M or Met) or tryptophan (W or Trp)) or pyroglutamate conversion sites (i.e., glutamine (Q or Gln)), wherein modification at such sites prevent deamidation and/or oxidation and/or pyroglutamate conversion, respectively.

[00145] To prevent the formation of deamidated variants, asparagine (N or Asn) may be mutated to alanine (A or Ala), glutamine (Q or Gln) or serine (S or Ser). To prevent the formation of oxidated variants, methionine (Met) or tryptophan (W or Trp) may be mutated to leucine (L) or isoleucine (I). To prevent the formation of pyroglutamate variants, glutamine (Q or Gln) may be mutated to glutamate (E or Glu). (Amphlett, G. et al., *Pharm. Biotechnol.*, 9:1-140 (1996)). Alternatively, or in addition, one or more alterations (e.g., substitutions) of framework region residues may be in the Fc region in the parent antibody.

[00146] One useful procedure for generating such modified antibodies is called "alanine scanning mutagenesis" (Cunningham and Wells (1989) *Science* 244:1081-1085). Here, one or more of the hypervariable region residue(s) are replaced by alanine or polyalanine residue(s) to affect the interaction of the amino acids with the antigen. Those hypervariable region residue(s) demonstrating functional sensitivity to the substitutions then are refined by introducing further or other mutations at or for the sites of substitution. Thus, while the site for introducing an amino acid sequence variation is predetermined, the nature of the mutation *per se* need not be

predetermined. The ala-mutants produced this way are screened for their biological activity (i.e., binding affinity or hemolysis assay) as described herein.

[00147] Even more substantial modifications in the antibodies or fragments thereof (e.g., antigen-binding fragments) biological properties are accomplished by selecting substitutions that differ significantly in their effect on maintaining (a) the structure of the polypeptide backbone in the area of the substitution, for example, as a sheet or helical conformation, (b) the charge or hydrophobicity of the molecule at the target site, or (c) the bulk of the side chain. Naturally occurring residues are divided into groups based on common side-chain properties:

- (1) hydrophobic: norleucine, met, ala, val, leu, ile;
- (2) neutral hydrophilic: cys, ser, thr, asn, gln;
- (3) acidic: asp, glu;
- (4) basic: his, lys, arg;
- (5) residues that influence chain orientation: gly, pro; and
- (6) aromatic: trp, tyr, phe.

[00148] Non-conservative substitutions will entail exchanging a member of one of these classes for another class.

[00149] In another embodiment, the sites selected for modification are modified, and those modifications with improved binding affinity are selected by phage display.

[00150] Nucleic acid molecules encoding amino acid sequence mutants or modified amino acid sequences are prepared by a variety of methods known in the art. These methods include, but are not limited to, oligonucleotide-mediated (or site-directed) mutagenesis, PCR mutagenesis, and cassette mutagenesis of an earlier prepared variant or a non-variant version of the parent antibody. One method for making mutants or variants or modified amino acid sequences is site directed mutagenesis (see, e.g., Kunkel (1985) *Proc. Natl. Acad. Sci. USA* 82:488).

[00151] In certain embodiments, the modified antibody will only have a single hypervariable region residue substituted. In other embodiments, two or more of the hypervariable region residues of the parent antibody will have been substituted, e.g., from about two to about ten hypervariable region substitutions. Ordinarily, the modified antibody will have an amino acid sequence having at least 75% amino acid sequence identity or similarity (defined above in Definition section) with the amino acid sequence of either the heavy or light chain variable domain of the parent antibody, more preferably at least 80%, more preferably at least 85%, more preferably at least 90%, and most preferably at least 95%.

[00152] Following production of the modified antibody, the biological activity of that molecule relative to the parent antibody is determined. As noted above, this may involve determining the binding affinity and/or other biological activities of the antibody variant, or fragment thereof (e.g., antigen-binding fragment). In some embodiments of the disclosure, a panel of modified antibodies is prepared and screened for binding affinity for the antigen such as Factor D or a fragment thereof. One or more of the antibody mutants or modified antibodies selected from this initial screen are optionally subjected to one or more further biological activity assays to confirm that the antibody variant(s), or fragments thereof (e.g., antigen-binding fragments) are indeed useful, *e.g.*, for preclinical studies.

[00153] The modified anti-Factor D antibodies described herein may be subjected to further modifications, oftentimes depending on the intended use of the modified antibody. Such modifications may involve further alteration of the amino acid sequence, fusion to heterologous polypeptide(s) and/or covalent modifications such as those elaborated below. With respect to amino acid sequence alterations, exemplary modifications are elaborated above. For example, any cysteine residue not involved in maintaining the proper conformation of the modified antibody also may be substituted, generally with serine, to improve the oxidative stability of the molecule and prevent aberrant cross linking. Conversely, cysteine bond(s) may be added to the antibody to improve its stability (particularly where the antibody is an antibody fragment such as an Fv fragment).

[00154] Another type of amino acid mutant has an altered glycosylation pattern. This may be achieved by deleting one or more carbohydrate moieties found in the antibody, and/or adding one or more glycosylation sites that are not present in the antibody. Glycosylation of antibodies, or antibody fragments (e.g., antigen-binding fragments) is typically either N-linked or O-linked. N-linked refers to the attachment of the carbohydrate moiety to the side chain of an asparagine residue. The tripeptide sequences asparagine-X-serine and asparagine-X-threonine, where X is any amino acid except proline, are the recognition sequences for enzymatic attachment of the carbohydrate moiety to the asparagine side chain. Thus, the presence of either of these tripeptide sequences in a polypeptide creates a potential glycosylation site. O-linked glycosylation refers to the attachment of one of the sugars N-acetylgalactosamine, galactose, or xylose to a hydroxyamino acid, most commonly serine or threonine, although 5-hydroxyproline or 5-hydroxylysine may also be used. Addition of glycosylation sites to the antibody is conveniently accomplished by altering the amino acid sequence such that it contains one or more of the above-described tripeptide sequences (for N-linked glycosylation sites). The

alteration may also be made by the addition of, or substitution by, one or more serine or threonine residues to the sequence of the original antibody (for O-linked glycosylation sites).

Affinity and Biological Activity of Anti-Factor D Antibodies and Variants Thereof

[00155] Antibodies having characteristics identified herein as being desirable in an anti-Factor D antibody, may be screened for desirable properties such as factor D-binding affinity and factor D-inhibiting activity *in vitro* or *in vivo*.

a. Affinity

[00156] In some aspects, the anti-Factor D antibody variants used in the conjugates of the disclosure compete with the parent anti-Factor D antibody from which they are generated. Anti-Factor D antibody variants that bind to the same epitope as the parent anti-Factor D antibody are also provided.

[00157] To determine whether an anti-Factor D antibody variant bind to the same epitope on human Factor D bound by a reference anti-Factor D antibody, a cross-blocking assay may be performed (Antibodies, A Laboratory Manual, Cold Spring Harbor Laboratory, Ed Harlow and David Lane (1988)). Alternatively, epitope mapping may be performed to determine whether an anti-Factor D antibody binds an epitope of interest (Champe et al. (1995) *J. Biol. Chem.* 270: 1388-1394. Antibody affinities, for example for human Factor D, may be determined using standard methods, including the surface plasmon resonance (SPR) assay described in more details in the Examples.

[00158] In some aspects, the factor D binding affinity of the anti-Factor D antibody variant used in the conjugates of the disclosure is comparable to that of the parent anti-Factor D antibody from which it is generated. In some aspects, the factor D binding affinity of anti-Factor D antibody variant used in the conjugates of the disclosure is within 10-fold, 7-fold, 5-fold, 2-fold or 1-fold of that of the parent anti-Factor D antibody.

[00159] In some embodiments, the disclosure provides a conjugate comprising an anti-Factor D antibody, wherein the affinity of the antibody in its monovalent form to Factor D (e.g., affinity of the antibody as a Fab fragment to Factor D) is 20 nM (20×10^{-9} M) or better. In another embodiment, the disclosure provides a conjugate comprising an anti-Factor D antibody, wherein the affinity of the antibody in its monovalent form to Factor D (e.g., affinity of the antibody as a Fab fragment to Factor D) is 10 nM (10×10^{-9} M) or better. In another embodiment, the disclosure provides a conjugate comprising an anti-Factor D antibody, wherein the affinity of the antibody in its monovalent form to Factor D (e.g., affinity of the antibody as a Fab fragment to Factor D) is 1.0 nM (1.0×10^{-9} M) or better. In another embodiment, the

disclosure provides a conjugate comprising an anti-Factor D antibody, wherein the affinity of the antibody in its monovalent form to Factor D (e.g., affinity of the antibody as a Fab fragment to Factor D) is 0.5 nM (0.5×10^{-9} M) or better. In another embodiment, the disclosure provides a conjugate comprising an anti-Factor D antibody, wherein the affinity of the antibody in its monovalent form to Factor D (e.g., affinity of the antibody as a Fab fragment to Factor D) is 1.0 pM (1.0×10^{-12} M) or better. In another embodiment, the disclosure provides a conjugate comprising an anti-Factor D antibody, wherein the affinity of the antibody in its monovalent form to Factor D (e.g., affinity of the antibody as a Fab fragment to Factor D) is 0.5 pM (0.5×10^{-12} M) or better.

[00160] In another embodiment, the disclosure provides a conjugate comprising an anti-Factor D antibody, wherein the affinity of the antibody in its bivalent form to Factor D (e.g., affinity of the antibody as an IgG to Factor D) is 10.0 nM (10.0×10^{-9} M) or better. In another embodiment, the disclosure provides a conjugate comprising an anti-Factor D antibody, wherein the affinity of the antibody in its bivalent form to Factor D (e.g., affinity of the antibody as an IgG to Factor D) is 5.0 nM (5.0×10^{-9} M) or better. In another embodiment, the disclosure provides a conjugate comprising an anti-Factor D antibody, wherein the affinity of the antibody in its bivalent form to Factor D (e.g., affinity of the antibody as an IgG to Factor D) is 1.0 nM (1.0×10^{-9} M) or better. In another embodiment, the disclosure provides a conjugate comprising an anti-Factor D antibody, wherein the affinity of the antibody in its bivalent form to Factor D (e.g., affinity of the antibody as an IgG to Factor D) is 0.5 nM (0.5×10^{-9} M) or better. In another embodiment, the disclosure provides a conjugate comprising an anti-Factor D antibody, wherein the affinity of the antibody in its bivalent form to Factor D (e.g., affinity of the antibody as an IgG to Factor D) is 5.0 pM (5.0×10^{-12} M) or better. In another embodiment, the disclosure provides a conjugate comprising an anti-Factor D antibody, wherein the affinity of the antibody in its bivalent form to Factor D (e.g., affinity of the antibody as an IgG to Factor D) is 2.0 pM (2.0×10^{-12} M) or better. In another embodiment, the disclosure provides a conjugate comprising an anti-Factor D antibody, wherein the affinity of the antibody in its bivalent form to Factor D (e.g., affinity of the antibody as an IgG to Factor D) is 1.0 pM (1.0×10^{-12} M) or better. In another embodiment, the disclosure provides a conjugate comprising an anti-Factor D antibody, wherein the affinity of the antibody in its bivalent form to Factor D (e.g., affinity of the antibody as an IgG to Factor D) is 0.5 pM (0.5×10^{-12} M) or better.

[00161] In another embodiment, the disclosure provides a conjugate comprising an anti-Factor D antibody, wherein the affinity of the antibody in its monovalent form to Factor D (e.g., affinity of the antibody as a Fab fragment to Factor D) is between 0.5 mM (0.5×10^{-6} M) and 0.5

pM (0.5×10^{-12} M). In another embodiment, the disclosure provides a conjugate comprising an anti-Factor D antibody, wherein the affinity of the antibody in its monovalent form to Factor D (e.g., affinity of the antibody as a Fab fragment to Factor D) is between 15 nM (15×10^{-9} M) and 0.1 nM (0.1×10^{-9} M). In another embodiment, the disclosure provides a conjugate comprising an anti-Factor D antibody, wherein the affinity of the antibody in its monovalent form to Factor D (e.g., affinity of the antibody as a Fab fragment to Factor D) is between 5.5 nM (5.5×10^{-9} M) and 1 nM (1×10^{-9} M). In another embodiment, the disclosure provides a conjugate comprising an anti-Factor D antibody, wherein the affinity of the antibody in its monovalent form to Factor D (e.g., affinity of the antibody as a Fab fragment to Factor D) is between 0.5 pM (0.5×10^{-12} M) and 50 pM (5×10^{-11} M).

[00162] In another embodiment, the disclosure provides a conjugate comprising an anti-Factor D antibody, wherein the affinity of the antibody in its bivalent form to Factor D (e.g., affinity of the antibody as an IgG to Factor D) is between 0.5 mM (0.5×10^{-6} M) and 0.5 pM (0.5×10^{-12} M). In another embodiment, the disclosure provides a conjugate comprising an anti-Factor D antibody, or antibody variants thereof, wherein the affinity of the antibody in its bivalent form to Factor D (e.g., affinity of the antibody as an IgG to Factor D) is between 10 nM (10×10^{-9} M) and 0.05 nM (0.05×10^{-9} M). In another embodiment, the disclosure provides a conjugate comprising an anti-Factor D antibody, wherein the affinity of the antibody in its bivalent form to Factor D (e.g., affinity of the antibody as an IgG to Factor D) is between 5.5 nM (5.5×10^{-9} M) and 1 nM (1×10^{-9} M). In another embodiment the disclosure provides a conjugate comprising an anti-Factor D antibody, wherein the affinity of the antibody in its bivalent form to Factor D (e.g., affinity of the antibody as an IgG to Factor D) is between 0.5 pM (0.5×10^{-12} M) and 50 pM (5×10^{-11} M).

[00163] In another embodiment, the disclosure provides a conjugate comprising an anti-Factor D antibody, wherein the affinity of the antibody in its monovalent form to Factor D (e.g., affinity of the antibody as a Fab fragment to Factor D) is about 1.4 pM (1.4×10^{-12} M). In another embodiment, the disclosure provides a conjugate comprising an anti-Factor D antibody, wherein the affinity of the antibody in its bivalent form to Factor D (e.g., affinity of the antibody as a IgG to Factor D) is about 1.1 pM (1.1×10^{-12} M). In another embodiment, the disclosure provides a conjugate comprising an anti-Factor D antibody, wherein the affinity of the antibody in its monovalent form to Factor D (e.g., affinity of the antibody as a Fab fragment to Factor D) is about 0.19 nM (0.19×10^{-9} M). In another embodiment, the disclosure provides a conjugate comprising an anti-Factor D antibody, wherein the affinity of the antibody in its bivalent form to Factor D (e.g., affinity of the antibody as a IgG to Factor D) is about 0.08 nM (0.08×10^{-9} M). In

another embodiment, the disclosure provides a conjugate comprising an anti-Factor D antibody, wherein the affinity of the antibody in its monovalent form to Factor D (e.g., affinity of the antibody as a Fab fragment to Factor D) is about 12.3 nM (12.3×10^{-9} M). In another embodiment, the disclosure provides a conjugate comprising an anti-Factor D antibody, wherein the affinity of the antibody in its bivalent form to Factor D (e.g., affinity of the antibody as an IgG to Factor D) is about 9.0 nM (9.0×10^{-9} M).

[00164] In another embodiment, the disclosure provides a conjugate comprising an anti-Factor D antibody, wherein the affinity of the antibody in its monovalent form to Factor D (e.g., affinity of the antibody as a Fab fragment to Factor D) is about 1.4 pM (1.4×10^{-12} M) $\pm$ 0.5. In another embodiment, the disclosure provides a conjugate comprising an anti-Factor D antibody, wherein the affinity of the antibody in its bivalent form to Factor D (e.g., affinity of the antibody as an IgG to Factor D) is about 1.1 pM (1.1×10^{-12} M) $\pm$ 0.6. In another embodiment, the disclosure provides a conjugate comprising an anti-Factor D antibody, wherein the affinity of the antibody in its monovalent form to Factor D (e.g., affinity of the antibody as a Fab fragment to Factor D) is about 0.19 nM (0.19×10^{-9} M) $\pm$.01. In another embodiment, the disclosure provides a conjugate comprising an anti-Factor D antibody, wherein the affinity of the antibody in its bivalent form to Factor D (e.g., affinity of the antibody as a IgG to Factor D) is about 0.08 nM (0.08×10^{-9} M) $\pm$ 0.01. In another embodiment, the disclosure provides a conjugate comprising an anti-Factor D antibody, wherein the affinity of the antibody in its monovalent form to Factor D (e.g., affinity of the antibody as a Fab fragment to Factor D) is about 12.3 nM (12.3×10^{-9} M) $\pm$ 2. In another embodiment, the disclosure provides a conjugate comprising an anti-Factor D antibody, wherein the affinity of the antibody in its bivalent form to Factor D (e.g., affinity of the antibody as a IgG to Factor D) is about 9.0 nM (9.0×10^{-9} M) $\pm$ 1.

[00165] In another embodiment, an anti-Factor D antibody used in the conjugates of the disclosure may have an affinity in its monovalent form to Factor D (e.g., affinity of the antibody as a Fab fragment to Factor D) of about 1.4 pM (1.4×10^{-12} M) $\pm$ 2. In another embodiment, an anti-Factor D antibody used in the conjugates of the disclosure may have an affinity in its bivalent form to Factor D (e.g., affinity of the antibody as a IgG to Factor D) of about 1.1 pM (1.1×10^{-12} M) $\pm$ 2. In another embodiment, an anti-Factor D antibody used in the conjugates of the disclosure may have an affinity in its monovalent form to Factor D (e.g., affinity of the antibody as a Fab fragment to Factor D) is about 0.19 nM (0.19×10^{-9} M) $\pm$ 2. In another embodiment, an anti-Factor D antibody, or antibody variant thereof, used in the conjugates of the disclosure may have an affinity in its bivalent form to Factor D (e.g., affinity of the antibody as a IgG to Factor D) is about 0.08 nM (0.08×10^{-9} M) $\pm$ 2. In another embodiment, an anti-

Factor D antibody used in the conjugates of the disclosure may have an affinity in its monovalent form to Factor D (e.g., affinity of the antibody as a Fab fragment to Factor D) is about 12.3 nM (12.3×10^{-9} M) $\pm$ 2. In another embodiment, an anti-Factor D antibody used in the conjugates of the disclosure may have an affinity in its bivalent form to Factor D (e.g., affinity of the antibody as a IgG to Factor D) is about 9.0 nM (9.0×10^{-9} M) $\pm$ 2.

[00166] As is well-established in the art, binding affinity of a ligand to its receptor can be determined using any of a variety of assays, and expressed in terms of a variety of quantitative values. Accordingly, in some embodiments, the binding affinity is expressed as K_D values and reflects intrinsic binding affinity (e.g., with minimized avidity effects). Generally and preferably, binding affinity is measured *in vitro*, whether in a cell-free or cell-associated setting. As described in greater detail herein, fold difference in binding affinity can be quantified in terms of the ratio of the monovalent binding affinity value of a humanized antibody (e.g., in Fab form) and the monovalent binding affinity value of a reference/comparator antibody (e.g., in Fab form) (e.g., a murine antibody having donor hypervariable region sequences), wherein the binding affinity values are determined under similar assay conditions. Thus, in some embodiments, the fold difference in binding affinity is determined as the ratio of the K_D values of the humanized antibody in Fab form and said reference/comparator Fab antibody. For example, in some embodiments, if an antibody of the disclosure (A) has an affinity that is “3-fold lower” than the affinity of a reference antibody (M), then if the K_D value for A is 3x, the K_D value of M would be 1x, and the ratio of K_D of A to K_D of M would be 3:1. Conversely, in some embodiments, if an antibody of the disclosure (C) has an affinity that is “3-fold greater” than the affinity of a reference antibody (R), then if the K_D value for C is 1x, the K_D value of R would be 3x, and the ratio of K_D of C to K_D of R would be 1:3. Any of a number of assays known in the art, including those described herein, can be used to obtain binding affinity measurements, including, for example, Biacore, radioimmunoassay (RIA) and ELISA.

[00167] Further, K_D values for an antibody used in the conjugates of the disclosure may vary depending on conditions of the particular assay used. For example, in some embodiments, binding affinity measurements may be obtained in an assay wherein the Fab or antibody is immobilized and binding of the ligand, i.e., Factor D, is measured or alternatively, the ligand, i.e., Factor D, for the Fab or antibody is immobilized and binding of the Fab or antibody is measured. In some embodiments, the binding affinity measurements may be obtained in an assay wherein the regeneration conditions may comprise (1) 10mM glycine or 4M $MgCl_2$ at pH 1.5, and (2) pH between pH of 1.0 and pH of 7.5, including pH of 1.5, pH of 5.0, pH of 6.0 and pH of 7.2. In some embodiments, the binding affinity measurements may be obtained in an

assay wherein the binding conditions may comprise (1) PBS or HEPES-buffered saline and (2) Tween-20, i.e., 0.1% Tween-20. In some embodiments, the binding affinity measurements may be obtained in an assay wherein the source of the ligand, i.e., Factor D, may be from commercially available sources. In some embodiments, binding affinity measurements may be obtained in an assay wherein (1) the Fab or antibody is immobilized and binding of the ligand, i.e., Factor D is measured, (2) the regeneration conditions comprise 4M MgCl₂ at pH 7.2 and (3) the binding conditions comprise HEPES-buffered saline, pH 7.2 containing 0.1% Tween-20. In some embodiments, binding affinity measurements may be obtained in an assay wherein (1) the ligand, i.e., Factor D, is immobilized and binding of the Fab or antibody is measured, (2) the regeneration conditions comprise 10mM glycine at pH 1.5 and (3) the binding conditions comprise PBS buffer.

b. Biological Activity

[00168] To determine whether an anti-Factor D antibody, or variant or fragment thereof (e.g. antigen-binding fragment) is capable of binding to Factor D and exerting a biological effect, for example, inhibition of alternative pathway hemolysis, hemolytic inhibition assays using rabbit RBCs may be used, including those described in Example 2. Such hemolytic inhibition may be determined using standard assays (Kostavasili et al. (1997) *J of Immunology* 158:1763-72; Wiesmann et al. (2006) *Nature* 444:159-60). Activation of complement in such assays may be initiated with serum or plasma. Appropriate concentrations of Factor D in serum or plasma (Pascual et al. (1998) *Kidney International* 34:529-536; Complement Facts Book, Bernard J. Morley and Mark J. Walport, editors, Academic Press (2000); Barnum et al. (1984) *J. Immunol. Methods*, 67: 303-309) can be routinely determined according to methods known in the art, including those that have been described in references such as Pascual et al. (1998) *Kidney International* 34:529-536 and Barnum et al. (1984) *J. Immunol. Methods* 67:303-309. The present disclosure relates generally to antibodies capable of inhibiting biological activities associated with Factor D. For example, at a concentration of 18 µg/ml (equivalent to about 1.5 times the molar concentration of human factor D in the blood; molar ratio of anti-Factor D antibody to Factor D of about 1.5:1), significant inhibition of the alternative complement activity by the antibody can be observed (see, e.g., US Patent No. 6,956,107)

[00169] In some embodiments, the present disclosure is directed to conjugates comprising anti-Factor D antibodies, wherein a Fab fragment of such antibodies inhibits alternative pathway hemolysis with IC₅₀ values less than 30 nM. In some embodiments, the disclosure is directed to conjugates comprising anti-Factor D antibodies, wherein a Fab fragment of such antibodies

inhibits alternative pathway hemolysis with IC_{50} values less than 15 nM. In some embodiments, the disclosure is directed to conjugates comprising anti-Factor D antibodies, wherein a Fab fragment of such antibodies inhibits alternative pathway hemolysis with IC_{50} values less than 10 nM. In some embodiments, the disclosure is directed to conjugates comprising anti-Factor D antibodies, wherein a Fab fragment of such antibodies inhibits alternative pathway hemolysis with IC_{50} values less than 5 nM.

[00170] In some embodiments, the disclosure is directed to conjugates comprising anti-Factor D antibodies, wherein a Fab fragment of such antibodies inhibits alternative pathway hemolysis with IC_{50} values between 30 nM and 2 nM. In some embodiments, the disclosure is directed to conjugates comprising anti-Factor D antibodies, wherein a Fab fragment of such antibodies inhibits alternative pathway hemolysis with IC_{50} values between 25 nM and 7 nM. In some embodiments, the disclosure is directed to conjugates comprising anti-Factor D antibodies, wherein a Fab fragment of such antibodies inhibits alternative pathway hemolysis with IC_{50} values between 20 nM and 12 nM. In some embodiments, the disclosure is directed to conjugates comprising anti-Factor D antibodies, wherein a Fab fragment of such antibodies inhibits alternative pathway hemolysis with IC_{50} values between 30 nM and 15 nM. In some embodiments, the disclosure is directed to conjugates comprising anti-Factor D antibodies, wherein a Fab fragment of such antibodies inhibits alternative pathway hemolysis with IC_{50} values between 12 nM and 8 nM. In some embodiments, the disclosure is directed to conjugates comprising anti-Factor D antibodies, wherein a Fab fragment of such antibodies inhibits alternative pathway hemolysis with IC_{50} values between 7 nM and 2 nM. In some embodiments, the disclosure is directed to conjugates comprising anti-Factor D antibodies, wherein a Fab fragment of such antibodies inhibits alternative pathway hemolysis with IC_{50} values between 6 nM and 3 nM. In some embodiments, the disclosure is directed to conjugates comprising anti-Factor D antibodies, wherein a Fab fragment of such antibodies inhibits alternative pathway hemolysis with IC_{50} values between 8 nM and 5 nM. In some embodiments, the disclosure is directed to conjugates comprising anti-Factor D antibodies, wherein a Fab fragment of such antibodies inhibits alternative pathway hemolysis with IC_{50} values between 5 nM and 2 nM. In some embodiments, the disclosure is directed to conjugates comprising anti-Factor D antibodies, wherein a Fab fragment of such antibodies inhibits alternative pathway hemolysis with IC_{50} values between 10 nM and 5 nM. In some embodiments, the disclosure is directed to conjugates comprising anti-Factor D antibodies, wherein a Fab fragment of such antibodies inhibits alternative pathway hemolysis with IC_{50} values between 8 nM and 2 nM. In some embodiments, the disclosure is directed to conjugates

comprising anti-Factor D antibodies, wherein a Fab fragment of such antibodies inhibits alternative pathway hemolysis with IC_{50} values between 7 nM and 3 nM. In some embodiments, the disclosure is directed to conjugates comprising anti-Factor D antibodies, wherein a Fab fragment of such antibodies inhibits alternative pathway hemolysis with IC_{50} values between 6 nM and 4 nM. In another embodiment, the disclosure is directed to conjugates comprising anti-Factor D antibodies, wherein a Fab fragment of such antibodies inhibits alternative pathway hemolysis with an IC_{50} value of about $4.7 \text{ nM} \pm 0.6 \text{ nM}$. In another embodiment, the disclosure is directed to anti-Factor D antibodies, wherein a Fab fragment of such antibodies inhibits alternative pathway hemolysis with an IC_{50} value of about $6.4 \text{ nM} \pm 0.6 \text{ nM}$. In another embodiment, the disclosure is directed to conjugates comprising anti-Factor D antibodies, wherein a Fab fragment of such antibodies inhibits alternative pathway hemolysis with an IC_{50} value of about $3.5 \text{ nM} \pm 0.5 \text{ nM}$. In another embodiment, the disclosure is directed to conjugates comprising anti-Factor D antibodies, wherein a Fab fragment of such antibodies inhibits alternative pathway hemolysis with an IC_{50} value of about $4.4 \text{ nM} \pm 1.5 \text{ nM}$. In another embodiment, the disclosure is directed to conjugates comprising anti-Factor D antibodies, wherein a Fab fragment of such antibodies inhibits alternative pathway hemolysis with an IC_{50} value of about $10.2 \text{ nM} \pm 0.8 \text{ nM}$. In another embodiment, the disclosure is directed to conjugates comprising anti-Factor D antibodies, wherein a Fab fragment of such antibodies inhibits alternative pathway hemolysis with an IC_{50} value of about $23.9 \text{ nM} \pm 5.0 \text{ nM}$.

[00171] In some embodiments, the disclosure is directed to conjugates comprising anti-Factor D antibodies, wherein a Fab fragment of such antibodies inhibits alternative pathway hemolysis with IC_{90} values less than 80 nM. In some embodiments, the disclosure is directed to conjugates comprising anti-Factor D antibodies, wherein a Fab fragment of such antibodies inhibits alternative pathway hemolysis with IC_{90} values less than 50 nM. In some embodiments, the disclosure is directed to conjugates comprising anti-Factor D antibodies, wherein a Fab fragment of such antibodies inhibits alternative pathway hemolysis with IC_{90} values less than 40 nM. In some embodiments, the disclosure is directed to conjugates comprising anti-Factor D antibodies, wherein a Fab fragment of such antibodies inhibits alternative pathway hemolysis with IC_{90} values less than 20 nM. In some embodiments, the disclosure is directed to conjugates comprising anti-Factor D antibodies, wherein a Fab fragment of such antibodies inhibits alternative pathway hemolysis with IC_{50} values less than 15 nM.

[00172] In some embodiments, the disclosure is directed to conjugates comprising anti-Factor D antibodies, wherein a Fab fragment of such antibodies inhibits alternative pathway hemolysis with IC_{90} values between 80 nM and 10 nM. In some embodiments, the disclosure is

directed to conjugates comprising anti-Factor D antibodies, wherein a Fab fragment of such antibodies inhibits alternative pathway hemolysis with IC_{90} values between 75 nM and 15 nM. In some embodiments, the disclosure is directed to conjugates comprising anti-Factor D antibodies, wherein a Fab fragment of such antibodies inhibits alternative pathway hemolysis with IC_{90} values between 70 nM and 20 nM. In some embodiments, the disclosure is directed to conjugates comprising anti-Factor D antibodies, wherein a Fab fragment of such antibodies inhibits alternative pathway hemolysis with IC_{90} values between 65 nM and 25 nM. In some embodiments, the disclosure is directed to conjugates comprising anti-Factor D antibodies, wherein a Fab fragment of such antibodies inhibits alternative pathway hemolysis with IC_{90} values between 60 nM and 30 nM. In some embodiments, the disclosure is directed to conjugates comprising anti-Factor D antibodies, wherein a Fab fragment of such antibodies inhibits alternative pathway hemolysis with IC_{90} values between 55 nM and 35 nM. In some embodiments, the disclosure is directed to conjugates comprising anti-Factor D antibodies, wherein a Fab fragment of such antibodies inhibits alternative pathway hemolysis with IC_{90} values between 50 nM and 40 nM. In some embodiments, the disclosure is directed to conjugates comprising anti-Factor D antibodies, wherein a Fab fragment of such antibodies inhibits alternative pathway hemolysis with IC_{90} values between 80 nM and 70 nM. In some embodiments, the disclosure is directed to conjugates comprising anti-Factor D antibodies, wherein a Fab fragment of such antibodies inhibits alternative pathway hemolysis with IC_{90} values between 55 nM and 25 nM. In some embodiments, the disclosure is directed to conjugates comprising anti-Factor D antibodies, wherein a Fab fragment of such antibodies inhibits alternative pathway hemolysis with IC_{90} values between 16 nM and 12 nM. In another embodiment, the disclosure is directed to conjugates comprising anti-Factor D antibodies, wherein a Fab fragment of such antibodies inhibits alternative pathway hemolysis with an IC_{90} value of about $14.0 \text{ nM} \pm 1.0 \text{ nM}$. In another embodiment, the disclosure is directed to conjugates comprising anti-Factor D antibodies, wherein a Fab fragment of such antibodies inhibits alternative pathway hemolysis with an IC_{90} value of about $38.0 \text{ nM} \pm 11.0 \text{ nM}$. In another embodiment, the disclosure is directed to conjugates comprising anti-Factor D antibodies, wherein a Fab fragment of such antibodies inhibits alternative pathway hemolysis with an IC_{90} value of about $72.6 \text{ nM} \pm 4.8 \text{ nM}$.

[00173] In some embodiments, the disclosure is directed to conjugates comprising an anti-Factor D antibody wherein a Fab fragment of such antibodies inhibits alternative pathway hemolysis in an antibody to Factor D molar ratio of about 0.05:1 (0.05) to about 10:1 (10), or about 0.09:1 (0.09) to about 8:1 (8), or about 0.1:1 (0.1) to about 6:1 (6), or about 0.15:1 (0.15)

to about 5:1 (5), or about 0.19:1 (0.19) to about 4:1 (4), or about 0.2:1 (0.2) to about 3:1 (3), or about 0.3:1 (0.3) to about 2:1 (2), or about 0.4:1 (0.4) to about 1:1 (1), or about 0.5:1 (0.5) to about 1:2 (0.5), or about 0.6:1 (0.6) to about 1:3 (0.33), or about 0.7:1 (0.7) to about 1:4 (0.25), or about 0.8:1 (0.8) to about 1:5 (0.2) or about 0.9:1 (0.9) to about 1:6 (0.17).

[00174] In some embodiments, the disclosure is directed to conjugates comprising fragments of humanized anti-Factor D antibodies (e.g. antigen-binding fragments). The antibody fragments of the present disclosure may, for example, be Fv, Fab, Fab-SH, Fab'-SH, Fab', Fab-C, Fab'-C, Fab'-C-SH, Fab-C-SH, scFv, diabody, or F(ab')₂, dAb, complementarity determining region (CDR) fragments, linear antibodies, single-chain antibody molecules, minibodies, diabodies, or multispecific antibodies formed from antibody fragments. In a further embodiment, the disclosure is directed to conjugates comprising a humanized anti-Factor D antibody fragment (e.g. antigen-binding fragment) that is capable of penetrating substantially all of the retina. In an even further embodiment, the disclosure is directed to conjugates comprising a humanized anti-Factor D antibody fragment (e.g. antigen-binding fragment) that is capable of penetrating throughout the entire thickness of the retina.

[00175] In some embodiments, the disclosure is directed to conjugates comprising anti-Factor D antibodies, wherein an unconjugated Fab fragment of such antibodies has a half-life of at least 3, 5, 7, 10 or 12 days after administration into a mammalian eye (e.g. human) via a single intravitreal injection. In another embodiment, the disclosure is directed to conjugates comprising humanized anti-Factor D antibodies, wherein an unconjugated Fab fragment of such antibodies inhibits alternative pathway (AP) complement activation for at least 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 105, 110 or 115 days after administration into a mammalian eye (e.g. human) via a single intravitreal injection. In another embodiment, the disclosure is directed to conjugates comprising humanized anti-Factor D antibodies, wherein the concentration of an unconjugated Fab fragment of such antibodies that inhibits alternative pathway (AP) complement activation is maintained in retinal tissue for at least 40, 45, 50, 55, 60, 65, 70, 75, 80 or 85 days after administration into a mammalian eye (e.g. human) via a single intravitreal injection. In another embodiment, the disclosure is directed to conjugates comprising humanized anti-Factor D antibodies, wherein the concentration of an unconjugated Fab fragment of such antibodies that inhibits alternative pathway (AP) complement activation is maintained in the vitreous humor for at least 80, 85, 90, 95, 100, 105, 110 or 115 days after administration into a mammalian eye (e.g. human) via a single intravitreal injection.

Construction of Anti-Factor D Antibody or Antibody Variant–Polymer Conjugates*a. Multi-armed Polymers*

[00176] In some aspects, the conjugates of the present disclosure can be made by derivatizing the anti-Factor D antibodies or antibody variants described herein by conjugating the antibodies or variants thereof with a multi-armed polymer. It will be appreciated that any multi-armed polymer that provides the conjugate with the desired size or that has the selected average molecular weight as described herein is suitable for use in constructing the antibody-polymer conjugates of the disclosure.

[00177] Many polymers are suitable for use in pharmaceuticals. *See, e.g.*, Davis et al., *Biomedical Polymers: Polymeric Materials and Pharmaceuticals for Biomedical Use*, pp. 441-451 (1980). In all embodiments of the present disclosure, a non-proteinaceous polymer is used to form the conjugates of the disclosure. The non-proteinaceous polymer ordinarily is a hydrophilic synthetic polymer, i.e., a polymer not otherwise found in nature. However, polymers which exist in nature and are produced by recombinant or *in vitro* methods may also be useful, as are polymers which are isolated from native sources.

[00178] In some aspects, the anti-Factor D antibodies or antibody variants are derivatized by conjugating (e.g., covalently linking) the antibodies or variants thereof to a multi-armed polyol. Thus, in some embodiments, the disclosure is directed to a conjugate comprising one or more anti-Factor D antibody or antibody variant disclosed herein covalently linked to one or more multi-armed polyol. The polyol employed can be any water-soluble poly (alkylene oxide) polymer and can have a linear or branched chain. Suitable polyols include those substituted at one or more hydroxyl positions with a chemical group, such as an alkyl group having between one and four carbons. Typically, the polyol is a poly(alkylene glycol), such as polyethylene glycol (PEG), and thus, for ease of description, the remainder of the discussion relates to an exemplary embodiment wherein the polyol employed is PEG, and the process of conjugating the polyol to a polypeptide is termed "PEGylation." However, those skilled in the art will recognize that other polyols, such as, for example, poly(propylene glycol) and polyethylene-polypropylene glycol copolymers, can be employed using the techniques for conjugation described herein for PEG.

[00179] The polyols used to form the conjugates of the present disclosure are multi-armed polyols. As used herein, "multi-armed polyol" refers to a polyol comprising a core structure to which at least two arms are attached. The multi-armed polyol may be, for example, a dimer

(two arms), a tetramer (four arms), a hexamer (six arms), an octamer (eight arms), etc. In some aspects, the multi-armed polyol is a multi-armed PEG.

[00180] The weight average molecular weight of the multi-armed PEG used in the PEGylation of the anti-Factor D antibodies and antibody variants can vary, and typically may range from about 500 to about 300,000 daltons (D). In some embodiments, the weight average molecular weight of the multi-armed PEG is from about 1,000 to about 100,000 D, and, in some embodiments, from about 20,000 to about 60,000 D. In some embodiments, PEGylation is carried out with a multi-armed PEG having a weight average molecular weight of about 40,000 D.

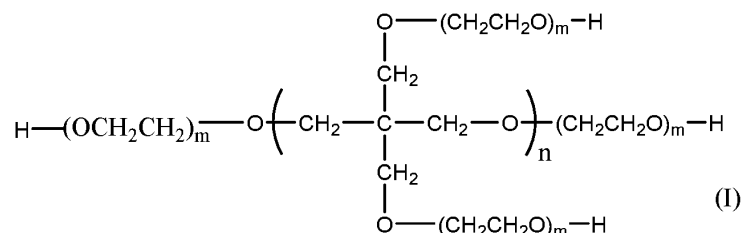
[00181] A variety of methods for PEGylating proteins are known in the art. Specific methods of producing proteins conjugated to PEG include the methods described in U.S. Pat. No. 4,179,337, U.S. Pat. No. 4,935,465, and U.S. Patent No. 5,849,535, all of which are herein incorporated by reference in their entirety. Typically the protein is covalently bonded via one or more of the amino acid residues of the protein to a terminal reactive group on the polymer. The polymer with the reactive group(s) is designated herein as an activated or functionalized polymer (e.g., a functionalized PEG). The reactive group selectively reacts with free sulfhydryl or amino or other reactive groups on the antibody or antibody variant. The multi-armed PEG polymer can be coupled to the sulfhydryl or amino or other reactive group on the antibody or antibody variant in either a random or a site specific manner. It will be understood, however, that the type and amount of the reactive group chosen, as well as the type of polymer employed, to obtain optimum results, will depend on the particular antibody or antibody variant employed to limit, and preferably substantially prevent, having the reactive group react with too many active groups on the antibody. As it may not be possible to sufficiently limit or prevent this in some instances, typically from about 0.05 to about 1000 moles, or, in some embodiments, from about 0.05 to about 200 moles, of functionalized polymer per mole of antibody, depending on antibody concentration, may be employed. The final amount of functionalized polymer per mole of antibody is a balance to maintain optimum activity, while at the same time optimizing, if possible, the vitreous humor, retina, and/or aqueous humor half-life of the antibody.

[00182] While the residues may be any reactive amino acids on the antibody or antibody variant, such as the N-terminal amino acid group, in some embodiments, the reactive amino acid is cysteine, which is linked to the reactive group of the functionalized polymer through its free thiol group as shown, for example, in WO 99/03887, WO 94/12219, WO 94/22466, U.S. Patent No. 5,206,344, U.S. Patent No. 5,166,322, and U.S. Patent No. 5,206,344, all of which are herein incorporated by reference in their entirety. In such embodiments, the polymer may

comprise at least one terminal reactive group that is capable of reacting specifically with the free sulfhydryl or thiol group(s) on the parental antibody. Such groups include, but are not limited to, maleimide, a sulfhydryl, a thiol, trifluoromethanesulfonate, tosylate, aziridine, epoxide, a pyridyl disulfide, succinimidyl ester, -NH_2 , an aldehyde, a haloacetate, a haloacetamide, and a para-nitrophenyl carbonate, among others. The polymer can be coupled to the parental antibody using any protocol suitable for the chemistry of the coupling system selected, such as the protocols and systems described in U.S. Pat. No. 4,179,337, U.S. Pat. No. 7,122,636, and Jevsevar, et al., *Biotech J.*, Vol. 5, pp. 113-128 (2010). Alternatively, the reactive amino acid may be lysine, which is linked to the reactive group of the functionalized polymer through its free epsilon-amino group (*see, e.g.*, WO 93/00109, incorporated by reference herein), or glutamic or aspartic acid, which is linked to the polymer through an amide bond. The reactive group of the polymer can then react with, for example, the α (alpha) and ϵ (epsilon) amines or sulfhydryl groups of proteins to form a covalent bond. It will be appreciated that the present disclosure is not limited to conjugates utilizing any particular type of linkage between an antibody or antibody fragment and a polymer.

[00183] Suitable functionalized multi-armed PEGs for use in preparing the conjugates of the disclosure can be produced by a number of conventional reactions. For example, a N-hydroxysuccinimide ester of a PEG (M-NHS-PEG) can be prepared from a PEG-monomethyl ether by reaction with N,N'-dicyclohexylcarbodiimide (DCC) and N-hydroxysuccinimide (NHS), according to the method of Buckmann and Merr, *Makromol. Chem.*, Vol. 182, pp. 1379-1384 (1981). In addition, a PEG terminal hydroxy group can be converted to an amino group, for example, by reaction with thionyl bromide to form PEG-Br, followed by aminolysis with excess ammonia to form PEG-NH₂. The PEG-NH₂ can then be conjugated to the antibody or antibody variant of interest using standard coupling reagents, such as Woodward's Reagent K. Furthermore, a PEG terminal-CH₂OH group can be converted to an aldehyde group, for example, by oxidation with MnO₂. The aldehyde group can be conjugated to the antibody or antibody variant by reductive alkylation with a reagent such as cyanoborohydride.

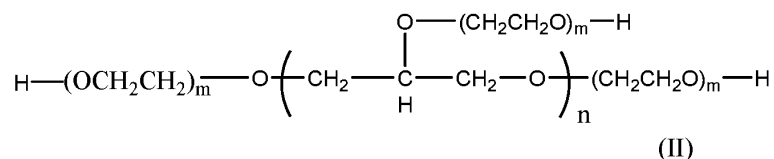
[00184] In some embodiments, the multi-armed PEG used to prepare the conjugates of the present disclosure has the structure of general formula (I):



wherein each m denotes the length or size of the particular arm of the polyol (PEG) and is independently an integer of from about 45 to about 1000, or from about 3 to about 250, or from about 50 to about 200, or from about 100 to about 150; and n is an integer from about 1 to about 10.

[00185] In some embodiments, the multi-armed PEG has the structure of general formula (I), wherein n is 1, and the multi-armed PEG is a tetramer. In another embodiment, the multi-armed PEG has the structure of general formula (I), wherein n is 2, and the multi-armed PEG is a hexamer. In another embodiment, the multi-armed PEG has the structure of general formula (I), wherein n is 3, and the multi-armed PEG is an octamer.

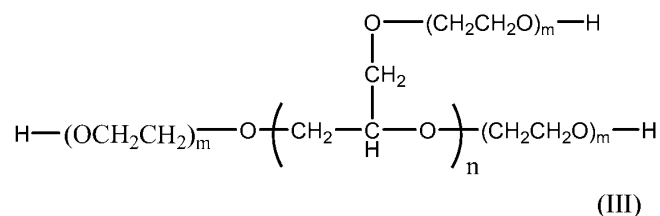
[00186] In another aspect, the multi-armed PEG used to prepare the conjugates of the present disclosure has the structure of general formula (II):



wherein each m denotes the length or size of the particular arm of the polyol (PEG) and is independently an integer of from about 45 to about 1000, or from about 3 to about 250, or from about 50 to about 200, or from about 100 to about 150; and n is an integer from about 1 to about 10.

[00187] In some embodiments, the multi-armed PEG has the structure of general formula (II), wherein n is 2, and the multi-armed PEG is a tetramer. In another embodiment, the multi-armed PEG has the structure of general formula (II), wherein n is 4, and the multi-armed PEG is a hexamer. In another embodiment, the multi-armed PEG has the structure of general formula (II), wherein n is 6, and the multi-armed PEG is an octamer.

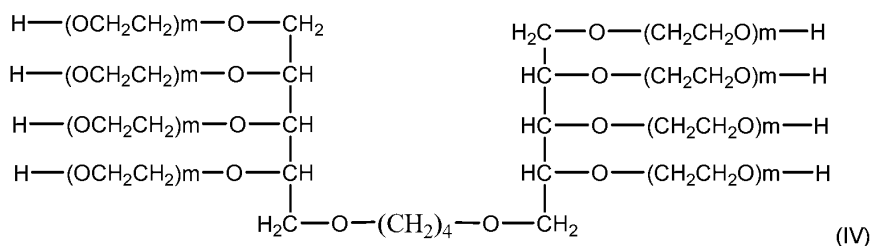
[00188] In another aspect, the multi-armed PEG used to prepare the conjugates of the present disclosure has the structure of general formula (III):



wherein each m denotes the length or size of the particular arm of the polyol (PEG) and is independently an integer of from about 45 to about 1000, or from about 3 to about 250, or from about 50 to about 200, or from about 100 to about 150; and n is an integer from about 1 to about 10.

[00189] In some embodiments, the multi-armed PEG has the structure of general formula (III), wherein n is 2, and the multi-armed PEG is a tetramer. In another embodiment, the multi-armed PEG has the structure of general formula (III), wherein n is 4, and the multi-armed PEG is a hexamer. In another embodiment, the multi-armed PEG has the structure of general formula (III), wherein n is 6, and the multi-armed PEG is an octamer.

[00190] In another aspect, the multi-armed PEG used to prepare the conjugates of the present disclosure has the structure of general formula (IV):

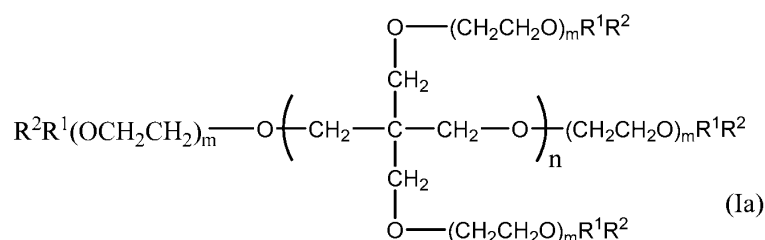


wherein each m denotes the length or size of the particular arm of the polyol (PEG) and is independently an integer of from about 45 to about 1000, or from about 3 to about 250, or from about 50 to about 200, or from about 100 to about 150.

[00191] The multi-armed PEG having the structure of any of general formulas (I) to (IV) may be functionalized to, for example, attach a terminal reactive group suitable for reacting with or conjugating to the antibody (e.g., antibody fragment) using any of the techniques described above to produce a functionalized multi-armed PEG. In other embodiments, however, the multi-armed PEG can be covalently linked to the anti-Factor D antibodies or antibody variants through a multifunctional crosslinking agent which reacts with the PEG and one or more amino

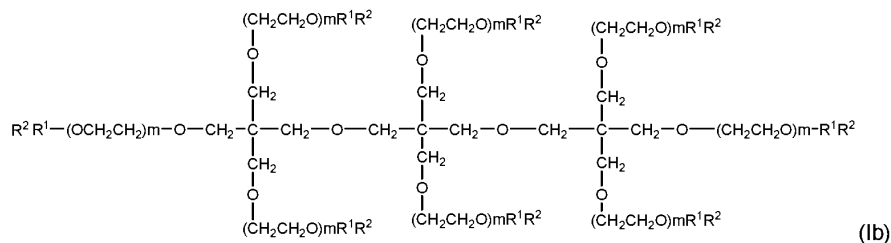
acid residues of the antibody or antibody variant to be linked, as described in, for example, U.S. Pat. No. 7,122,636, which is herein incorporated by reference in its entirety.

[00192] In other aspects, the multi-armed PEG used to prepare the conjugates of the present disclosure is a functionalized multi-armed PEG comprising at least one terminal reactive group. The terminal reactive group can conjugate directly to the anti-Factor D antibodies or antibody variants to form the conjugates of the present disclosure. In some embodiments, the functionalized multi-armed PEG has the structure of general formula (Ia):



wherein each m denotes the length or size of the particular arm of the polyol (PEG) and is independently an integer of from about 45 to about 1000, or from about 3 to about 250, or from about 50 to about 200, or from about 100 to about 150; and n is an integer from about 1 to about 10; each R^1 is independently either absent, or is a linking group; and each R^2 is independently either hydrogen or a terminal reactive group; wherein at least one R^2 is a terminal reactive group. In some embodiments, R^2 is independently selected from the group consisting of a thiol reactive group, an amino reactive group, and combinations thereof.

[00193] In some embodiments, the functionalized multi-armed PEG has the structure of general formula (Ia), wherein n is an integer from 1 to 3. In some embodiments, the functionalized multi-armed PEG has the structure of general formula (Ia), wherein n is 1, and the multi-armed PEG is a tetramer. In another embodiment, the functionalized multi-armed PEG has the structure of general formula (Ia), wherein n is 2, and the multi-armed PEG is a hexamer. In another embodiment, the functionalized multi-armed PEG has the structure of general formula (Ia), wherein n is 3, and the multi-armed PEG is an octamer. In such embodiments, the octamer has the structure of general formula (Ib):



wherein m , R^1 , and R^2 are as defined above. In particular, in one embodiment, each m denotes the length or size of the particular arm of the polyol (PEG) and is independently an integer of from about 45 to about 1000, or from about 3 to about 250, or from about 50 to about 200, or from about 100 to about 150; each R^1 is independently either absent, or is a linking group; and each R^2 is independently either hydrogen or a terminal reactive group; wherein at least one R^2 is a terminal reactive group. In some embodiments, R^2 is independently selected from the group consisting of a thiol reactive group, an amino reactive group, and combinations thereof.

[00194] Multi-armed PEGs having the structure of general formula (Ib) have a tripentaerythritol (TP) core structure, and are also referred to herein as TP octamers.

[00195] In some embodiments, the functionalized multi-armed PEG has the structure of general formula (Ia) or (Ib), wherein each R^1 , when present, is the same or different, and R^1 and

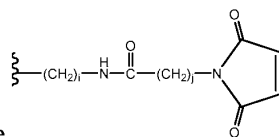
R^2 when taken together are selected from the group consisting of $\text{---}(\text{CH}_2)_i\text{---}R^2$;
 $\text{---}(\text{CH}_2)_i\text{---}NH\text{---}R^2$; $\text{---}(\text{CH}_2)_i\text{---}O\text{---}C(=O)\text{---}R^2$; $\text{---}(\text{CH}_2)_i\text{---}O\text{---}C(=O)\text{---}O\text{---}R^2$; $\text{---}(\text{CH}_2)_i\text{---}O\text{---}C(=O)\text{---}NH\text{---}R^2$;
 $\text{---}(\text{CH}_2)_i\text{---}C(=O)\text{---}R^2$; $\text{---}(\text{CH}_2)_i\text{---}C(=O)\text{---}O\text{---}R^2$; $\text{---}(\text{CH}_2)_i\text{---}C(=O)\text{---}NH\text{---}R^2$;
 $\text{---}(\text{CH}_2)_i\text{---}NH\text{---}C(=O)\text{---}R^2$; $\text{---}(\text{CH}_2)_i\text{---}NH\text{---}C(=O)\text{---}(\text{CH}_2)_j\text{---}R^2$; $\text{---}(\text{CH}_2)_i\text{---}NH\text{---}C(=O)\text{---}O\text{---}R^2$;
 $\text{---}(\text{CH}_2)_i\text{---}NH\text{---}C(=O)\text{---}NH\text{---}R^2$; $\text{---}C(=O)\text{---}(\text{CH}_2)_i\text{---}C(=O)\text{---}R^2$; $\text{---}C(=O)\text{---}(\text{CH}_2)_i\text{---}C(=O)\text{---}O\text{---}R^2$; and
 $\text{---}C(=O)\text{---}(\text{CH}_2)_i\text{---}C(=O)\text{---}NH\text{---}R^2$; and combinations thereof; wherein each i is independently an integer of 0-10; j is an integer of 0-10; and R^2 is as defined herein. In some embodiments, each R^1 is a linking group.

[00196] In some embodiments, the functionalized multi-armed PEG has the structure of general formula (Ia) or (Ib), wherein R^1 and R^2 , when taken together, are

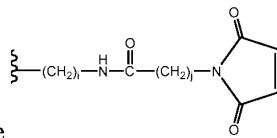
$\text{---}(\text{CH}_2)_i\text{---}NH\text{---}C(=O)\text{---}(\text{CH}_2)_j\text{---}R^2$, wherein i , j , and R^2 are as defined herein. In some embodiments, R^1 and R^2 , when taken together, are $\text{---}(\text{CH}_2)_i\text{---}NH\text{---}C(=O)\text{---}(\text{CH}_2)_j\text{---}R^2$, wherein i is 2; j is 2 or 3, and R^2 is as defined herein.

[00197] In some aspects, the functionalized multi-armed PEG has the structure of general formula (Ia) or (Ib), wherein each R^2 is independently selected from the group consisting of a maleimide, a sulfhydryl, a thiol, trifluoromethanesulfonate, tosylate, aziridine, epoxide, a pyridyl disulfide, succinimidyl ester, $-NH_2$, an aldehyde, a haloacetate, a haloacetamide, and a para-nitrophenyl carbonate. In some embodiments, each R^2 is independently a haloacetate selected from the group consisting of bromoacetate, iodoacetate, chloroacetate, and combinations thereof. In some embodiments, each R^2 is independently a haloacetamide selected from the group consisting of bromoacetamide, iodoacetamide, chloroacetamide, and combinations thereof. In some embodiments, R^2 is a maleimide.

[00198] In some embodiments, the functionalized multi-armed PEG has the structure of general formula (Ia) or (Ib), wherein each R^2 is a maleimide. In some embodiments, the functionalized multi-armed PEG has the structure of general formula (Ia) or (Ib), wherein R^1 and

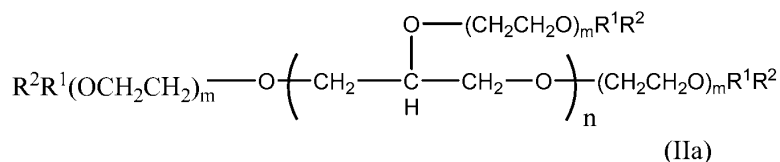


R^2 , when taken together, are , wherein i and j are as defined above. In one embodiment, the functionalized multi-armed PEG has the structure of general formula (Ia)



or (Ib), wherein R^1 and R^2 , when taken together, are , wherein i is 2 and j is 2.

[00199] In another aspect, the functionalized multi-armed PEG used to prepare the conjugates of the present disclosure has the structure of general formula (IIa):

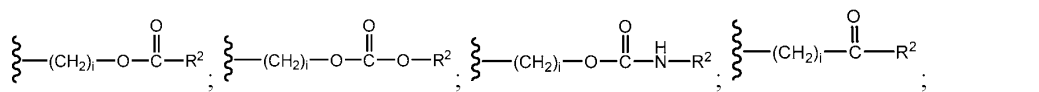
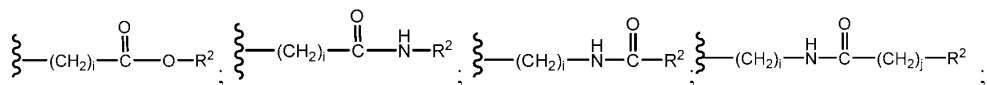
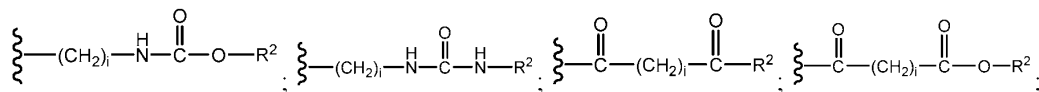


wherein each m denotes the length or size of the particular arm of the polyol (PEG) and is independently an integer of about 45 to about 1000, or from about 3 to about 250, or from about 50 to about 200, or from about 100 to about 150; and n is an integer from about 1 to about 10; each R^1 is independently either absent, or is a linking group; and each R^2 is independently either hydrogen or a terminal reactive group; wherein at least one R^2 is a terminal reactive group. In some embodiments, R^2 is independently selected from the group consisting of a thiol reactive group, an amino reactive group, and combinations thereof.

[00200] In some embodiments, the functionalized multi-armed PEG has the structure of general formula (IIa), wherein n is an integer from 2 to 6. In some embodiments, the functionalized multi-armed PEG has the structure of general formula (IIa), wherein n is 3. In another embodiment, the functionalized multi-armed PEG has the structure of general formula (IIa), wherein n is 2, and the multi-armed PEG is a tetramer. In another embodiment, the functionalized multi-armed PEG has the structure of general formula (IIa), wherein n is 4, and the multi-armed PEG is a hexamer. In another embodiment, the functionalized multi-armed PEG has the structure of general formula (IIa), wherein n is 6, and the multi-armed PEG is an octamer. Octamers having the structure of general formula (IIa) have a hexaglycerin (HG) core structure, and are also referred to herein as HG octamers.

[00201] In some embodiments, the functionalized multi-armed PEG has the structure of general formula (IIa), wherein each R^1 , when present, is the same or different, and R^1 and R^2

when taken together are selected from the group consisting of $\xi-(CH_2)_i-R^2$; $\xi-(CH_2)_i-NH-R^2$;



and $\xi-C(=O)-(CH_2)_i-C(=O)-NH-R^2$; and combinations thereof; wherein each i is independently an integer of 0-10; j is an integer of 0-10; and R^2 is as defined herein. In some embodiments, each R^1 is a linking group.

[00202] In some embodiments, the functionalized multi-armed PEG has the structure of

general formula (IIa), wherein R^1 and R^2 , when taken together, are $\xi-(CH_2)_i-NH-C(=O)-(CH_2)_j-R^2$,

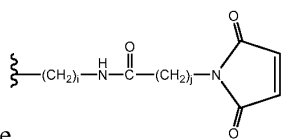
wherein i , j , and R^2 are as defined herein. In some embodiments, R^1 and R^2 , when taken

together, are $\xi-(CH_2)_i-NH-C(=O)-(CH_2)_j-R^2$, wherein i is 2; j is 2 or 3, and R^2 is as defined herein.

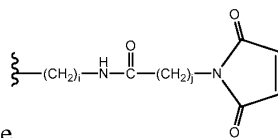
[00203] In some aspects, the functionalized multi-armed PEG has the structure of general formula (IIa), wherein each R^2 is independently selected from the group consisting of a maleimide, a sulfhydryl, a thiol, trifluoromethanesulfonate, tosylate, aziridine, epoxide, a

pyridyl disulfide, succinimidyl ester, -NH_2 , an aldehyde, a haloacetate, a haloacetamide, and a para-nitrophenyl carbonate. In some embodiments, each R^2 is independently a haloacetate selected from the group consisting of bromoacetate, iodoacetate, chloroacetate, and combinations thereof. In some embodiments, each R^2 is independently a haloacetamide selected from the group consisting of bromoacetamide, iodoacetamide, chloroacetamide, and combinations thereof. In some embodiments, R^2 is a maleimide.

[00204] In some embodiments, the functionalized multi-armed PEG has the structure of general formula (IIa), wherein each R^2 is a maleimide. In some embodiments, the functionalized multi-armed PEG has the structure of general formula (IIa), wherein R^1 and R^2 ,

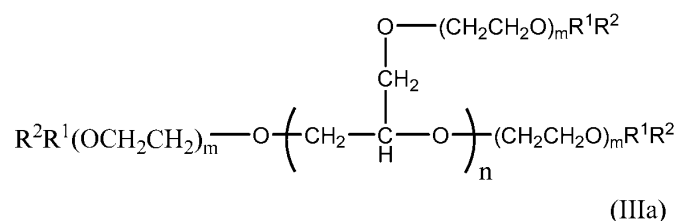


when taken together, are , wherein i and j are as defined above. In some embodiments, the functionalized multi-armed PEG has the structure of general formula (IIa),



wherein R^1 and R^2 , when taken together, are , wherein i is 2 and j is 2.

[00205] In another aspect, the functionalized multi-armed PEG has the structure of general formula (IIIa):



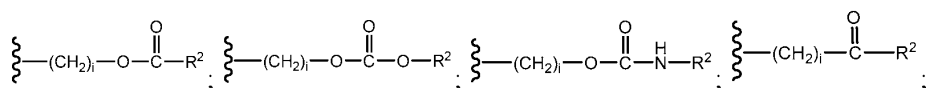
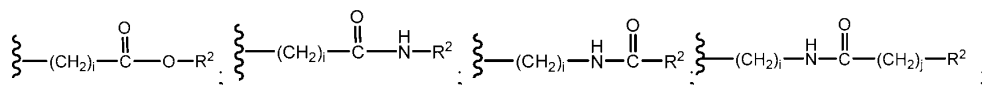
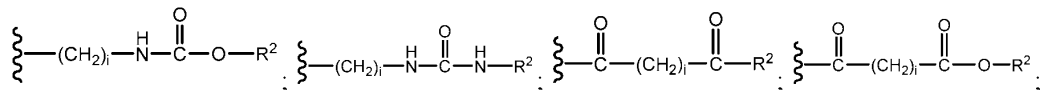
wherein each m denotes the length or size of the particular arm of the polyol (PEG) and is independently an integer of from about 45 to about 1000, or from about 3 to about 250, or from about 50 to about 200, or from about 100 to about 150; and n is an integer from about 1 to about 10; each R^1 is independently either absent, or is a linking group; and each R^2 is independently either hydrogen or a terminal reactive group; wherein at least one R^2 is a terminal reactive group. In some embodiments, R^2 is independently selected from the group consisting of a thiol reactive group, an amino reactive group, and combinations thereof.

[00206] In some embodiments, the functionalized multi-armed PEG has the structure of general formula (IIIa), wherein n is an integer from 2 to 6. In some embodiments, the functionalized multi-armed PEG has the structure of general formula (IIIa), wherein n is 2, and

the multi-armed PEG is a tetramer. In another embodiment, the functionalized multi-armed PEG has the structure of general formula (IIIa), wherein n is 4, and the multi-armed PEG is a hexamer. In another embodiment, the functionalized multi-armed PEG has the structure of general formula (IIIa), wherein n is 6, and the multi-armed PEG is an octamer. Octamers having the structure of general formula (IIIa) have a hexaglycerol (HGEO) core structure, and are also referred to herein as HGEO octamers.

[00207] In some embodiments, the functionalized multi-armed PEG has the structure of general formula (IIIa), wherein each R^1 , when present, is the same or different, and R^1 and R^2

when taken together are selected from the group consisting of $\zeta-(CH_2)_i-R^2$; $\zeta-(CH_2)_i-NH-R^2$;



and $\zeta-C(=O)-(CH_2)_i-C(=O)-NH-R^2$; and combinations thereof; wherein each i is independently an

integer of 0-10; j is an integer of 0-10; and R^2 is as defined herein. In some embodiments, each R^1 is a linking group.

[00208] In some embodiments, the functionalized multi-armed PEG has the structure of

general formula (IIIa), wherein R^1 and R^2 , when taken together, are $\zeta-(CH_2)_i-NH-C(=O)-(CH_2)_j-R^2$,

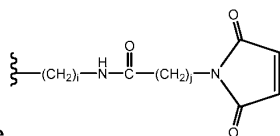
wherein i, j, and R^2 are as defined herein. In some embodiments, R^1 and R^2 , when taken

together, are $\zeta-(CH_2)_i-NH-C(=O)-(CH_2)_j-R^2$, wherein i is 2; j is 2 or 3, and R^2 is as defined herein.

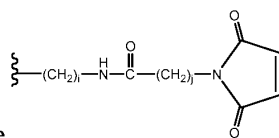
[00209] In some aspects, the functionalized multi-armed PEG has the structure of general formula (IIIa), wherein each R^2 is independently selected from the group consisting of a maleimide, a sulfhydryl, a thiol, trifluoromethanesulfonate, tosylate, aziridine, epoxide, a pyridyl disulfide, succinimidyl ester, $-NH_2$, an aldehyde, a haloacetate, a haloacetamide, and a para-nitrophenyl carbonate. In some embodiments, each R^2 is independently a haloacetate selected from the group consisting of bromoacetate, iodoacetate, chloroacetate, and combinations thereof. In some embodiments, each R^2 is independently a haloacetamide selected

from the group consisting of bromoacetamide, iodoacetamide, chloroacetamide, and combinations thereof. In some embodiments, R^2 is a maleimide.

[00210] In some embodiments, the functionalized multi-armed PEG has the structure of general formula (IIIa), wherein each R^2 is a maleimide. In some embodiments, the functionalized multi-armed PEG has the structure of general formula (IIIa), wherein R^1 and R^2 ,

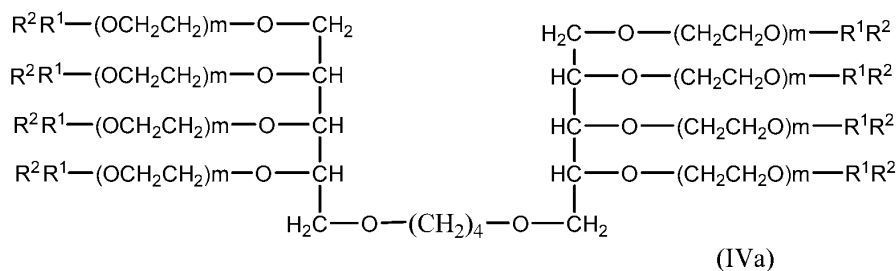


when taken together, are i and j are as defined above. In some embodiments, the functionalized multi-armed PEG has the structure of general formula



(IIIa), wherein R^1 and R^2 , when taken together, are i is 3 and j is 2.

[00211] In another aspect, the functionalized multi-armed PEG has the structure of general formula (IVa):



wherein each m denotes the length or size of the particular arm of the polyol (PEG) and is independently an integer of from about 45 to about 1000, or from about 3 to about 250, or from about 50 to about 200, or from about 100 to about 150; each R^1 is independently either absent, or is a linking group; and each R^2 is independently either hydrogen or a terminal reactive group; wherein at least one R^2 is a terminal reactive group. In some embodiments, R^2 is independently selected from the group consisting of a thiol reactive group, an amino reactive group, and combinations thereof.

[00212] Multi-armed PEGs having the structure of general formula (IVa) have a butanediol core structure, and are also referred to herein as DX octamers.

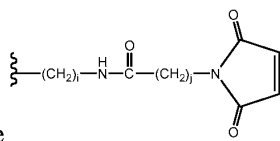
[00213] In some embodiments, the functionalized multi-armed PEG has the structure of general formula (IVa), wherein each R^1 , when present, is the same or different, and R^1 and R^2

when taken together are selected from the group consisting of $\begin{array}{c} \text{---} \\ \text{---} \end{array} \text{---}(\text{CH}_2)_i\text{---R}^2$; $\begin{array}{c} \text{---} \\ \text{---} \end{array} \text{---}(\text{CH}_2)_i\text{---NH---R}^2$;
 $\begin{array}{c} \text{---} \\ \text{---} \end{array} \text{---}(\text{CH}_2)_i\text{---O---C(=O)---R}^2$; $\begin{array}{c} \text{---} \\ \text{---} \end{array} \text{---}(\text{CH}_2)_i\text{---O---C(=O)---O---R}^2$; $\begin{array}{c} \text{---} \\ \text{---} \end{array} \text{---}(\text{CH}_2)_i\text{---O---C(=O)---NH---R}^2$; $\begin{array}{c} \text{---} \\ \text{---} \end{array} \text{---}(\text{CH}_2)_i\text{---C(=O)---R}^2$;
 $\begin{array}{c} \text{---} \\ \text{---} \end{array} \text{---}(\text{CH}_2)_i\text{---C(=O)---O---R}^2$; $\begin{array}{c} \text{---} \\ \text{---} \end{array} \text{---}(\text{CH}_2)_i\text{---C(=O)---NH---R}^2$; $\begin{array}{c} \text{---} \\ \text{---} \end{array} \text{---}(\text{CH}_2)_i\text{---NH---C(=O)---R}^2$; $\begin{array}{c} \text{---} \\ \text{---} \end{array} \text{---}(\text{CH}_2)_i\text{---NH---C(=O)---(CH}_2)_j\text{---R}^2$;
 $\begin{array}{c} \text{---} \\ \text{---} \end{array} \text{---}(\text{CH}_2)_i\text{---NH---C(=O)---O---R}^2$; $\begin{array}{c} \text{---} \\ \text{---} \end{array} \text{---}(\text{CH}_2)_i\text{---NH---C(=O)---NH---R}^2$; $\begin{array}{c} \text{---} \\ \text{---} \end{array} \text{---C(=O)---(CH}_2)_i\text{---C(=O)---R}^2$; $\begin{array}{c} \text{---} \\ \text{---} \end{array} \text{---C(=O)---(CH}_2)_i\text{---C(=O)---O---R}^2$;
 and $\begin{array}{c} \text{---} \\ \text{---} \end{array} \text{---C(=O)---(CH}_2)_i\text{---C(=O)---NH---R}^2$; and combinations thereof; wherein each i is independently an integer of 0-10; j is an integer of 0-10; and R^2 is as defined herein. In some embodiments, each R^1 is a linking group.

[00214] In some embodiments, the functionalized multi-armed PEG has the structure of general formula (IVa), wherein R^1 and R^2 , when taken together, are $\begin{array}{c} \text{---} \\ \text{---} \end{array} \text{---}(\text{CH}_2)_i\text{---NH---C(=O)---(CH}_2)_j\text{---R}^2$, wherein i , j , and R^2 are as defined herein. In some embodiments, R^1 and R^2 , when taken together, are $\begin{array}{c} \text{---} \\ \text{---} \end{array} \text{---}(\text{CH}_2)_i\text{---NH---C(=O)---(CH}_2)_j\text{---R}^2$, wherein i is 2; j is 2 or 3, and R^2 is as defined herein.

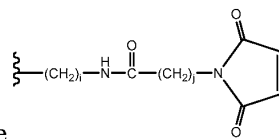
[00215] In some aspects, each R^2 is independently selected from the group consisting of a maleimide, a sulfhydryl, a thiol, trifluoromethanesulfonate, tosylate, aziridine, epoxide, a pyridyl disulfide, succinimidyl ester, ---NH_2 , an aldehyde, a haloacetate, a haloacetamide, and a para-nitrophenyl carbonate. In some embodiments, each R^2 is independently a haloacetate selected from the group consisting of bromoacetate, iodoacetate, chloroacetate, and combinations thereof. In some embodiments, each R^2 is independently a haloacetamide selected from the group consisting of bromoacetamide, iodoacetamide, chloroacetamide, and combinations thereof. In some embodiments, R^2 is a maleimide.

[00216] In some embodiments, the functionalized multi-armed PEG has the structure of general formula (IVa), wherein each R^2 is a maleimide. In some embodiments, the functionalized multi-armed PEG has the structure of general formula (IVa), wherein R^1 and R^2 ,



when taken together, are $\begin{array}{c} \text{---} \\ \text{---} \end{array} \text{---}(\text{CH}_2)_i\text{---NH---C(=O)---(CH}_2)_j\text{---}$, wherein i and j are as defined above. In some embodiments, the functionalized multi-armed PEG has the structure of general formula

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(IVa), wherein R^1 and R^2 , when taken together, are $-(CH_2)_i-$, wherein i is 3 and j is 2.

[00217] The multi-armed PEGs used to prepare the conjugates of the disclosure preferably will have a low polydispersity of PEG chain (arm) length. In particular, a high polydispersity of the multi-armed PEG used to prepare the conjugate may in some instances complicate the analysis of the final conjugate, in particular making an accurate determination of the number of antibodies (e.g., Fabs) per PEG more difficult and uncertain. Accordingly, the PEG used to form the conjugate will typically have a polydispersity (determined using methods known in the art) within a range of about 1 to about 1.35, and in various embodiments will have a polydispersity of about 1 to about 1.25, about 1 to about 1.2, about 1 to about 1.15, about 1 to about 1.1, about 1.05, or even about 1.

[00218] Other functionalized multi-armed PEGs suitable for use in the present disclosure are described in U.S. Pat. App. Publ. No. 2011/0286956, and U.S. Pat. App. Publ. No. 2015/0073155, both of which are herein incorporated by reference in their entirety.

[00219] Functionalized multi-armed PEGs suitable for use in the present disclosure can also be purchased from a number of vendors. For example, JenKem Technology, USA sells maleimide-functionalized PEG octamers (e.g., 8ARM (TP)-PEG-MAL and 8ARM (HG)-PEG-MAL) and tetramers. NOF America Corp. also sells maleimide functionalized PEG octamers (e.g., Sunbright® HGEO-400MA; Sunbright® DX-400MA) and tetramers (e.g., Sunbright® PTE-400MA). Such octamers and tetramers are available in a variety of molecular weights, including an average molecular weight of 40,000 D.

b. Conjugates

[00220] In some embodiments, the disclosure is directed to a conjugate comprising one or more anti-Factor D antibody or antibody variant disclosed herein and one or more multi-armed polyol, wherein the conjugate is prepared by covalently linking at least one anti-Factor D antibody or antibody variant to the polyol. In some embodiments, the multi-armed polyol is a PEG. In some embodiments, the PEG is an octamer. In some embodiments, the PEG has the structure of general formula (Ia), (Ib), (IIa), (IIIa), or (IVa).

[00221] The conjugates of the present disclosure may be characterized by the number of anti-Factor D antibodies or antibody variants conjugated to each multi-armed PEG. This is referred to herein as “fabylation” or “degree of fabylation”. The number of anti-Factor D

antibodies or antibody variants conjugated to each PEG may vary depending on a variety of factors, including: 1) the number of arms in the PEG; 2) the number and/or reactivity of the terminal reactive groups on the PEG; 3) the core structure of the PEG; and/or, 4) PEGylation reaction conditions.

[00222] In one preferred embodiment, the conjugate of the disclosure comprises an eight-armed PEG, wherein at least one anti-Factor D antibody or antibody variant is covalently linked to the PEG. In another embodiment, the conjugate of the disclosure comprises an eight-armed PEG, wherein at least two anti-Factor D antibodies or antibody variants are covalently linked to the PEG. In another embodiment, the conjugate of the disclosure comprises an eight-armed PEG, wherein at least three anti-Factor D antibodies or antibody variants are covalently linked to the PEG. In another embodiment, the conjugate of the disclosure comprises an eight-armed PEG, wherein at least four anti-Factor D antibodies or antibody variants are covalently linked to the PEG. In another embodiment, the conjugate of the disclosure comprises an eight-armed PEG, wherein at least five anti-Factor D antibodies or antibody variants are covalently linked to the PEG. In another embodiment, the conjugate of the disclosure comprises an eight-armed PEG, wherein at least six anti-Factor D antibodies or antibody variants are covalently linked to the PEG. In another embodiment, the conjugate comprises an eight-armed PEG, wherein at least seven anti-Factor D antibodies or antibody variants are covalently linked to the PEG. In another embodiment, the conjugate of the disclosure comprises an eight-armed PEG, wherein eight anti-Factor D antibodies or antibody variants are covalently linked to the PEG. In some embodiments, the conjugate of the disclosure comprises an eight-armed PEG, wherein from 5-8 anti-Factor D antibodies or antibody variants are covalently linked to the PEG. In another embodiment, the conjugate of the disclosure comprises an eight-armed PEG, wherein from 6-8 anti-Factor D antibodies or antibody variants are covalently linked to the PEG. In another embodiment, the conjugate of the disclosure comprises an eight-armed PEG, wherein from 7-8 anti-Factor D antibodies or antibody variants are covalently linked to the PEG.

[00223] In some embodiments, the conjugate of the disclosure comprises a multi-armed PEG having the structure of any one of general formulas (Ia), (Ib), (IIa), (IIIa), or (IVa). In such embodiments, at least one R^2 is covalently linked to an anti-Factor D antibody or antibody variant described herein. In some embodiments, the multi-armed PEG having the structure of any one of general formulas (Ia), (Ib), (IIa), (IIIa), or (IVa) is an octamer, and at least two, at least three, at least four, at least five, at least six, at least seven, or all eight R^2 groups are covalently linked to an anti-Factor D antibody or antibody variant described herein.

[00224] In some aspects, the conjugates of the present disclosure include species wherein the multi-armed polyol is covalently attached to a specific site or specific sites on the parental antibody; i.e., polymer attachment is targeted to a particular region or a particular amino acid residue or residues in the parental antibody or antibody fragments. Standard mutagenesis techniques can be used to alter the number and/or location of potential PEGylation sites in the parental antibody or antibody fragments. Thus, to the extent that amino acid substitutions introduce or replace amino acids such as cysteine and lysine, the anti-Factor D antibodies and variants thereof of the present disclosure can contain a greater or lesser number of potential PEGylation sites than a native sequence anti-Factor D (shown in Figure 1).

[00225] As discussed above, site specific conjugation of polymers is most commonly achieved by attachment to cysteine residues in the parental antibody or antibody fragment. In such embodiments, the coupling chemistry can, for example, utilize the free sulfhydryl group of a cysteine residue not in a disulfide bridge in the parental antibody.

[00226] In some embodiments, one or more cysteine residue(s) naturally present in the parental antibody is (are) used as attachment site(s) for polymer conjugation. In other embodiments, free amino groups on the antibody or antibody variant can be thiolated with 2-imino-thiolane (Traut's reagent) and then coupled to, e.g., a maleimide-functionalized PEG, as described in Pedley, et al., *Br. J. Cancer*, Vol. 70, pp. 1126-1130 (1994). In another embodiment, one or more cysteine residue(s) is (are) engineered into a selected site or sites in the parental antibody for the purpose of providing a specific attachment site or sites for polymer.

[00227] Cysteine engineered antibodies have been described previously (U.S. Pat. Pub. No. 2007/0092940 and Junutula, J. R., et al, *J. Immunol Methods*, Vol. 332(1-2), pp. 41-52 (2008), all herein incorporated by reference in their entirety). In some embodiments, cysteine engineered antibodies can be parental antibodies. These are useful for generating antibody fragments having a free cysteine in a particular location, typically in a constant domain, e.g., C_L or C_{H1}. A parent antibody engineered to contain a cysteine is referred to herein as a "ThioMab" and Fab fragments produced from such cysteine engineered antibodies, regardless of the method of production, are referred to herein as "ThioFabs." As described previously (*see, e.g.*, U.S. Pat. Pub. No. 2007/0092940 and Junutula, J. R., et al, *J. Immunol Methods*, Vol. 332(1-2), pp. 41-52 (2008)), mutants with replaced ("engineered") cysteine (Cys) residues are evaluated for the reactivity of the newly introduced, engineered cysteine thiol groups. The thiol reactivity value is a relative, numerical term in the range of 0 to 1.0 and can be measured for any cysteine engineered antibody. In addition to having a reactive thiol group, ThioMabs should be selected such that they retain antigen binding capability. The design, selection, and preparation of

cysteine engineered antibodies were described in detail previously (*see, e.g.*, WO 2011/069104, which is herein incorporated by reference). In some embodiments, engineered cysteines are introduced into the constant domains of heavy or light chains. As such, the cysteine engineered antibodies retain the antigen binding capability of their wild type, parent antibody counterparts and, as such, are capable of binding specifically, to antigens.

[00228] In some aspects, the present disclosure relates to antibody fragment-polymer conjugates, wherein the antibody fragment is a Fab, and the polymer is attached to one or more cysteine residue in the light or heavy chain of the Fab fragment that would ordinarily form the inter-chain disulfide bond linking the light and heavy chains.

[00229] In another aspect, the present disclosure relates to antibody fragment-polymer conjugates, wherein the antibody fragment is a Fab-C, and the polymer attachment is targeted to the hinge region of the Fab-C fragment. In some embodiments, one or more cysteine residue(s) naturally present in the hinge region of the antibody fragment is (are) used to attach the polymer. In another embodiment, one or more cysteine residues is (are) engineered into the hinge region of the Fab-C fragment for the purpose of providing a specific attachment site or sites for polymer. In some embodiments, an anti-Factor D antibody variant Fab fragment disclosed herein is modified by adding one cysteine at the C'-terminal end for the purpose of providing one attachment site for polymer conjugation. In another embodiment, an anti-Factor D antibody variant Fab fragment described herein is modified by adding four additional residues, Cys-Pro-Pro-Cys (SEQ ID NO: 21), at the C'-terminal end for the purpose of providing two attachment sites for polymer conjugation. In still another embodiment, an anti-Factor D antibody variant Fab fragment described herein is modified by adding four additional residues, Ser-Pro-Pro-Cys (SEQ ID NO: 111), at the C'-terminal end for the purpose of providing one attachment site for polymer conjugation. In still another embodiment, an anti-Factor D antibody variant Fab fragment described herein is modified by adding four additional residues, Cys-Pro-Pro-Ser (SEQ ID NO: 112), at the C'-terminal end for the purpose of providing one attachment site for polymer conjugation. In still another embodiment, an anti-Factor D antibody variant Fab fragment described herein is modified by adding four additional residues, Ala-Pro-Pro-Cys (SEQ ID NO: 113), at the C'-terminal end for the purpose of providing one attachment site for polymer conjugation. In still another embodiment, an anti-Factor D antibody variant Fab fragment described herein is modified by adding four additional residues, Ser-Gly-Gly-Cys (SEQ ID NO: 114), at the C'-terminal end for the purpose of providing one attachment site for polymer conjugation. In still another embodiment, an anti-Factor D antibody variant Fab

fragment described herein has a C'-terminal end that has been modified to end in "CYGPPC", providing one attachment site for polymer conjugation.

[00230] The degree and sites of PEGylation can also be manipulated by adjusting reaction conditions, such as the relative concentrations of the functionalized PEG and the protein as well as the pH. Suitable conditions for a desired degree of PEGylation can be determined empirically by varying the parameters of standard PEGylation reactions.

[00231] PEGylation of anti-Factor D antibodies and antibody variants is carried out by any convenient method. Suitable PEGylation conditions are set forth in WO 2011/069104 and WO 03/029420, both of which are herein incorporated by reference in their entirety.

c. Characterization and Activity

[00232] The PEGylated proteins can be characterized by SDS-PAGE, gel filtration, NMR, peptide mapping, liquid chromatography-mass spectrophotometry, and *in vitro* biological assays. The extent of fabylation is typically first shown by SDS-PAGE. Polyacrylamide gel electrophoresis in 10% SDS is typically run in 10 mM Tris-HCl pH 8.0, 100 mM NaCl as elution buffer. To demonstrate which residue is PEGylated, peptide mapping using proteases such as trypsin and Lys-C protease can be performed. Thus, samples of PEGylated and non-PEGylated antibodies can be digested with a protease such as Lys-C protease and the resulting peptides separated by a technique such as reverse phase HPLC. The chromatographic pattern of peptides produced can be compared to a peptide map previously determined for the anti-Factor D polypeptide.

[00233] Each peak can then be analyzed by mass spectrometry to verify the size of the conjugate in the peak. Depending on the PEG used in the conjugation, and the size of the conjugate in the peak, the number of antibodies or variants thereof conjugated to the PEG can be estimated. The fragment(s) that conjugated to PEG groups are usually not retained on the HPLC column after injection and disappear from the chromatograph. Such disappearance from the chromatograph is an indication of PEGylation on that particular fragment that should contain at least one PEGylatable amino acid residue. PEGylated anti-Factor D antibodies and antibody variants may further be assayed for ability to interact with Factor D and other biological activities using known methods in the art.

[00234] PEGylation changes the physical and chemical properties of the antibody drug, and may results in improved pharmacokinetic behaviors, including but not limited to: improved stability; decreased immunogenicity; increased hydrodynamic radius (RH); and/or extended circulating life, as well as increased ocular residence time.

[00235] In some embodiments, the conjugates of the present disclosure have an increased half-life after administration into a mammalian eye (e.g. human) via a single intravitreal injection, as compared to the corresponding unconjugated anti-Factor D antibody or antibody variant. In some embodiments, the increase in half-life is at least 1.4 times, or at least 1.5 times, or at least 1.8 times, or at least 2 times the half-life of the corresponding unconjugated anti-Factor D antibody or antibody variant.

[00236] In some embodiments, the conjugates of the present disclosure may have a hydrodynamic radius (RH), as determined using methods known in the art, of from about 3 nm to about 30 nm or more, or alternatively from about 5 nm to about 25 nm, and in some embodiments may be about 5 nm, about 10 nm, about 15 nm, about 20 nm, about 25 nm, or more.

[00237] In some embodiments, the conjugates of the present disclosure may exhibit a stability, characterized by the %loss of binding capacity (e.g., fD-binding capacity) per month measured using methods known in the art (e.g., when exposed to physiological conditions), of about 15%, about 12%, about 10%, about 8%, or even less.

[00238] In some embodiments, the conjugates of the present disclosure may exhibit an IC₅₀ potency value, as determined using a time-resolved fluorescence energy transfer (TR-FRET) assay of Factor D-dependent Factor B activation, as detailed in the examples. In some embodiments, the conjugates inhibit Factor D-dependent Factor B activation with IC₅₀ values of from about 25 pM to about 10 nM, or from about 25 pM to about 5 nM, or from about 25 pM to about 1 nM, or from about 25 pM to about 750 pM, or from about 25 pM to about 500 pM.

[00239] In some embodiments, the conjugate has a viscosity that makes it suitable for administration through a narrow bore needle. In some embodiments, the viscosity of the conjugate is less than 800 cP, less than 700 cP, less than 600 cP, less than 500 cP, less than 400 cP, less than 300 cP, less than 200 cP, less than 100 cP, less than 50 cP, or less than 30 cP at a concentration of 150-250 mg/ml. In some embodiments, the viscosity of the conjugate is less than 300 cP at a concentration of 200 mg/ml.

Pharmaceutical Formulations

[00240] Therapeutic formulations of the conjugates of the present disclosure thereof may be prepared for storage as lyophilized formulations or aqueous solutions by mixing the conjugate having the desired degree of purity with optional "pharmaceutically-acceptable" carriers, excipients or stabilizers typically employed in the art (all of which are termed "excipients"). For example, buffering agents, stabilizing agents, preservatives, isotonicifiers, non-

ionic detergents, antioxidants and other miscellaneous additives. (See Remington's Pharmaceutical Sciences, 16th edition, A. Osol, Ed. (1980)). Such additives must be nontoxic to the recipients at the dosages and concentrations employed.

[00241] Buffering agents help to maintain the pH in the range which approximates physiological conditions. They are preferably present at concentration ranging from about 2 mM to about 50 mM. Suitable buffering agents for use with the present disclosure include both organic and inorganic acids and salts thereof such as citrate buffers (e.g., monosodium citrate-disodium citrate mixture, citric acid-trisodium citrate mixture, citric acid-monosodium citrate mixture, etc.), succinate buffers (e.g., succinic acid-monosodium succinate mixture, succinic acid-sodium hydroxide mixture, succinic acid-disodium succinate mixture, etc.), tartrate buffers (e.g., tartaric acid-sodium tartrate mixture, tartaric acid-potassium tartrate mixture, tartaric acid-sodium hydroxide mixture, etc.), fumarate buffers (e.g., fumaric acid-monosodium fumarate mixture, etc.), fumarate buffers (e.g., fumaric acid-monosodium fumarate mixture, fumaric acid-disodium fumarate mixture, monosodium fumarate-disodium fumarate mixture, etc.), gluconate buffers (e.g., gluconic acid-sodium glyconate mixture, gluconic acid-sodium hydroxide mixture, gluconic acid-potassium glyconate mixture, etc.), oxalate buffer (e.g., oxalic acid-sodium oxalate mixture, oxalic acid-sodium hydroxide mixture, oxalic acid-potassium oxalate mixture, etc.), lactate buffers (e.g., lactic acid-sodium lactate mixture, lactic acid-sodium hydroxide mixture, lactic acid-potassium lactate mixture, etc.) and acetate buffers (e.g., acetic acid-sodium acetate mixture, acetic acid-sodium hydroxide mixture, etc.). Additionally, there may be mentioned phosphate buffers, histidine buffers and trimethylamine salts such as Tris.

[00242] Preservatives may be added to retard microbial growth, and may be added in amounts ranging from 0.2%-1% (w/v). Suitable preservatives for use with the present disclosure include phenol, benzyl alcohol, meta-cresol, methyl paraben, propyl paraben, octadecyldimethylbenzyl ammonium chloride, benzalconium halides (e.g., chloride, bromide, iodide), hexamethonium chloride, alkyl parabens such as methyl or propyl paraben, catechol, resorcinol, cyclohexanol, and 3-pentanol.

[00243] Isotonicifiers sometimes known as "stabilizers" may be added to ensure isotonicity of liquid compositions of the present disclosure and include polyhydric sugar alcohols, preferably trihydric or higher sugar alcohols, such as glycerin, erythritol, arabitol, xylitol, sorbitol and mannitol.

[00244] Stabilizers refer to a broad category of excipients which can range in function from a bulking agent to an additive which solubilizes the therapeutic agent or helps to prevent denaturation or adherence to the container wall. Typical stabilizers can be polyhydric sugar

alcohols (enumerated above); amino acids such as arginine, lysine, glycine, glutamine, asparagine, histidine, alanine, ornithine, L-leucine, 2-phenylalanine, glutamic acid, threonine, etc., organic sugars or sugar alcohols, such as lactose, trehalose, stachyose, mannitol, sorbitol, xylitol, ribitol, myoinositol, galactitol, glycerol and the like, including cyclitols such as inositol; polyethylene glycol; amino acid polymers; sulfur containing reducing agents, such as urea, glutathione, thiocetic acid, sodium thioglycolate, thioglycerol, .alpha.-monothioglycerol and sodium thio sulfate; low molecular weight polypeptides (i.e., <10 residues); proteins such as human serum albumin, bovine serum albumin, gelatin or immunoglobulins; hydrophylic polymers, such as polyvinylpyrrolidone monosaccharides, such as xylose, mannose, fructose, glucose; disaccharides such as lactose, maltose, sucrose and trisaccharides such as raffinose; polysaccharides such as dextran. Stabilizers may be present in the range from 0.1 to 10,000 weights per part of weight active protein.

[00245] Non-ionic surfactants or detergents (also known as "wetting agents") may be added to help solubilize the therapeutic agent as well as to protect the therapeutic protein against agitation-induced aggregation, which also permits the formulation to be exposed to shear surface stressed without causing denaturation of the protein. Suitable non-ionic surfactants include polysorbates (20, 80, etc.), polyoxamers (184, 188 etc.), Pluronic® polyols, polyoxyethylene sorbitan monoethers (Tween®-20, Tween®-80, etc.). Non-ionic surfactants may be present in a range of about 0.05 mg/ml to about 1.0 mg/ml, preferably about 0.07 mg/ml to about 0.2 mg/ml.

[00246] Additional miscellaneous excipients include bulking agents, (e.g. starch), chelating agents (e.g. EDTA), antioxidants (e.g., ascorbic acid, methionine, vitamin E), and cosolvents. The formulation herein may also contain more than one active ingredient as necessary for the particular indication being treated. In some embodiments, the active ingredients have complementary activities that do not adversely affect each other. For example, it may be desirable to further provide an immunosuppressive agent. Such molecules are suitably present in combination in amounts that are effective for the purpose intended. The active ingredients may also be entrapped in microcapsule prepared, for example, by coacervation techniques or by interfacial polymerization, for example, hydroxymethylcellulose or gelatin-microcapsule and poly-(methylmethacrylate) microcapsule, respectively, in colloidal drug delivery systems (for example, liposomes, albumin microspheres, microemulsions, nano-particles and nanocapsules) or in macroemulsions. Such techniques are disclosed in Remington's Pharmaceutical Sciences, 16th edition, A. Osal, Ed. (1980).

[00247] The formulations to be used for *in vivo* administration must be sterile. This is readily accomplished, for example, by filtration through sterile filtration membranes. Sustained-

release preparations may be prepared. Suitable examples of sustained-release preparations include semi-permeable matrices of solid hydrophobic polymers containing the antibody, or antibody variant or fragment (e.g. antigen-binding fragment) thereof, which matrices are in the form of shaped articles, e.g., films, or microcapsules. Examples of sustained-release matrices include polyesters, hydrogels (for example, poly(2-hydroxyethyl-methacrylate), or poly(vinylalcohol)), polylactides (U.S. Pat. No. 3,773,919), copolymers of L-glutamic acid and ethyl-L-glutamate, non-degradable ethylene-vinyl acetate, degradable lactic acid-glycolic acid copolymers such as the LUPRON DEPOT™ (injectable microspheres composed of lactic acid-glycolic acid copolymer and leuprolide acetate), and poly-D- (-)-3-hydroxybutyric acid. While polymers such as ethylene-vinyl acetate and lactic acid-glycolic acid enable release of molecules for over 100 days, certain hydrogels release proteins for shorter time periods. When encapsulated antibodies remain in the body for a long time, they may denature or aggregate as a result of exposure to moisture at 37° C resulting in a loss of biological activity and possible changes in immunogenicity. Rational strategies can be devised for stabilization depending on the mechanism involved. For example, if the aggregation mechanism is discovered to be intermolecular S--S bond formation through thio-disulfide interchange, stabilization may be achieved by modifying sulfhydryl residues, lyophilizing from acidic solutions, controlling moisture content, using appropriate additives, and developing specific polymer matrix compositions.

[00248] The conjugates of the disclosure for prevention or treatment of an ocular disease or condition are typically administered by ocular, intraocular, and/or intravitreal injection, and/or juxtasceral injection, and/or subtenon injection, and/or superchoroidal injection and/or topical administration in the form of eye drops and/or ointment. Such conjugates of the disclosure may be delivered by a variety of methods, e.g. intravitreally as a device and/or a depot that allows for slow release of the compound into the vitreous, including those described in references such as *Intraocular Drug Delivery*, Jaffe, Jaffe, Ashton, and Pearson, editors, Taylor & Francis (March 2006). In one example, a device may be in the form of a min pump and/or a matrix and/or a passive diffusion system and/or encapsulated cells that release the compound for a prolonged period of time (*Intraocular Drug Delivery*, Jaffe, Jaffe, Ashton, and Pearson, editors, Taylor & Francis (March 2006)). Other methods of administration may also be used, which includes but is not limited to, topical, parenteral, subcutaneous, intraperitoneal, intrapulmonary, intranasal, and intralesional administration. Parenteral infusions include intramuscular, intravenous, intraarterial, intraperitoneal, or subcutaneous administration.

[00249] Formulations for ocular, intraocular or intravitreal administration can be prepared by methods and using ingredients known in the art. A main requirement for efficient treatment is proper penetration through the eye. Unlike diseases of the front of the eye, where drugs can be delivered topically, retinal diseases require a more site-specific approach. Eye drops and ointments rarely penetrate the back of the eye, and the blood-ocular barrier hinders penetration of systemically administered drugs into ocular tissue. Accordingly, usually the method of choice for drug delivery to treat retinal disease, such as AMD and CNV, is direct intravitreal injection. Intravitreal injections are usually repeated at intervals which depend on the patient's condition, and the properties and half-life of the drug delivered. For intraocular (e.g. intravitreal) penetration, usually molecules of smaller size are preferred. In one embodiment, administration is intravitreal using a narrow bore needle. In one embodiment, the narrow bore needle is 30, 29, 28, 27, 26, 25, 24, 23, or 22 gauge.

[00250] The efficacy of the treatment of complement-associated eye conditions, such as AMD or CNV, can be measured by various endpoints commonly used in evaluating intraocular diseases. For example, vision loss can be assessed. Vision loss can be evaluated by, but not limited to, e.g., measuring by the mean change in best correction visual acuity (BCVA) from baseline to a desired time point (e.g., where the BCVA is based on Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity chart and assessment at a test distance of 4 meters), measuring the proportion of subjects who lose fewer than 15 letters in visual acuity at a desired time point compared to baseline, measuring the proportion of subjects who gain greater than or equal to 15 letters in visual acuity at a desired time point compared to baseline, measuring the proportion of subjects with a visual-acuity Snellen equivalent of 20/2000 or worse at a desired time point, measuring the NEI Visual Functioning Questionnaire, measuring the size of CNV and amount of leakage of CNV at a desired time point, e.g., by fluorescein angiography, etc. Ocular assessments can be done, e.g., which include, but are not limited to, e.g., performing eye exam, measuring intraocular pressure, assessing visual acuity, measuring slitlamp pressure, assessing intraocular inflammation, etc.

[00251] The amount of antibody or antibody variant thereof which will be effective in the treatment of a particular disorder or condition will depend on the nature of the disorder or condition, and can be determined by standard clinical techniques. Where possible, it is desirable to determine the dose-response curve and the pharmaceutical compositions of the disclosure first *in vitro*, and then in useful animal model systems prior to testing in humans.

[00252] In some embodiments, the antibodies and conjugates described herein may be formulated to provide a concentration of antibody in the formulations of at least 50 mg/mL, at

least 75 mg/mL, at least 100 mg/mL, at least 125 mg/mL, at least 150 mg/mL, at least 175 mg/mL, at least 200 mg/mL, at least 225 mg/mL, at least 250 mg/mL, at least 275 mg/mL, at least 300 mg/mL, at least 325 mg/mL, at least 350 mg/mL, at least 375 mg/mL, at least 400 mg/mL, at least 425 mg/mL, at least 450 mg/mL, at least 475 mg/mL, or at least 500 mg/mL. In some embodiments, the antibody in the formulation is in an amount of at least 100 mg/mL. In some embodiments, the antibody in the formulation is in an amount of at least 200 mg/mL. In some embodiments, the antibody in the formulation is in an amount of at least 300 mg/mL. In some embodiments, the antibodies and conjugates described herein may be formulated to provide a concentration of antibody in the formulations of from about 50 mg/mL to about 500 mg/mL, about 50 mg/mL to about 300 mg/mL, about 100 mg/mL to about 500 mg/mL, about 100 mg/mL to about 300 mg/mL, about 200 mg/mL to about 500 mg/mL, about 200 mg/mL to about 400 mg/mL, about 200 mg/mL to about 300 mg/mL, or about 250 mg/mL to about 375 mg/mL.

[00253] In some embodiments, an aqueous solution of conjugate comprising therapeutic polypeptide, antibody, or antibody variant thereof, or fragment thereof (e.g. antigen-binding fragment), is administered by subcutaneous injection. In another embodiment, an aqueous solution of conjugate comprising therapeutic polypeptide, antibody, or antibody variant thereof, or fragment thereof (e.g. antigen-binding fragment) is administered by intravitreal injection. Each dose may range from about 0.3 mg to about 30 mg per eye.

[00254] The dosing schedule for subcutaneous administration may vary from once a month to daily depending on a number of clinical factors, including the type of disease, severity of disease, and the subject's sensitivity to the therapeutic agent.

Articles of Manufacture and Kits

[00255] Another embodiment of the disclosure is an article of manufacture containing materials useful for the treatment, prevention and/or diagnosis of conditions targeted by the antibodies of the disclosure, or variants thereof or fragments thereof (e.g. antigen-binding fragments). For example, the disclosure concerns an article of manufacture containing materials useful for the treatment, prevention and/or diagnosis of complement-associated disorders. The article of manufacture comprises a container and a label or package insert on or associated with the container. Suitable containers include, for example, bottles, vials, syringes, etc. The containers may be formed from a variety of materials such as glass or plastic. The container holds a composition which is effective for treating, preventing and/or diagnosis of the complement-associated condition and may have a sterile access port (for example the container

may be an intravenous solution bag or a vial having a stopper pierceable by a hypodermic injection needle). At least one active agent in the composition is an anti-Factor D antibody conjugate of the disclosure. The label or package insert indicates that the composition is useful for treatment, prevention and/or diagnosis of a particular condition.

[00256] Package insert refers to instructions customarily included in commercial packages of therapeutic products that contain information about the indications, usage, dosage, administration, contraindications and/or warnings concerning the use of such therapeutic products. In some embodiments, the label or package insert indicates that the composition is used for treating complement-associated disorders, such as, for example, any of the conditions listed before, including eye disorders, e.g. age-related macular degeneration (AMD). The label or package insert will further comprise instructions for administering the antibody composition to the patient.

[00257] Additionally, the article of manufacture may further comprise a second container comprising a pharmaceutically-acceptable buffer, such as bacteriostatic water for injection (BWFI), phosphate-buffered saline, Ringer's solution and dextrose solution. It may further include other materials desirable from a commercial and user standpoint, including other buffers, diluents, filters, needles, and syringes.

[00258] In another embodiment, kits are also provided that are useful for various purposes, e.g., for treatment, prevention and/or diagnosis of complement-associated disorders, for complement-associated hemolysis assays, for purification or immunoprecipitation of Factor D polypeptide from cells. For isolation and purification of Factor D polypeptide, the kit can contain an anti-Factor D antibody coupled to beads (e.g., sepharose beads). Kits can be provided which contain the antibodies for detection and quantitation of Factor D polypeptide *in vitro*, e.g., in an ELISA or a Western blot. As with the article of manufacture, the kit comprises a container and a label or package insert on or associated with the container. The container holds a composition comprising a conjugate of the disclosure comprising at least one anti-Factor antibody. Additional containers may be included that contain, e.g., diluents and buffers, control antibodies. The label or package insert may provide a description of the composition as well as instructions for the intended *in vitro* or detection use. The label or package insert may provide instructions for the administration (e.g. the antibody, or antibody fragment thereof (e.g. antigen-binding fragment) to a subject.

Therapeutic Uses

[00259] The conjugates of the present disclosure may be used to treat a mammal. In some embodiments, the conjugate is administered to a nonhuman mammal for the purposes of obtaining preclinical data, for example. Exemplary nonhuman mammals to be treated include nonhuman primates, dogs, cats, rodents and other mammals in which preclinical studies are performed. Such mammals may be established animal models for a disease to be treated with the antibody, or may be used to study toxicity of the antibody of interest. In each of these embodiments, dose escalation studies may be performed on the mammal.

[00260] The conjugate is administered by any suitable means, including parenteral, subcutaneous, intraperitoneal, intrapulmonary, and intranasal, and, if desired for local immunosuppressive treatment, intralesional administration. Parenteral infusions include intramuscular, intravenous, intraarterial, intraperitoneal, or subcutaneous administration. In addition, the conjugate is suitably administered by pulse infusion, particularly with declining doses of the antibody, or antibody variant thereof or fragment thereof (e.g. antigen-binding fragment). In some embodiments, the dosing is given by injections, such as intravenous or subcutaneous injections, depending in part on whether the administration is brief or chronic. In one embodiment, administration is intravitreal using a narrow bore needle. In one embodiment, the narrow bore needle is 30, 29, 28, 27, 26, 25, 24, 23, or 22 gauge. In one embodiment, the dosing is administered using an implantable port delivery system.

[00261] For the prevention or treatment of disease, the appropriate dosage of the conjugate will depend on the type of disease to be treated, the severity and course of the disease, whether the antibody is administered for preventive or therapeutic purposes, previous therapy, the patient's clinical history and response to the antibody and the discretion of the attending physician.

[00262] Depending on the type and severity of the disease, a sufficient amount of conjugate may be administered to provide from about 1 to about 25 mg/eye (i.e., from about 0.015 mg/kg to about 0.36 mg/kg, assuming one eye is treated) of the antibody to the patient, whether, for example, by one or more separate administrations, or by continuous infusion. A typical daily dosage of the conjugate might be sufficient to provide the antibody in a range from about 1 to about 20 mg/eye or more, or from about 1 to about 15 mg/eye or more, depending on the factors mentioned above. For repeated administrations over several days or longer, depending on the condition, the treatment is sustained until a desired suppression of disease symptoms occurs. However, other dosage regimens may be useful. The progress of this therapy

is easily monitored by conventional techniques and assays. An exemplary dosing regimen is disclosed in WO 94/04188.

[00263] The conjugate compositions may be formulated, dosed and administered in a manner consistent with good medical practice. Factors for consideration in this context include the particular disorder being treated, the particular mammal being treated, the clinical condition of the individual patient, the cause of the disorder, the site of delivery of the agent, the method of administration, the scheduling of administration, and other factors known to medical practitioners. The "therapeutically effective amount" of the conjugate to be administered will be governed by such considerations, and is the minimum amount necessary to prevent, ameliorate, or treat a disease or disorder. The conjugate need not be, but is optionally formulated with one or more agents currently used to prevent or treat the disorder in question. The effective amount of such other agents depends on the amount of antibody, or antibody variant thereof or fragment thereof (e.g. antigen-binding fragment), present in the formulation, the type of disorder or treatment, and other factors discussed above. These are generally used in the same dosages and with administration routes as used hereinbefore or about from 1 to 99% of the heretofore employed dosages.

[00264] The antibodies disclosed herein which recognize Factor D as their target and the conjugates comprising these antibodies may be used to treat complement-mediated (complement-associated) disorders in a subject. These disorders are associated with excessive or uncontrolled complement activation. They include: complement activation during cardiopulmonary bypass operations; complement activation due to ischemia-reperfusion following acute myocardial infarction, aneurysm, stroke, hemorrhagic shock, crush injury, multiple organ failure, hypobolemic shock and intestinal ischemia. These disorders can also include disease or condition is an inflammatory condition such as severe burns, endotoxemia, septic shock, adult respiratory distress syndrome, hemodialysis, anaphylactic shock, severe asthma, angioedema, Crohn's disease, sickle cell anemia, poststreptococcal glomerulonephritis and pancreatitis. The disorder may be the result of an adverse drug reaction, drug allergy, IL-2 induced vascular leakage syndrome or radiographic contrast media allergy. The disorder may be systemic. It may also include autoimmune disease such as systemic lupus erythematosus, myasthenia gravis, rheumatoid arthritis, Alzheimer's disease and multiple sclerosis. Complement activation is also associated with transplant rejection. Recently there has been a strong correlation shown between complement activation and ocular diseases such as age-related macular degeneration, diabetic retinopathy and other ischemia-related retinopathies, choroidal neovascularization (CNV), uveitis, diabetic macular edema, pathological myopia, von Hippel-

Lindau disease, histoplasmosis of the eye, Central Retinal Vein Occlusion (CRVO), corneal neovascularization, and retinal neovascularization. In one embodiment, the complement-associated disorder is a complement-associated eye condition. In one embodiment, the complement-associated eye condition is selected from the group consisting of age-related macular degeneration (AMD), including dry and wet (non-exudative and exudative) forms, choroidal neovascularization (CNV), uveitis, diabetic retinopathy, ischemia-related retinopathy, diabetic macular edema, pathological myopia, von Hippel-Lindau disease, histoplasmosis of the eye, Central Retinal Vein Occlusion (CRVO), corneal neovascularization, and retinal neovascularization. In one embodiment, the complement-associated eye condition is selected from intermediate dry form AMD or geographic atrophy (GA).

[00265] A conjugate comprising Factor D antagonist can be administered alone or in combination with at least a second therapeutic compound. Administration of the conjugate and any second therapeutic compound can be done simultaneously, e.g., as a single composition or as two or more distinct compositions using the same or different administration routes. Alternatively, or additionally the administration can be done sequentially, in any order. In certain embodiments, intervals ranging from minutes to days, to weeks to months, can be present between the administrations of the two or more compositions. For example, the conjugate comprising the Factor D antagonist may be administered first, followed by the second therapeutic compound. However, simultaneous administration or administration of the second therapeutic compound prior to the conjugate is also contemplated. In one example, the Factor D antagonist is an anti-Factor D antibody. In a further example, the anti-Factor D antibody is an anti-Factor D antibody variant described herein. In some embodiments, the second therapeutic compound is selected from an HTRA1 antagonist, an ANG2 antagonist (such as anti-ANG2 antibodies as disclosed, for example, in US20090304694 A1), a TIE2 antagonist (such as anti-TIE2 antibodies as disclosed, for example, in US Patent No. 6,376,653), a VEGF antagonist (such as VEGF antagonists as disclosed, for example, in US Patent No. 6,884,879 issued Feb. 26, 2015 and WO98/45331 (bevacizumab and other humanized anti-VEGF antibodies); WO2005/012359 and WO2005/044853 (G6 or B20 series antibodies (e.g. G6-31, B20-4.1), and a second complement component antagonist. In one example, the second therapeutic compound is a HTRA1 antagonist, an ANG2 antagonist, a TIE2 antagonist, or a VEGF antagonist. In a further example, the HTRA1 antagonist is an anti-HTRA1 antibody. In another embodiment, the ANG2 antagonist is an anti-ANG2 antibody. In another embodiment, the TIE2 antagonist is an anti-TIE2 antibody. In some embodiments, the VEGF antagonist is selected from a VEGF

trap (such as aflibercept (Eylea®) and an anti-VEGF antibody (such as bevacizumab (Avastin®) or ranabizumab (Lucentis®)).

[00266] Other therapeutic agents suitable for combined administration with the conjugates comprising an anti-Factor D antibody as disclosed herein are antagonists of various members of the classical or alternative complement pathway (complement inhibitors). Thus, the conjugates disclosed herein may be administered in combination with antagonists of one or more of the C1, C2, C3, C4, C5, C6, C7, C8, and C9 complement components. In some embodiments, the conjugates comprising anti-Factor D disclosed herein are combined with antagonists of the C2 and/or C4 and/or C5 complement components, such as anti-C2 and/or anti-C4 and/or anti-C5 antibodies. Such antibodies are known in the art and/or are commercially available. An anti-C5 antibody eculizumab (Alexion, Cheshire, CT, USA), has been approved for the treatment of Paroxysmal nocturnal hemoglobinuria (PNH) and atypical hemolytic uremic syndrome (aHUS). Other complement inhibitors are disclosed, for example, in US Publication No. 20050036991 A1. Thus, the conjugates comprising anti-Factor D antibody as disclosed herein may be administered in combination with an effective amount of one or more complement inhibitors, including, without limitation, anti-C2 and anti-C5 antibodies, optionally in combination with at least one additional Factor D antagonist/antibody.

[00267] In some embodiments, the treatment of the present disclosure for complement-mediated disorders in a human subject with a complement-mediated disorder comprises administering to the subject an effective amount of a therapeutic compound, such as a Factor D antagonist or a conjugate comprising the Factor D antagonist, and further comprising administering to the subject an effective amount of a second therapeutic compound, that is a HTRA1 antagonist, an ANG2 antagonist, a TIE2 antagonist, a VEGF antagonist, and/or an antagonist of one or more of the C1, C2, C3, C4, C5, C6, C7, C8, and C9 complement components. In one example, the Factor D antagonist is an anti-Factor D antibody, and the conjugate comprises one or more anti-factor D antibody. In a further example, the anti-Factor D antibody is an anti-Factor D antibody variant described herein, and the conjugate comprises one or more anti-Factor D antibody variant. In one example, the HTRA antagonist is an anti-HTRA1 antibody. In another example, the ANG2 antagonist is an anti-ANG2 antibody. In another example, the TIE2 antagonist is an anti-TIE2 antibody. In another example, the VEGF antagonist is an anti-VEGF antibody. In another embodiment, the antagonist of the C2 and/or C4 and/or C5 complement components is as anti-C2 and/or anti-C4 and/or anti-C5 antibody. In one example, the complement-mediated disorder is a complement-associated eye condition. In one example, the ocular disorder is age-related macular degeneration (AMD), including non-

exudative (e.g. intermediate dry AMD or geographic atrophy (GA)) and exudative (e.g. wet AMD (choroidal neovascularization (CNV)) AMD, diabetic retinopathy (DR), endophthalmitis and uveitis. In one example, the complement-associated eye condition is intermediate dry AMD. In one example, the complement-associated eye condition is geographic atrophy. In one example, the complement-associated eye condition is wet AMD (choroidal neovascularization (CNV)).

[00268] Combined administration herein includes co-administration, using separate formulations or a single pharmaceutical formulation, and consecutive administration in either order, wherein generally there is a time period while both (or all) active agents simultaneously exert their biological activities.

EXAMPLES

[00269] The following examples are offered by way of illustration and not by way of limitation. Commercially available reagents referred to in the examples were used according to manufacturer's instructions unless otherwise indicated. The source of those cells identified in the following examples, and throughout the specification, by ATCC accession numbers is the American Type Culture Collection, 10801 University Boulevard, Manassas, VA 20110-2209.

Example 1: Generation of Anti-Factor D Antibody Variants

[00270] Lampalizumab, a humanized anti-Factor D Fab fragment that potently inhibits Factor D and the alternative complement pathway, through binding to an exosite on factor D is currently in clinical development for the treatment of geographic atrophy (GA), an advanced form of dry AMD. Lampalizumab (FCFD4515S; hereinafter "aFD") is an antibody Fab fragment comprised of a 214 residue light chain (SEQ ID NO:1) and a 223 residue heavy chain (SEQ ID NO:2).

[00271] While results of a phase II human clinical trial in GA indicate that a treatment effect is obtained with monthly intravitreal injection of aFD, there exist incentives to use higher drug doses to achieve even better efficacy. Meanwhile, less frequent dosing would provide improved convenience to the patient, have potential benefits of decreased infection rate and increased clinical efficacy, and could facilitate treatment of patients with less advanced forms of dry AMD.

[00272] Efforts were made to further improve the wild type aFD (WT)'s physical and chemical stabilities, especially under low pH conditions and/or at high concentrations under neutral pH. Aspartic acid residues Asp-30 on the light chain and Asp-62 on the heavy chain

(Figure 1A) have been identified as prone to isomerization. Asp isomerization involves dehydration to form a cyclic imide intermediate (Asu) that is normally long-lived at pH<8 and detected as a basic peak upon ion exchange chromatography (IEC). Formation of the cyclic intermediate is accelerated at lower pH. Hydrolysis of the cyclic intermediate to form Asp or Iso-Asp, yielding the same charge state as the starting material and thus not detectable by IEC, is faster at higher pH. Isomerization of Asp-62 (Asp-61 according to Kabat numbering) does not appear to affect potency since it is not in contact with factor D in the crystal structure of the Fab:FD complex. Katschke et al. (2012) *J. Biol. Chem.* 287:12886. Asp-30, together with light chain residues Asp-32 and Asp-92, make an electrostatic contact with basic residues on factor D. Isomerization of Asp-30 is quite rapid and presumed to account for an observed loss in potency of the antibody. Isomerization of Asp residues 32 and 92 could also have an effect on FD-binding but the rates are known to be very slow. Formation of the cyclic imide, or its subsequent hydrolysis to iso-aspartic acid, at position 30 could negatively impact antigen binding through perturbation of the electrostatic interaction. Antigen-binding measurements on the isolated basic fraction suggest that the cyclic intermediate form is fully active, consistent with iso-aspartic acid formation as the cause of loss in binding.

[00273] Asn-103 (Asn-101 according to Kabat numbering) on the heavy chain is susceptible to deamidation, a reaction that proceeds with higher rate at neutral as compared with slightly acidic pH (6-7). Deamidation can be detected as the appearance of an acidic peak upon IEC. Asn deamidation, like Asp isomerization, proceeds through a cyclic Asu intermediate. However, since formation of Asu from Asn only occurs at higher pH where Asu is hydrolyzed to form Asp or Iso-Asp, usually only the acidic peak is detected. The side chain of Asn-103 forms a hydrogen bond with factor D residue Arg-172. The effect of deamidation at this site, or formation of the cyclic imide intermediate, Asu, on antigen binding is unknown.

[00274] The aFD.WT has a lower pI (7.1) than a typical humanized Fab (pI 8-9). The composition of CDR-L1 (Figure 1A) results in a negative charge cluster on the VL domain. These features may affect solubility of the molecule, especially at low pH and low ionic strength. In addition, high concentration formulations of aFD.WT, even at neutral pH and physiological ionic strength, may have the tendency to form non-covalent dimers at a faster rate at 37°C.

[00275] Several variants of aFD.WT were produced for the purpose of improving stabilities. Point mutations were introduced by site-directed mutagenesis using the QuikChangeII® (Agilent) mutagenesis kit following the protocol supplied with the kit. Oligonucleotide primers specifying the required codon changes were synthesized. Plasmids

with designed changes were identified and confirmed by DNA sequencing. For small scale expression and purification, DNA was transformed into *E. coli* strain 64B4. Single colonies were picked into 5 mL LB media (media prep code A2008) containing 50 µg/mL carbenecillin (media prep code A3232) and grown overnight in 14 mL culture tubes with shaking at 200 RPM in an Innova incubator at 37 °C. These cultures were used to inoculate 250 mLs of complete soy crap media (media prep code A4564), 50 µg/mL carbenecillin, in a 1 L baffled shake flask. Cultures were grown overnight at 30 °C with shaking at 200 RPM and then harvested by centrifugation. The cell pellet was lysed using PopCulture media (Invitrogen), and Fabs purified on Gravitrap Protein G columns (GE Healthcare), following protocols supplied by the manufacturers. For larger scale production of Fabs, cell paste from 10 L fermentation of transformed cells was suspended in extraction buffer and homogenized using a microfluidizer. Fabs were captured by immunoaffinity chromatography on Protein G- Sepharose or kappa-select and eluted with a low pH buffer. The low pH eluate was adjusted to pH 5 and further purified by cation exchange chromatography on an S-Sepharose column. Identities of the purified proteins were confirmed by mass spectroscopy and the pooled fractions were concentrated to about 10 mg/mL, and exchanged into PBS buffer (pH 7.3) (also referred to herein as “PBS”; 8 mM dibasic sodium phosphate (Na₂HPO₄), 2 mM monobasic potassium phosphate (KH₂PO₄), 140 mM NaCl, 2.7 mM KCl), via diafiltration.

Example 2: Bioactivities of the Anti-Factor D Antibody Variants

[00276] Promising single and combination mutants were tested for factor D (fD) binding affinity and ability to inhibit factor D activities.

a. Factor D Binding Affinity by Surface Plasmon Resonance (SPR) Measurements

[00277] Kinetics and binding constant K_D for factor D binding to immobilized aFD.WT and variants thereof was determined by surface plasmon resonance (SPR) measurements on a Biacore®T200 instrument. Antibody Fab fragments were immobilized on a Series S CM5 sensor chip using the anti-huFab capture kit (GE healthcare Cat. # 28-9583-25) following a protocol described by the manufacturer. Kinetics of binding were calculated from sensorgrams recorded for injection of 60 µL aliquots of solutions of human factor D varied in concentration from 0.39 nM to 25 nM in 2-fold increments. The flow rate was 30 µL/minute, the running buffer was HBS-P+, the temperature of analysis was 25 °C, real-time reference cell subtraction was employed, and dissociation following factor D injection was followed for 10 minutes. After subtraction of the sensorgram observed for injection of running buffer, data were analyzed

according to a 1:1 model using BiaEval software v4.1 (GE Healthcare) to extract the kinetics and affinity constants.

Table 1. Effect of mutations on affinity for factor D

Mutant	SPR K_D (pM)	Variant #
aFD.WT	≤ 10	
VL-D28S	≤ 10	AFD.v1
VL-D30E	≤ 10	AFD.v2
VL-D31S	≤ 10	AFD.v3
VL-D32S	26	AFD.v4
VL-D28S:D31S:D32S	280	AFD.v5
VL-D30E:D31S VH-D62E ("TM")	≤ 10	AFD.v6
VL-D30E:D31S VH-D62E VL-D92E ("TM.D92E")	≤ 10	AFD.v7
VL-D28S:D30E:D31S VH-D62E ("SIESD")	16.7 $\pm$ 4.4	AFD.v8
VL-D28S:D30E:D31S VH-D62E VL-N34S	30	AFD.v9
VL-D28S:D30E:D31S VH-D62E VL-D92E	70	AFD.v10
VL-D28S:D30E:D31S:D92E VH-D62E:N103S	102	AFD.v15
VL-D28S:D30E:D31S VH-D62E VH-N52S	70	AFD.v11
VL-D28S:D30E:D31S VH-D62E VH-N103D	23	AFD.v12
VL-D28S:D30E:D31S VH-D62E VH-N103Q	60	AFD.v13
VL-D28S:D30E:D31S VH-D62E VH-N103S ("SIESD.N103S")	25.6 $\pm$ 6.3	AFD.v14

[00278] Mutants are named and numbered based on location in aFD.WT's light chain variable domain (VL; SEQ ID NO:3) and heavy chain variable domain (VH; SEQ ID NO:4). Single letter code for the wild-type residue followed by sequence position followed by single letter code for the substituted amino acid. Multiple changes on the same domain are separated by a colon.

[00279] As shown in Table 1, aFD.WT has a high affinity for fD, at the limit (~ 10 pM KD) that can be determined with SPR technology. Aspartic acid residues 28, 30, and 31 in

CDR-L1 could be individually substituted with Ser, Glu, and Ser, respectively, without apparent effect on affinity for fD (Table 1). In contrast, replacement of CDR-L1 Asp32 with Ser resulted in a significant loss in fD-binding whether tested individually (AFD.v4) or in combination with D28S and D31S mutants (AFD.v5). fD affinities equivalent to the wild-type molecule were determined for a triple mutant ("TM" (AFD.v6)) combining VL-D30E, D31S and VH-D62E and for a quad mutant (TM.D92E (AFD.v7)) which adds VL-D92E to TM (AFD.v6). The VH-D62E is a replacement at a site that undergoes isomerization without apparent effect on fD-binding; VL-Asp92 is an antigen contact residue with a slow rate of isomerization. The quad mutant "SIESD" (AFD.v8) combining VL-D28S, D30E, D31S and VH-D62E shows a small (~2-fold) loss in affinity for fD. In the context of SIESD (AFD.v8), the VL-D92E replacement resulted in a further loss in affinity for fD (see AFD.v10 (SIESD.D92E in Table 1)).

[00280] Potential sites of deamidation were tested for replacement with other residues. Both VL-N34 and VH-N52 are in contact with fD in the co-crystal structure but neither of these sites show significant rates of deamidation under neutral pH conditions. Ser substitution at these sites resulted in a loss in affinity (Table 1; AFD.v9 and AFD.v11). VH residue Asn-103 does contact fD and has a measureable rate of deamidation in PBS. Substitution of Asn-103 with Asp or Ser in the context of SIESD (AFD.v8) resulted in small, acceptable losses in affinity for fD (see AFD.v12 (SIESD.N103D) and AFD.v14 (SIESD.N103S)) (Table 1). A Gln substitution for Asn-103 resulted in a larger decrease in binding affinity (see AFD.v13 (SIESD.N103Q) (Table 1). Similar to SIESD (AFD.v8), SIESD.N103S.D92E (AFD.v15) which added VL-D92E to the penta mutant SIESD.N103S (AFD.v14) resulted in a further 4-fold decrease in affinity for fD.

b. Factor D Inhibition Assays

[00281] aFD.WT and variants were tested for their abilities to inhibit Factor D-induced complement activation, using an alternative pathway (AP) hemolysis assay. The AP hemolysis assay using rabbit erythrocytes (Er) has been previously described. Pangburn (1998), *Methods. Enzymol.* 162:639; Katschke et al. (2009) *J. Biol. Chem.* 284:10473. Er (Colorado Serum) were washed three times with 0.5% bovine skin gelatin in veronal buffer (GVB) and re-suspended. Dilutions of aFDs were prepared at a 2X concentration and added to 96-well polypropylene plates. Er suspension were mixed with GVB/0.1M EGTA/0.1M MgCl₂ and added to the plates. Complement activation was initiated by the addition of C1q-depleted human serum to avoid any complement activation through the classical pathway (CompTech; diluted 1:3 in GVB). After a 30 minute incubation at room temperature, the reaction stopped by adding 10 mM EDTA in

GVB. The plates were centrifuged and the supernatants transferred. The absorbance of the supernatant was read at 412 nm. The AFD.Ab concentrations causing half-maximal inhibition (IC₅₀) were determined by a nonlinear regression analysis.

Table 2. Inhibitory potency of AFD.Ab variants

Sample	IC ₅₀ (nM)*
	AP Hemolysis
WT (aFD.WT)	3.4
SIESD (AFD.v8)	4.2
SIESD.N103S (AFD.v14)	4.1
TM.D92E (AFD.v7)	3.8

*RSE= ±30%

[00282] As shown in Table 2, variants SIESD (AFD.v8), SIESD.N103S (AFD.v14), and TM.D92E (AFD.v7) have potencies for inhibiting fD-dependent complement activation activities that are equivalent to aFD.WT, given the standard error in IC₅₀ measurement of ±30%.

c. Binding Capacity over Prolonged Time

[00283] SPR was also used to measure total binding of AFD.Ab variants to fD over time under defined conditions. The standard error in these measurements is ±10%. Figure 2A shows that at pH 5.5, loss in binding was about 40% in one month for aFD.WT and AFD.Ab variants, D30E (AFD.v2) and TM (AFD.v6), whereas loss of binding for SIESD (AFD.v8) and SIESD.N103S (AFD.v14) was smaller at about 15%, even for prolonged period of time (70 days). As a comparison, an anti-VEGF antibody Fab fragment (aVEGF) showed no loss in binding over 70 days. Addition of salt to the pH 7.4 condition seemed to enhance the rate of loss in binding for aFD.WT and aVEGF (data not shown). As shown in Figure 2B, in the presence of PBS (with Fab protein concentration at 100 mg/ml), D30E (AFD.v2) and TM (AFD.v6) had equivalent rates of loss in binding that was slower than observed for aFD.WT. The loss in binding after 10 weeks at 37 °C was about 30% for aFD.WT, and 20% for D30E (AFD.v2) and TM (AFD.v6) variants of anti-factor D. Loss in binding after 10 weeks at 37 °C was only 10% for SIESD.N103S (AFD.14; Figure 2B), no greater than the experimental error, and equivalent to that observed for aVEGF under the same conditions. The thermal stress in PBS experiment at 100 mg/mL Fab concentration was repeated for SIESD (AFD.v8) in order to collect data out to 70 days. As shown in Figure 2C, loss in binding at 70 days was less than 10% for SIESD (AFD.v8).

Example 3. Anti-Factor D Antibody Variants with Improved Stability

[00284] Based on the affinity assays above, several single and combination anti-Factor D antibody variants were selected for further stability analysis.

a. Solubility

[00285] Samples were initially tested for solubility at low ionic strength and pH 6. Samples were first prepared in 20 mM His-HCl pH 5 buffer by concentration to ~100 mg/mL using Amicon Centrifrep YM-10 centrifugal filter units. These solutions at pH 5 and low ionic strength did not show turbidity upon visual inspection. Samples were centrifuged at 14,000xg for 10 minutes to pellet any insoluble material. No pellet was observed, and the protein concentration of the solution was determined by UV absorbance measurements. Samples (~1 mL) were placed in Slide-A-Lyzer cassettes of 10 K MWCO (Pierce) and dialyzed overnight at 4 °C versus 1 L of 20 mM His buffer, pH 6, followed by visual inspection for turbidity. Photographs of the solutions were taken and are provided in Figure 6. At pH 6 and low ionic strength conditions (~ 100 mg/ml in 20 mM His-HCl, pH 6), aFD.WT and D30E (AFD.v2) solutions were noticeably turbid, TM (AFD.v6) solution was less turbid and the solution of SIESD (AFD.v8) was clear (Figure 6). After centrifugation as above, whereby large pellets were visually observed for aFD.WT and AFD.v2, a smaller pellet for TM (AFD.v6), and no pellet for SIESD (AFD.v8), protein concentrations of the supernatants were determined by UV absorbance measurements (Table 3). aFD.WT and D30E (AFD.v2) showed solubilities of less than 50 mg/ml, TM (AFD.v6) showed solubility approaching 100 mg/mL and SIESD (AFD.v8) was fully soluble under these conditions. The small reduction in protein concentration for SIESD (AFD.v8) after pH 6 dialysis relative to the pH 5 starting concentration reflects a dilution effect upon dialysis rather than precipitation of AFD.v8 since no pellet was observed upon centrifugation.

Table 3. Solubility of AFD.Ab Variants (~ 100 mg/ml in 20 mM His-HCl, pH 6)

AFD.Ab Variant #	Concentration at pH 5, before pH 6 dialysis (mg/ml)	Concentration after pH 6 dialysis at 4°C and centrifugation (mg/ml)
aFD.WT	102	40
AFD.v2 (D30E)	102	14
AFD.v6 (TM)	102	92
AFD.v8 (SIESD)	100	94

[00286] Further variants AFD.v3, AFD.v12, AFD.v13 and AFD.v14 were tested in no salt solubility tests. After dialysis into pH 6 buffer at 4°C and incubation overnight at 37°C, all of the protein solutions except aFD.WT were clear (Figure 7). Measurements of protein concentration after 37 °C incubation and centrifugation (Table 4) indicate that all the variants were more soluble than aFD.WT. The turbid solution of aFD.WT (Figure 7, top row) became clear when subsequently dialyzed versus PBS (pH 7.3), a salt (NaCl) containing buffer, which suggests that the precipitation was reversible with salt addition and/or increase in pH (Figure 7, bottom row). The solubility data on AFD.v3 indicates that the single amino acid change D31S, removal of 1 negatively charged residue, can result in increased solubility. The further amino acid changes in AFD.v8, AFD.v12, AFD.v13 and AFD.v14 also result in increased solubility.

Table 4. Solubility of AFD.Ab Variants at pH 6, no salt

Condition	aFD.WT	AFD.v3 (D31S)	AFD.v8 (SIESD)	AFD.v12 (SIESD.N103D)	AFD.v13 (SIESD.N103Q)	AFD.v14 (SIESD.N103S)
Concentration at pH 5, before pH 6 dialysis (mg/ml)	112	106	120	118	109	103
Concentration after pH 6 dialysis at 4°C, incubation at 37 °C overnight and centrifugation (mg/ml)	63	97	99	94	96	80

[00287] aFD.WT, SIESD (AFD.v8) and SIESD.N103S (AFD.v14) were also tested for solubility under conditions of physiological pH (pH 7.3) and ionic strength. For solubility testing under physiological pH and ionic strength, samples were dialyzed overnight versus PBS,

and then concentrated to 227-372 mg/mL using Amicon Centriprep YM-10 centrifugal filter units. After overnight incubation at 4 °C, samples were visually inspected for turbidity, a portion was centrifuged to remove precipitated protein and the concentration of protein was determined by UV absorbance measurements and reported in Table 5. Prior to centrifugation, the aFD.WT sample was turbid whereas the solutions of SIESD (AFD.v8) and SIESD.N103S (AFD.v14) were clear (aFD.WT, AFD.v8 and AFD.v14 shown in Figure 8). The concentration of AFD.v14 was 344 mg/mL for the solution in the photograph (Figure 8) which was then further concentrated to 372 mg/mL. The concentration of AFD.v8 was 269 mg/ml for the solution in Figure 8. The concentration of aFD.WT was 227 mg/mL for the solution in Figure 8. After centrifugation, a pellet was observed with the aFD.WT solution, but no pellet was observed for the solutions of SIESD (AFD.v8) and SIESD.N103S (AFD.v14). The protein concentration data (Table 5) indicated that aFD.WT can only be concentrated to 227 mg/mL in PBS before precipitation is observed, whereas the solubility limits are higher for SIESD (AFD.v8) (≥ 269 mg/mL) and SIESD.N103S (AFD.v14) (≥ 372 mg/mL). Since no precipitate was observed for SIESD (AFD.v8) at 269 mg/mL, and no attempt was made to further concentrate the solution, this is the lower limit of solubility for this variant in PBS. Similarly, the lower limit of solubility for SIESD.N103S (AFD.v14) in PBS is 372 mg/mL. The 269 mg/mL solution of SIESD (AFD.v8) in PBS remained clear after 4 weeks of incubation at 2-8°C. Similarly, there was not any apparent increase in turbidity for the 372 mg/mL solution of SIESD.N103S (AFD.v14) in PBS after 3 weeks of incubation at 2-8°C. At this concentration, there was a very small change in % aggregate as measured using size-exclusion chromatography (SEC) (Figure 9), increasing from 0.9% to 2.1% in 3 weeks at 2-8°C (SEC data prior to 3 week incubation (0.9% aggregate) is shown in Figure 9; SEC data after 3 week incubation is data not shown).

Table 5. Solubility of AFD.Ab Variants (in PBS (pH 7.3))

AFD.Ab Variant #	Isoelectric point (pI)*	Concentration after centrifugation (mg/ml)
aFD.WT	7.1	227
SIESD (AFD.v8)	7.3	269
SIESD.N103S (AFD.v14)	7.4	372

* pI values were determined by imaged capillary isoelectric focusing (icIEF)

[00288] Solubilities of variants SIESD (AFD.v8) and SIESD.N103S (AFD.v14) were also compared in a buffer of pH 5.5 (20 mM HCl pH 5.5), and varied NaCl concentration, that may be representative of formulations used for drugs administered via intravitreal injection.

Solutions of about 100 mg/mL protein concentration were prepared and dialyzed against a test buffer. These solutions were then concentrated using Amicon Centriprep YM-10 centrifugal filter units. The concentrations obtained whereby the solutions remained visibly clear at ambient temperature are reported in Table 6. SIESD (AFD.v8) has high solubility, up to 314 mg/mL, at pH 5.5 and low NaCl concentration. High concentrations of SIESD.N103S (AFD.v14) were also achievable, up to 278 mg/mL with addition of 100 mM NaCl.

Table 6. Solubility of AFD.Ab variants at pH 5.5 (20 mM His-HCl pH 5.5) and varied NaCl concentration

NaCl Concentration, mM	SIESD(AFD.v8) mg/mL	SIESD.N103S(AFD.v14) mg/mL
0	314	NT
50	290	200
100	NT	278

NT=not tested

[00289] Although SIESD.N103S (AFD.v14) has two (2) fewer negatively charged residues in comparison to aFD.WT, these changes in charge do not result in a significant change in pI (Table 5), as measured by imaged capillary isoelectric focusing (iCIEF) (Salas-Solano et al, *J. Sep Sci*, 35(22): 3124 (2012)). Proteins are expected to have minimum solubility at pH values close to the pI (Green, A.A., *J. Biol. Chem.*, 93: 517-542 (1931)). For SIESD.N103S (AFD.v14) the increased solubility in PBS (pH 7.3) is not correlated with change in pI. Rather, the Asp to Ser amino acid changes in LC-CDR-L1 (VL-D28S and D31S) appear to alter the charge distribution on the surface of the molecule.

b. Isomerization and Deamidation

[00290] To simulate the exposure of variants to a variety of conditions that may be found in long-acting delivery systems, antibodies were stressed under varied pH and salt conditions for several weeks at 37°C. Specifically, antibodies were evaluated in the following five different formulations:

Formulation 1: 10 mg/mL, 10 mM phosphate buffer at pH 2.5,

Formulation 2: 10 mg/mL, 10 mM histidine HCl at pH 5.5,

Formulation 3: 10 mg/mL, 10 mM phosphate buffer at pH 7.4 ("low salt"),

Formulation 4: 10 mg/mL, pH 7.4 PBS ("high salt"; 10 mM phosphate, 137 mM NaCl);

and,

Formulation 5: 100 mg/mL, pH 7.4 PBS.

[00291] All solutions had 0.02% PS20, were incubated at 37°C and were sampled every 2 weeks. The low salt conditions (pH 2.5, 5.5, and 7.4) were to evaluate the effect of chemical degradation in liquid formulations. PBS was used as a mimic of the pH and ionic strength of human vitreous. In addition, comparing the 10 mM phosphate, pH 7.4, to PBS condition should reveal ionic strength effects on chemical and physical stability. The PBS samples were buffer exchanged regularly during incubation to simulate the exchange of vitreous. The wild type AFD (“WT” or “aFD.WT”) and aVEGF were evaluated in all 5 conditions. D30E (AFD.v2) and TM (AFD.v6) variants were tested in all formulations except number 4. SIESD (AFD.v8) and SIESD.N103S (AFD.v14) were tested in formulations 2 and 5.

[00292] The chemical degradation being quantified were deamidation, which is characterized by the formation of acidic peaks, and the dehydration step of isomerization, which is characterized by the formation of a long-lived succinimide (Asu) intermediate detected as basic peaks. Anionic exchange chromatography (Dionex ProPac SAX-10 columns) (IEC) was used to quantify the appearance of Asn deamidated and Asp dehydrated species within antibody samples in different formulations.

[00293] For all conditions tested, aFD.WT shows the greatest rate in loss of main peak and increase in basic peak amongst the tested antibodies. This is most noticeable at pH 5.5 where aVEGF, D30E (AFD.v2), TM (AFD.v6), SIESD (AFD.v8), and SIESD.N103S (AFD.v14) all show significantly lower rates of main peak loss than aFD.WT, see Figure 3A. SIESD.N103S (AFD.v14) shows the slowest rate of main peak loss with the rate similar to aVEGF at pH 5.5 (Figure 3A) and even slower than aVEGF in PBS (Figure 3B). As shown in Figure 4B (100 mg/ml of Fab in PBS (pH 7.3), D30E (AFD.v2) shows approximately half the rate of basic peak formation as aFD.WT whereas TM (AFD.v6), SIESD (AFD.v8), and SIESD.N103S (AFD.v14) show negligible basic peak formation. In contrast, as shown in Figure 4B (100 mg/ml of Fab in PBS (pH 7.3), the rate of acidic peak generation for aFD.WT and D30E (AFD.v2) are equivalent for PBS condition and about 2-fold slower than determined for TM (AFD.v6) and SIESD (AFD.v8). Acidic peak formation for SIESD.N103S (AFD.v14) in PBS is essentially negligible.

c. Aggregation

[00294] Size exclusion chromatography (SEC) was utilized to quantify the formation of aggregates and monomers for tested antibodies. Column used was TSK-GEL Super SW2000 (Tosoh Biosci.). Materials and conditions were used based on the manufacturer’s instructions (www.tskgel.com).

[00295] The % monomers over time based on SEC data for tested antibodies at 100 mg/ml of Fab formulated in PBS at 37°C are shown in Figure 5. aFD.WT shows a decrease in monomer peak fraction by 3-4% per month. AFD.v2 (D30E) which has no change in negative charge compared to aFD.WT shows a similar rate of monomer loss. AFD.v6, AFD.v8 and AFD.v14 show a decreased rate of monomer loss. The differences in monomer content at day zero reflect minor variations in the homogeneity of the purified preparations. The aggregation rate for D30E (AFD.v2) and TM (AFD.v6) is comparable at pH 5.5 and 7.4 (no salt) at 10 mg/ml protein concentration. The addition of salt at pH 7.4 does not affect the rate of aggregation for AFD.Ab variants but it doubles the rate of aggregation for aVEGF. Aggregation is protein concentration dependent since increasing the concentration from 10 mg/mL to 100 mg/mL in PBS increases the rate of aggregation for all samples tested (Table 7). Aggregation at 10 mg/mL concentration in 10 mM phosphate buffer pH 7.4 and no NaCl, and at 10 mg/mL concentration in PBS was minimal (Table 7). At 100 mg/mL concentration in PBS, the loss in monomer is much greater for aFD.WT and D30E (AFD.v2) (5.8% and 7.3% in 40 days, respectively) than for aVEGF, TM (AFD.v6), SIESD (AFD.v8), and SIESD.N103S (AFD.v14) (1.8%, 1.5%, 0.7%, and 1.5% in 40 days, respectively) at 100 mg/mL in PBS at 37 °C. These data suggest that AFD.v6, AFD.v8 and AFD.v14 have less aggregation than aFD.WT and AFD.v2 and may be more suitable as therapeutics as they may be less prone to *in vivo* immunogenicity.

Table 7. Effect of salt and protein concentration on aggregation of AFD.Ab variants and aVEGF as determined by SEC at 40 days

Formulation Conditions	Decrease in % Monomer after 40 Days					
	aFD. WT	D30E (AFD.v2)	TM (AFD.v6)	SIESD (AFD.v8)	SIESD.N103S (AFD.v14)	aVEGF
10 mg/mL in 10 mM sodium phosphate pH 7.4	1.6	2.1	.9			.36
10 mg/mL in PBS	1.5		.8			.63
100 mg/mL in PBS	5.8	7.3	1.5	0.7	1.5	1.78

[00296] To detect fragmentation formed as a function of pH, capillary electrophoresis sodium dodecyl sulfate (CE-SDS) was performed using a Beckman PA800 System with an uncoated fused-silica capillary with a 50 µm internal diameter (Polymicro Technologies, Inc.). Samples were prepared by a Beckman Coulter NXp Liquid Handling Robot with automation equivalent to Q12695. Samples were injected into the capillary at a voltage of 5 kV for 15 seconds and then mobilized at a voltage of 15 kV for 30 minutes. All samples were run at

ambient temperature. The electropherograms of all tested antibodies are similar to that of aFD.WT. Only at pH 2.5 was significant fragmentation observed. At no condition were higher molecular weight species observed, indicating that any aggregates formed are SDS-dissociable and not covalently linked.

[00297] The above stability results show that the triple (TM (AFD.v6)) and quad (SIESD (AFD.v8)) mutant variants of anti-Factor D have chemical stability that is significantly improved over aFD.WT or D30E (AFD.v2). In this series, SIESD.N103S (AFD.14) has the highest chemical stability at pH 5.5 and in PBS, similar to the stability of aVEGF. Both isomerization and deamidation sites have been removed and solubility at neutral pH has been increased while maintaining the fD binding affinity. Based on the above findings, the selected anti-Factor D variants described herein, particularly the SIESD (AFD.v8) and SIESD.N103S (AFD.v14) variants, are suitable for both high concentration formulation and for long acting delivery via, e.g., a port delivery system (PDS) device. For example, long acting delivery using a permanent, refillable device, such as a port delivery system may require high concentration formulation and low tendency to aggregate under physiological conditions of pH (~ 7.3) and ionic strength (~ 150 mM NaCl).

List of HVR Sequences (substitutions in variants are underlined)

SEQ ID NO:	Description	Sequence
5	HVR-L1 of WT	ITSTDIDDDMN
6	HVR-L2 of WT/TM (AFD.v6)/TM.92E (AFD.v7)/SIESD (AFD.v8)/SIESD.N103S (AFD.v14)	GGNTLRP
7	HVR-L3 of WT/TM (AFD.v6)/SIESD (AFD.v8)/SIESD.N103S (AFD.v14)	LQSDSLPYT
8	HVR-H1 of WT/TM (AFD.v6)/TM.92E (AFD.v7)/SIESD (AFD.v8)/SIESD.N103S (AFD.v14)	GYTFTNYGMN
9	HVR-H2 of WT	WINTYTGETTYADDFKG
10	HVR-H3 of WT/TM (AFD.v6)/TM.92E (AFD.v7)/SIESD (AFD.v8)	EGGVNN
11	HVR-L1 of TM (AFD.v6)/TM.D92E (AFD.v7)	ITSTDIESDMN
12	HVR-H2 of TM (AFD.v6)/TM.92E (AFD.v7)/SIESD (AFD.v8)/SIESD.N103S (AFD.v14)	WINTYTGETTYAEDFKG
13	HVR-L3 of TM.D92E (AFD.v7)	LQSES ¹ LPYT
14	HVR-L1 of SIESD (AFD.v8)/SIESD.N103S (AFD.v14)	ITST ¹ SIESDMN
15	HVR-H3 of SIESD.N103S (AFD.v14)	EGGV ¹ SN

Example 4: Stability of High Concentration Formulation of SIESD (AFD.v8)

[00298] Based on the stability studies above, AFD.v8 was assessed for suitability for high concentration formulations in low ionic strength, pH 5.5 buffer by performing a thermal (37 °C) stress test. A solution of about 100 mg/mL AFD.v8 was prepared and dialyzed versus 20 mM histidine hydrochloride (His-HCl), pH 5.5, then concentrated using Amicon YM-10 centrifugal filter units. Protein concentration upon removal from the filter units was determined to be 272 mg/mL using absorbance measurements at 280 nm. Aliquots of 100 µL were filtered through 0.22 µm cellulose acetate filters using sterilized Spin-X (Costar) centrifuge tube filters. The filtered solutions contained in snap-cap eppendorf tubes were sealed with parafilm and placed in a warm room maintained at 37 °C. At pre-determined times of 0, 1, 2, 4, and 8 months a tube was removed, diluted 10-fold by addition of 900 µL storage buffer (10 mM His-HCl, pH 5.5, 10% trehalose, 0.01% polysorbate 20) and stored frozen at -70 °C until analysis could be performed. Samples were analyzed for generation of charge variants by ion-exchange chromatography (IEC), presence of aggregates by size-exclusion chromatography (SEC), retention of antigen-binding capacity by surface plasmon resonance (SPR) measurements, and specific chemical changes in the variable domains by peptide mapping. IEC was performed as described in Example 3 (paragraph 00292), with SEC done as described in Example 3 (paragraph 00294). SPR and peptide mapping was done as described below.

a. Peptide Mapping

[00299] Samples of AFD.v8 were diluted with RCM buffer (6M guanidine HCl, 360mM Tris, 2mM EDTA, pH 8.6) to 1 mg/mL in a 1.5 mL eppendorf tube. The reduction reaction was initiated by adding 1M dithiothreitol (DTT) to a final concentration of 20 mM and then incubating at 37°C for 1 hour. Following reduction, the alkylation reaction was carried out by adding 1M iodo acetic acid (IAA) to a final concentration of 50mM and incubating in the dark at room temperature for 15 minutes. The reduced and alkylated samples were buffer exchanged into the digest buffer (25mM Tris, 2.0M CaCl₂, pH 8.2) using G-25 Minitrapp columns. Trypsin was added in a 1:40 trypsin to protein ratio (by mass) and the digestion was allowed to go to completion by incubating at 37°C for 4 hours.

LC/MS-MS

[00300] A Waters H-Class Acquity connected to a Thermo Orbitrap Q Exactive mass spectrometer were used for LC/MS-MS analysis. 10 µg of trypsin digested samples were loaded onto the Waters Acquity UPLC CSH column and run using the following LC conditions:

Mobile phase A – 0.1% FA in H₂O

Mobile phase B – 0.1% FA in ACN

Column temperature: 77°C

Flow rate: 0.2mL/min

Time (minutes)	%B
0	1.0
2	1.0
7	13.0
42	35.0
44.1	95.0
46.0	95.0
46.1	1.0
64	1.0

[00301] For the mass spectral analysis, full MS1 scans were detected at 35K resolution using the FTMS (Fourier transform MS, Orbitrap). The top eight ions detected (dynamic exclusion off) in the full MS1 scans were selected for HCD fragmentation in data dependent MS2 scans, which were detected using the FTMS. Downstream data analysis including extracted ion chromatographs and quantification of native and post-translationally modified peptides were performed using Thermo Scientific's XCalibur software.

b. Binding Capacity by SPR Measurements

[00302] Functional activity for binding to immobilized human factor D was assessed by SPR measurements. A Series S, CM5 sensor chip was docked into a Biacore® T200 instrument¹ (GE Healthcare), primed with 1X running buffer and normalized with 70% glycerol following a protocol supplied by the manufacturer. The sensor chip surface was activated for amine-coupling of antigens using the amine coupling kit with the materials provided and the protocol suggested by the manufacturer. On a flow cell of the sensor chip human factor D (fD) was covalently immobilized by injecting a solution containing 100 µg/mL fD prepared by dilution of fD (2.4 mg/mL) with 10 mM sodium acetate pH 5. The flow rate was 10 µL/minute and an injection volume of 70 µL was used. This yielded a typical coupling density across multiple experiments of about 5000 Resonance Units (RU) for fD. Unreacted amine coupling sites were blocked by injection of 70 µL 1 M ethanolamine.

[00303] Antigen-binding active concentrations of AFD were determined using the calibration-dependent concentration analysis routine of the Biacore® T200 evaluation software. A standard curve of unstressed AFD was prepared through gravimetric dilution of standards to 5 µg/mL followed by serial 2-fold dilutions to produce samples of 2.5, 1.25, 0.625, 0.313, 0.156, and 0.078 µg/mL. Test samples were prepared by gravimetric dilution to obtain protein concentrations of about 0.5, 1.0, or 1.5 µg/mL. All samples (200 µL volume) were prepared using 1X running buffer (10 mM HEPES pH 7.4, 150 mM NaCl, 0.01% PS20). 60 µL aliquots were injected over the specific antigen surface using a flow rate of 10 µL/minute with the sensor chip maintained at 25 °C and primed with 1X running buffer. Antibody bound to specific antigen was determined from the SPR signal near the end of the sample injection. Bound antibody was eluted at the end of each binding cycle through injection of 30 µL of 10 mM Gly-HCl pH 2.1 to cause dissociation of the antibody-antigen complex. The standard curve of starting material was used to determine the relationship of SPR signal to antibody concentration using a four-parameter function to analyze the data. Parameters calculated from the standard curve were used to calculate the antigen-binding concentration of test samples based on the observed SPR signal. The ratio of this concentration to the protein concentration determined by absorbance measurements gives the fraction or percent binding.

c. Results

[00304] Results of this thermal stress test indicate that AFD.v8 is a stable molecule in high concentration formulation. Greater than 80% of antigen-binding capacity (Figure 10A) was maintained after 4 months at 37 °C. Very little aggregate formation occurred at 4 months and the protein was nearly 100% monomer by SEC (Figure 10B). Some chemical changes took place by 4 months as indicated by the increase in acidic species (Figure 10B, %Acidic – IEC) to approximately 15% and basic species to approximately 20% (Figure 10B, %Basic – IEC). After 8 months at 37 °C there was an additional increase in acidic and basic species, a loss in monomer content, and a decrease in factor D-binding capacity. Peptide mapping suggests that the acidic species primarily arose from deamidation of CDR-H3 Asn-103 (Asn-101 according to Kabat numbering) (Figure 10B, CDR-H3 N101% deamidation) whereas basic variants were contributed by pyroglutamic acid formation at the N-terminus of the heavy chain (Figure 10B, HC-E1 % succinimide) and isomerization of CDR-H3 residue Glu-99 (Glu-95 according to Kabat numbering) (Figure 10B, CDR-H3 E97 % isomerization). Since Asn-103 and Glu-99 (Asn-101 and Glu-95, respectively, according to Kabat numbering) are in contact with factor D in the co-crystal structure of lamaplizumab and factor D (Katschke KJ, Jr., Wu P, Ganesan R,

Kelley RF, Mathieu MA, Hass PE, Murray J, Kirchhofer D, Weismann C, van Lookeren Campagne M, "Inhibiting alternative pathway complement activation by targeting the factor D exosite", *J. Biol. Chem.* (2012) 287:12886-92), but the N-terminus of the heavy chain is not, it is likely that Asn-103 deamidation and Glu-99 isomerization, as well as the decrease in monomer content, directly contribute to the loss in factor D-binding at 8 months. Nonetheless, given the slow rate of these chemical and physical changes, coupled with the expected further decrease in rate at lower temperature, a high concentration liquid formulation of AFD.v8 stored at 2-8 °C or frozen at -20 °C would appear to give acceptable shelf-life.

Example 5: Rabbit pK for AFD.v8/v14

[00305] *In vivo* pK studies for AFD.v8 and AFD.v14 were performed in rabbits. pK parameters were determined from single dose experiments because humanized antibodies are immunogenic in rabbits upon repeat dosing or when exposure is increased through sustained delivery formulations.

[00306] The animals' care was in accordance with Genentech Institutional Animal Care and Use Committee guidelines. Naïve New Zealand White (NZW) rabbits (41 male animals; 3.1 kg to 4.1 kg and approximately 4 months of age at the time of dosing) were assigned to dose groups and dosed with the test items at Charles River Laboratories.

[00307] SIESD(AFD.v8), SIESD.N103S(AFD.v14) or ranibizumab were administered via a single bilateral intravitreal injection to rabbits and observed for up to 27 days. Topical antibiotic (tobramycin ophthalmic ointment) was applied to both eyes twice on the day before treatment, immediately following the injection, and twice on the day following the injection, with the exception of animals sent to necropsy on Days 1 and 2. Prior to dosing, mydriatic drops (1% tropicamide) were applied to each eye for full pupil dilation. Animals were sedated with isoflurane/oxygen gas prior to and during the procedure. Alcaine (0.5%) was also applied to each eye prior to injection. The conjunctivae was flushed with benzalkonium chloride (ZephiranTM) diluted in sterile water, U.S.P. to 1:10,000 (v/v)

[00308] Syringes were filled under a laminar flow hood immediately prior to dosing. Fabs were administered by a single 30 µL intravitreal injection (0.3 mg dose) to both eyes in all animals. Doses were administered by a board-certified veterinary ophthalmologist using sterilized 100 µL Hamilton Luer Lock syringes with a 30-gauge x 1/2" needle. In order to mimic clinical dosing, eyes were dosed in the infero-temporal quadrants, i.e., in 5 o'clock and 7 o'clock positions for the left and right eyes, respectively (when facing the animal). The eyes

were examined by slit-lamp biomicroscopy and/or indirect ophthalmoscopy immediately following treatment.

[00309] All animals underwent exsanguination by incision of the axillary or femoral arteries following anesthesia by intravenous injection of sodium pentobarbital. Aqueous humor, vitreous humor and retina tissue were collected, snap frozen in liquid nitrogen and stored at -80°C. Antibody Fab in retina was extracted by homogenization in 50 mM Tris-HCl pH 8.0, 1 M NaCl. Determination of vitreous and retinal concentrations of test articles was by GRIP ELISA as described below. Values below the LLOQ were not used in pharmacokinetic analysis or for graphical or summary purposes. Pharmacokinetic parameters were determined by non-compartmental analysis with nominal time and dose (Phoenix WinNonlin, Pharsight Corp, Mountain View, CA).

[00310] Analyses of SIESD (AFD.v8), SIESD.N103S (AFD.v14) and ranibizumab were done in the generic immunoglobulin pharmacokinetic (GRIP) ELISA, with the exceptions noted herein. Sheep anti-human-IgG (The Binding Site; San Diego, CA) was diluted to 1000 ng/mL in 0.5 M carbonate/bicarbonate, pH 9.6, and coated onto 384-well ELISA plates (Nunc; Neptune, NJ) during an overnight incubation at 4°C. Plates were washed with PBS plus 0.05% Tween-20 and blocked during a 1- to 2-hour incubation with PBS plus 0.5% bovine serum albumin (BSA). This and all subsequent incubations were performed at room temperature with gentle agitation. The standard curves were prepared by serially diluting AFD.v8, AFD.v14 or ranibizumab from 40 - 0.625 ng/mL in assay buffer (PBS, 0.5% BSA, 15 ppm Proclin, 0.05% Tween 20, 0.25% CHAPS, 5 mM EDTA, 0.35M NaCl, (pH 7.4)). The rabbit vitreous or retinal homogenate samples were diluted a minimum of 1:100 or 1:50, respectively, in assay buffer. The diluted standards, controls, and samples were then incubated on the washed plates for 1 – 2 hours. Following a wash step, plate-bound AFD.v8, AFD.v14 or ranibizumab was detected during a 1.5 hour incubation with HRP-conjugated sheep anti-human IgG mAb (Bethyl Laboratories Inc; Montgomery, TX) diluted to 83.3 ng/mL in assay diluent (PBS + 0.5% BSA + 0.05% Tween 20 + 10ppm Proclin). After a final wash, tetramethyl benzidine peroxidase substrate (Moss, Inc., Pasadena, MD) was added, color was developed for 10 -15 minutes, and the reaction was stopped with 1 M phosphoric acid. The plates were read at 450 nm with a 620 nm reference using a microplate reader (Multiscan Ascent, Thermo Fischer; Waltham, MA). The concentrations of AFD.v8, AFD.v14 or ranibizumab were calculated from a four-parameter fit of the respective standard curve using in-house Excel-based software. Taking into account the minimum dilution in vitreous or retinal homogenate, the minimum quantifiable

concentration of AFD.v8, AFD.v14 or ranibizumab in rabbit vitreous or retinal homogenate was 62.5 ng/mL or 31.25 ng/mL, respectively.

[00311] Time-dependent concentration curves observed for intravitreal injection of 0.3 mg SIESD (AFD.v8), SIESD.N103S (AFD.v14), or a comparator dose of ranibizumab (anti-VEGF), are shown in Figure 11.

[00312] Analysis of the vitreal data using a non-compartmental model indicated that both SIESD (AFD.v8) and SIESD.N103S (AFD.v14) have clearance properties very similar to ranibizumab. All three proteins gave very similar exposure, as reflected in the AUC parameter, in the three ocular compartments: vitreous humor, aqueous humor, and retina. PK parameters calculated for ranibizumab were consistent with results of earlier studies in rabbits (Gaudreault et al, *Retina*, 27:1260-6 (2007)). Both SIESD (AFD.v8) and SIESD.N103S (AFD.v14) show target-independent ocular clearance properties that render these molecules suitable for development.

Example 6: Viscosity for AFD.v8/v14

[00313] As low viscosity is important for intravitreal administration, viscosity for SIESD (AFD.v8) and SIESD.N103S (AFD.v14) was measured at different protein concentrations in a pH 5.5, low salt buffer. Viscosity measurements were performed on a TA Instruments cone and plate rheometer thermostatted at 25 °C using a shear rate of 1000 s⁻¹.

[00314] aFD.WT, SIESD (AFD.v8) and SIESD.N103S (AFD.v14) gave similar profiles of viscosity dependence on protein concentration with viscosities acceptable for intravitreal injection (<30 cP) even at concentrations exceeding 200 mg/mL (Figure 12).

Example 7. Anti-Factor D Antibody Variants Further Modified for Polymer Conjugation

[00315] The aFD.WT and variants described in the above Examples are Fab fragments. While the variable domains of their light and heavy chains (VL and VH) vary in sequences as shown in Figure 1B, their constant domains CL and CH1 remain the same. In particular, the CH1 domain of the heavy chain ends at the Threonine residue as shown in Figure 1A (SEQ ID NO:2) Figure 1C (SEQ ID NO: 27) and Figure 1D (SEQ ID NO: 29). In order to prepare the AFD.Ab variants for polymer conjugation such as PEGylation, the heavy chains of the Fab fragments were further modified by adding the first cysteine residue from the hinge region of the Fab' counterpart (e.g., Cys-modified HC (Fab-C) for AFD.v8 (SEQ ID NO: 30) and Cys-modified HC (Fab-C) for AFD.v14 (SEQ ID NO: 32)), so that the added cysteine serves as the attachment site of PEG polymer. The resulting fragment can therefore be conjugated with one

arm of the multi-arm PEG. The heavy chains of the Fab fragments were also modified by adding the first four residues from the hinge region of the Fab' counterpart, namely Cys-Pro-Pro-Cys (SEQ ID NO: 21) (e.g., Cys-Pro-Pro-Cys-modified HC for AFD.v8 (SEQ ID NO: 31) and Cys-Pro-Pro-Cys-modified HC for AFD.v14 (SEQ ID NO: 33)), so that the two added Cys both serve as attachment sites for PEG, resulting in a modified AFD.Ab Fab fragment capable of attaching two PEG molecules.

[00316] The Cys-modified and Cys-Pro-Pro-Cys-modified variants were prepared using the QuikChangeII® (Agilent) mutagenesis kit following the protocol supplied with the kit. Oligonucleotide primers specifying the required codon changes were synthesized. Plasmids with designed changes were identified and confirmed by DNA sequencing. For small scale expression, DNA was transformed into E. coli strain 64B4. Single colonies were picked into 5 mL LB media (media prep code A2008) containing 50 µg/mL carbenicillin (media prep code A3232) and grown overnight in 14 mL culture tubes with shaking at 200 RPM in an Innova incubator at 37 °C. These cultures were used to inoculate 250 mLs of complete soy crap media (media prep code A4564), 50 µg/mL carbenicillin, in a 1 L baffled shake flask. Cultures were grown overnight at 30 °C with shaking at 200 RPM and then harvested by centrifugation. The cell pellet was lysed using PopCulture media (Invitrogen), and Fab-C purified as described in Example 1. For larger scale production of Fab-C, cell paste from 10 L fermentation of transformed cells was suspended in extraction buffer and homogenized using a microfluidizer, and the Fab-C was purified as described in Example 8.

Example 8: Preparation of AFD.v14 Conjugates

[00317] The AFD.v14 variant containing the Cys-modified HC (SEQ ID NO: 32) prepared in Example 7 (referred to herein as the "Cys-modified AFD.v14 variant" or "AFD.v14.C") was conjugated with commercially available maleimide-functionalized multi-armed PEGs having varying core structures.

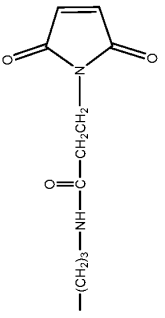
a. Maleimide-Functionalized Multi-Armed PEGs

[00318] The maleimide-functionalized multi-armed PEGs detailed in Table 8, below, were used in the conjugation reactions:

Table 8. Maleimide-functionalized multi-armed PEGs

PEG	Vendor	Core structure	Functional Group (X)	* Poly-Dispersity	Average MW
8ARM (TP)-PEG-MAL	JenKem Technology, USA			~1.04	40,000
8ARM-PEG-MAL	JenKem Technology, USA			~1.08	40,000
Sunbright® HGEO-400MA	NOF America Corp.			~1.33	40,000
Sunbright® DX-400MA	NOF America Corp.			~1.01	40,000

Table 8. Maleimide-functionalized multi-armed PEGs

PEG	Vendor	Core structure	Functional Group (X)	* Poly-Dispersity	Average MW
Sunbright® PTE-400MA	NOF America Corp.	$ \begin{array}{c} \text{O}(\text{CH}_2\text{CH}_2\text{O})_m\text{---X} \\ \\ \text{CH}_2 \\ \\ \text{X---}(\text{OCH}_2\text{CH}_2)_m\text{---O---CH}_2\text{---C---CH}_2\text{---O}(\text{CH}_2\text{CH}_2\text{O})_m\text{---X} \\ \qquad \qquad \qquad \\ \text{CH}_2 \qquad \qquad \qquad \text{CH}_2 \\ \qquad \qquad \qquad \\ \text{O}(\text{CH}_2\text{CH}_2\text{O})_m\text{---X} \end{array} $		--	40,000

* As provided by vendor. Note that this refers to the PEG chain length.

[00319] The 8ARM (TP)-PEG-MAL (JenKem Technology, USA) and Sunbright® HGEO-400MA (NOF America, Corp.) were analyzed using MALDI to compare the homogeneity of PEG octamers containing either the TP core or the HGEO core. The results are set forth in Figures 13A and 13B.

[00320] As can be seen from Figures 13A and 13B, the 8ARM (TP)-PEG-MAL containing the TP core was more homogeneous than the Sunbright® HGEO-400MA containing the HGEO core.

b. Conjugation of Cys-Modified AFD.v14 Variant and Maleimide-Functionalized Multi-Armed PEGs

[00321] The Cys-modified AFD.v14 variant prepared in Example 7 was captured using Gamma Plus resin, with 6.5 mM GSH pH 8.5 wash for 5 column volumes to deblock c-terminal cysteine and disrupt Fab-C dimer formation, followed by elution into 0.1M acetic acid pH 2.9. The Cys-modified AFD.v14 monomer was further isolated using SP Sepharose High Performance strong cation exchange resin (from GE Healthcare) in 25 mM sodium acetate pH 5.0, with 0.05% Triton X-100 + 0.05% Triton X-114 for 19 hours for endotoxin removal. Elution was performed with gradient between 0-20% 25 mM sodium acetate pH 5.0 + 1 M NaCl over 20 column volumes. The monomeric Fab-C with deblocked c-terminal cysteine was then prepared for PEGylation by titrating to pH 6.5 using 1 M HEPES pH 7.2. The Cys-modified AFD.v14 Fab-C was then conjugated to the maleimide-functionalized multi-armed PEG in 25 mM sodium acetate pH 6.5, 150 mM NaCl, 4 mM EDTA, at a concentration around 5 mg/mL. The Cys-modified AFD.v14 variant was not further concentrated in order to minimize cysteine reactivity loss due to Fab-C dimerization. After equilibrating to room temperature, the maleimide-functionalized multi-armed PEG was resuspended in 25mM sodium acetate pH 5.0 to a concentration of 10 mg/mL. The pH was kept below pH 6 to avoid maleimide ring opening. Once the PEG was solubilized, it was added to the Fab-C pool at a molar ratio of 0.1125:1 PEG to Fab-C. The mixture was then left at room temperature with gentle shaking overnight. The following day, the conjugation efficiency (# Fab/PEG) was checked by SEC-MALS.

Example 9: Purification and Characterization of AFD.v14 Conjugates

[00322] The conjugates prepared in Example 8 were purified and analyzed using SEC-MALS to confirm PEGylation and determine conjugation efficiency for different PEG core structures. Unless otherwise indicated, conjugation efficiency was determined by Size Exclusion Chromatography (SEC) using a 300 x 8 mm Shodex OH pak SB-804 HQ run at 0.8 mL/minute using phosphate buffered saline (PBS) pH 7.2, 150 mM NaCl under isocratic

conditions. Molar mass was determined using in-line static Multi-Angle laser Light Scattering (MALS) by Wyatt Technology. Photon correlation spectroscopy was used to determine hydrodynamic radii (RH), using Quasi-Elastic Light Scattering (QELS), a single photon counting module with detection at a 99.0°, also by Wyatt Technology. Raw data was worked up using Wyatt's proprietary Astra software, where molar mass and RH constants were set using a rituximab standard.

a. Cys-Modified AFD.v14-8ARM (TP)-PEG-MAL Conjugate

[00323] The Cys-modified AFD.v14-8ARM (TP)-PEG-MAL conjugate (containing the TP core structure) (hereinafter the “AFD.v14 TP conjugate” or “AFD.v14.C + TP octamer”) prepared in Example 8 was purified using SEC on a Sephacryl S-300 HR (GE Healthcare) column in 20 mM His-acetate, pH 5.5, 50 mM NaCl (isocratic gradient). Molar mass and conjugation efficiency were determined using in-line static Multi-Angle laser Light Scattering (MALS) by Wyatt Technology and Shodex OH pak SB-804 (Figure 14C). Raw data was analyzed using Wyatt's proprietary Astra software, where molar mass constants were set using a rituximab standard. Molar mass was used to estimate the average number of AFD.v14 variants attached to each PEG. The results are shown in Figures 14A, 14B, and 14C and in Table 9.

Table 9

Fraction #	Molar Mass (g/mol)	Estimated Fabylation*
B2	502,000	agg
B3	470,200	n/d
B4	453,200	n/d
B5	444,300	8 Fabs/PEG
B6	430,400	8 Fabs/PEG
B7	410,900	8 Fabs/PEG
C1	388,100	7 Fabs/PEG
C2	349,100	6-7 Fabs/PEG

agg = aggregates; n/d = not determined

* B5-B7 are deemed to be 8 Fabs/PEG based on %error in the MALS measurements.

[00324] As can be seen from Table 9, conjugation of the Cys-modified AFD.v14 variant (AFD.v14.C) with a multi-armed PEG octamer having the TP core produced conjugates comprising 8 Fabs/PEG, demonstrating that good conjugation efficiency can be achieved with PEG octamers comprising a TP core (e.g., approximately 45% recovery of 8 Fabs/PEG from conjugation).

b. Cys-Modified AFD.v14-8ARM-PEG-MAL Conjugate

[00325] The Cys-modified AFD.v14-8ARM-PEG-MAL conjugate (containing the HG core structure (JenKem)) (hereinafter the “AFD.v14 HG conjugate” or the “AFD.v14.C + HG octamer”) prepared in Example 8 was purified using SEC on a Sephacryl S-300 HR (GE Healthcare) column in 20 mM His-acetate, pH 5.5, 50 mM NaCl (isocratic gradient). Molar mass and conjugation efficiency was determined using Tosoh G3000PW column and in-line static MALS by Wyatt Technology. Photon correlation spectroscopy was used to determine hydrodynamic radii (RH), using Quasi-Elastic Light Scattering (QELS), a single photon counting module with detection at a 99°, also by Wyatt Technology. Raw data was analyzed using Wyatt’s proprietary Astra software, where molar mass and RH constants were set using a rituximab standard. Molar mass was used to estimate the number of AFD.v14 variants attached to each PEG. The results are shown in Figures 15A, 15B, and 15C and in Table 10.

Table 10

Fraction #	Mw (kDa)	Estimated Fabylation	R_H (nm)
A6	1146.6 (± 0.1%)	agg	16.0 (± 4.9%)
B3	861.6 (± 0.1%)	agg	14.5 (± 4.0%)
B6	758.3 (± 0.1%)	agg	13.7 (± 3.8%)
C1	649.3 (± 3.8%)	n/d	13.5 (± 3.8%)
C6	562.6 (± 0.1%)	n/d	12.8 (± 3.6%)
D2	546.7 (± 0.1%)	n/d	12.8 (± 3.7%)
D4	536.6 (± 0.1%)	n/d	12.6 (± 3.6%)
E2	525.4 (± 0.1%)	n/d	12.5 (± 3.5%)
E5	489.2 (± 0.2%)	8 Fab/PEG	12.3 (± 3.7%)
F1	409.2 (± 0.2%)	7-8 Fab/PEG	10.8 (± 3.7%)
F4	342.2 (± 0.1%)	6-7 Fab/PEG	9.7 (± 2.9%)
F6	325.5 (± 0.2%)	6 Fab/PEG	9.5 (± 0.3%)
G2	302.4 (± 0.2%)	5-6 Fab/PEG	9.3 (± 3.1%)

agg = aggregates; n/d = not determined

[00326] As can be seen from Table 10, conjugation of the Cys-modified AFD.v14 variant (AFD.v14.C) with a PEG octamer comprising the HG core produced conjugates comprising 8 Fabs/PEG. The recovery of conjugates comprising 8 Fabs/PEG (approximately 20% recovery), however, was about half the amount of conjugates comprising 8 Fabs/PEG that was recovered when using the conjugate with the TP core. Conjugation with the HG core also produced more conjugates comprising 5-7 Fabs/PEG, than was observed with the TP core, and significantly more aggregates.

[00327] In an effort to improve Fabylation estimate and RH measurement, the product containing fractions obtained following the S-300 purification were pooled and alternately analyzed using SEC-MALS on a 10/300 Sephacryl S-400 HR (GE Healthcare) column in PBS, pH 7.4, run at 0.25 mL/minute. Molar mass and RH were determined as described above. The SEC and MALS results are set forth in Figures 16A and 16B.

[00328] The conjugates prepared using the 8ARM-PEG-MAL (HG core) and analyzed using Sephacryl S-400 HR had an average RH of 12.2 nm ($\pm$ 4.5%), an average molar mass of 340.3 kDa ($\pm$ 8.9%), and an average of 6.4 Fabs/PEG.

c. Cys-Modified AFD.v14-HGEO-400MA Conjugate

[00329] The Cys-modified AFD.v14-HGEO-400MA conjugate (containing the Sunbright® HGEO-400MA PEG) (hereinafter the “AFD.v14 HGEO conjugate” or “AFD.v14.C + HGEO octamer”) prepared in Example 8 was purified using SEC on a Sephacryl S-300 HR (GE Healthcare) column in 20 mM His-acetate, pH 5.5, 50 mM NaCl (isocratic gradient). Molar mass, conjugation efficiency, and RH were determined as described above using Sephacryl S-400 HR, run at 0.25 mL/minute in PBS, pH 7.4.

[00330] The results are set forth in Figures 17A and 17B. The conjugates prepared using the Sunbright® HGEO-400MA PEG (HGEO core) had an average RH of 15.2 nm ($\pm$ 4.5%), an average molar mass of 423.8 kDa ($\pm$ 10.6%), and an average of 8.2 Fabs/PEG.

[00331] Following purification of the AFD.v14 HGEO conjugates using SEC on the Sephacryl S-300 HR column, conjugation efficiency and molar mass were alternately determined using Tosoh G3000PW column and in-line static MALS by Wyatt Technology, as described above. Molar mass was used to estimate the number of AFD.v14 variants attached to each PEG. The results from this analysis are set forth in Figures 18A and 18B, and in Table 11.

Table 11

Fraction #	Molar Mass (g/mol)	Estimated Fabylation
B1	2,145,000 ($\pm$ 0.8%)	agg
B2	665,800 ($\pm$ 0.7%)	agg
B3	426,400 ($\pm$ 0.8%)	8 Fabs/PEG
B4	296,400 ($\pm$ 0.8%)	6 Fabs/PEG
B5	246,200 ($\pm$ 0.8%)	5 Fabs/PEG
B6	215,000 ($\pm$ 0.8%)	n/d

agg = aggregates; n/d = not determined

[00332] As can be seen from Table 11, conjugation of the Cys-modified AFD.v14 variant (AFD.v14.C) with a PEG octamer comprising the HGEO core produced conjugates comprising 8 Fabs/PEG. Conjugation with the HGEO core also produced more conjugates comprising 5-6 Fabs/PEG, than was observed with the TP core. Finally, conjugation with the HEGO core resulted in more aggregates, and a lower conjugation efficiency, as compared to the TP core.

Example 10: Enrichment of AFD.v14 Conjugates

[00333] One way to increase the Fab concentration in an intravitreal formulation without significantly increasing formulation viscosity is to increase the percentage of highly fablylated conjugates in the formulation. In this example, cation exchange chromatography was used to enrich for highly fablylated conjugates.

[00334] Fractions B4-B7 (estimated fablylation of 8 Fab/PEG) from the SEC purification of the AFD.v14.C + TP octamer described in Example 9a were pooled (about 45% recovery), and subjected to cation exchange chromatography (CEX) using SP Sepharose High Performance strong cation exchange resin (GE Healthcare) in 25 mM sodium acetate pH 5.0, with 0.05% Triton X-100 + 0.05% Triton X-114 wash for 19 hours to remove endotoxin, followed by gradient elution between 10-20% using 25 mM sodium acetate pH 5.0 plus 1 M NaCl over 50 column volumes (CV). Fractions were analyzed using SEC-MALS + QELS using Shodex OH pak SB-804 HQ, as described above. The results are set forth in Figures 19A, 19B, 19C, and Table 12.

Table 12

Fraction #	Molar mass (g/mol)	Estimated Fablylation	GEL Lane #
3B11	335,000	6 Fabs/PEG	1, 8
3E12	367,100	7 Fabs/PEG	2, 9
4A7	414,200	8 Fabs/PEG	3, 10
4C5	430,000	8 Fabs/PEG	4, 11
4F3	483,900	n/d	5, 12
4H9	567,400	n/d	6, 13

[00335] The conjugate containing fractions obtained following CEX on SP Sepharose resin were pooled and analyzed using a 300 x 8 mm Shodex OH pak SB-804 HQ, run at 0.8 mL/minute using phosphate buffered saline (PBS), pH 7.4, 150 mM NaCl, under isocratic conditions. Molar mass and RH were determined as described above. The MALS results are set forth in Figure 20.

[00336] Following enrichment, conjugates prepared using the 8ARM (TP)-PEG-MAL (TP core) were obtained that had an average RH of 10.5 nm ($\pm$ 2.5%), an average molar mass of 407.1 kDa ($\pm$ 0.2%), and an average of 7.8 Fabs/PEG.

[00337] The conjugate containing fractions obtained following cation exchange chromatography purification of the TP conjugate described above were pooled (CEX pool) and compared to pooled fractions obtained following SEC using Sephacryl S-300 HR (GE Healthcare) (see Example 9a) (S300 pool), and pooled fractions obtained following SEC using Sephacryl S-400 HR (GE Healthcare) in 20 mM His-acetate, pH 5.5, 50 mM NaCl (isocratic gradient) (data not shown) (S400 pool). The pooled fractions were subject to capillary SDS gel electrophoresis (CE-SDS), and the results are set forth in Figures 21A and 21B.

[00338] As can be seen from Figures 21A and 21B, purification on S-300 and S-400 resin gave similar results. Enrichment of the conjugates using CEX, however, visibly enriched the amount of conjugates comprising 8 Fabs/PEG, while removing lower and higher molecular weight contaminants.

Example 11: Comparison of PEG Cores

[00339] The properties of conjugates prepared in Example 8, comprising either the 8ARM-(TP)-PEG-MAL (containing the TP core structure), the 8ARM-PEG-MAL (containing the HG core structure (JenKem)), or the Sunbright®-DX-400MA PEG (containing the butanediol core structure, referred to herein as the “AFD.v14 DX conjugate” or the “AFD.v14.C + DX octamer”), were compared using SEC-MALS. The HG and DX conjugates were purified using SEC on a Sephacryl S-300 HR (GE Healthcare) column in 20 mM His-acetate, pH 5.5, 50 mM NaCl (isocratic gradient). For the TP conjugate, pooled fractions obtained following purification on Sephacryl S-300 HR as described in Example 9a (“CEX load”) and pooled fractions obtained following the CEX enrichment as described in Example 10 (“TP final”) were used. Molar mass and conjugation efficiency was determined using MALS by Wyatt Technology and a 300 x 8 mm Shodex OH pak SB-804 HQ run at 0.8 mL/minute using phosphate buffered saline (PBS) pH 7.2, 150 mM NaCl under isocratic conditions. RH was determined as described above. The results are set forth in Figures 22A, 22B, and Table 13.

Table 13

Conjugate	PEG Core Structure	M _w (kDa)	Polydispersity (M _w /M _n)	R _H (nm)	Gel Lane #
AFD.v14.C + TP octamer*	Tripentaerythritol (TP)	407.1	1.004	10.5	6, 12
AFD.v14.C + HG octamer	Hexaglycerol (HG, JenKem)	539.1	1.289	12.8	4, 10
AFD.v14.C + DX octamer	Butanediol (DX)	355.6	1.005	9.2	3, 9

*Data is for TP final. Gel lanes 5 and 11 (Figure 22A) were CEX load.

[00340] Polydispersity was determined using methods known in the art, and in particular was determined using Astra software commercially available from Wyatt Technology.

[00341] As can be observed from these results, although the AFD.v14 DX conjugate had a low polydispersity, it did not provide as high a conjugation efficiency as the AFD.v14.C + TP octamer.

Example 12: Viscosity of AFD.v14 Conjugates

[00342] As low viscosity is important for intravitreal administration, viscosity of the Cys-modified AFD.v14 variant (AFD.v14.C) conjugated to either a PEG octamer (8ARM (HG)-PEG-MAL from JenKem Technology, USA; the AFD.v14.C + HG octamer) or a PEG tetramer (Sunbright® PTE-400MA from NOF America Corp.), prepared in Example 8, was measured at different protein concentrations in a pH 7.4 phosphate buffered saline (PBS) solution. Viscosity measurements were performed on a TA Instruments cone and plate rheometer thermostatted at 40 °C using a shear rate of 1000 s⁻¹. The results are shown in Figure 23.

[00343] As can be seen from Figure 23, conjugation of the AFD.v14 variant to the HGEO octamer allowed for a greater protein concentration, as compared to conjugation to the tetramer, at comparable viscosity.

[00344] The viscosity of the AFD.v14 HGEO conjugate (AFD.v14.C + HGEO octamer) at different protein concentrations was compared to that of the AFD.v14.C + TP octamer. Viscosity was measured at different protein concentrations at pH 6.5 in 20mM His-Ace, 50 mM NaCl formulation. Viscosity measurements were performed on a TA Instruments cone and plate rheometer thermostatted at 20 °C using a shear rate of 1000 s⁻¹. The results are set forth in Figure 24.

[00345] As can be seen from Figure 24, the AFD.v14.C + TP octamer had a lower viscosity than the AFD.v14.C + HGEO octamer, at comparable protein concentrations.

Example 13: Thermal Stability of AFD.v14 Conjugates

[00346] To simulate the exposure of the AFD.v14 conjugates to conditions that may be found in long-acting delivery systems, samples of the AFD.v14.C + TP octamer (prepared in Example 8) were stressed under two different pH and salt conditions for several weeks at 37°C. Specifically, conjugates were evaluated in the following formulations:

[00347] Formulation 1: 10 mg/mL, PBS; and,

[00348] Formulation 2: 10 mg/mL, 20 mM histidine HCl, 50 mM NaCl, at pH 6.5.

[00349] PBS was used as a mimic of the pH and ionic strength of human vitreous.

Aliquots (100 µL) of solutions of AFD.v14-TP conjugate, formulated at 10 mg/mL in PBS or 20 mM His-acetate pH 6.5, 50 mM NaCl, were sterile filtered by centrifugal filtration using 0.22 µm Costar® Spin-X centrifuge tubes (Corning) and then incubated at 37 °C for 0, 2, 4, or 8 weeks (T0, T2w, T4w, or T8w, respectively). Incubations were terminated by freezing at -70 °C. After thawing, samples were analyzed by SEC-MALS using a Shodex OH pak SB-804 HQ as described above, CE-SDS and by biacore to assess fD-binding capacity, as described below. The relative peak area for the conjugate determined by CE-SDS as a function of incubation time is shown in Figures 25A and 25B, suggesting a 1%/week decrease in conjugate at 37 °C. A similar change in conjugate, with increase in free Fab and dimer species, is observed by SEC-MALS (Figure 26). No change in binding capacity greater than the standard error in the measurements (±10%) was determined for incubation of the conjugate at 37 °C (Figure 28). The binding capacity remained steady even after 8 weeks at 37 °C in phosphate buffered saline (PBS) and after 4 weeks at pH 6.5.

a. CE-SDS Analysis

[00350] Material and Reagents: AFD.v14.C + TP octamer samples were thawed from -70 °C before use. Potassium cyanide (KCN) and 3-(2-furoyl)quinoline-2-carboxaldehyde (FQ) reagents were purchased from Molecular Probes (Eugene, OR, USA). Monobasic and dibasic sodium phosphate, dimethyl sulfoxide (DMSO), dithiothreitol (DTT) and N-ethylmaleimide were purchased from Sigma-Aldrich (St. Louis, MO, USA). Sodium dodecyl sulfate (SDS), 0.1 M sodium hydroxide (NaOH) and 0.1 M hydrochloric acid (HCl) reagents were purchased from J.T. Baker (Phillipsburg, NJ, USA). Replaceable sieving gel was purchased from Beckman Coulter, Inc. (Fullerton, CA, USA).

[00351] Solutions: Aqueous solutions were prepared with deionized 18.2 MΩ water from a Millipore purification system (Billerica, MA, USA). Solutions of 0.1M sodium phosphate, pH 6.7 reaction buffer and 4% SDS were filtered through a 0.2 µm membrane filter (Millipore,

Bedford, MA, USA) and diluted before use. Stock solutions of 20 mM fluorogenic FQ were prepared in Dimethyl sulfoxide (DMSO) and stored in the dark at -20 °C. Aliquots were thawed and diluted with water before use.

[00352] FQ Labeling Procedure: Solutions of AFD.v14.C + TP octamer (300 µg) were exchanged into 0.5 mL sodium phosphate reaction buffer using NAP-5 gel filtration columns (GE Healthcare, Piscataway, NJ, USA) to remove potentially competing formulation constituents. A 250 µL aliquot of the desalted conjugate was mixed with 30 µL of 150 mM N-ethylmaleimide dissolved in 4% SDS and incubated for 5 minutes at 70°C to control disulfide reshuffling under denaturing conditions (*see, e.g.*, Michels, D.A., Brady, L.J., Guo, A., Balland, A., *Anal Chem* 2007, 79, 5963-5971). Ten microliters of each 2.5 mM FQ and 30 mM KCN reagents were added to the SDS-AFD.v14 solution, and the final solution was incubated for 10 minutes at 50°C before diluted threefold with 1% SDS to quench the reaction. For reducing analysis, aliquots of the diluted samples were incubated with 50 mM DTT for 10 minutes at 70°C.

[00353] CE-SDS Analysis: Separation of AFD.v14.C + TP octamer samples was performed with 31.2 cm (21 cm effective length) fused-silica capillaries of 50 µm ID (Polymicro technologies, Phoenix, AZ, USA) encased in 40°C thermal controlled cartridges. Fully automated Beckman PA800+ systems (Beckman Coulter, Brea, CA, USA) were equipped with LIF detection and used 32 Karat version 9.1 to control the instrument. The LIF detector used a 3.5 mW argon-ion laser having an excitation at 488 nm; emission was collected through a 600 ± 20 nm bandpass filter (Edmund Optics, Barrington, NJ, USA). Voltage was applied in the negative mode (reverse polarity). Sample solutions were introduced electrokinetically at 5 kV for 25 s and separated at 17 kV. Between runs, the capillary was washed with 0.1 M NaOH, 0.1 M HCl and Beckman gel buffer for 5 minutes, 1 minute, 1 minute and 10 minutes, respectively. (*see, e.g.*, Michels, et al., *Anal Chem* 2007, 79, 5963-5971; Michels, et al., *Electrophoresis* 2012, 33, 815-826.)

b. Binding Capacity

[00354] The following materials were purchased from GE Healthcare: Series S CM5 Sensor Chips (cat#BR-1005-30); 10 X Biacore® running buffer (cat#BR-1006-71); 0.1 M Hepes pH 7.4, 1.5 M NaCl, 0.5% Polysorbate® 20; regeneration solution (cat#BR-1003-55); 10 mM Gly-HCl pH 2.1; and, amine coupling kit (cat#BR-1000-50). A Series S, CM5 sensor chip was docked into a Biacore® T200 instrument (GE Healthcare), primed with 1X running buffer and normalized with 70% glycerol following a protocol supplied by the manufacturer. The

sensor chip surface was activated for amine-coupling of antigens using the amine coupling kit with the materials provided and the protocol suggested by the manufacturer. Human factor D (fD) was covalently immobilized by injecting a solution containing 100 µg/mL antigen prepared by dilution of fD (PUR#20491, 2.4 mg/mL) with 10 mM sodium acetate pH 5. The flow rate was 10 µL/minute and an injection volume of 70 µL was used. This yielded a typical coupling density across multiple experiments of about 5000 Resonance Units (RU) for fD. Unreacted amine coupling sites were blocked by injection of 70 µL 1 M ethanolamine. Antigen-binding active concentrations of antibody Fab were determined using the calibration-dependent concentration analysis routine of the Biacore® T200 evaluation software. A standard curve of AFD.v14.C + TP octamer was prepared through gravimetric dilution of a stock solution to 5 µg/mL followed by serial 2-fold dilutions to produce samples of 2.5, 1.25, 0.625, 0.313, 0.156, and 0.078 µg/mL. Test samples were prepared by gravimetric dilution to obtain protein concentrations of about 0.5, 1.0, or 1.5 µg/mL. All samples (200 µL volume) were prepared using 1X running buffer. 60 µL aliquots were injected over the specific antigen surface using a flow rate of 10 µL/minute with the sensor chip maintained at 25 °C and primed with 1X running buffer. Antibody bound to specific antigen was determined from the SPR signal near the end of the sample injection. Bound antibody was eluted at the end of each binding cycle through injection of 30 µL of 10 mM Gly-HCl pH 2.1 to cause dissociation of the antibody-antigen complex. The standard curve of AFD.v14.C + TP octamer was used to determine the relationship of SPR signal to antibody concentration using a four-parameter function to analyze the data. Parameters calculated from the standard curve were used to calculate the antigen-binding concentration of test samples based on the observed SPR signal. The ratio of this concentration to the protein concentration determined by absorbance measurements gives the fraction or percent binding.

Example 14: Cynomolgus Monkey PK for AFD.v14 Conjugate

[00355] *In vivo* pK studies for the AFD.v14.C + TP octamer, prepared in Example 8, and purified as described in Examples 9a and 10, were performed in Cynomolgus monkey. PK parameters were determined from single dose experiments. Unconjugated, unmodified AFD.v14 (SIESD.N103S) was used as a control. The animals' care was in accordance with Genentech Institutional Animal Care and Use Committee guidelines.

a. Study Parameters

[00356] Cynomolgus monkeys (28 male animals; 2 kg to 4 kg and approximately 2-7 years in age at the time of dosing) were assigned to one of four dosing groups. Group 1

(control) animals (4 animals) received a single bilateral intravitreal dose of 5 mg/eye (10 mg/animal) of AFD.v14, through a 30 gauge needle (100 µl dose volume). Group 2 and 3 animals (10 animals in each group) received a bilateral intravitreal dose of 1 or 4 mg/eye (2 or 8 mg/animal), respectively based on Fab weight, of the AFD.v14.C + TP octamer through a 30-gauge needle (2 injections in each eye of 50 µl; 100 µl total dose volume). Animals were sedated (10 mg/kg ketamine HCl, 0.5 mg/kg diazepam) and treated with topical proparacaine prior to injection. The AFD.v14 or AFD.v14.C + TP octamer was then administered through the sclera and pars plana, 4 mm posterior to the limbus, with the needle directed posterior to the lens into the midvitreal. The Group 4 animals (4 animals) received a single IV bolus (1 mL) of the AFD.v14.C + TP octamer at 0.4 mg/animal. For IV administration, the AFD.v14.C + TP octamer was formulated as 10 mM sodium succinate, 10% trehalose, and 0.05% Tween-20 (pH 5.0).

[00357] Ocular tissues were collected from Groups 1, 2, and 3. One animal (2 eyes) from Group 1 and two animals (4 eyes) from each of Groups 2 and 3 were euthanized at the following times after dosing: Group 1 – days 1 (24 hours), 2, 4, and 8; Groups 2 and 3 – days 1 (24 hours), 4, 8, 12, and 20. After euthanasia, both eyes were enucleated, and vitreous humor, aqueous humor, and retinal tissue were collected from both eyes. The entire retinal layer was collected using filter paper days after flash freezing of the eyes. The AFD.v14 and AFD.v14.C + TP octamer concentrations were determined in the vitreous and aqueous humor and retinal tissues.

[00358] All blood samples (approximately 1 mL) were collected via a femoral or cephalic vein. Samples were drawn at the following times after IVT or IV dosing: Group 1 – 1 hour, 6 hours, and days 1 (24 hours), 2, 3, 4, 5, and 7; Groups 2 and 3 – 1 hour, 6 hours, and days 1 (24 hours), 2, 4, 6, 8, 12, and 20; Group 4 – 1 hour, 6 hours, and days 1 (24 hours), 2, 4, 7, 11, 14, 17, 21, 24, and 28. Within one hour of blood collection, samples were clotted at room temperature, and serum was separated by centrifugation and stored at -60°C to -80°C.

[00359] Details of the study protocol are set forth in Table 14.

Table 14. Cynomolgus Monkey pK Study Parameters

Group	Dose	Route	Number of Animals	Ocular time points (days)	Serum time points
1	5 mg/eye	IVT (bilateral)	4	1, 2, 4, 8	1 and 6 hr; 1, 2, 3, 4, 5, 7 days
2	1 mg/eye	IVT (bilateral)	10	1, 4, 8, 12, 20	6 hr; 1, 2, 4, 5, 8, 12, 20 days

Group	Dose	Route	Number of Animals	Ocular time points (days)	Serum time points
3	4 mg/eye	IVT (bilateral)	10	1, 4, 8, 12, 20	6 hr; 1, 2, 4, 6, 8, 12, 20 days
4	0.4 mg/animal	IV	4	n/a	6 hr; 1, 2, 4, 7, 11, 14, 17, 21, 24, 28 days

b. Pharmacokinetics Assay for AFD.v14 and AFD.v14.C + TP octamer

[00360] A Gyrolab XP assay was used to quantify AFD.v14 and AFD.v14.C + TP octamer in cynomolgus monkey serum, vitreous humor, aqueous humor, and retinal homogenate. Samples were diluted 1:4 – 1:3000 in sample buffer (phosphate buffered saline (PBS), 0.5% bovine serum albumin (BSA), 15 ppm Proclin (Sigma-Aldrich), 0.05% Tween 20, 0.25% CHAPS, 50 µg/mL muIgG (Equitech Bio, Cat. #SLM66), 5 mM EDTA (pH 7.4)). The AFD.v14 and AFD.v14.C + TP octamer standard curves were prepared by serially diluting AFD.v14 or AFD.v14.C + TP octamer from 2.06 - 1500ng/mL in sample buffer. Capture and detection reagents were applied at 100 µg/mL of biotin-conjugated goat anti-human IgG (HC + LC, Bethyl, Cat#A80-319B) in PBS/0.01% Tween 20/0.02% NaN₃ and Alexa-anti-CDR (clone 234, Genentech) at 25 nM in Rxxip F (Gyrolab). The assay was run on a Gyrolab Bioaffy 200 CD, and wash steps used PBS/0.01% Tween 20/0.02% NaN₃ followed by Gyros pH 11 wash buffer. The instrument was run and data analyzed as described by the manufacturer with a 1% PMT setting. The concentrations of AFD.v14 and AFD.v14.C + TP octamer were determined from a five-parameter fit of its standard curve. The minimum quantifiable concentration was 8.24 ng/mL (0.16 nM) for AFD.v14 and AFD.v14.C + TP octamer in cynomolgus monkey serum, vitreous humor, aqueous humor and retinal homogenate.

[00361] The vitreous humor, aqueous humor, and retinal pK results are set forth in Figures 29A (vitreous) and 29B (vitreous, normalized), Figures 30A (aqueous) and 30B (aqueous, normalized), and Figures 31A (retina) and 31B (retina, normalized) and in Tables 15-17 below.

Table 15. Vitreous PK for AFD.v14 control (Group 1) and AFD.v14.C + TP octamer (Groups 2 and 3)

Group	Dose (µg/eye)	T _{1/2} (days)	AUC (Day*µg/mL)	AUC/dose (Day*µg/mL/mg dose)	T _{1/2} ext [*]	V _{ss} (mL)	Cl (mL/day)
1	5000	2.7	--	--	--	3	0.79
2	1000	3.5	2530	2100	1.3	2.3	0.47
3	4000	5	7730	1980	1.9	3.4	0.46

*increase compared to control

Table 16. Aqueous PK for AFD.v14.C + TP octamer

Group	Dose ($\mu\text{g}/\text{eye}$)	$T_{1/2}$ (days)	AUC_{last} ($\text{Day} \cdot \mu\text{g}/\text{mL}$)	V_z (mL)	Cl/F (mL/Day)
2	1000	3	434	12	2.73
3	4000	5.2	1430	20	2.58

Table 17. Retinal PK for AFD.v14.C + TP octamer

Group	Dose ($\mu\text{g}/\text{eye}$)	$T_{1/2}$ (days)	AUC_{last} ($\text{Day} \cdot \mu\text{g}/\text{mL}$)	V_z (mL)	Cl/F (mL/Day)
2	1000	3.6	31	196	38
3	4000	5.9	98	309	36

[00362] As can be seen from Table 15, the vitreal terminal half-life for both Group 2 (3.5 days) and Group 3 (5 days) was longer than that of the unconjugated AFD.v14 control (Group 1), and longer than the average half-life of unconjugated lampalizumab and ranibizumab Fabs (about 2.34 days). The average AUC/mg-dose for conjugated AFD.v14 Groups 2 and 3 (about 2040) was higher than the average AUC/mg-dose for the unconjugated lampalizumab Fab (about 1733). Based on vitreal terminal half-life, the 4.0 mg/eye dose cleared more slowly than the 1.0 mg/eye dose. As can be seen from Tables 16 and 17, and Figures 30 and 31, a longer terminal half-life was also observed in aqueous humor and retina for Groups 2 and 3 (conjugated AFD.v14), as compared to unconjugated Fab.

[00363] The serum pK results for Groups 1-3 are set forth in Figures 32A and 32B (normalized), and the serum pK results for Group 4 are set forth in Figure 32C.

[00364] As can be seen from Figures 32A and 32B, the serum pK curves for Groups 2 and 3 (AFD.v14.C + TP octamer) are parallel to each other (Figure 32A), and overlap after dose normalization (Figure 32B). The serum AUC for Groups 2 and 3 is dose proportional, up until the last measured time point.

[00365] The terminal half-life for Group 4 (AFD.v14.C + TP octamer; IV dose) was 7.5 days, and the clearance was 15.8 mL/day (5.64 mL/kg/day (average weight of Group 4 monkeys was 2.8 kg)). On measurement days 21, 24, and 28, the serum concentration dropped below the limit of detection for 3 out of the 4 Group 4 monkeys.

c. Pharmacodynamics Assay for factor D in Cynomolgus Monkey Serum

[00366] A sandwich ELISA was used to quantify factor D (fD) in cynomolgus monkey serum, vitreous humor, aqueous humor and retinal homogenate. Mouse anti-human factor D clone 4676 (Genentech) was diluted to 1 $\mu\text{g}/\text{mL}$ in coating buffer (0.05M Sodium Carbonate, pH 9.6) and incubated overnight at 4°C on 384-well Maxisorp plates (Thermo Scientific, Cat# 464718). Plates were washed with PBS plus 0.05% Tween 20 and blocked during a 2 hour

incubation with PBS plus 0.5% bovine serum albumin (BSA). This and all subsequent incubations were performed at room temperature with gentle agitation. The cynomolgus monkey fD standard curve was prepared by serially diluting fD from 0.04 - 5 ng/mL in sample buffer (assay buffer supplemented with 500 ng/mL of the AFD.v14 therapeutic and 50 µg/mL mouse IgG). The serum samples and controls were diluted to a minimum of 1:100 in sample buffer. The vitreous humor, aqueous humor, and retinal homogenate samples and controls were diluted to a minimum of 1:10 in sample buffer. The diluted standards, controls, and samples were then incubated on the plates for 2 hours, and plate-bound fD/AFD.Ab complex was detected using biotin-conjugated mouse-anti-CDR mAb to AFD.Ab (clone 242, 1 µg/mL) for one hour followed by High Sensitivity SA-HRP (3 ng/mL, Pierce Cat.#21130) also for one hour. After a final wash, tetramethyl benzidine (Moss, Cat.# TMBE-1000) was added and color was developed for 10-15 minutes, and the reaction was stopped with 1 M phosphoric acid. The plates were read at 450 nm with a 620 nm reference using a microplate reader. The concentrations of fD were determined from a four parameter fit of the standard curve. The minimum quantifiable concentration in cynomolgus monkey serum was 3.9 ng/mL (0.16 nM). The minimum quantifiable concentration in cynomolgus monkey vitreous humor, aqueous humor and retinal homogenate was 0.39 ng/ml (0.016nM).

[00367] The average serum fD and AFD.v14.C + TP octamer concentrations for Groups 2, 3, and 4 are set forth in Figure 33A. As can be seen from Figure 33A, the serum fD concentration was higher than the AFD.Ab concentration at all time points tested. These results indicate that systemic AP complement activity is maintained in all groups.

[00368] The average ocular fD and AFD.v14.C + TP octamer concentrations for Groups 2 and 3 are set forth in Figure 33B. As can be seen from Figure 33B, the AFD.Ab concentration in the vitreous humor, aqueous humor, and retinal homogenate exceeded the fD concentration at all time points tested.

Example 15: Potency of Anti-Factor D Antibody Variants and Conjugates for Inhibition of Factor D

[00369] The potency of AFD.Ab variants or conjugates comprising a Cys-modified Fab variant for inhibition of Factor D are determined in a time-resolved fluorescence energy transfer (TR-FRET) assay of Factor D-dependent factor B activation.

[00370] The Cys-modified AFD.v14 variant (AFD.v14.C), and the AFD.v8 variant containing the Cys-modified HC (SEQ ID NO: 30) prepared in Example 7 (the "Cys-modified AFD.v8 variant" or "AFD.v8.C") were each conjugated with a maleimide-functionalized multi-

armed PEG tetramer (Sunbright® PTE-400MA from NOF America Corp.) according to the procedure set forth in Example 8, to form conjugates (referred to hereinafter as the “AFD.v14 tetramer” or the “AFD.v8 tetramer”, respectively).

[00371] Dilutions of the AFD.Ab Fab variant, conjugate, or Fab control were prepared in enzymatic reaction buffer (ERB; 75 mM NaCl, 1 mM MgCl₂, 25 mM Tris, 0.005% polysorbate 20, pH 7.3) at a 4x concentration and combined in equal volumes with 0.5 nM or 0.2 nM factor D (125 pM or 50 pM, respectively) (fD, Complement Technology; Tyler, TX) or ERB (no enzyme control). Ranibizumab (anti-VEGF) was used as the negative control. The Factor D/AFD.Ab or Factor D/conjugate mixtures (7 µl/well) were added to 364-well Proxiplate F plus black plates (Perkin Elmer Health Sciences; Waltham, MA) followed by 7 µl/well of substrate. The substrate consisted of a mixture of C3b (Complement Technology) at 7 µg/mL (40 nM) and factor B (Complement Technology) at 1 µg/mL (15 nM). The AFD.Ab Fab or conjugate, enzyme, cofactor, and substrate were incubated for 45 minutes at room temperature with gentle agitation. The reaction was stopped with 7 µl/well of a detection reagent cocktail mixture consisting of biotinylated anti-factor Bb (2F12, GNE PRO282909) at 8 nM, Europium-conjugated anti-factor Ba (custom conjugation of 1C3, GNE PRO282908 by Life Technologies; Madison, WI) at 4 nM, and streptavidin-Alexa 647 at 25 nM. The plate was incubated at room temperature in the dark for 30 minutes. Time-resolved fluorescence energy transfer was detected with a PHERAstar FS microplate reader (BMG LabTech; Cary, NC) by exciting at 337 nm and detecting Europium emission at 620 nm and Alexa fluor emission at 665 nm. The AFD.Ab or conjugate concentrations causing half-maximal inhibition (IC₅₀) were determined by nonlinear regression analysis using a four-parameter fit model (KaleidaGraph Synergy Software; Reading, PA).

[00372] Inhibition curves for the TR-FRET assay are shown in Figure 34A (Table 18). Lampalizumab has an IC₅₀ for inhibition of Factor D-dependent fB activation of 24 pM, and the standard error in IC₅₀ is ± 25%. The IC₅₀ for AFD.v8 and AFD.v14 is comparable to that measured for lampalizumab. See Figure 34A (Table 18). The difference in IC₅₀ for the conjugated Cys-modified AFD.Ab versions (AFD.v8 tetramer and AFD.v14 tetramer) compared to the unconjugated Fab is likely due to difficulty in handling more viscous PEGylated molecules (Figure 34A, Table 18).

Table 18: IC₅₀ of Factor D-dependent Factor B Activation (50 pM fD)

Molecule	Average IC₅₀ fB Activation (pM)
AFD.v8	27.65
AFD.v14	34.03
AFD.v8 tetramer	11.03
AFD.v14 tetramer	14.77
Ranibizumab	n/a
Lampalizumab	24.38

[00373] The potency of the AFD.v14.C + TP octamer for inhibition of Factor D was also determined in a TR-FRET assay of Factor D-dependent factor B activation using the procedure described above, with addition of 125 pM fD. The IC₅₀ for the AFD.v14.C + TP octamer (AFD.v14.C + TP octamer) was compared to AFD.v14, Cys-modified AFD.v14 (“AFD.v14.C”), and lampalizumab. Ranibizumab was used as the negative control. The results are set forth in Figure 34B and Table 19.

Table 19: IC₅₀ of Factor D-dependent Factor B Activation (125 pM fD)

Molecule	Average IC₅₀ fB Activation (pM)
Lampalizumab	72
AFD.v14	87
AFD.v14 TP octamer (S200 pool)*	104
AFD.v14 TP octamer (CEX pool)^	77
AFD.v14.C	72
Ranibizumab	n/a

* Obtained following purification using SEC on a Sephacryl S-200 HR (GE Healthcare) column.

^ Obtained following CEX enrichment (Example 10).

[00374] The IC₅₀ of the AFD.v14 TP octamer (both S300 pool and CEX pool) is potent, and is comparable to that measured for unconjugated Fab (lampalizumab, AFD.v14, AFD.v14.C). Enrichment of the AFD.v14 TP octamer using cation exchange chromatography resulted in a more potent product.

Example 16: Effect of Anti-Factor D Antibody Variants and Conjugates on Systemic Alternative Complement Pathway Activity

[00375] Lampalizumab has previously been shown to transiently inhibit systemic complement function in cynomolgus monkeys (*see* Loyet, et al., *J. Pharmacol. Exp. Ther.*,

2014, Vol. 351, pp. 527-537). In the current example, the effect of intravitreal administration of an anti-Factor D antibody variant or an AFD.Ab conjugate on systemic alternative complement pathway (AP) activity was evaluated in cynomolgus monkeys.

a. Pharmacokinetic/Pharmacodynamic Studies in Cynomolgus Monkeys

[00376] The AFD.Ab variant and conjugate were administered by a single-dose IVT or intravenous injection to male cynomolgus monkeys (*M. fascicularis*) of Chinese origin to assess the pharmacokinetics (PK) and pharmacodynamics (PD) of the molecules. These studies were conducted at Covance Laboratories (Madison, WI). All procedures were conducted in compliance with the US Department of Agriculture Animal Welfare Act Regulations (9 CFR 3), Guide for the Care and Use of Laboratory Animals, and the Office of Laboratory Animal Welfare.

[00377] Four studies were performed. In the first (control) study (Study 1, n=10), lampalizumab was administered to both eyes, in two 50 µL IVT doses, separated by 15 minutes. These animals received 10 mg/eye for a total of 20 mg/animal. Blood was collected predose (day -2) and post dose at the following time points: 45 minutes, and 2, 6, 10, 24, 34, 48, 96, 120, 154, 192, 288, and 384 hours. After blood collections at 24, 48, 120, 192, and 384 hours, two animals per group were removed from the study and euthanized to collect ocular matrix. The lampalizumab control Study has previously been described in Loyet, et al., *J. Pharmacol. Exp. Ther.*, 2014, 351:527-537.

[00378] In Study 2 (n=3), AFD.v14 was administered to both eyes, in two 50 µL IVT doses, separated by 15 minutes. These animals received 25 mg/eye for a total of 50 mg/animal. Blood was collected predose (day -1 and -3) and post dose at the following time points: 30 minutes, and 2, 8, 24, 48, and 96 hours.

[00379] In Study 3 (n=10), the AFD.v14.C + TP octamer was administered to both eyes, in two 50 µL IVT doses, separated by 15 minutes, to provide 3.9 mg/eye of AFD.v14, for a total of 7.8 mg/animal of AFD.v14. Blood was collected predose (week -1 and week -2) and post dose at the following time points: 1, 6, 24, 48, 72, 96, 144, 192, 288, and 480 hours. Two animals per group at each time point (at 24, 96, 192, 288, and 480 hours) were removed from the study and euthanized to collect ocular matrix.

[00380] In Study 4, the AFD.v14.C + HG octamer was administered to both eyes in two 50 µL IVT doses, separated by 15 minutes, to provide either 7.1 mg/eye of AFD.v14 (n=2) or 11.8 mg/eye of AFD.v14 (n=1), for a total of 14.2 mg/animal or 23.6 mg/animal of AFD.v14.

Blood was collected predose (day -7 and -1) and post dose at the following time points: 1, 6, 24, 96, and 168 hours.

[00381] For all studies, predose and postdose serum samples were collected from each animal via the femoral vein for PK and PD analyses. At each time point, whole blood was collected into serum separator tubes, allowed to clot at ambient temperature for at least 20 minutes, then centrifuged in a refrigerated centrifuge set at a temperature range of 2°C–8°C. The serum was harvested within 20 minutes of centrifugation and stored between –60°C and –80°C until analysis.

b. Total AFD.v14/conjugate analysis

[00382] A Gyrolab XP assay was used to quantify AFD.v14, AFD.v14.C + TP octamer, and AFD.v14.C + HG octamer in cynomolgus monkey serum. Samples were diluted 1:4 – 1:3000 in sample buffer (phosphate buffered saline (PBS), 0.5% bovine serum albumin (BSA), 15 ppm Proclin (Sigma-Aldrich), 0.05% Tween 20, 0.25% CHAPS, 50 µg/mL muIgG (Equitech Bio, Cat. #SLM66), 5 mM EDTA (pH 7.4)). The AFD.v14 and AFD.v14 TP and HG conjugate standard curves were prepared by serially diluting AFD.v14, AFD.v14.C + TP octamer, or AFD.v14.C + HG octamer from 2.06 - 1500ng/mL in sample buffer. Capture and detection reagents were applied at 100 µg/mL of biotin-conjugated goat anti-human IgG (HC + LC, Bethyl, Cat#A80-319B) in PBS/0.01% Tween 20/0.02% NaN₃ and Alexa-anti-CDR (clone 234, Genentech) at 25 nM in Rexasip F (Gyrolab). The assay was run on a Gyrolab Bioaffy 200 CD, and wash steps used PBS/0.01% Tween 20/0.02% NaN₃ followed by Gyros pH 11 wash buffer. The instrument was run and data analyzed as described by the manufacturer with a 1% PMT setting. The concentrations of AFD.v14, AFD.v14.C + TP octamer, and AFD.v14.C + HG octamer were determined from a five-parameter fit of its standard curve. The minimum quantifiable concentration was 8.24 ng/mL (0.16 nM) for AFD.v14, AFD.v14.C + TP octamer, and AFD.v14.C + HG octamer in cynomolgus monkey serum.

c. Pharmacodynamics Assay for factor D in Cynomolgus Monkey Serum

[00383] A sandwich ELISA was used to quantify factor D (fD) in cynomolgus monkey serum. Mouse anti-human factor D clone 4676 (Genentech) was diluted to 1 µg/mL in coating buffer (0.05M Sodium Carbonate, pH 9.6) and incubated overnight at 4°C on 384-well Maxisorp plates (Thermo Scientific, Cat#. 464718). Plates were washed with PBS plus 0.05% Tween 20 and blocked during a 2 hour incubation with PBS plus 0.5% bovine serum albumin (BSA). This and all subsequent incubations were performed at room temperature with gentle agitation. The cynomolgus monkey fD standard curve was prepared by serially diluting fD from

0.04 - 5 ng/mL in sample buffer (assay buffer supplemented with 500 ng/mL of the AFD.v14 therapeutic and 50 µg/mL mouse IgG). The serum samples and controls were diluted to a minimum of 1:100 in sample buffer. The diluted standards, controls, and samples were then incubated on the plates for 2 hours, and plate-bound fD/AFD.Ab complex was detected using biotin-conjugated mouse-anti-CDR mAb to AFD.Ab (clone 242, 1 µg/mL) for one hour followed by High Sensitivity SA-HRP (3 ng/mL, Pierce Cat.#21130) also for one hour. After a final wash, tetramethyl benzidine (Moss, Cat.# TMBE-1000) was added and color was developed for 10-15 minutes, and the reaction was stopped with 1 M phosphoric acid. The plates were read at 450 nm with a 620 nm reference using a microplate reader. The concentrations of fD were determined from a four parameter fit of the standard curve. The minimum quantifiable concentration in cynomolgus monkey serum was 3.9 ng/mL (0.16 nM).

d. AP Hemolysis Assay

[00384] The ability of AFD.v14 and AFD.v14.C + TP octamer to inhibit AP activity was evaluated in a hemolytic assay in which serum (either human or monkey) was combined with rabbit erythrocytes, as designed and described by Pangburn (*Methods Enzymol*, 1988, 162:639–653) and Katschke et al. (*J. Biol. Chem.*, 2009, 284:10473–10479). To ensure complement activation did not occur through the classic complement pathway (CP), C1q-depleted human serum (Complement Technologies, Tyler, TX) was used, and the buffer included EGTA to chelate calcium, a cation essential for CP activity.

[00385] C1q-depleted human serum was used to activate the AP. The concentration of fD present in 10% C1q-depleted human serum was 9.6 nM in-well, a value in agreement with previously reported fD levels in serum (Barnum, et al., *J. Immunol. Methods*, 1984, 67:303–309; Loyet et al., *Invest. Ophthalmol. Vis. Sci.*, 2012, 53:6628–6637).

e. Determination of Inhibition of Systemic AP Activity in AFD.v14.C + HG octamer -Treated Cynomolgus Monkey Serum

[00386] To evaluate the time course and dose dependency of any potential inhibition of systemic AP activity subsequent to dosing with AFD.v14.C + HG octamer or AFD.v14.C + TP octamer, either a plate-based WIESLAB Complement System AP ELISA (the data from this assay are referred to in Figure 35 as “% AP complement activity”) or an ex vivo assay similar to the *in vitro* AP hemolysis assay described above was performed (the data from this assay are referred to in Figure 35 as “% relative hemolysis.”). In this assay, however, instead of adding a dilution curve of exogenous AFD.v14.C + HG octamer or AFD.v14.C + TP octamer to the serum samples, the samples themselves were serially diluted, with any inhibition of hemolytic

activity attributed to the injected dose of AFD.v14.C + HG octamer or AFD.v14.C + TP octamer.

[00387] Erythrocytes were prepared, and the assay was performed, as described above, for the AP hemolysis assay with the following modifications. To determine the absorbance corresponding to maximum lysis, total lysis controls were prepared with sterile water (80 μ l/well), whereas GVB was added to all other wells (50 μ l). Cynomolgus monkey serum samples were serially diluted 1:1.5 over six points and added along with a negative control (buffer only) to 96-well U-bottom polypropylene plates (30 μ l/well). The total lysis controls represented maximum (100%) hemolysis. Data points were collected in triplicate, and the mean percent maximum hemolysis was plotted against the reciprocal of the final serum dilution in the assay. The 50% maximal hemolysis (AH50) values, defined as 50% maximal hemolysis, were determined by nonlinear regression analysis using a four-parameter fit model. For those curves that did not reach saturation, the AH50 was estimated using a curve fit in which the upper asymptote was fixed at 100%. The percent relative hemolysis was calculated for each individual time point as $[(\text{postdose AH50 for the individual time point})/(\text{predose AH50})] \times 100$. The AH50 value for serum from each individual normal cynomolgus monkey can vary as much as 2-fold from the overall average of AH50 values. Therefore, the predose and postdose samples from each study animal were run on the same assay plate to ensure that postdose changes in AP activity were directly compared with the individual animal's baseline complement activity.

f. Results

[00388] The percent relative hemolysis in comparison to total fD and the therapeutic active is shown in Figures 35A (lampalizumab, 10 mg/eye), 35B (AFD.v14, 25 mg/eye), and 35C (AFD.v14.C + TP octamer, 3.9 mg/eye). The lampalizumab data (Figure 35A) is comparative data obtained following IVT administration of 10 mg/eye of lampalizumab, as described in Loyet, et al., *J. Pharmacol. Exp. Ther.*, 2014, 351:527-537). As can be seen from Figure 35B, administration of 25 mg/eye of AFD.v14 transiently inhibited systemic AP activity, with activity returning to baseline by 24 hours post administration, similar to results previously observed for lampalizumab (Figure 35A). In comparison, no systemic AP inhibition was observed following administration of 3.9 mg/eye of the AFD.v14.C + TP octamer (Figure 35C). Without wishing to be bound to any particular theory, it is believed that the slower clearance from the eye obtained with the conjugate compared to Fab (e.g., lampalizumab and AFD.v14) allows fD to saturate the AFD.Ab at earlier time points, preventing systemic complement inhibition.

[00389] The percent relative AP complement activity in comparison to total fD and total conjugate is shown in Figures 35D (AFD.v14.C + HG octamer, 7.1 mg/eye) and 35E (AFD.v14.C + HG octamer, 11.8 mg/eye). As can be seen from these figures, negligible systemic complement inhibition was observed for the AFD.v14.C + HG octamer for IVT dosage up to 11.8 mg/eye. Due to the slower clearance from the eye, the conjugate concentration remains below the molar concentration of fD, in particular at time points earlier than 10 hours. This is in contrast to similar eye-dosed concentrations of the AFD.Ab Fab in which at these early time points the molar concentration exceeds the molar fD concentration and leads to systemic AP inhibition.

[00390] Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the disclosure described herein. Such equivalents are intended to be encompassed by the following claims.

[00391] Although the foregoing disclosure has been described in some detail by way of illustration and example for purposes of clarity of understanding, the descriptions and examples should not be construed as limiting the scope of the disclosure. The disclosures of all patent and scientific literatures cited herein are expressly incorporated in their entirety by reference.

[00392] The foregoing written specification is considered to be sufficient to enable one skilled in the art to practice the disclosure. The present disclosure is not to be limited in scope by the construct deposited, since the deposited embodiment is intended as a single illustration of certain aspects of the disclosure and any constructs that are functionally equivalent are within the scope of this disclosure. Indeed, various modifications of the disclosure in addition to those shown and described herein will become apparent to those skilled in the art from the foregoing description and fall within the scope of the appended claims.

WE CLAIM:

1. A conjugate comprising one or more anti-Factor D antibody variant covalently linked to one or more polyols, wherein:
at least one anti-Factor D antibody variant in the conjugate comprises substitution of at least one target aspartic acid (D or Asp) residue within a hypervariable region (HVR) of a reference anti-Factor D antibody, wherein the target Asp residue is identified as prone to isomerization and the substitution is Asp to Glutamic acid (E or Glu), and wherein each antibody variant exhibits improved stability without significant loss of Factor D binding affinity when compared to the reference anti-Factor D antibody; and
the polyol is a multi-armed polyol.
2. The conjugate according to claim 1, wherein the Asp residue is within an Asp-Xaa motif, wherein Xaa is Asp, Gly, His, Ser or Thr.
3. The conjugate according to claim 2, wherein the target Asp residue is the first Asp of an Asp-Asp motif.
4. The conjugate according to claim 1, wherein at least one antibody variant in the conjugate further comprises substitution of serine (S or Ser) for additional at least one Asp residue within a HVR of a reference anti-Factor D antibody, wherein the resulting antibody variant has lower negative charge and exhibits improved solubility when compared to the reference anti-Factor D antibody.
5. The conjugate according to claim 1, wherein at least one antibody variant in the conjugate further comprises one or more Ser substitution for deamidation prone asparagine (N or Asn) residue within a HVR of a reference anti-Factor D antibody.
6. The conjugate according to claim 1, wherein the reference anti-Factor D antibody comprises the light chain variable domain sequence of SEQ ID NO:3.
7. The conjugate according to claim 6, wherein the reference anti-Factor D antibody further comprises the heavy chain variable domain sequence of SEQ ID NO:4.
8. The conjugate according to claim 7, wherein the reference anti-Factor D antibody comprises the light chain sequence of SEQ ID NO:1 and the heavy chain sequence of SEQ ID NO:2.

9. The conjugate according to claim 7, wherein the reference anti-Factor D antibody comprises the light chain sequence of SEQ ID NO:1 and a heavy chain sequence selected from the group consisting of SEQ ID NOs: 34-53 and 115.

10. The conjugate according to claim 8 or claim 9, wherein at least one antibody variant in the conjugate comprises a light chain HVR1 (HVR-L1) sequence of SEQ ID NO:11 and a heavy chain HVR2 (HVR-H2) sequence of SEQ ID NO:12.

11. The conjugate according to claim 10, wherein the antibody variant further comprises a light chain HVR3 (HVR-L3) sequence of SEQ ID NO:13.

12. The conjugate according to claim 8 or claim 9, wherein at least one antibody variant in the conjugate comprises a light chain HVR1 (HVR-L1) sequence of SEQ ID NO:14 and a heavy chain HVR2 (HVR-H2) sequence of SEQ ID NO:12.

13. The conjugate according to claim 12, wherein the antibody variant further comprises a heavy chain HVR3 (HVR-H3) sequence of SEQ ID NO:15.

14. A conjugate comprising one or more anti-Factor D antibody variant covalently linked to one or more polyols, wherein:

at least one anti-Factor D antibody variant in the conjugate comprises substitution at one or more positions within the HVRs of a reference anti-Factor D antibody, wherein said reference anti-Factor D antibody comprises light chain HVR-1 comprising the sequence ITSTDIDDDMN (SEQ ID NO: 5), light chain HVR-2 comprising the sequence GGNTLRP (SEQ ID NO: 6), light chain HVR-3 comprising the sequence LQSDSLPYT (SEQ ID NO: 7), heavy chain HVR-1 comprising the sequence GYTFTNYGMN (SEQ ID NO: 8), heavy chain HVR-2 comprising the sequence WINTYTGETTYADDFKG (SEQ ID NO: 9), and heavy chain HVR-3 comprising the sequence EGGVNN (SEQ ID NO: 10), and wherein said substitution is one or more of the following: (a) amino acid at position 5 of SEQ ID NO: 5 is S (a, b, and c disclosed in SEQ ID NO: 22); (b) amino acid at position 7 of SEQ ID NO: 5 is E; (c) amino acid at position 8 of SEQ ID NO: 5 is S; (d) amino acid at position 13 of SEQ ID NO: 9 is E (SEQ ID NO: 23); (e) amino acid at position 4 of SEQ ID NO: 7 is E (SEQ ID NO: 24); or (f) amino acid at position 5 of SEQ ID NO: 10 is S (SEQ ID NO: 25); and the polyol is a multi-armed polyol.

15. The conjugate according to claim 14, wherein said substitution is selected from the group consisting of:

- (i) substitutions (b)-(d);
- (ii) substitutions (b)-(e);
- 5 (iii) substitutions (a)-(d); and
- (iv) substitutions (a)-(d) and (f).

16. The conjugate according to claim 14 or claim 15, wherein the variant comprises a heavy chain constant domain amino acid sequence selected from the group consisting of SEQ ID NOs: 54-74 and 116.

17. A conjugate comprising one or more anti-Factor D antibody covalently linked to one or more polyols, wherein:

at least one anti-Factor D antibody in the conjugate is independently selected from the group consisting of:

- 5 a) an anti-Factor D antibody comprising a light chain variable domain amino acid sequence of SEQ ID NO:16, 18 or 19; and
 - b) an anti-Factor D antibody comprising a heavy chain variable domain amino acid sequence of SEQ ID NO:17 or 20; and
- the polyol is a multi-armed polyol.

18. The conjugate according to claim 17, wherein at least one anti-factor D antibody in the conjugate comprises a light chain variable domain amino acid sequence of SEQ ID NO:16, 18 or 19 and a heavy chain variable domain amino acid sequence of SEQ ID NO:17 or 20.

19. The conjugate according to claim 18, wherein the light chain variable domain amino acid sequence is according to SEQ ID NO:19 and the heavy chain variable domain amino acid sequence is according to SEQ ID NO:17.

20. The conjugate according to claim 18, wherein the light chain variable domain amino acid sequence is according to SEQ ID NO:19 and the heavy chain variable domain amino acid sequence is according to SEQ ID NO:20.

21. The conjugate according to any one of claims 17-20, wherein at least one anti-Factor D antibody comprises a heavy chain constant domain amino acid sequence selected from the group consisting of SEQ ID NOs: 55-74 and 116.

22. A conjugate comprising one or more anti-Factor D antibody covalently linked to one or more polyols, wherein:

at least one anti-Factor D antibody in the conjugate has a variable light chain comprising a HVR-L1 having the sequence of SEQ ID NO:11 or 14, a HVR-L2 having the sequence of SEQ ID NO:6, and a HVR-L3 having the sequence of SEQ ID NO:7 or 13; and a variable heavy chain comprising a HVR-H1 having the sequence of SEQ ID NO:8, a HVR-H2 having the sequence of SEQ ID NO:9 or 12, and a HVR-H3 having the sequence of SEQ ID NO:10 or 15; and

the polyol is a multi-armed polyol.

23. The conjugate according to claim 22, wherein each anti-Factor D antibody in the conjugate is independently selected from the group consisting of:

- (i) an anti-Factor D antibody having a variable light chain comprising a HVR-L1 having the sequence of SEQ ID NO:14, a HVR-L2 having the sequence of SEQ ID NO:6, and a HVR-L3 having the sequence of SEQ ID NO:7; and a variable heavy chain comprising a HVR-H1 having the sequence of SEQ ID NO:8, a HVR-H2 having the sequence of SEQ ID NO:12, and a HVR-H3 having the sequence of SEQ ID NO:10; and
- (ii) an anti-Factor D antibody having a variable light chain comprising a HVR-L1 sequence of SEQ ID NO: HVR-L1 having the sequence of SEQ ID NO: 14, a HVR-L2 having the sequence of SEQ ID NO:6, and a HVR-L3 having the sequence of SEQ ID NO:7; and a variable heavy chain comprising a HVR-H1 having the sequence of SEQ ID NO:8, a HVR-H2 having the sequence of SEQ ID NO:12, and a HVR-H3 having the sequence of SEQ ID NO:15.

24. The conjugate according to claim 22 or claim 23, wherein at least one anti-Factor D antibody has a heavy chain constant domain amino acid sequence selected from the group consisting of SEQ ID NOs: 55-74 and 116.

25. A conjugate comprising one or more anti-Factor D antibody covalently linked to one or more polyols, wherein:

at least one anti-Factor D antibody in the conjugate is selected from the group consisting of:

- 5 (i) an anti-Factor D antibody having a light chain having the amino acid sequence of SEQ ID NO: 26 and a heavy chain having the amino acid sequence of SEQ ID NO: 27;
- (ii) an anti-Factor D antibody having a light chain having the amino acid sequence of SEQ ID NO: 28 and a heavy chain having the amino acid sequence of SEQ ID NO: 29;
- 10 (iii) an anti-Factor D antibody having a light chain having the amino acid sequence of SEQ ID NO: 26 and a heavy chain having the amino acid sequence of SEQ ID NO: 30;
- (iv) an anti-Factor D antibody having a light chain having the amino acid sequence of SEQ ID NO: 26 and a heavy chain having the amino acid sequence of SEQ ID NO: 31;
- 15 (v) an anti-Factor D antibody having a light chain having the amino acid sequence of SEQ ID NO: 26 and a heavy chain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 75-92 and 117;
- 20 (vi) an anti-Factor D antibody having a light chain having the amino acid sequence of SEQ ID NO: 28 and a heavy chain having the amino acid sequence of SEQ ID NO: 32;
- (vii) an anti-Factor D antibody having a light chain having the amino acid sequence of SEQ ID NO: 28 and a heavy chain having the amino acid sequence of SEQ ID NO: 33; and,
- 25 (vii) an anti-Factor D antibody having a light chain having the amino acid sequence of SEQ ID NO: 28 and a heavy chain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 93-110 and 118; wherein
- the polyol is a multi-armed polyol.

26. The conjugate according to claim 25, wherein at least one anti-Factor D antibody in the conjugate is an anti-Factor D antibody having a light chain having the amino acid sequence of SEQ ID NO: 28 and a heavy chain having the amino acid sequence of SEQ ID NO: 32.

27. The conjugate according to claim 25, wherein at least one anti-Factor D antibody in the conjugate is an anti-Factor D antibody having a light chain having the amino acid sequence of SEQ ID NO: 26 and a heavy chain having the amino acid sequence of SEQ ID NO: 30.

28. The conjugate according to any one of claims 1-27, wherein the anti-Factor D antibody or the antibody variant is an antibody fragment selected from the group consisting of Fab, Fab', Fab'-SH, Fab-C, Fab-C-SH, and combinations thereof.

29. The conjugate according to claim 28, wherein at least one antibody fragment in the conjugate comprises one cysteine residue at the C'-terminal end.

30. The conjugate according to claim 28, wherein at least one antibody fragment in the conjugate comprises an amino acid sequence of SEQ ID NO: 21 at the C'-terminal end.

31. The conjugate according to claim 28, wherein at least one antibody fragment in the conjugate comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 111-114 at the C'-terminal end.

32. The conjugate according to any one of claims 1-31, wherein the polyol is covalently linked to at least one of the anti-Factor D antibodies or the antibody variants at a free sulfhydryl group of a cysteine residue.

33. The conjugate of claim 32, wherein the cysteine residue is an engineered cysteine.

34. The conjugate according to claim 32 or claim 33, wherein the cysteine residue is in a constant domain of the anti-Factor D antibody or the antibody variant.

35. The conjugate according to any one of claims 32 to 34, wherein the cysteine residue is at the C'-terminal end of the anti-Factor D antibody or the antibody variant.

36. The conjugate according to any one of claims 32 to 35, wherein the conjugate comprises at least two of the anti-Factor D antibodies or the antibody variants, and the polyol is covalently linked to each anti-Factor D antibody or antibody variant at a free sulfhydryl group of a cysteine residue.

37. The conjugate according to any one of claims 1-16, wherein at least one of the antibody variants comprises substitution of at least one amino acid residue within a constant domain of the reference anti-Factor D antibody, wherein the amino acid residue is substituted with Cys.

38. The conjugate according to claim 37, wherein the polyol is covalently linked to the antibody variant at a free sulfhydryl group of the substituted cysteine residue.

39. The conjugate according to any one of claims 1-38, wherein the polyol is covalently linked to at least one of the anti-Factor D antibodies or the antibody variants at a free amino group of a lysine residue.

40. The conjugate according to claim 39, wherein the lysine residue is within a constant domain of the anti-Factor D antibody or the antibody variant.

41. The conjugate according to any one of claims 1-40, wherein at least two of the anti-Factor D antibodies or the antibody variants are covalently linked to the polyol.

42. The conjugate according to claim 41, wherein at least three of the anti-Factor D antibodies or the antibody variants are covalently linked to the polyol.

43. The conjugate according to claim 42, wherein at least four of the anti-Factor D antibodies or the antibody variants are covalently linked to the polyol.

44. The conjugate according to claim 43, wherein at least five of the anti-Factor D antibodies or the antibody variants are covalently linked to the polyol.

45. The conjugate according to claim 44, wherein at least six of the anti-Factor D antibodies or the antibody variants are covalently linked to the polyol.

46. The conjugate according to claim 45, wherein at least seven of the anti-Factor D antibodies or the antibody variants are covalently linked to the polyol.

47. The conjugate according to claim 46, wherein eight of the anti-Factor D antibodies or the antibody variants are covalently linked to the polyol.

48. The conjugate according to any one of claims 1-47, wherein the multi-armed polyol is selected from the group consisting of a dimer, a tetramer, a hexamer, and an octamer.

49. The conjugate according to claim 48, wherein the multi-armed polyol is an octamer.

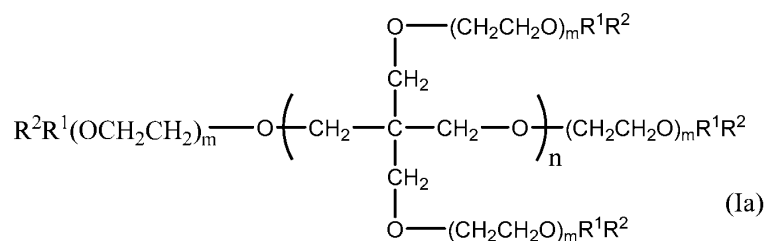
50. The conjugate according to any one of claims 1-49, wherein the polyol is polyethylene glycol.

51. The conjugate according to claim 50, wherein the polyethylene glycol has a weight average molecular weight of from about 500 D to about 300,000 D.

52. The conjugate according to claim 51, wherein the polyethylene glycol has a weight average molecular weight of from about 20,000 D to about 60,000 D.

53. The conjugate according to claim 52, wherein the polyethylene glycol has a weight average molecular weight of about 40,000 D.

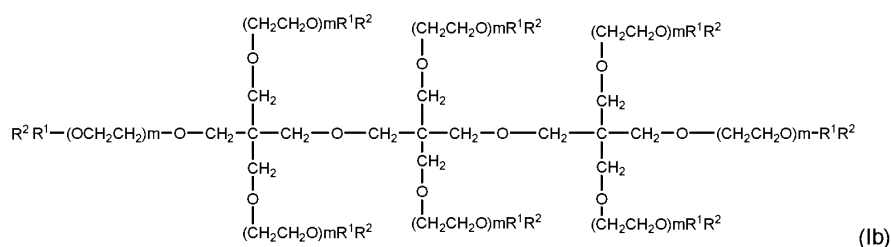
54. The conjugate according to any one of claims 50-53, wherein the polyethylene glycol has the structure of general formula (Ia):



5 wherein each m is independently an integer from 3-250; n is an integer from 1-10; each R¹ is independently either absent, or is a linking group; and each R² is independently either hydrogen or a terminal reactive group; wherein at least one R² is a terminal reactive group and is covalently linked to the anti-Factor D antibody or the antibody variant.

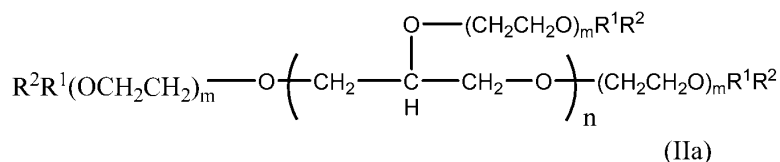
55. The conjugate according to any one of claims 50-53, wherein the polyethylene glycol has the structure of general formula (Ib):

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- wherein each m is independently an integer from 3-250; each R^1 is independently either absent, or is a linking group; and each R^2 is independently either hydrogen or a terminal reactive group; wherein at least one R^2 is a terminal reactive group and is covalently linked to the anti-Factor D antibody or the antibody variant.

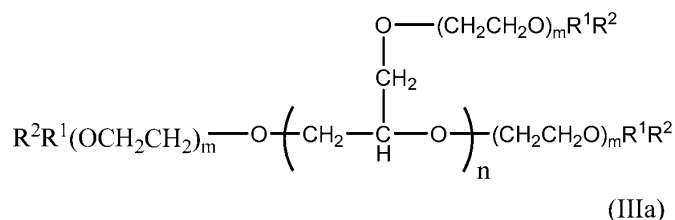
56. The conjugate according to any one of claims 50-53, wherein the polyethylene glycol has the structure of general formula (IIa):



- wherein each m is independently an integer of from 3-250; n is an integer from 1-10; each R^1 is independently either absent, or is a linking group; and each R^2 is independently either hydrogen or a terminal reactive group; wherein at least one R^2 is a terminal reactive group and is covalently linked to the anti-Factor D antibody or the antibody variant.

57. The conjugate according to claim 56, wherein n is 6.

58. The conjugate according to any one of claims 50-53, wherein the polyethylene glycol has the structure of general formula (IIIa):



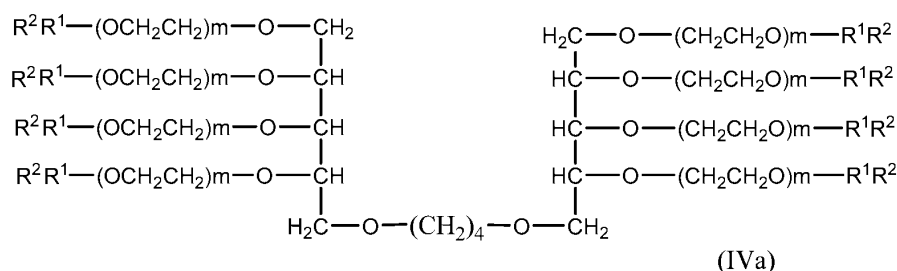
- wherein each m is independently an integer of from 3-250; n is an integer from 1-10; each R^1 is independently either absent, or is a linking group; and each R^2 is independently either hydrogen or a terminal reactive group; wherein at least one R^2 is a terminal reactive group and is covalently linked to the anti-Factor D antibody or the antibody variant.

59. The conjugate according to claim 58, wherein n is 2.

60. The conjugate according to claim 58, wherein n is 4.

61. The conjugate according to claim 58, wherein n is 6.

62. The conjugate according to any one of claims 50-53, wherein the polyethylene glycol has the structure of general formula (IVa):

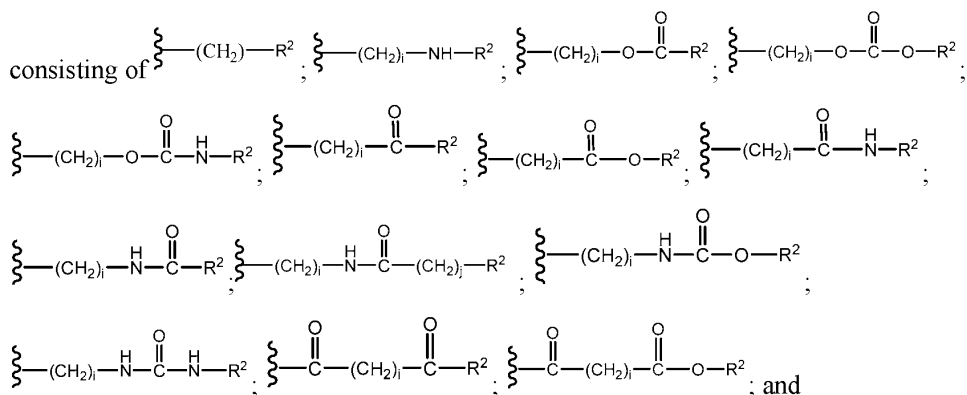


wherein each m is independently an integer of from 3-250; each R^1 is independently either absent, or is a linking group; and each R^2 is independently either hydrogen or a terminal reactive group; wherein at least one R^2 is a terminal reactive group and is covalently linked to the anti-Factor D antibody or the antibody variant.

63. The conjugate according to any one of claims 54-62, wherein m is an integer of 50-200.

64. The conjugate according to claim 63, wherein m is an integer of 100-150.

65. The conjugate according to any one of claims 54-64, wherein at least one R^1 is a linking group, wherein R^1 and R^2 when taken together are selected from the group



$$\xi - \overset{\text{O}}{\parallel}{\text{C}} - (\text{CH}_2)_j - \overset{\text{O}}{\parallel}{\text{C}} - \text{N} - \text{R}^2$$

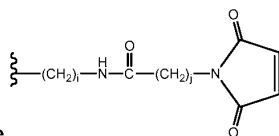
; and combinations thereof; wherein each i is independently an integer of 0-10; and j is an integer of 0-10.

66. The conjugate according to any one of claims 54-65, wherein each R² is independently selected from the group consisting of a thiol reactive group, an amino reactive group, and combinations thereof.

67. The conjugate according to claim 66, wherein each R² is independently selected from the group consisting of a maleimide, a sulfhydryl, a thiol, trifluoromethanesulfonate, tosylate, aziridine, epoxide, a pyridyl disulfide, succinimidyl ester, -NH₂, an aldehyde, a haloacetate, a haloacetamide, and a para-nitrophenyl carbonate.

68. The conjugate according to claim 67, wherein R² is a maleimide.

69. The conjugate according to any one of claims 54-68, wherein R^1 and R^2 ,

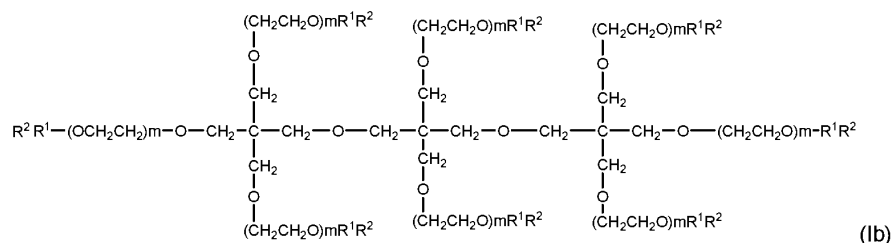


when taken together, are ≤ 10 , i is an integer of 0-10; and j is an integer of 0-10.

70. The conjugate according to any one of claims 54-58 or 61-69, wherein at least seven of the R² groups are covalently linked to one of the anti-Factor D antibodies or the antibody variants.

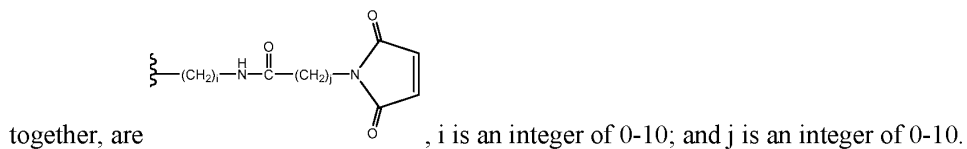
71. The conjugate according to claim 70, wherein eight of the R² groups are covalently linked to one of the anti-Factor D antibodies or the antibody variants.

72. The conjugate according to claim 26 or claim 27, wherein the polyethylene glycol has the structure of general formula (Ib):



- wherein each m is independently an integer from 3 - 250; each R^1 is independently either absent, or is a linking group; and each R^2 is independently either hydrogen or a terminal reactive group; wherein at least one R^2 is a terminal reactive group and is covalently linked to the anti-Factor D antibody or the antibody variant.

73. The conjugate according to claim 72, wherein R^1 and R^2 , when taken



74. The conjugate according to claim 73, wherein i is 2 and j is 2.
75. A conjugate according to any one of claims 1-74, wherein the conjugate is prepared by covalently linking at least one anti-Factor D antibody or antibody variant to the multi-armed polyol.
76. The conjugate of claim 75, wherein the multi-armed polyol is selected from the group consisting of a dimer, a tetramer, a hexamer, and an octamer.
77. The conjugate according to claim 75 or claim 76, wherein the polyol is a polyethylene glycol.
78. A pharmaceutical formulation comprising the conjugate according to any one of claims 1-77.
79. The pharmaceutical formulation according to claim 78, wherein the concentration of the anti-Factor D antibody or the antibody variant is at least 100 mg/ml.
80. The pharmaceutical formulation according to claim 79, wherein the concentration of the anti-Factor D antibody or the antibody variant is at least 200 mg/ml.
81. The pharmaceutical formulation according to claim 80, wherein the concentration of the anti-Factor D antibody or the antibody variant is at least 300 mg/ml.
82. The pharmaceutical formulation according to claim 78, wherein the concentration of the anti-Factor D antibody or the antibody variant is from about 50 mg/mL to about 300 mg/ml.

83. A long acting delivery device for ocular delivery comprising the pharmaceutical formulation according to any one of claims 78-82 and a means for delivering the formulation intravitreally to a patient, whereby the formulation remains effective on site for a prolonged period of time.

84. Use of the formulation according to any one of claims 78-82 or device of claim 83 in the manufacture of a medicament for treating a complement-associated disorder in a subject.

85. Use according to claim 84, wherein the complement-associated disorder is systemic.

86. Use according to claim 85, wherein the complement-associated disorder is an ocular disease.

87. Use according to claim 86, wherein the ocular disease is selected from the group consisting of age-related macular degeneration (AMD), including dry and wet (non-exudative and exudative) forms, diabetic retinopathy, ischemia-related retinopathy, choroidal neovascularization (CNV), uveitis, diabetic macular edema, pathological myopia, von Hippel-
5 Lindau disease, histoplasmosis of the eye, Central Retinal Vein Occlusion (CRVO), corneal neovascularization, and retinal neovascularization.

88. Use according to claim 87, wherein the ocular disease is selected from the group consisting of intermediate dry form AMD and geographic atrophy (GA).

89. The conjugate of any one of claims 1 to 77 for use in therapy.

90. The conjugate of any one of claims 1 to 77 for use in a method of treating a complement-associated disorder in a subject.

91. The conjugate of any one of claims 1 to 77 for use in a method of treating a systemic complement-associated disorder in a subject.

92. The conjugate of claim 91, wherein the complement-associated disorder is a complement-associated eye condition.

93. The conjugate of claim 92, wherein the complement-associated eye condition is selected from the group consisting of age-related macular degeneration (AMD), including dry and

wet (non-exudative and exudative) forms, choroidal neovascularization (CNV), uveitis, diabetic retinopathy, ischemia-related retinopathy, diabetic macular edema, pathological myopia, von
5 Hippel-Lindau disease, histoplasmosis of the eye, Central Retinal Vein Occlusion (CRVO), corneal neovascularization, and retinal neovascularization.

94. The conjugate of claim 92, wherein the complement-associated eye condition is selected from the group consisting of intermediate dry form AMD and geographic atrophy (GA).

95. A method of treating a complement-associated disorder in a subject comprising administering to the subject an effective amount of the conjugate of any one of claims 1 to 77, or the pharmaceutical formulation of any one of claims 78 to 82.

96. The method of claim 95, wherein the complement-associated disorder is systemic.

97. The method of claim 95, wherein the complement-associated disorder is a complement-associated eye condition.

98. The method of claim 97, wherein the complement-associated eye condition is selected from the group consisting of age-related macular degeneration (AMD), including dry and wet (non-exudative and exudative) forms, choroidal neovascularization (CNV), uveitis, diabetic retinopathy, ischemia-related retinopathy, diabetic macular edema, pathological myopia, von
5 Hippel-Lindau disease, histoplasmosis of the eye, Central Retinal Vein Occlusion (CRVO), corneal neovascularization, and retinal neovascularization.

99. The method of claim 97, wherein the complement-associated eye condition is selected from the group consisting of intermediate dry form AMD and geographic atrophy (GA).

100. The method of any one of claims 95 to 99, wherein the method comprises administering the conjugate or pharmaceutical formulation using an implantable port delivery system.

101. The method of any one of claims 95 to 100, wherein the method comprises administering the conjugate or pharmaceutical formulation by intravitreal administration.

102. The method of claim 101, wherein the intravitreal administration is through a narrow bore needle.

103. The method of claim 102, wherein the narrow bore needle is about 30, 29, 28, 27, 26, 25, 24, 23, or 22 gauge.

104. The method of any one of claims 95 to 103, further comprising administering an additional therapeutic agent to the individual.

105. The method of claim 104, wherein the additional therapeutic agent is selected from the group consisting of an ANG2 antagonist, a TIE2 antagonist, a VEGF antagonist, and a second complement component antagonist.

106. The method of claim 104, wherein the additional therapeutic agent is an anti-ANG2 antibody.

107. The method of claim 104, wherein the additional therapeutic agent is an anti-TIE2 antibody.

108. The method of claim 104, wherein the additional therapeutic agent is selected from the group consisting of a VEGF trap and an anti-VEGF antibody.

109. The method of claim 104, wherein the additional therapeutic agent is a second complement component antagonist, wherein the second complement component antagonist inhibits a complement component selected from the group consisting of C1, C2, C3, C4, C5, C6, C7, C8 and C9.

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WT Light Chain

DIQVTQSPSS L S A S V G D R V T I T C I I T S D I D D D M N W Y Q Q K P G K V P K L L I S G G N T L R P G V P S 60
 R F S G S G S G T D F T L T I S S L Q P E D V A T Y Y C L Q S D S L P Y I F G Q G T K V E I K R T V A A P S V F I F P P 120
 S D E Q L K S G T A S V V C L L N N F Y P R E A K V Q W K V D N A L Q S G N S Q E S V T E Q D S K D S T Y S L S S T L T 180
 L S K A D Y E K H K V Y A C E V T H Q G L S S P V T K S F N R G E C (SEQ ID NO:1) 214

WT Heavy Chain

E V Q L V Q S G P E L K K P G A S V K V S C K A S G Y T F T N Y G M N W V R Q A P G Q G L E W M G W I N T Y T G E T T Y 60
 A D D F K G R F V F S L D T S V S T A Y L Q I S S L K A E D T A V Y Y C E R E G G V N N W G Q G T L V T V S S A S T K G 120
 P S V F P L A P S S K S T S G G T A A L G C L V K D Y F P E P V T V S W N S G A L T S G V H T F P A V L Q S S G L Y S L 180
 S S W V T V P S S L G T Q T Y I C N V N H K P S N T K V D K K V E P K S C D K T H T (SEQ ID NO:2) 223

FIG. 1A

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VL Domain

WT DIQVTQSPSSL SASVGDRTVTITCIIISTIDIDDDMNWYQKPGKVPKLLISGGNTLRPGVPSRFSGSGSGTDFLTIISSLQP
 TM DIQVTQSPSSL SASVGDRTVTITCIIISTIDIESDMNWYQKPGKVPKLLISGGNTLRPGVPSRFSGSGSGTDFLTIISSLQP
 TM.D92E DIQVTQSPSSL SASVGDRTVTITCIIISTIDIESDMNWYQKPGKVPKLLISGGNTLRPGVPSRFSGSGSGTDFLTIISSLQP
 SIESD DIQVTQSPSSL SASVGDRTVTITCIIISTIDIESDMNWYQKPGKVPKLLISGGNTLRPGVPSRFSGSGSGTDFLTIISSLQP
 SIESD.N103S DIQVTQSPSSL SASVGDRTVTITCIIISTIDIESDMNWYQKPGKVPKLLISGGNTLRPGVPSRFSGSGSGTDFLTIISSLQP

WT EDVATYYCLOSDSLPYTFGQGTKEIK (SEQ ID NO:3)
 TM EDVATYYCLOSDSLPYTFGQGTKEIK (SEQ ID NO:16)
 TM.D92E EDVATYYCLOESLPYTFGQGTKEIK (SEQ ID NO:18)
 SIESD EDVATYYCLOSDSLPYTFGQGTKEIK (SEQ ID NO:19)
 SIESD.N103S EDVATYYCLOSDSLPYTFGQGTKEIK (SEQ ID NO:19)

VH Domain

WT EVQLVQSGPELKKPGASVKVSKASGYFTFTNYGMNWVRQAPGQGLEWMGWINTYTGTTTAYADDFKGRFVFSLDTSVSTAY
 TM EVQLVQSGPELKKPGASVKVSKASGYFTFTNYGMNWVRQAPGQGLEWMGWINTYTGTTTAYEDFKGRFVFSLDTSVSTAY
 TM.D92E EVQLVQSGPELKKPGASVKVSKASGYFTFTNYGMNWVRQAPGQGLEWMGWINTYTGTTTAYEDFKGRFVFSLDTSVSTAY
 SIESD EVQLVQSGPELKKPGASVKVSKASGYFTFTNYGMNWVRQAPGQGLEWMGWINTYTGTTTAYEDFKGRFVFSLDTSVSTAY
 SIESD.N103S EVQLVQSGPELKKPGASVKVSKASGYFTFTNYGMNWVRQAPGQGLEWMGWINTYTGTTTAYEDFKGRFVFSLDTSVSTAY

WT LQISSLKAEDTAVYYCEREGGVNNWGQGLTVTVSS (SEQ ID NO:4)
 TM LQISSLKAEDTAVYYCEREGGVNNWGQGLTVTVSS (SEQ ID NO:17)
 TM.D92E LQISSLKAEDTAVYYCEREGGVNNWGQGLTVTVSS (SEQ ID NO:17)
 SIESD LQISSLKAEDTAVYYCEREGGVNNWGQGLTVTVSS (SEQ ID NO:17)
 SIESD.N103S LQISSLKAEDTAVYYCEREGGVSNWGQGLTVTVSS (SEQ ID NO:20)

FIG. 1B

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SIESD (AFD.v8) Light Chain

DIQVTQSPSS LSASVGDRVIT ITCIIISIE SDMNWYQQKP GKVPKLLISG GNTLRPGVPS 60
 RFSGSGSGTD FTLTISSLQP EDVATYYCLO SDSLPYIFGQ GTKVEIKRTV AAPSVFIFPP 120
 SDEQLKSGTA SVVCLLNIFY PREAKVQWKV DNALQSGNSQ ESVTEQDSKD STYLSSTLT 180
 LSKADYEKHK VYACEVTHQG LSSPVTKSFN RGEC (SEQ ID NO:26) 214

SIESD (AFD.v8) Heavy Chain

EVQLVQSGPE LKPGASVKV SCKASGYTFT NYGMNwVRQA PGQGLEwMGw INTYTGETTY 60
~~A~~EDFKGRFVF SLDTSVSTAY LQISSLKAED TAVYYCEREG GVNNWGQGTL VTVSSASTKG 120
 PSVFPLAPSS KSTSGGTAAL GCLVKDYFPE PVTVSWNSGA LTSGVHTFPA VLQSSGLYSL 180
 SSWWTVPSSS LGTQTYICNV NHKPSNTKVD KKVEPKSCDK THT (SEQ ID NO:27) 223

Cys-Modified SIESD (AFD.v8) Heavy Chain

EVQLVQSGPE LKPGASVKV SCKASGYTFT NYGMNwVRQA PGQGLEwMGw INTYTGETTY 60
~~A~~EDFKGRFVF SLDTSVSTAY LQISSLKAED TAVYYCEREG GVNNWGQGTL VTVSSASTKG 120
 PSVFPLAPSS KSTSGGTAAL GCLVKDYFPE PVTVSWNSGA LTSGVHTFPA VLQSSGLYSL 180
 SSWWTVPSSS LGTQTYICNV NHKPSNTKVD KKVEPKSCDK THTC (SEQ ID NO:30) 223

Cys-Pro-Pro-Cys-Modified SIESD (AFD.v8) Heavy Chain

EVQLVQSGPE LKPGASVKV SCKASGYTFT NYGMNwVRQA PGQGLEwMGw INTYTGETTY 60
~~A~~EDFKGRFVF SLDTSVSTAY LQISSLKAED TAVYYCEREG GVNNWGQGTL VTVSSASTKG 120
 PSVFPLAPSS KSTSGGTAAL GCLVKDYFPE PVTVSWNSGA LTSGVHTFPA VLQSSGLYSL 180
 SSWWTVPSSS LGTQTYICNV NHKPSNTKVD KKVEPKSCDK THTCPPC (SEQ ID NO:31) 223

FIG. 1C

SIESD.N103S (AFD.v14) Light Chain

DIQVTQSPSS	LSASVGDRV	ITCIITISIE	SDMNWYQQKP	GKVPKLLISG	GNTLRPGVPS	60
RFSGSGGTD	FTLTISLQP	EDVATYYCLO	SDSLPYIFGQ	GTKVEIKRTV	AAPSVFIFPP	120
SDEQLKSGTA	SVVCLLNIFY	PREAKVQWKV	DNALQSGNSQ	ESVTEQDSKD	STYLSSTLT	180
LSKADYEKHK	VYACEVTHQG	LSSPVTKSFN	RGEC	(SEQ ID NO:28)		214

SIESD.N103S (AFD.v14) Heavy Chain

EVQLVQSGPE	LKPGASVKV	SKASGYTFT	NYGMNwVRQA	PGQGLEwMGw	INTYTGETTY	60
<u>A</u> EDFKGRFVF	SLDTSVSTAY	LQISSLKAED	TAVYYCEREG	<u>GV</u> SNwGQGT	VTVSSASTKG	120
PSVFPLAPSS	KSTSGGTAAL	GCLVKDYFPE	PVTVSwNSGA	LTSGVHTFPA	VLQSSGLYSL	180
SSWTVTPSSS	LGTQTYICNV	NHKPSNTKVD	KKVEPKSCDK	THT	(SEQ ID NO:29)	223

Cys-Modified SIESD.N103S (AFD.v14) Heavy Chain

EVQLVQSGPE	LKPGASVKV	SKASGYTFT	NYGMNwVRQA	PGQGLEwMGw	INTYTGETTY	60
<u>A</u> EDFKGRFVF	SLDTSVSTAY	LQISSLKAED	TAVYYCEREG	<u>GV</u> SNwGQGT	VTVSSASTKG	120
PSVFPLAPSS	KSTSGGTAAL	GCLVKDYFPE	PVTVSwNSGA	LTSGVHTFPA	VLQSSGLYSL	180
SSWTVTPSSS	LGTQTYICNV	NHKPSNTKVD	KKVEPKSCDK	THTC	(SEQ ID NO:32)	223

Cys-Pro-Pro-Cys-Modified SIESD.N103S (AFD.v14) Heavy Chain

EVQLVQSGPE	LKPGASVKV	SKASGYTFT	NYGMNwVRQA	PGQGLEwMGw	INTYTGETTY	60
<u>A</u> EDFKGRFVF	SLDTSVSTAY	LQISSLKAED	TAVYYCEREG	<u>GV</u> SNwGQGT	VTVSSASTKG	120
PSVFPLAPSS	KSTSGGTAAL	GCLVKDYFPE	PVTVSwNSGA	LTSGVHTFPA	VLQSSGLYSL	180
SSWTVTPSSS	LGTQTYICNV	NHKPSNTKVD	KKVEPKSCDK	THTCPPC	(SEQ ID NO:33)	223

FIG. 1D

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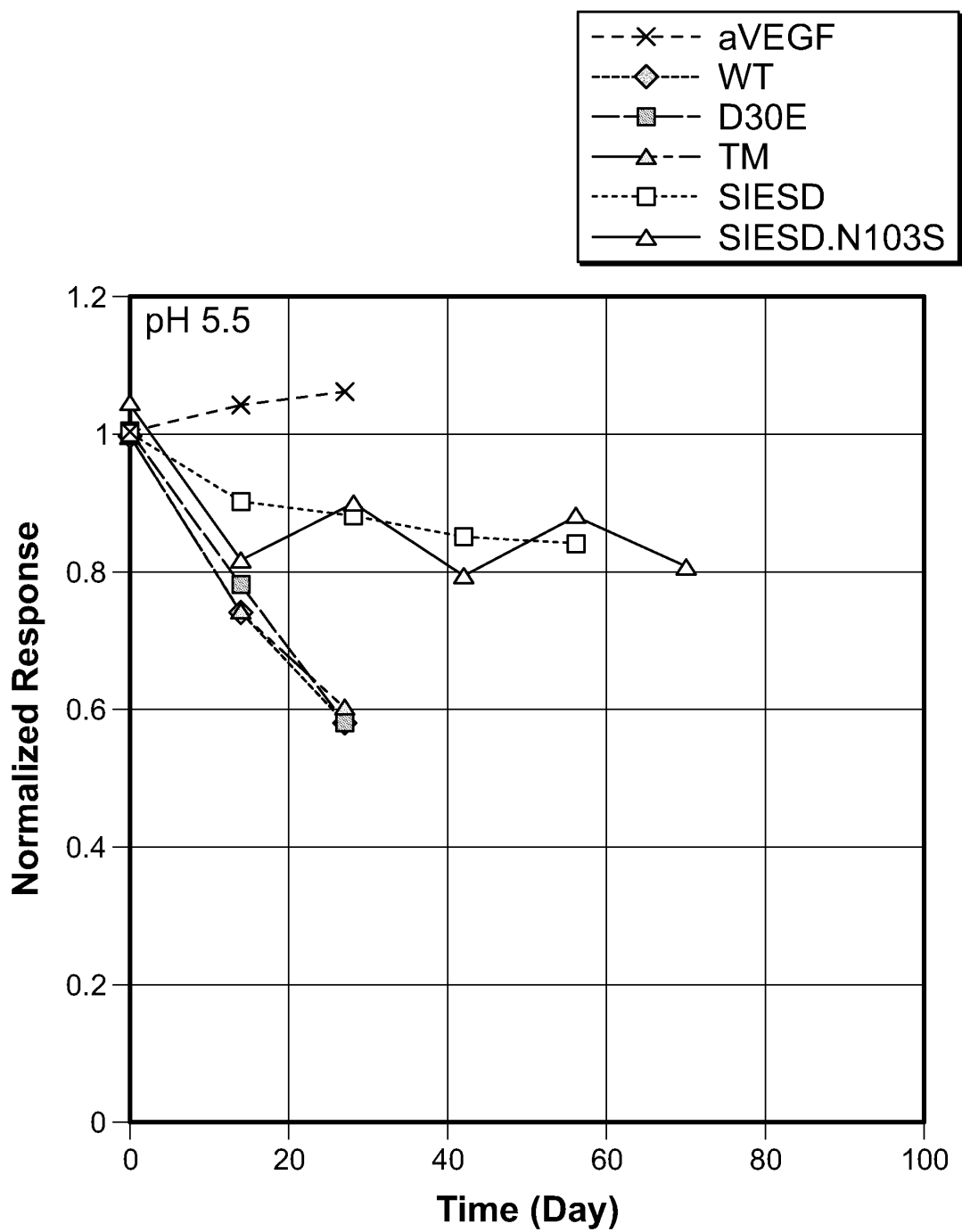


FIG. 2A

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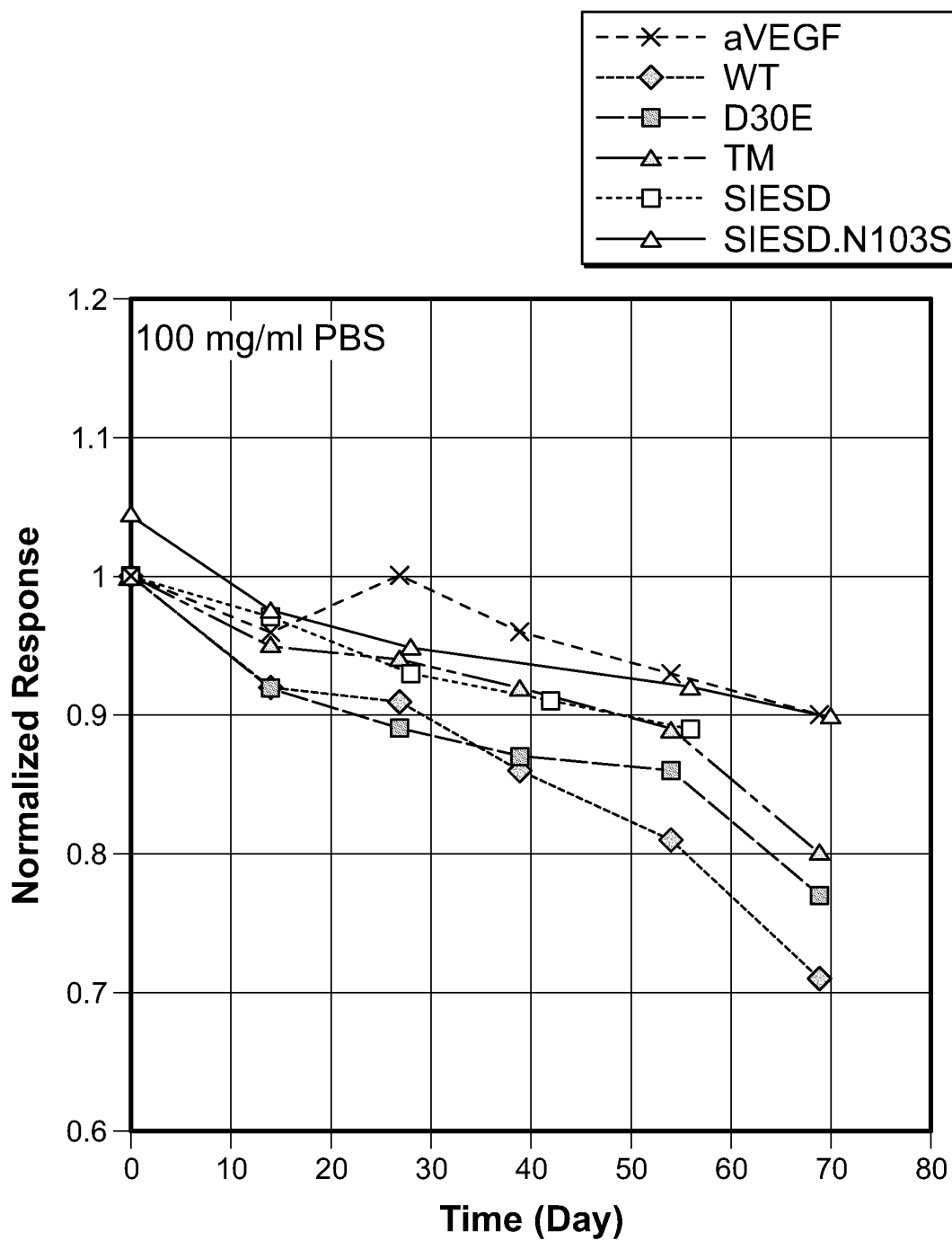


FIG. 2B

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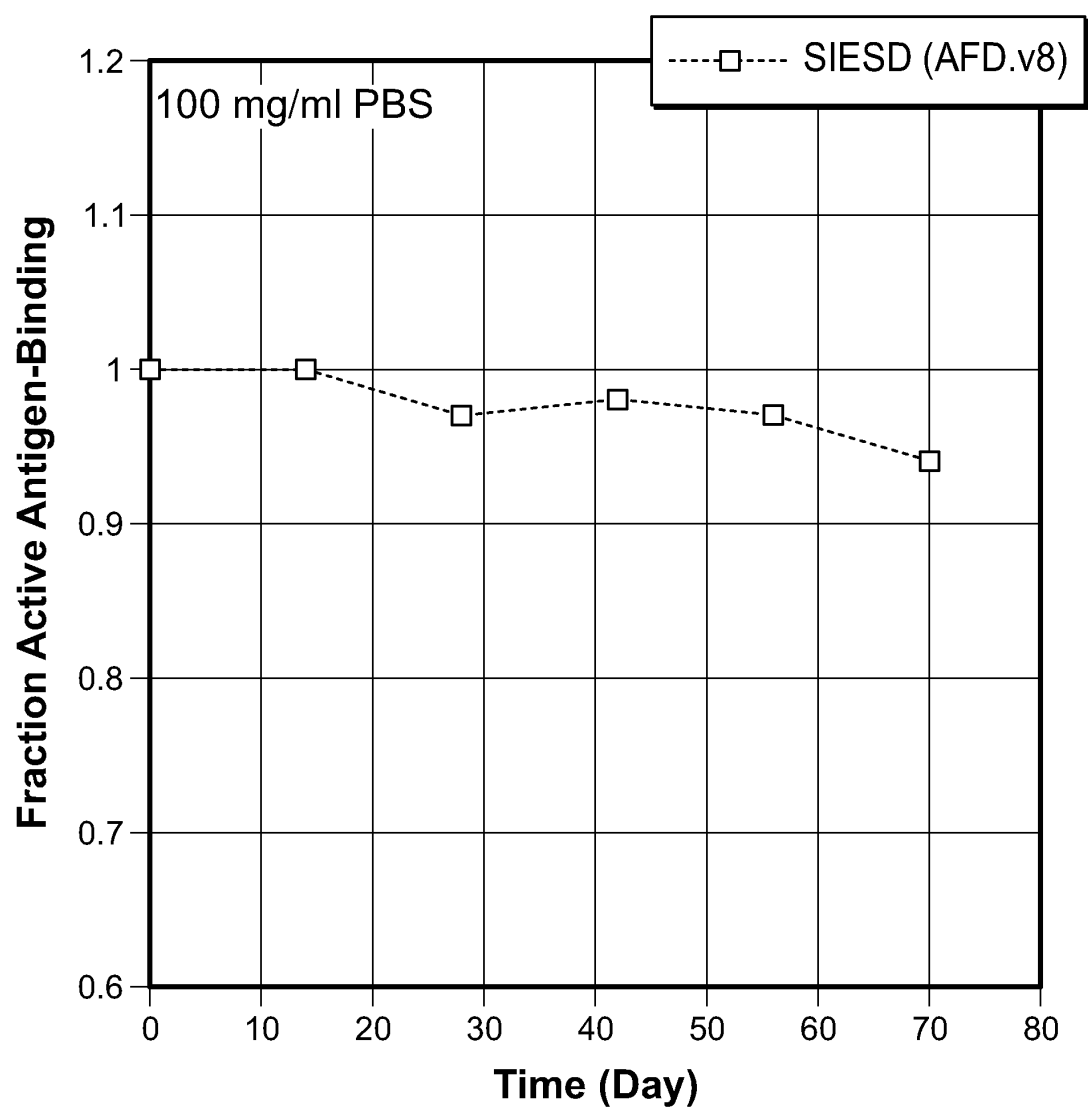


FIG. 2C

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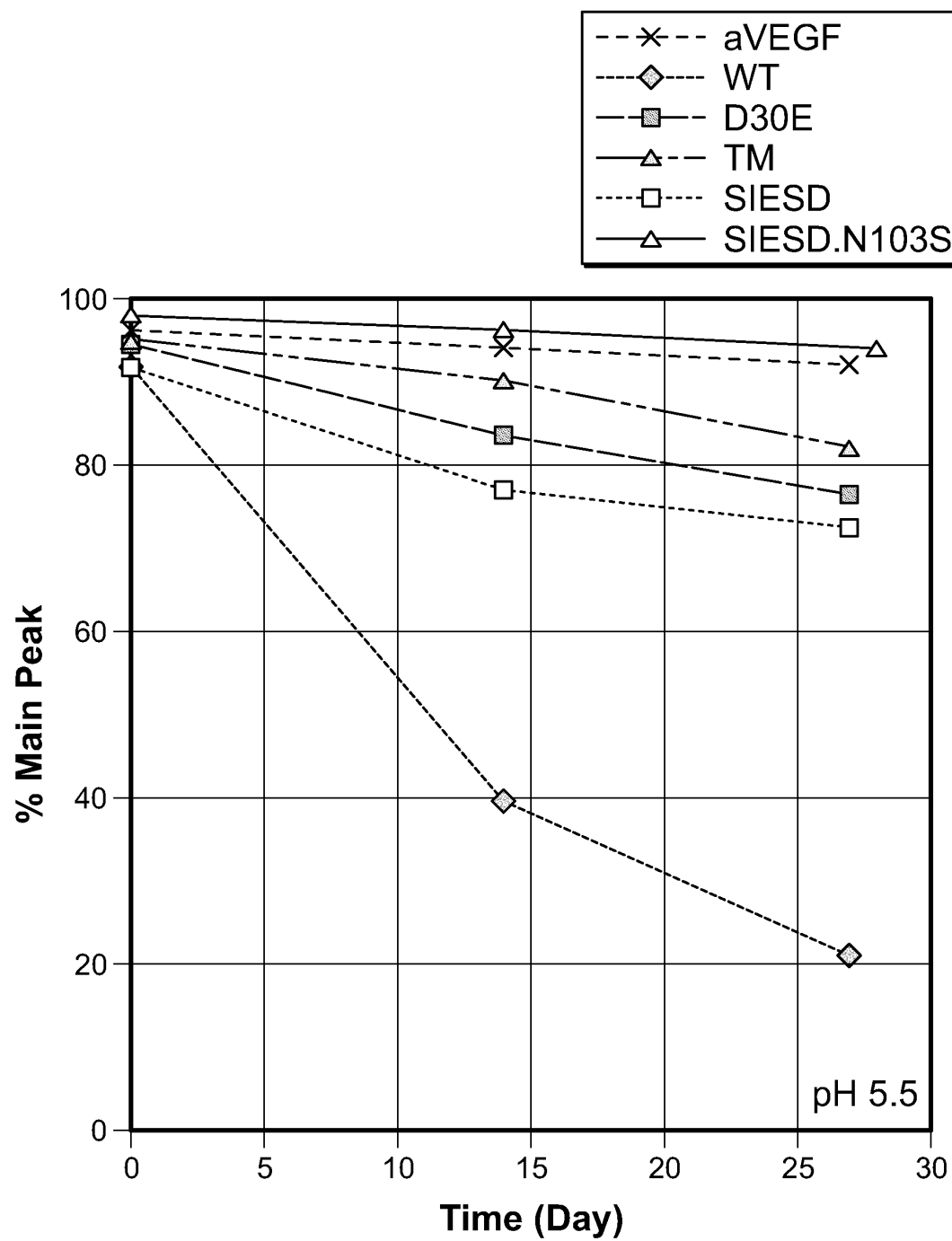


FIG. 3A

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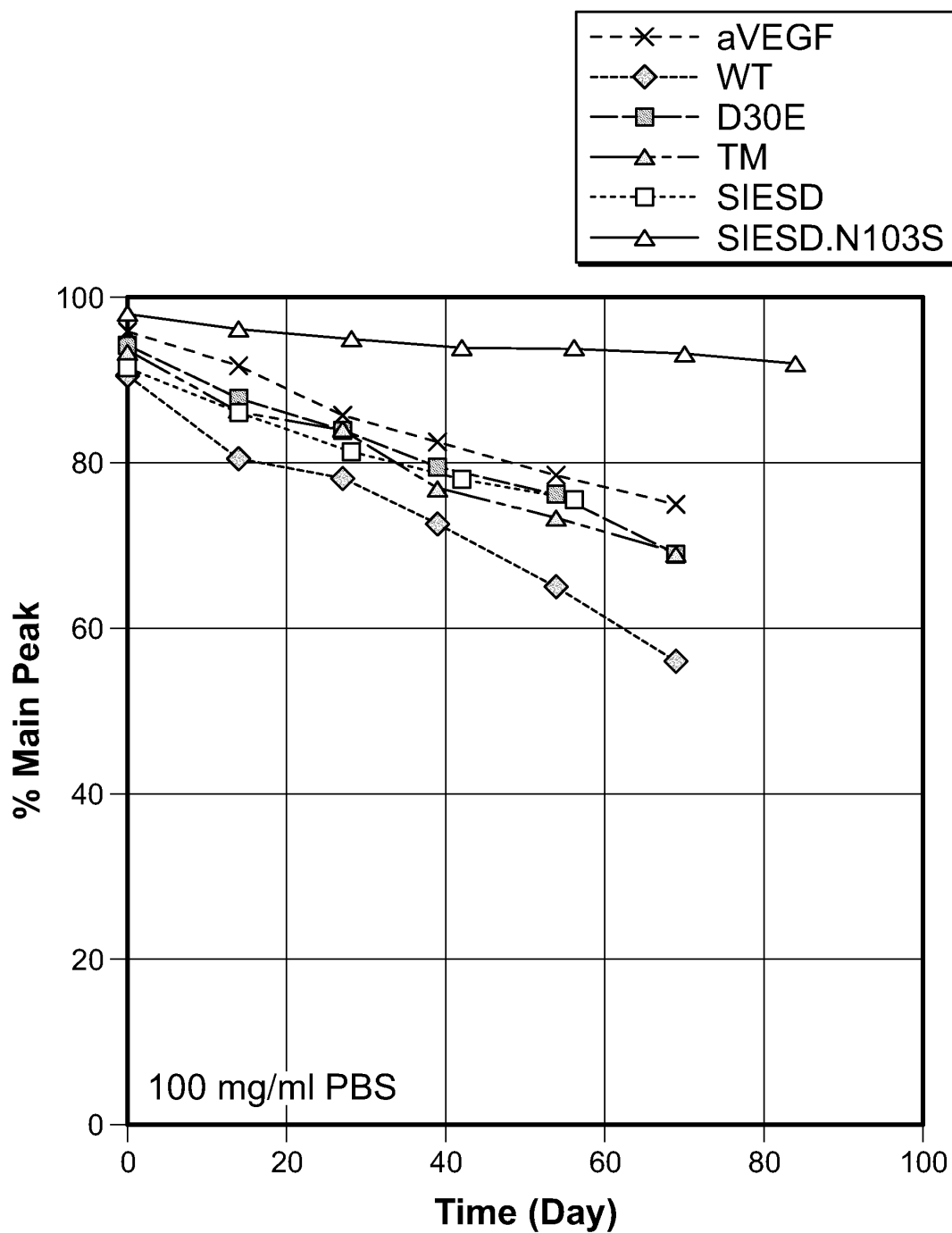


FIG. 3B

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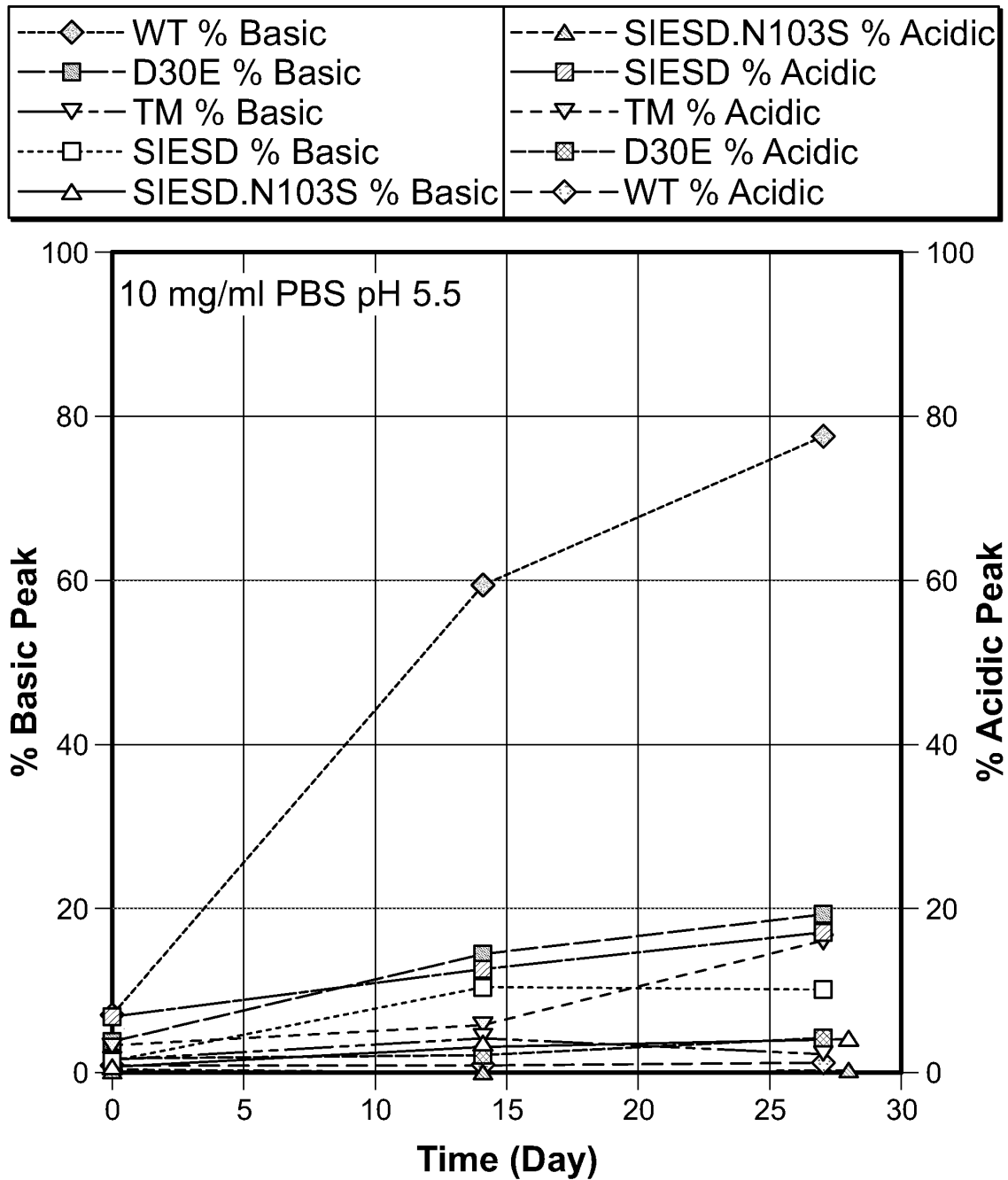


FIG. 4A

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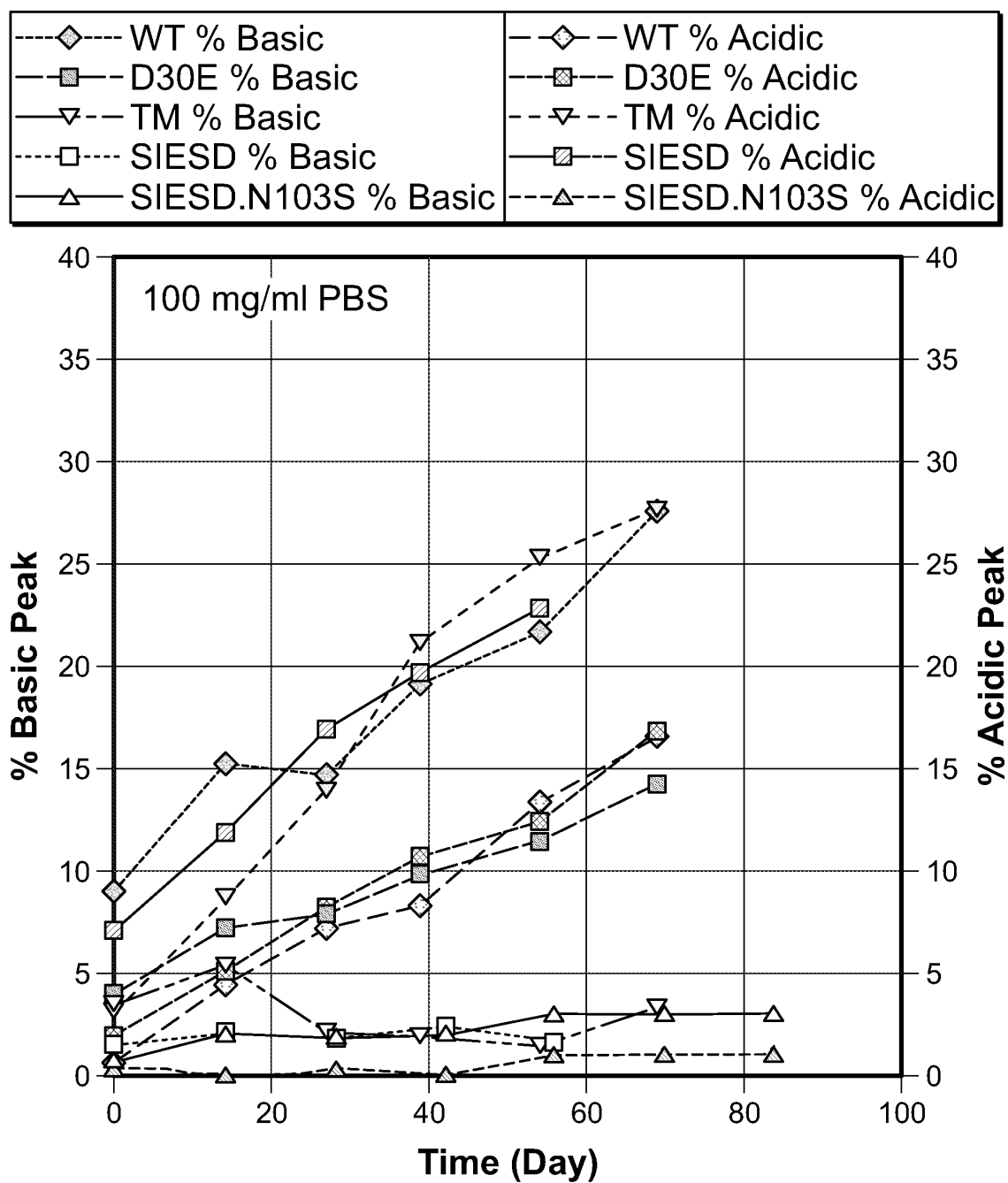


FIG. 4B

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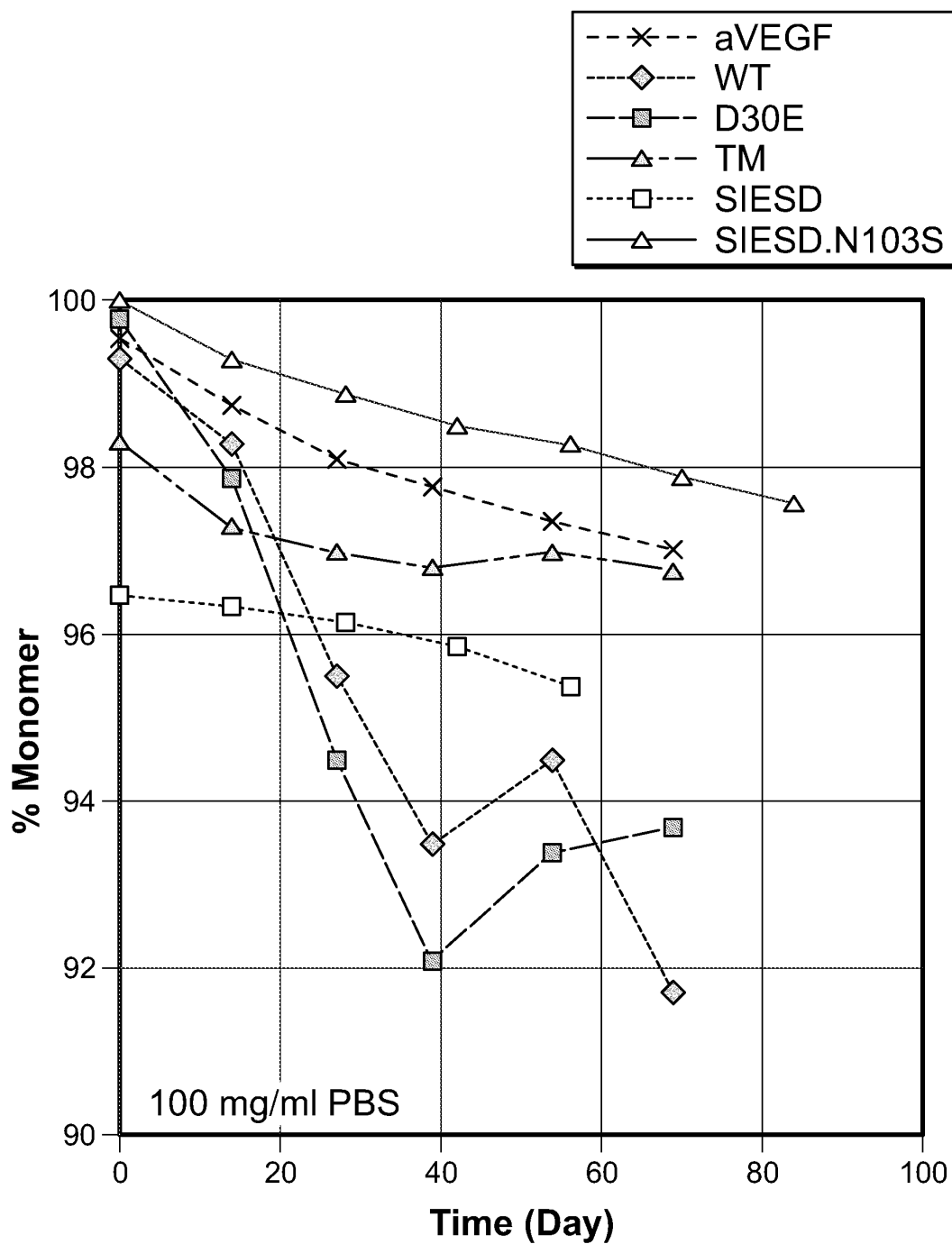


FIG. 5

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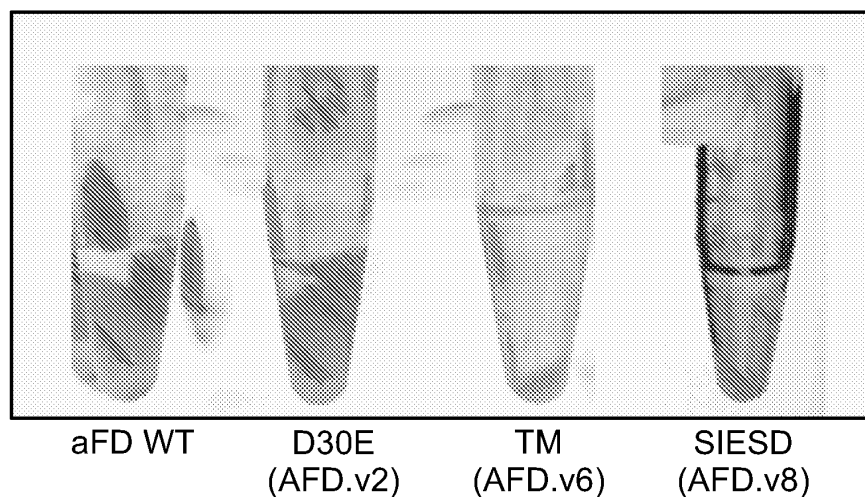


FIG. 6

Solutions after dialysis versus 20mM His-HCl pH 6.0 (top) and subsequent dialysis versus PBS (bottom)

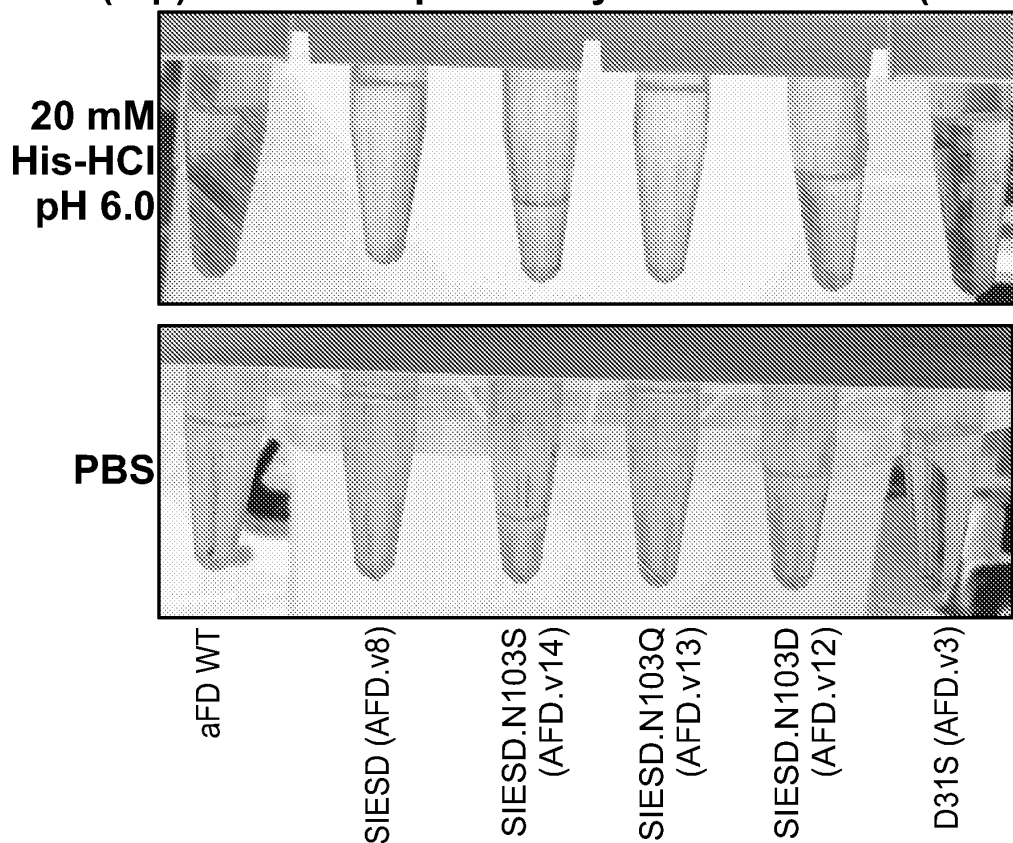


FIG. 7

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Protein Solutions in PBS Buffer

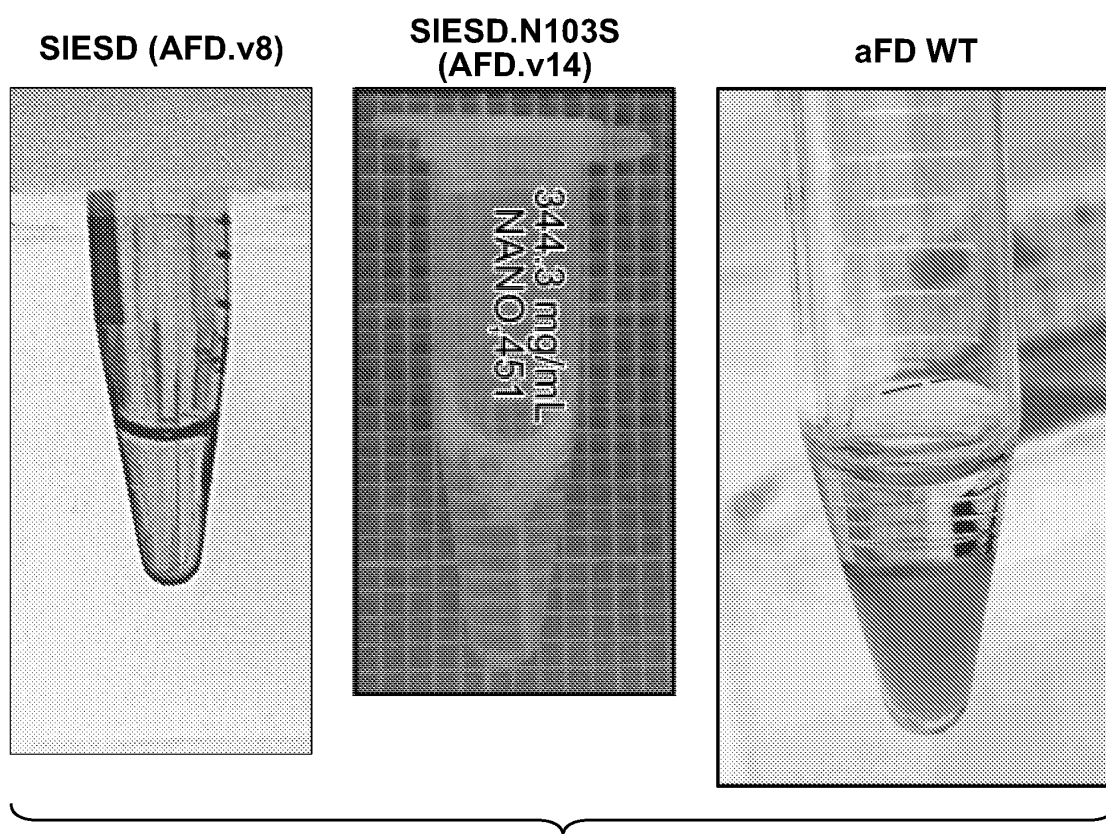
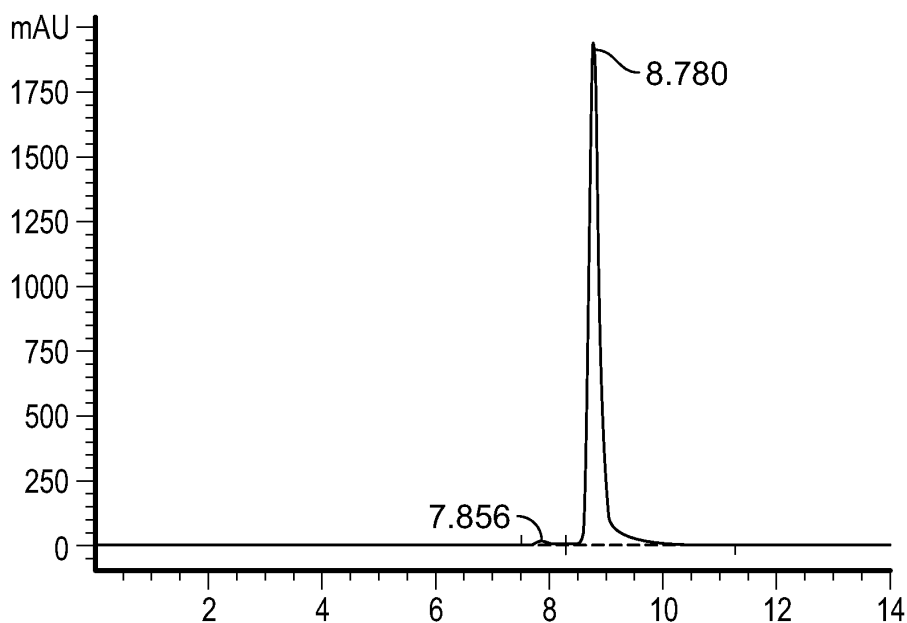


FIG. 8

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SEC Profile for 372 mg/mL SIESD.N103S (AFD.v14) in PBS

DAD1 A, Sig=280, 2 Ref=off

**Area Percent Report**

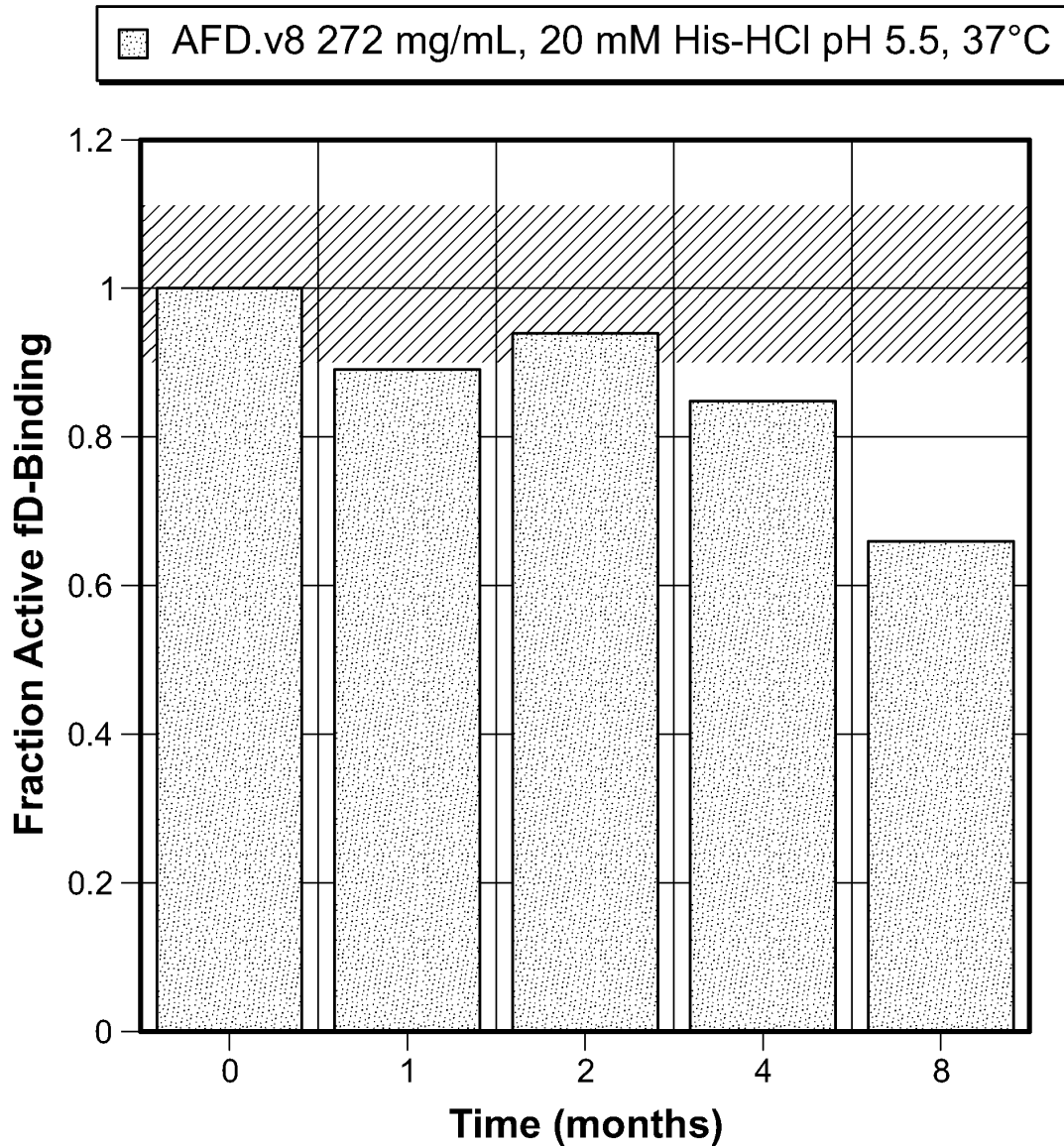
Sorted by : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 A, Sig=280, 2 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.856	VV	0.2537	241.13916	12.69158	0.94195
2	8.780	VB	0.1986	2.53587e4	1939.25708	99.05805
Totals:				2.55999e4	1951.94866	

FIG. 9

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SPR Measurements of factor D binding for high concentration formulation of AFD.v8 upon thermal stress at 37 °C**FIG. 10A**

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Assessment of chemical and physical stability for high concentration (272 mg/mL) formulation (20 mM His-HCL pH 5.5) of AFD.v8 stressed at 37 °C.

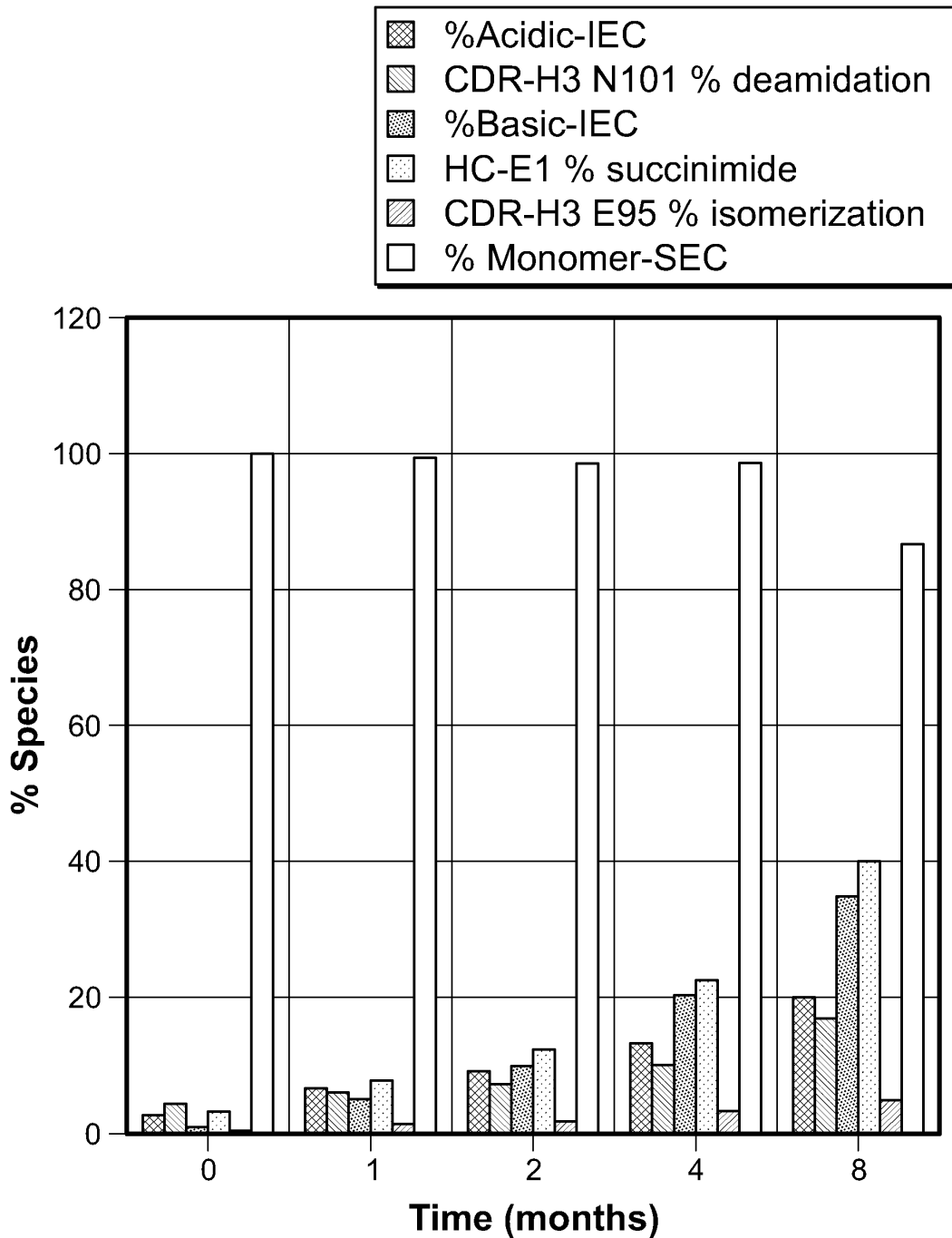
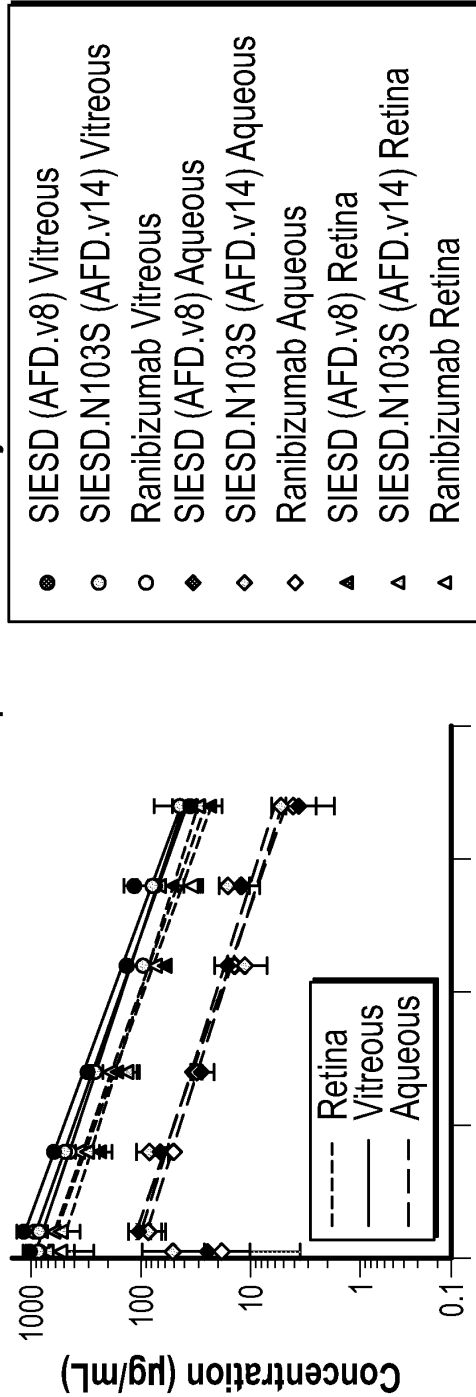


FIG. 10B

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Pharmacokinetics of AFD Variants upon Intravitreal Injection in Rabbits



Molecule*	Vitreous (Liquid)			Aqueous			Retina	
	Half-life (Days)	AUC _{all} (Day*µg/mL)	CL (mL/Day)	V _{ss} (mL)	Half-life (Days)	AUC _{all} (Day*µg/mL)	Half-life (Days)	AUC _{all} (Day*µg/mL)
SIESD (AFD.v8)	3.4	4460	0.22	1.0	3.5	411	3.4	2489
SIESD.N103S (AFD.v14)	3.7	3450	0.28	1.4	4.0	432	4.0	2199
Ranibizumab	3.5	3600	0.27	1.3	3.9	353	3.5	2453

*1 mg/eye dose, study 14-0995

FIG. 11

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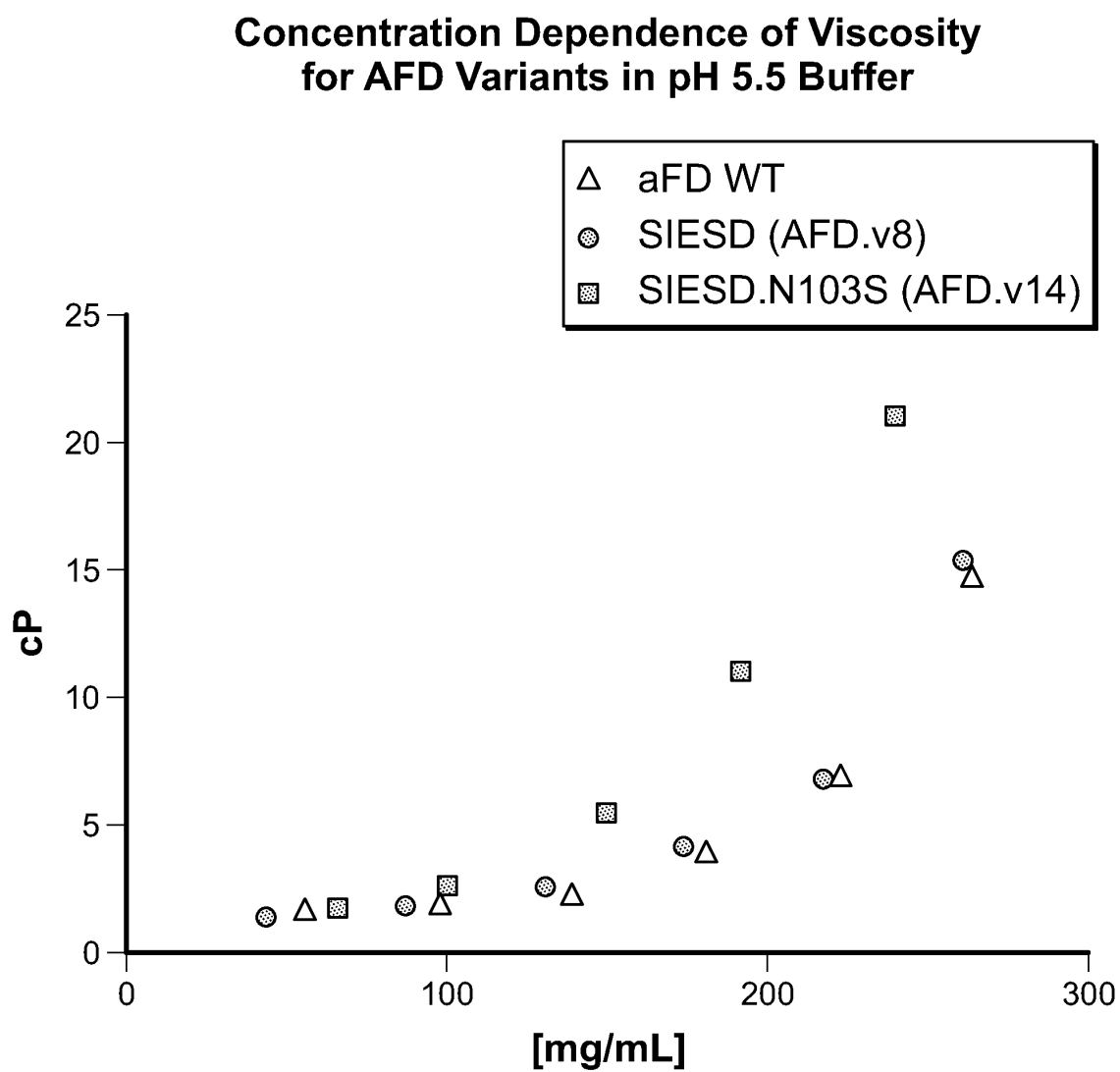
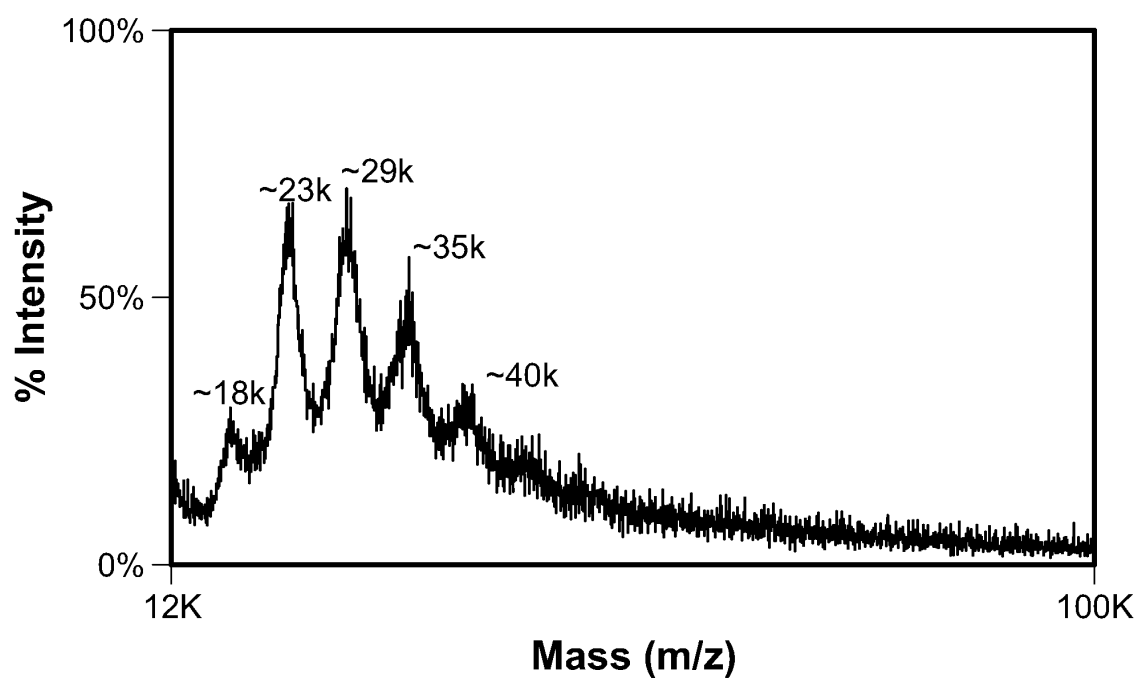


FIG. 12

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Hexaglycerol Core

Polydispersity ~1.33

**FIG. 13A**

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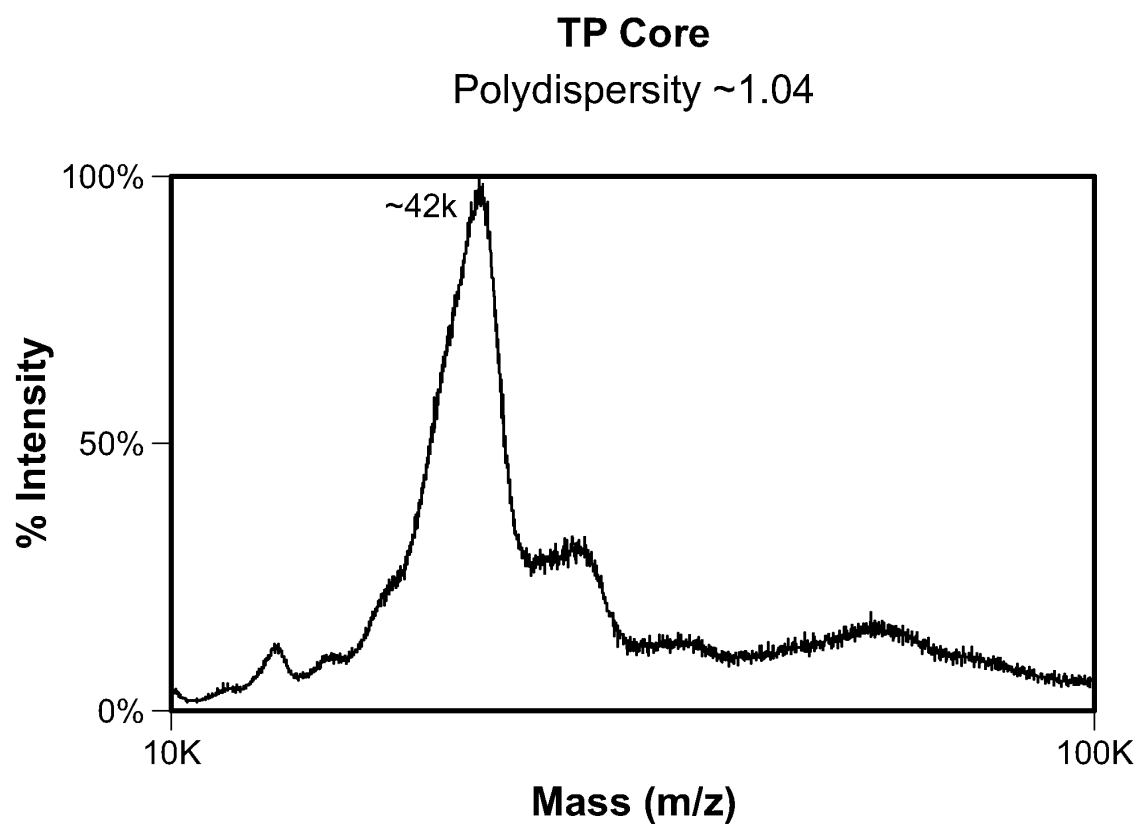


FIG. 13B

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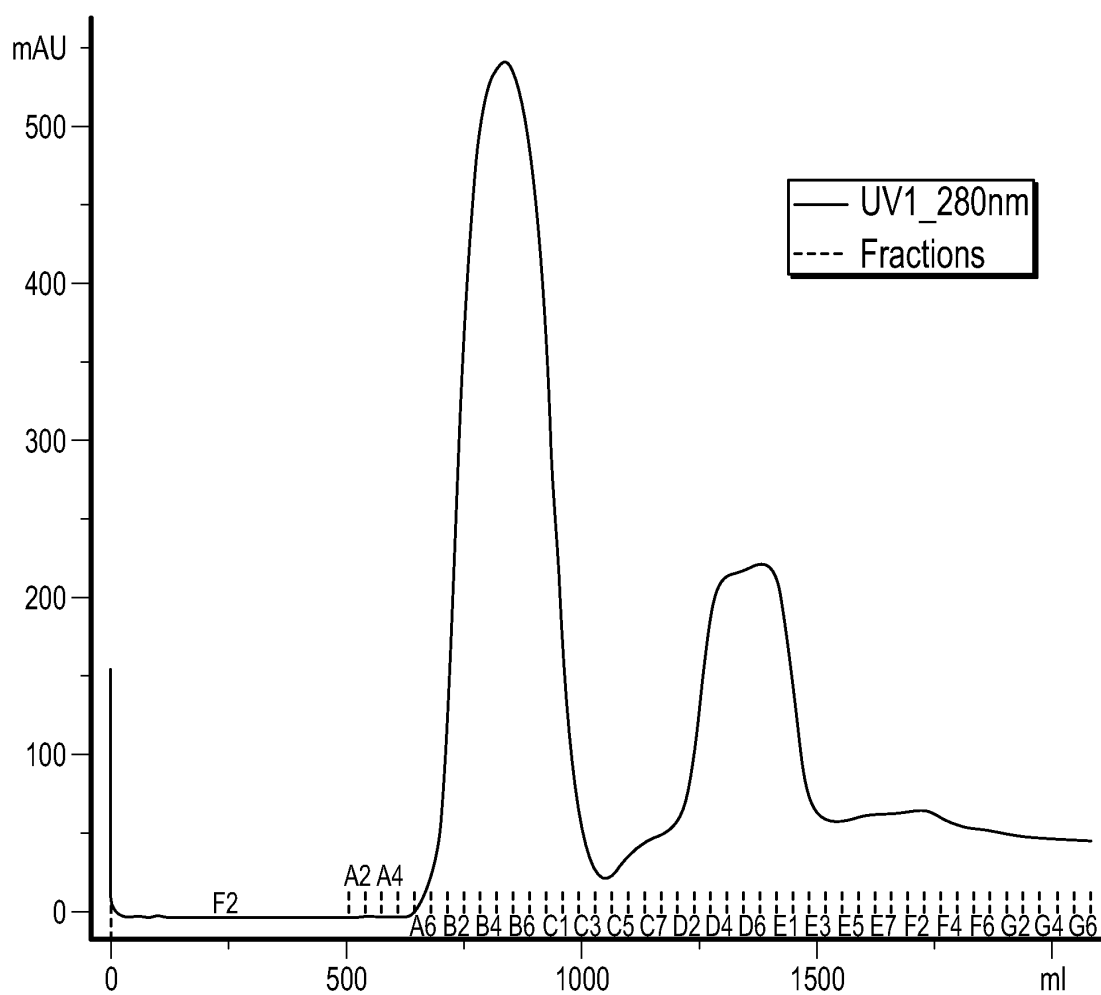
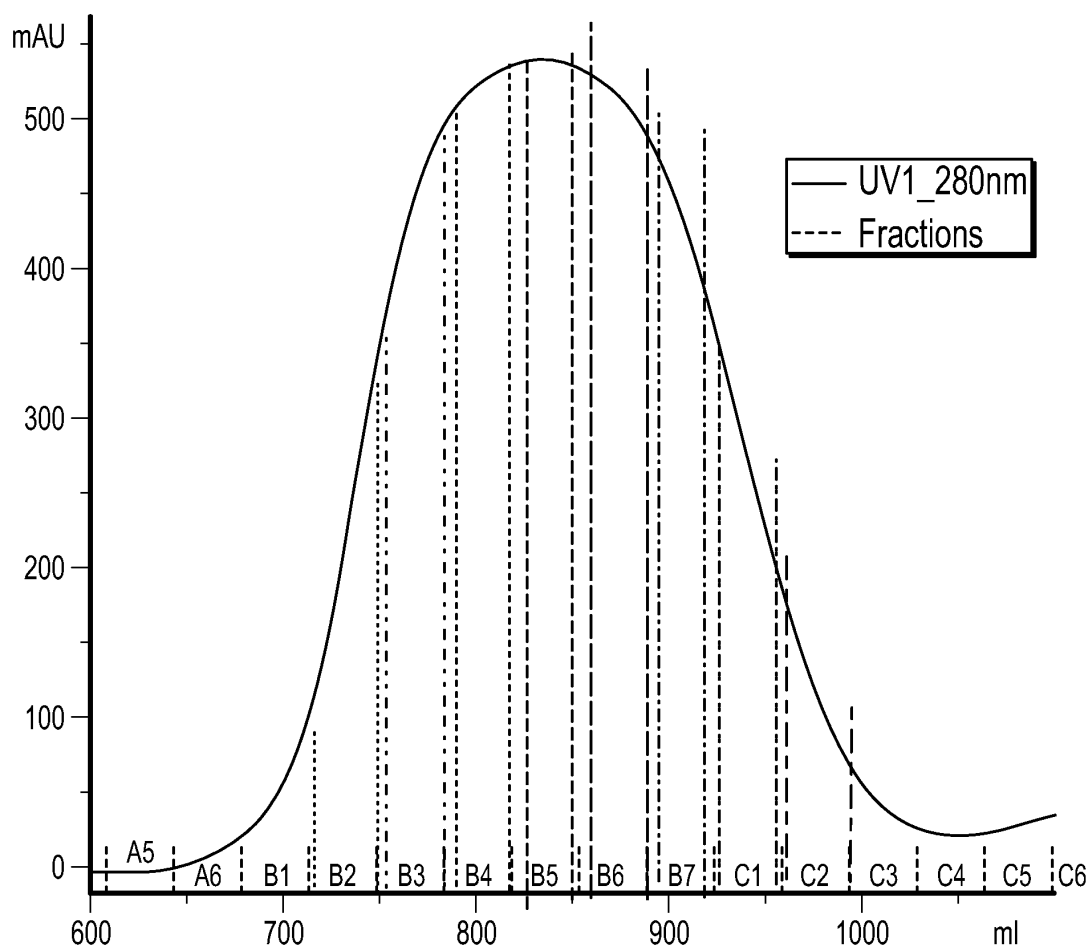
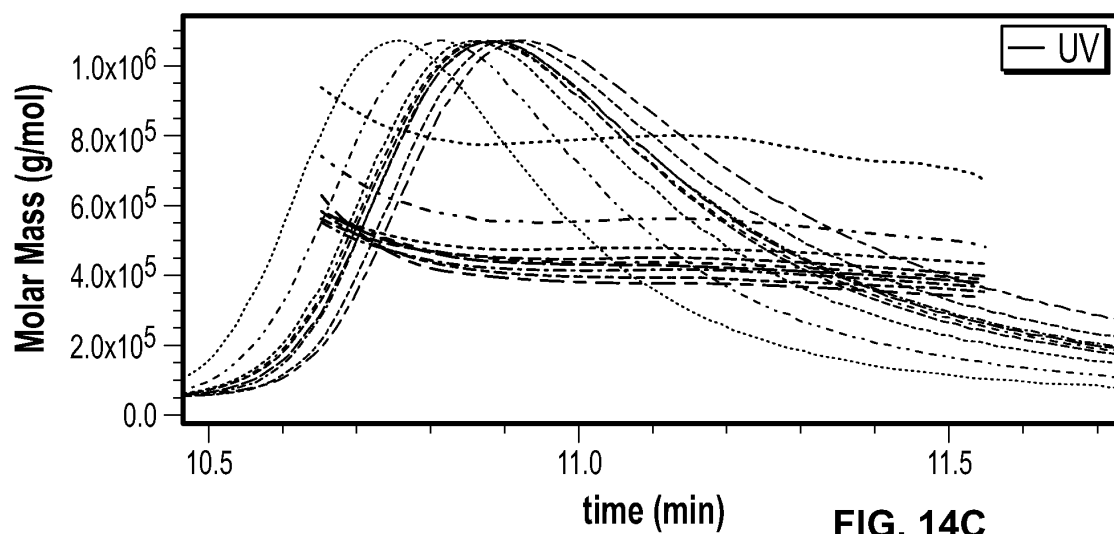


FIG. 14A

23/62**FIG. 14B****FIG. 14C**

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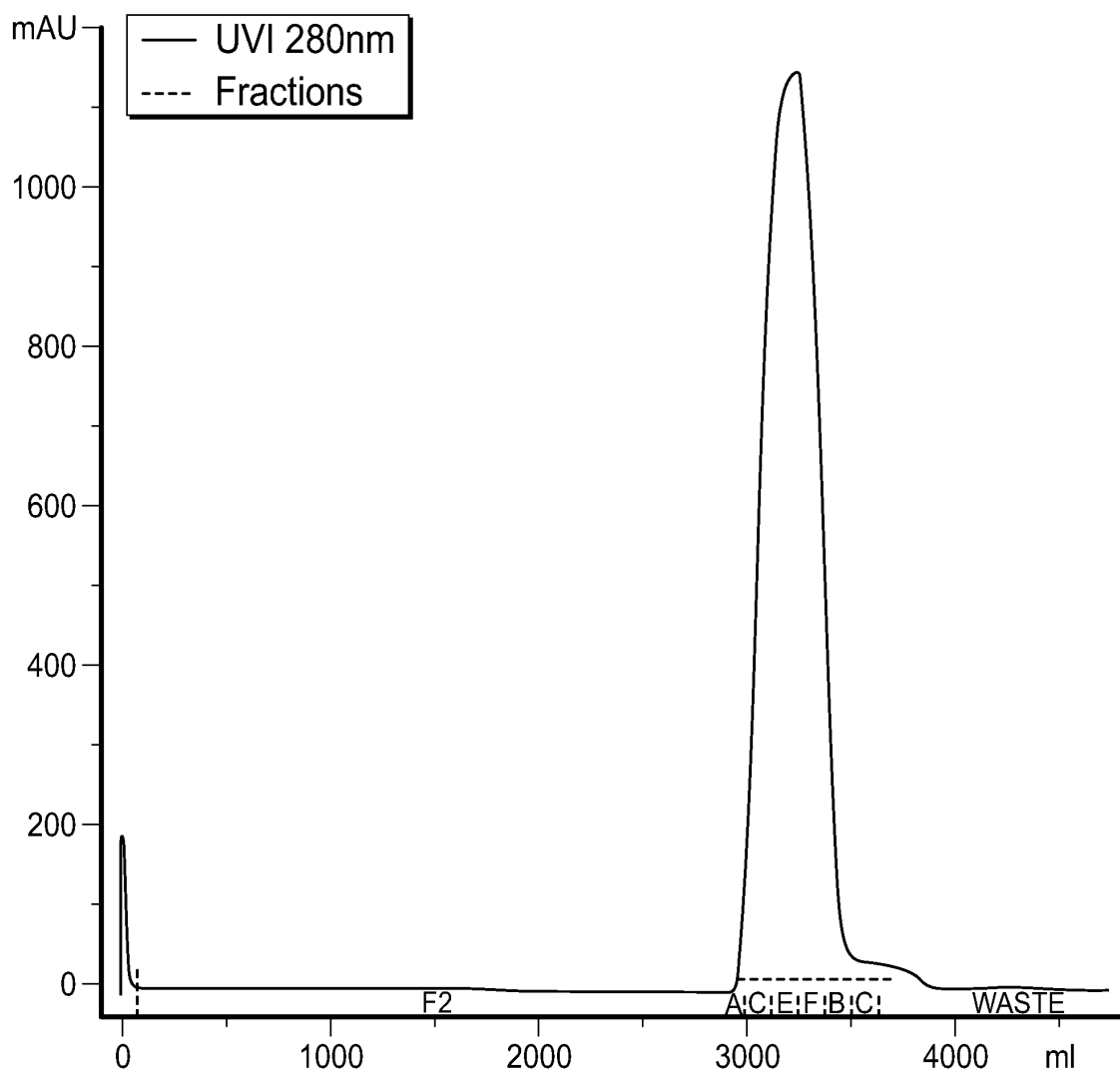


FIG. 15A

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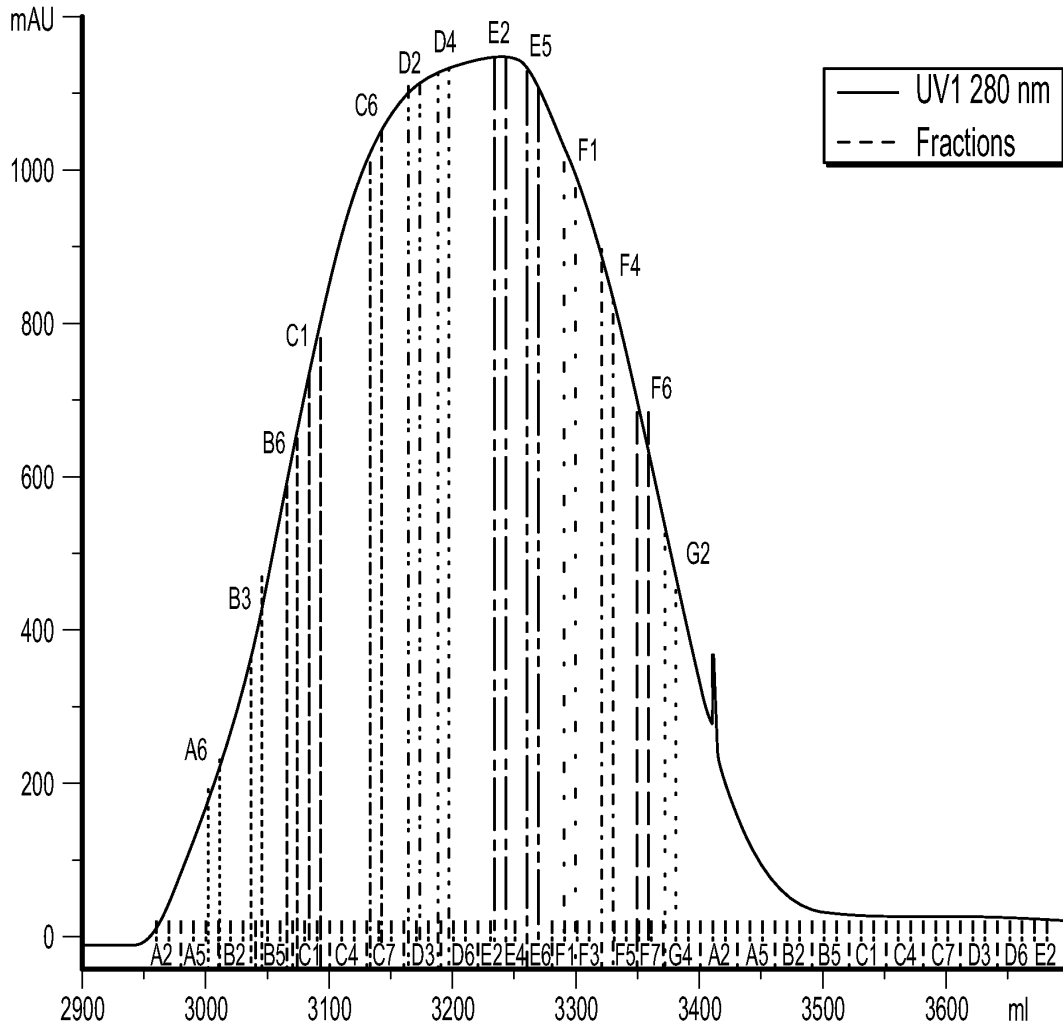


FIG. 15B

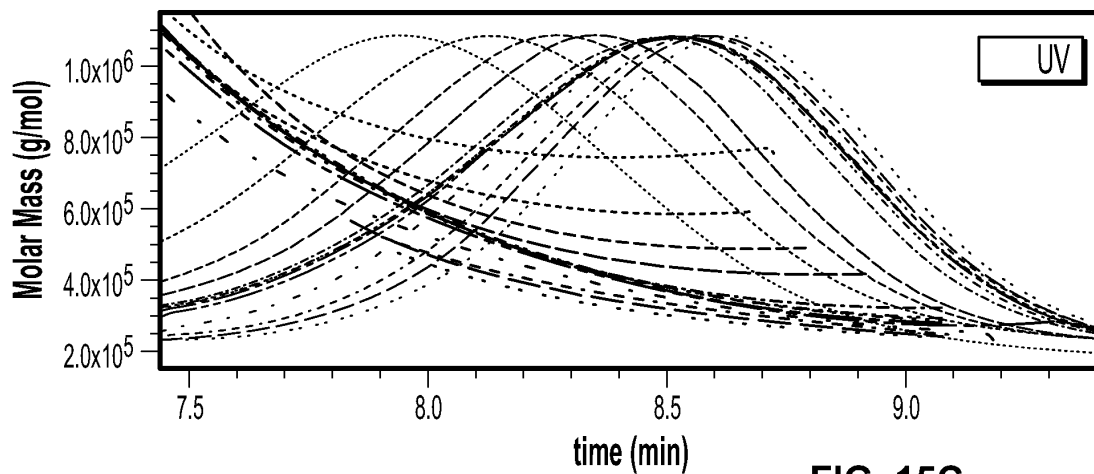
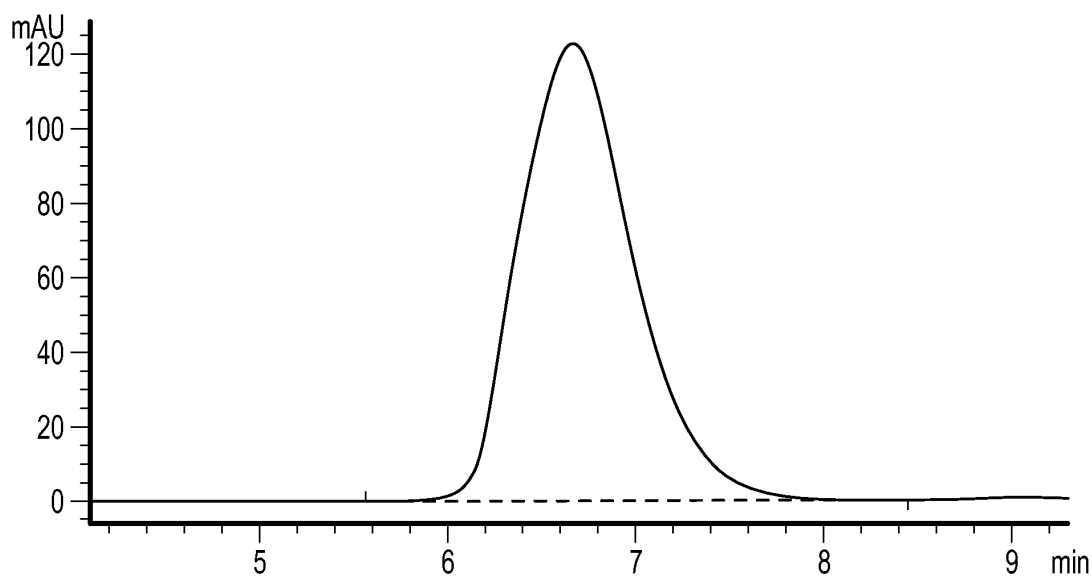
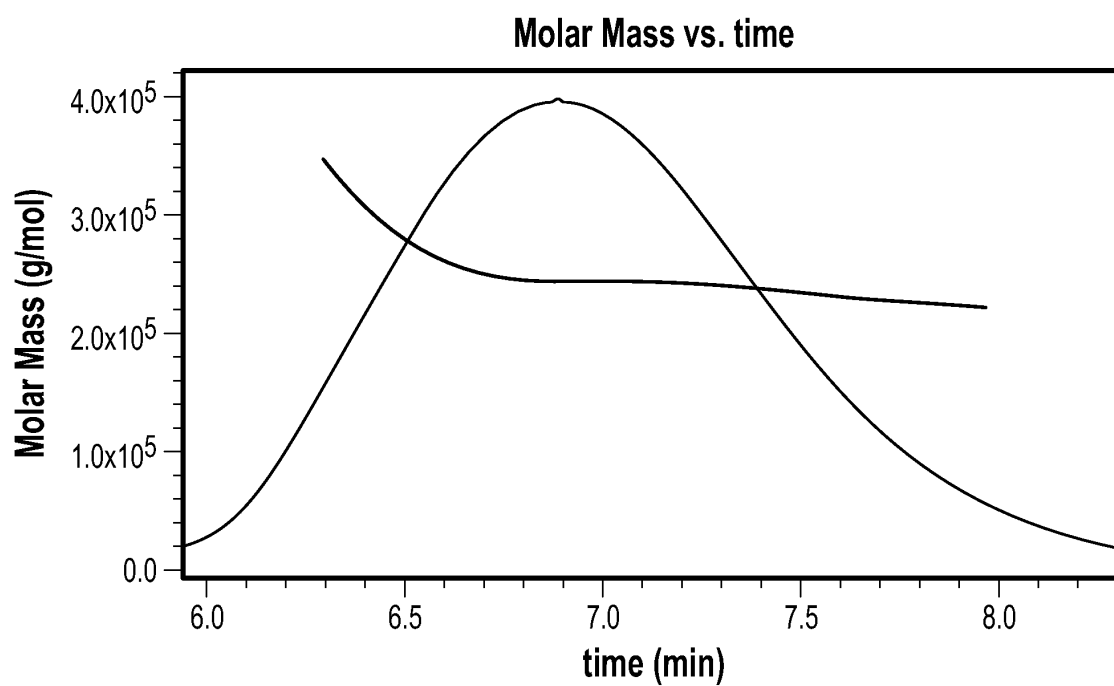
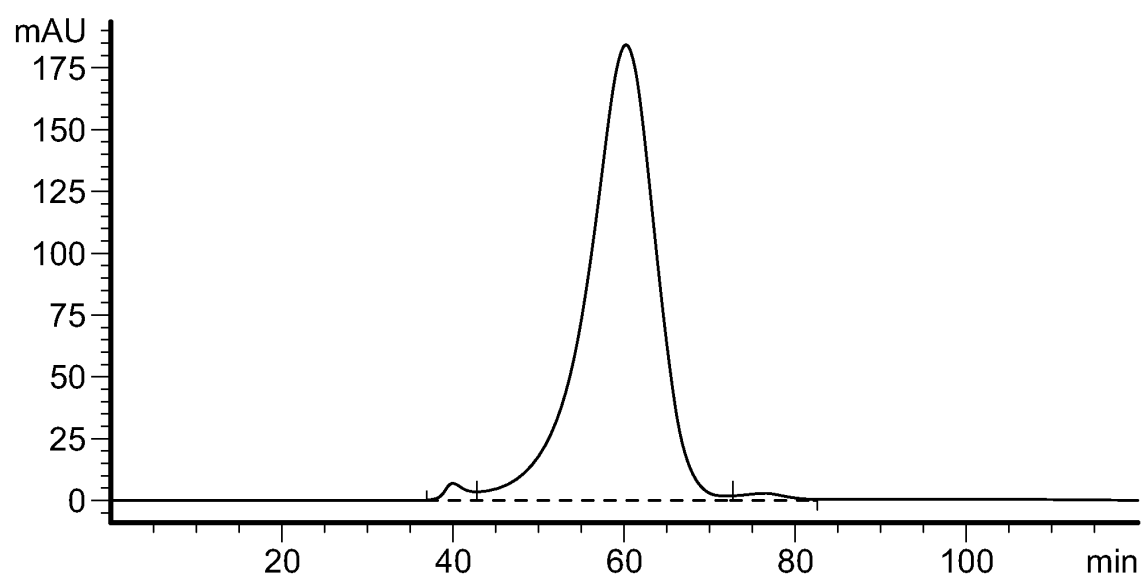


FIG. 15C

26/62**FIG. 16A****FIG. 16B**

27/62**FIG. 17A**

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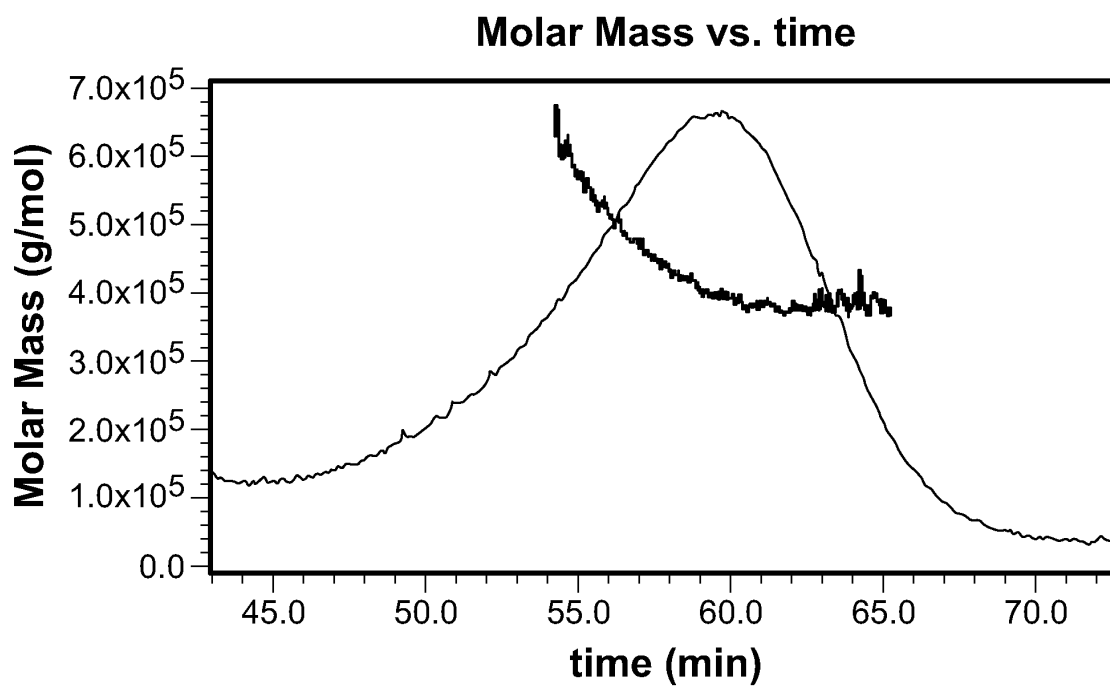


FIG. 17B

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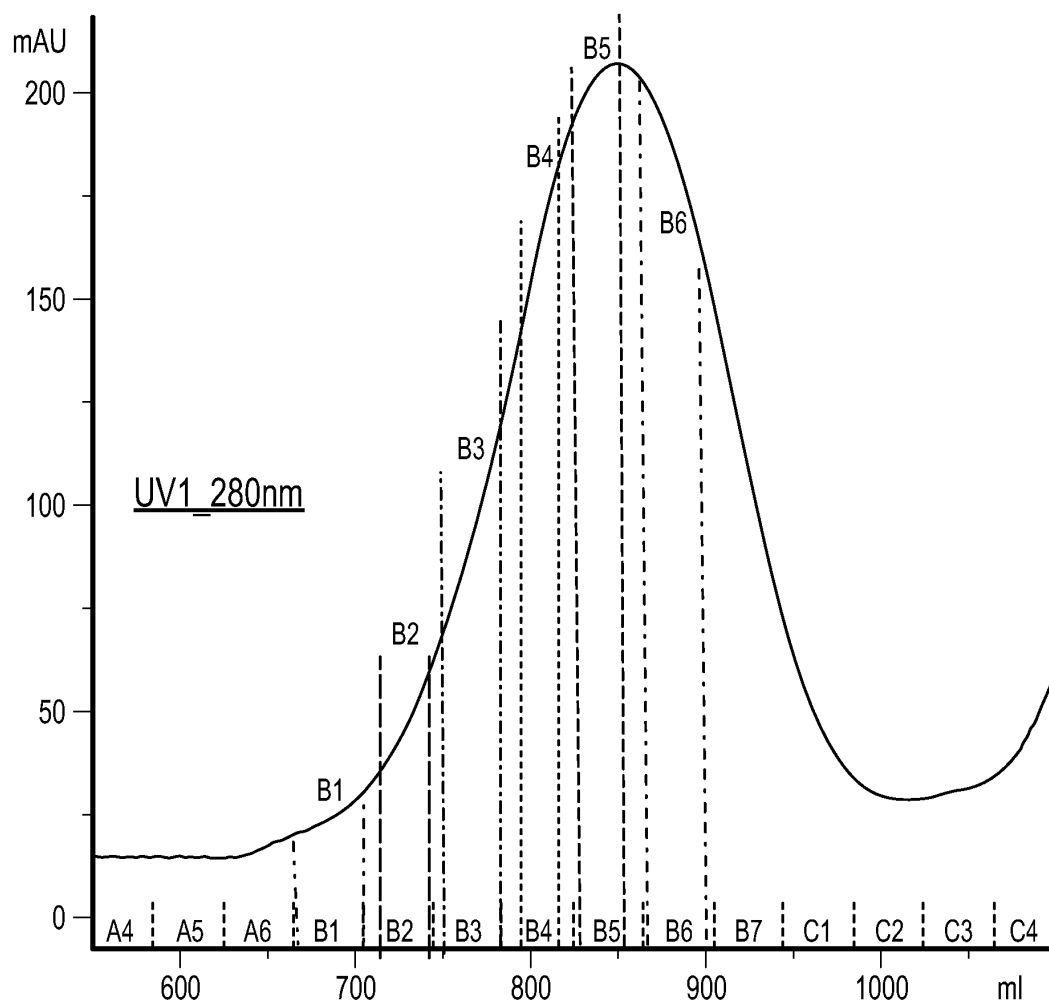


FIG. 18A

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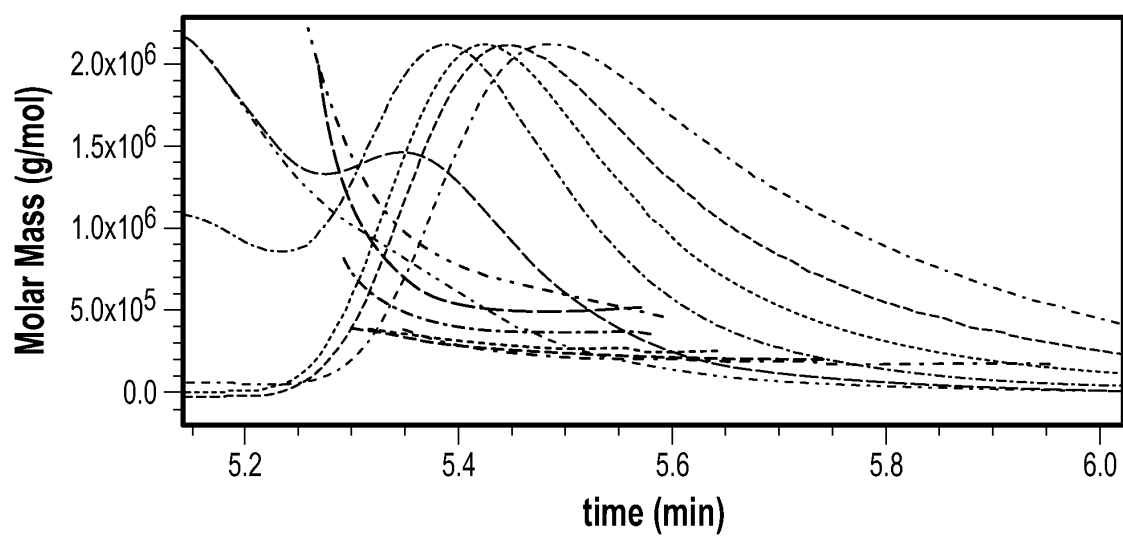


FIG. 18B

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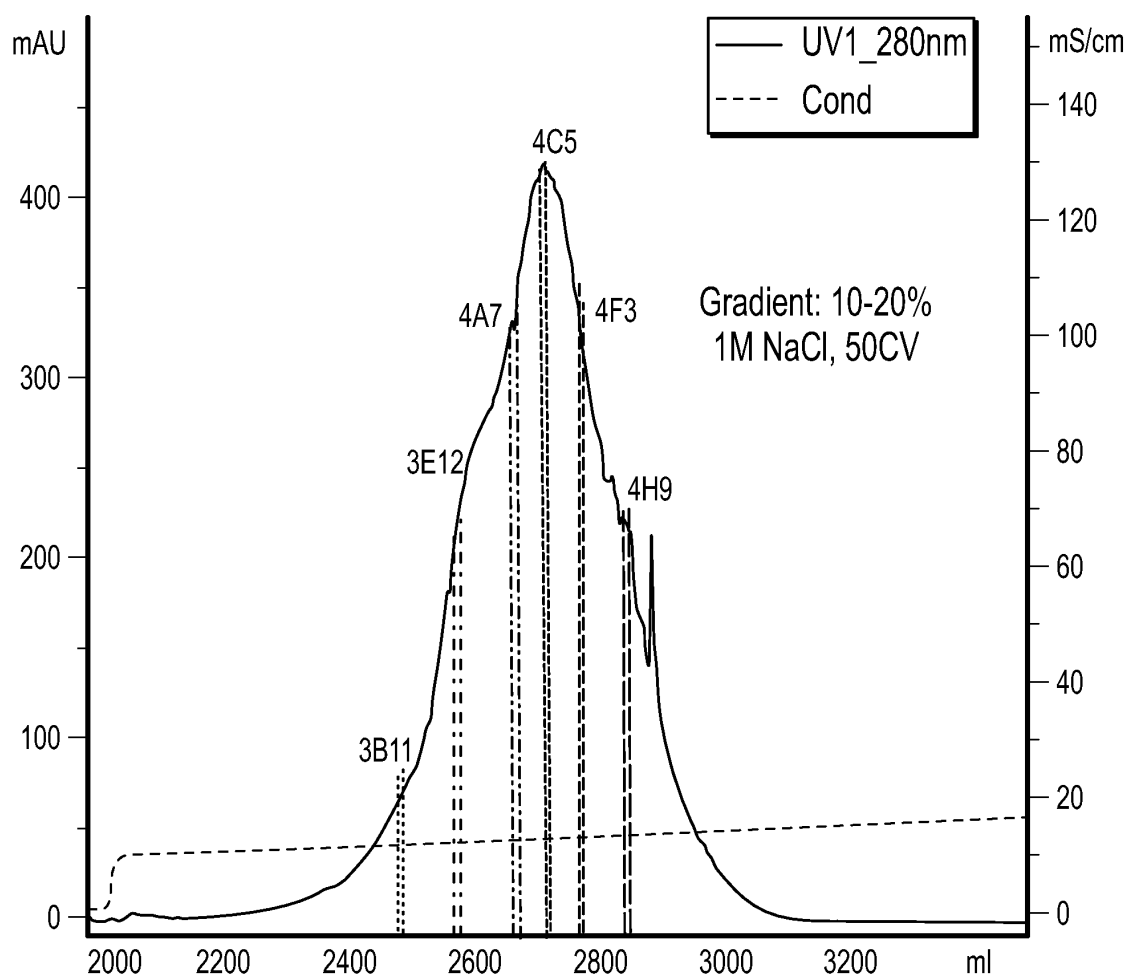


FIG. 19A

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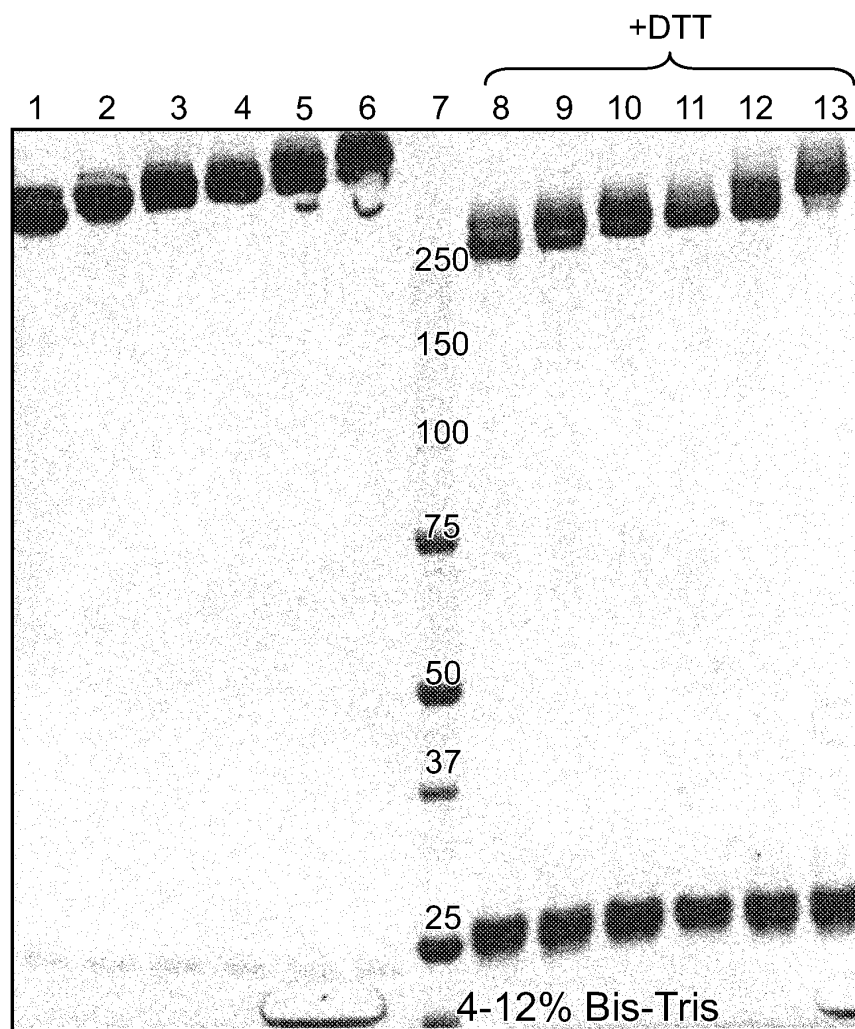


FIG. 19B

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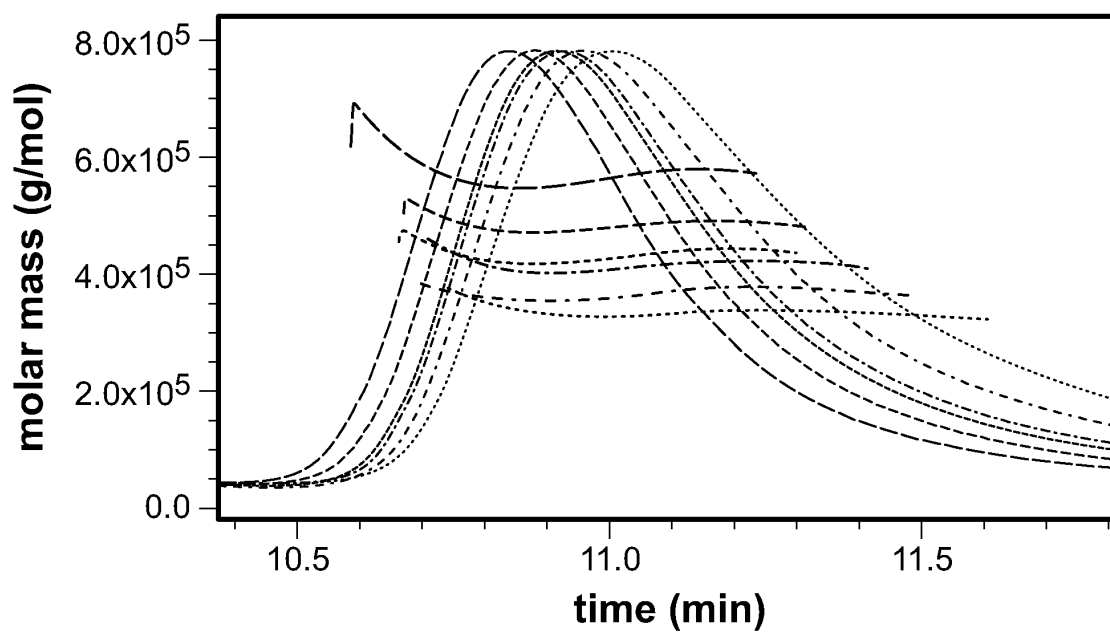


FIG. 19C

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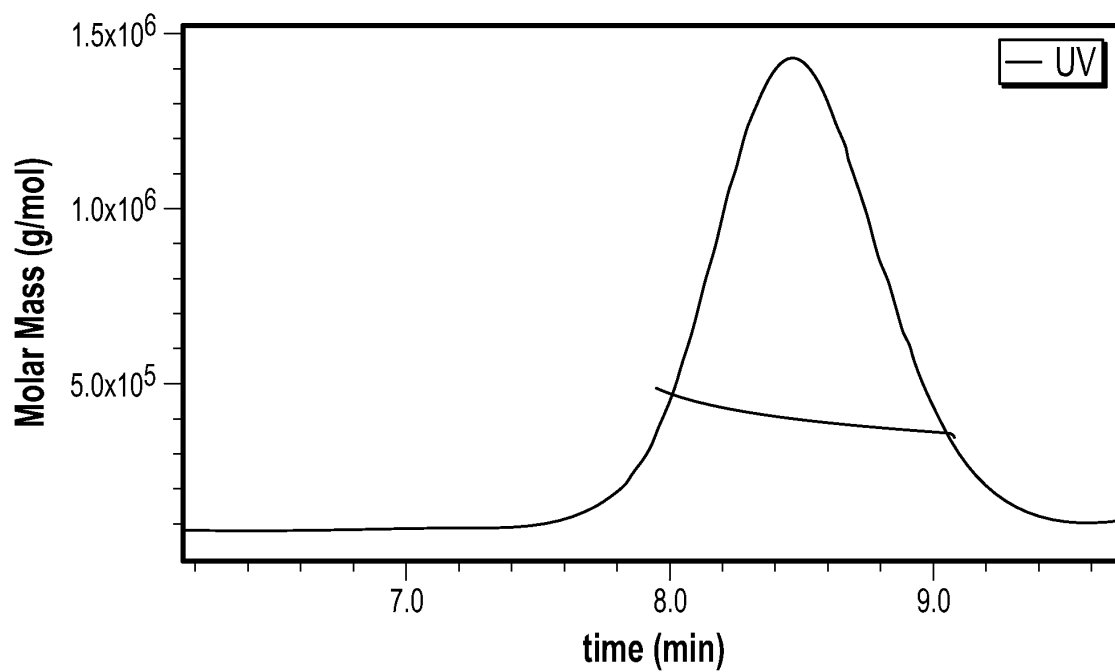


FIG. 20

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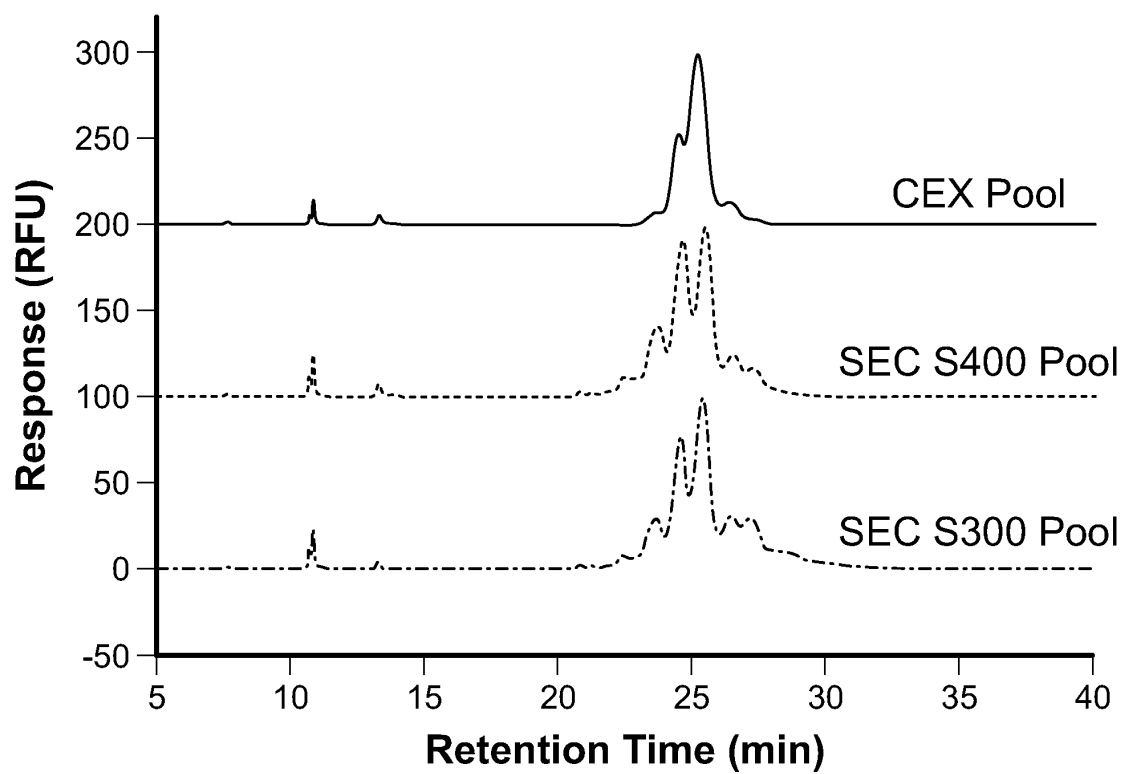


FIG. 21A

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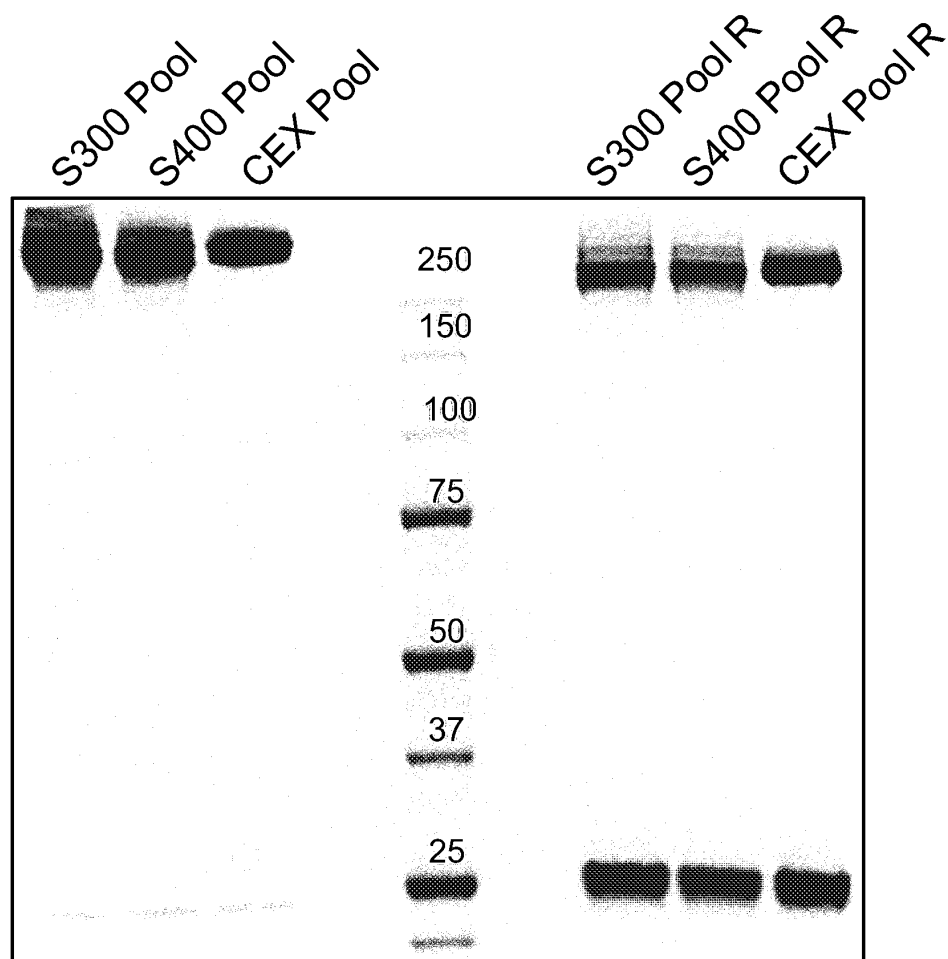


FIG. 21B

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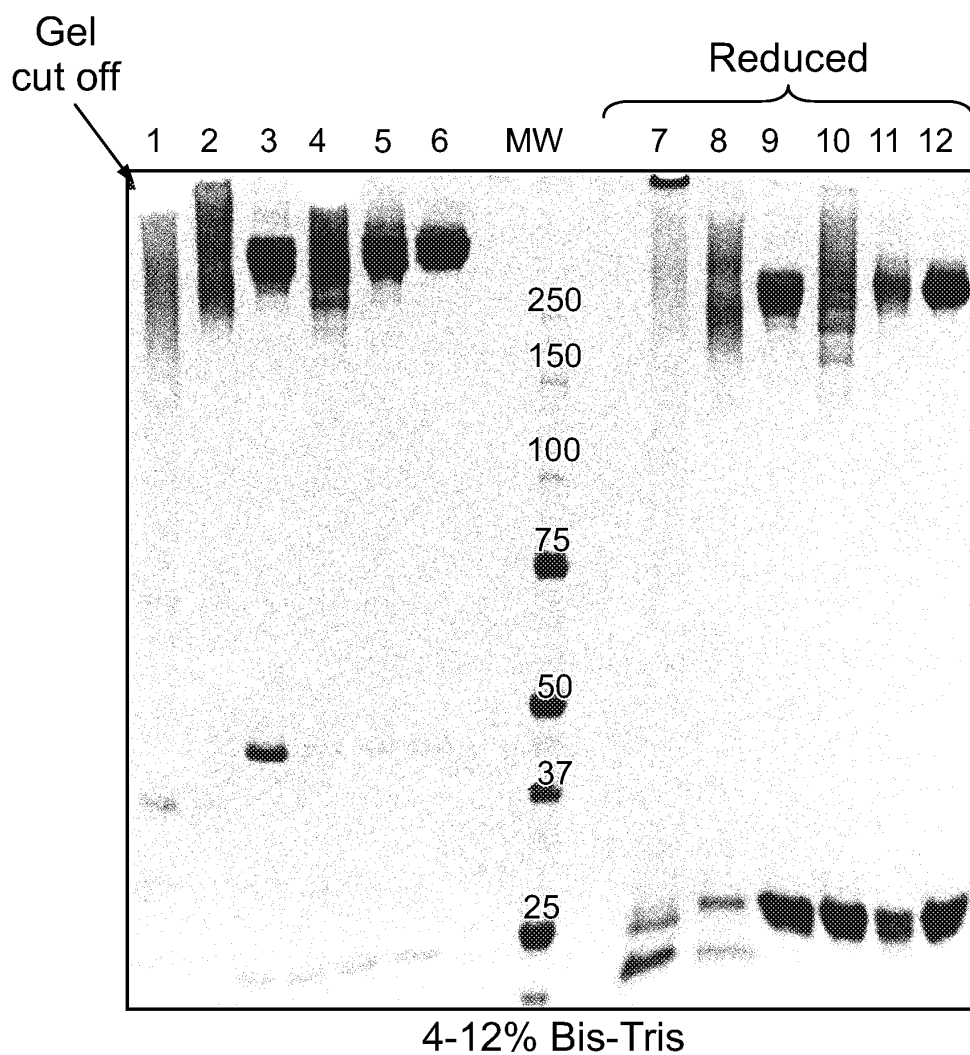


FIG. 22A

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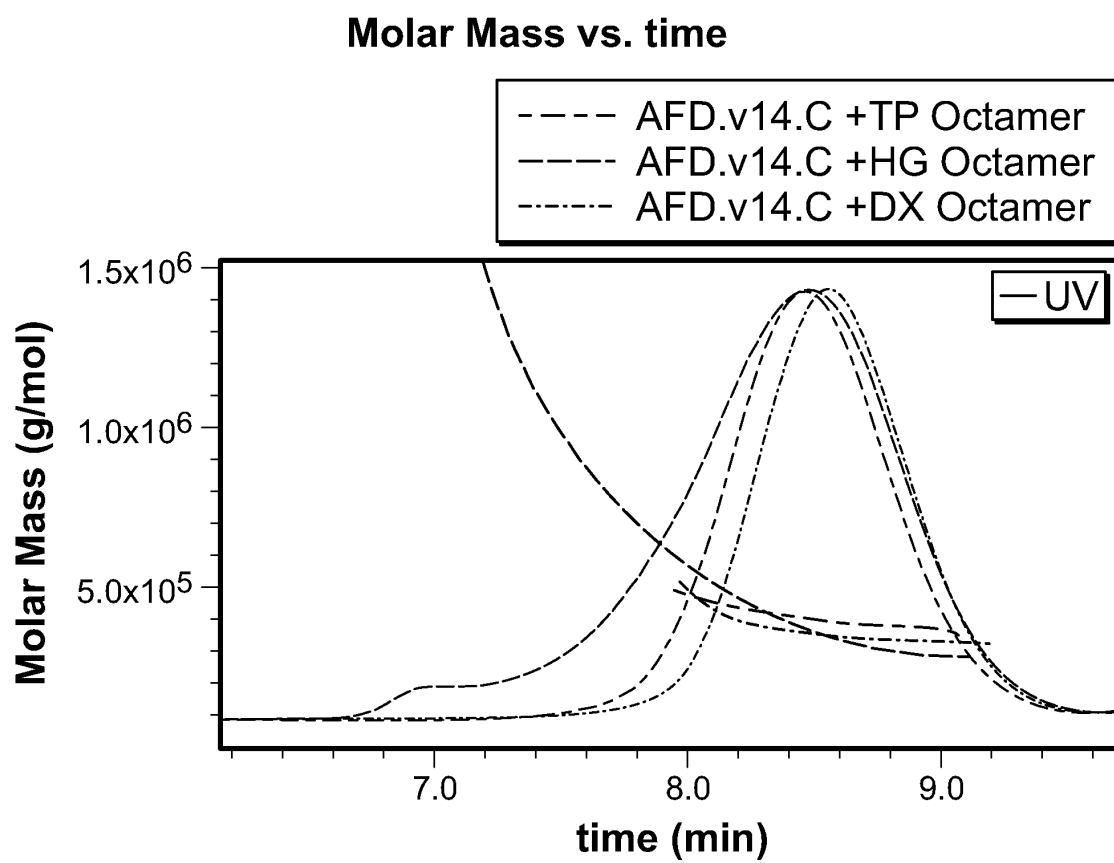


FIG. 22B

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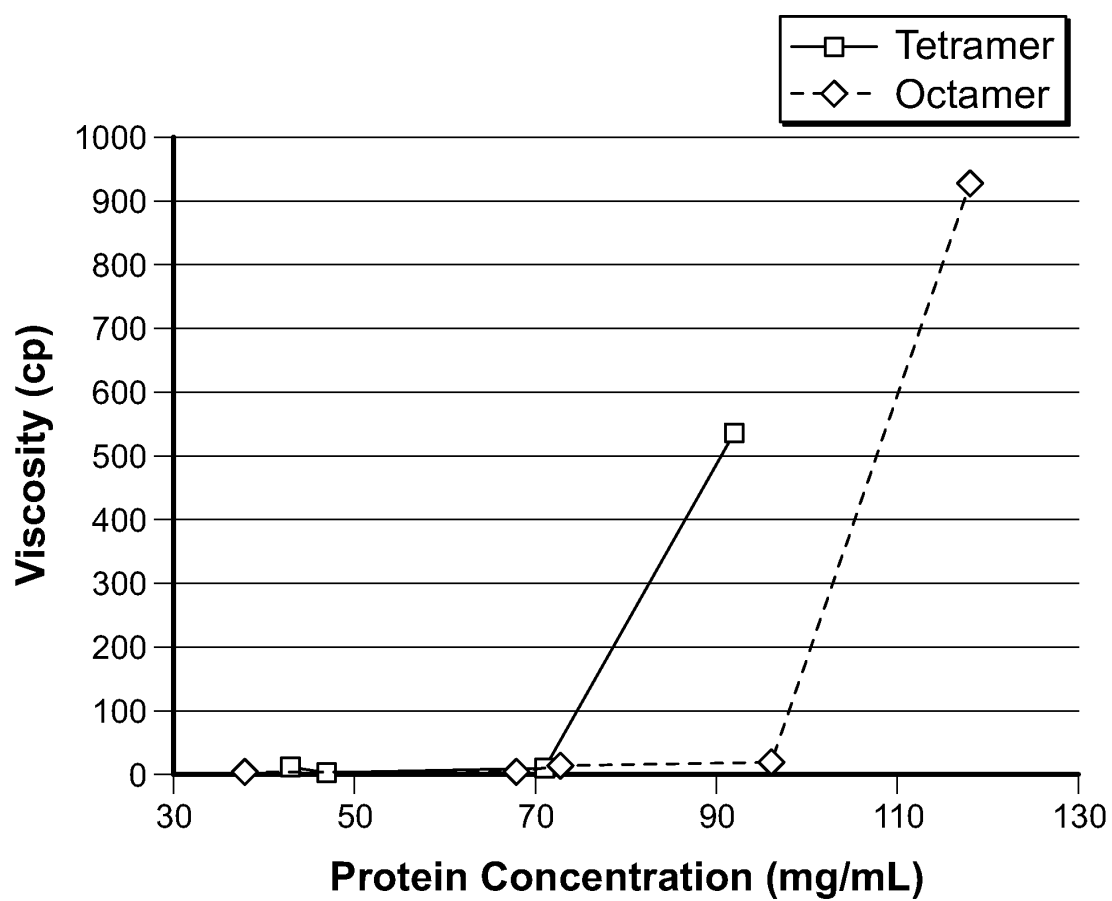


FIG. 23

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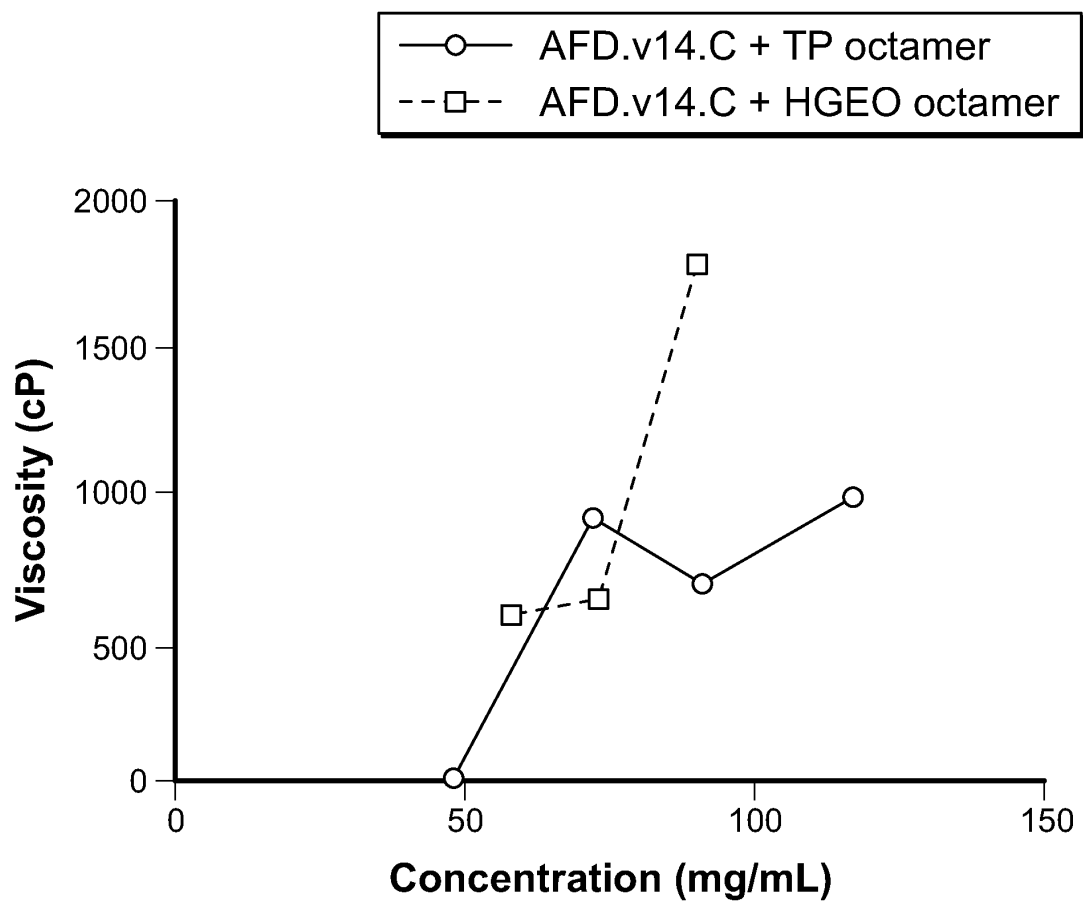
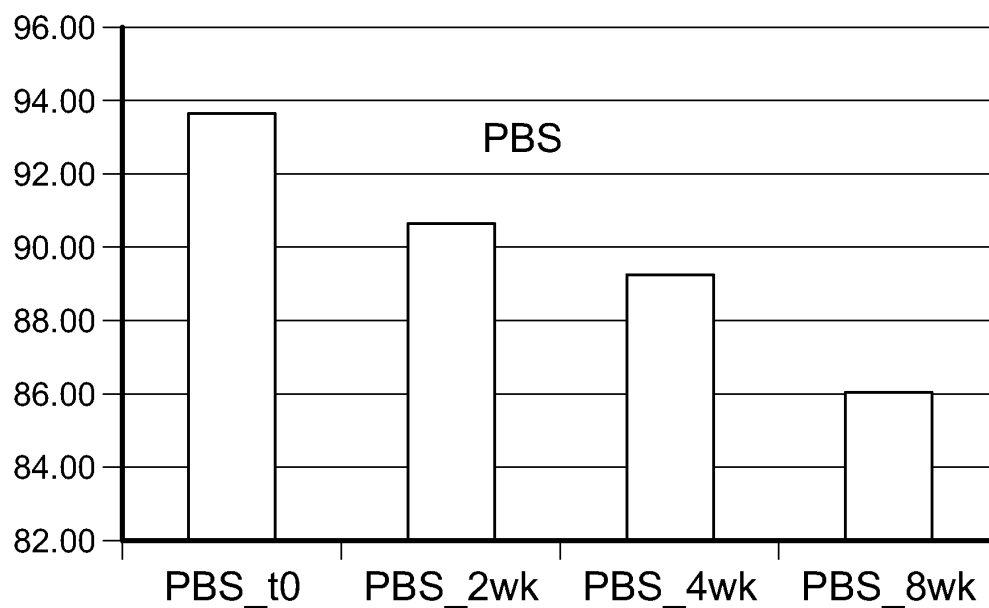
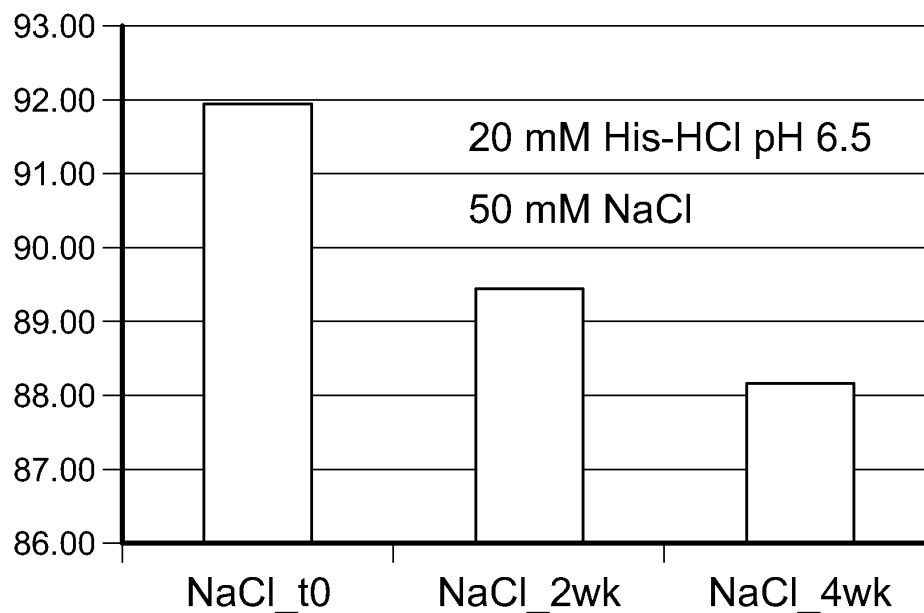
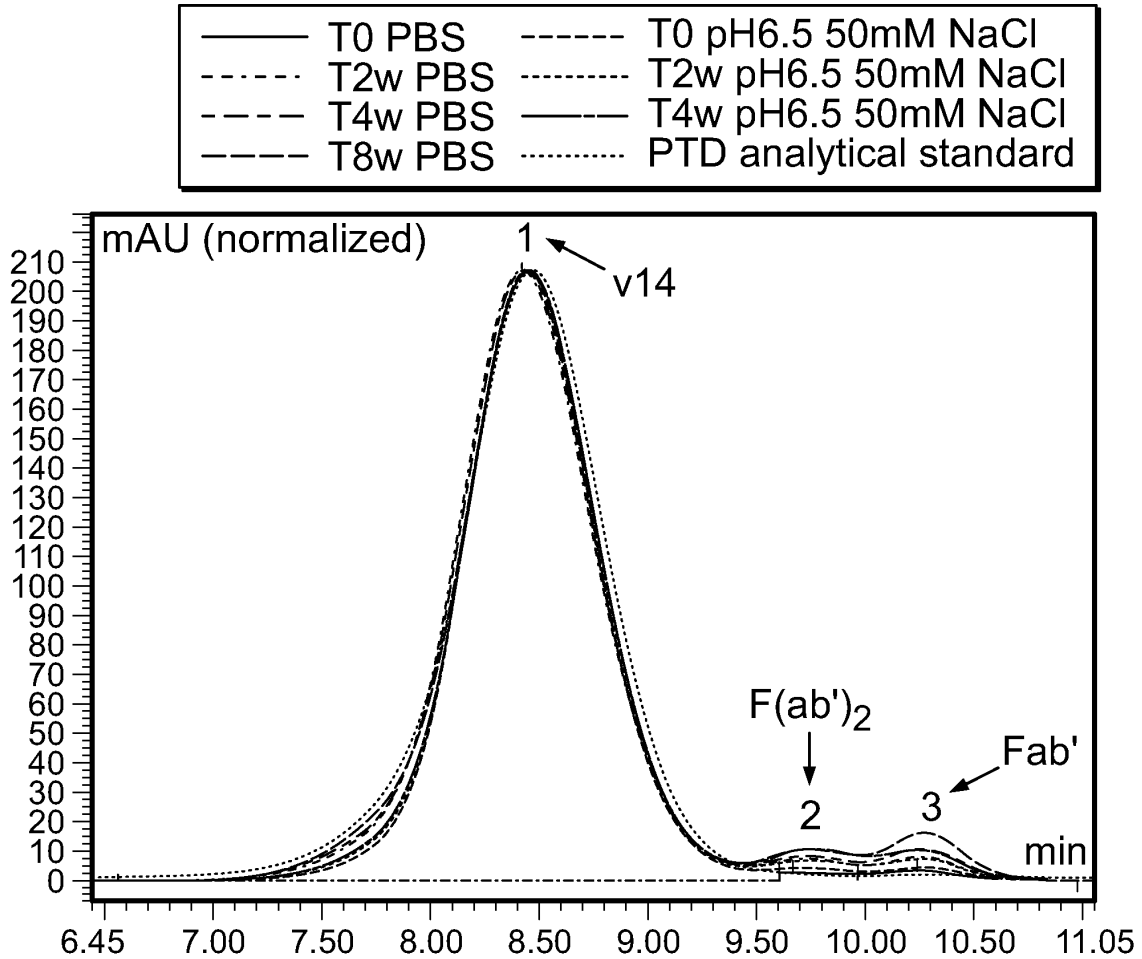


FIG. 24

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% Peak Area**FIG. 25A****% Peak Area****FIG. 25B**

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Sample ID	% Total		
	Peak 1	Peak 2	Peak 3
T0 PBS	98.48	0.58	0.94
T2w PBS	95.82	2.02	2.16
T4w PBS	94.85	2.32	2.84
T8w PBS	93.00	2.77	4.23
T0 pH6.5, 50mM NaCl	97.53	1.21	1.26
T2w pH6.5, 50mM NaCl	95.99	2.00	2.02
T4w pH6.5, 50mM NaCl	93.94	3.22	2.84
PTD std	100.00	0.00	0.00

FIG. 26

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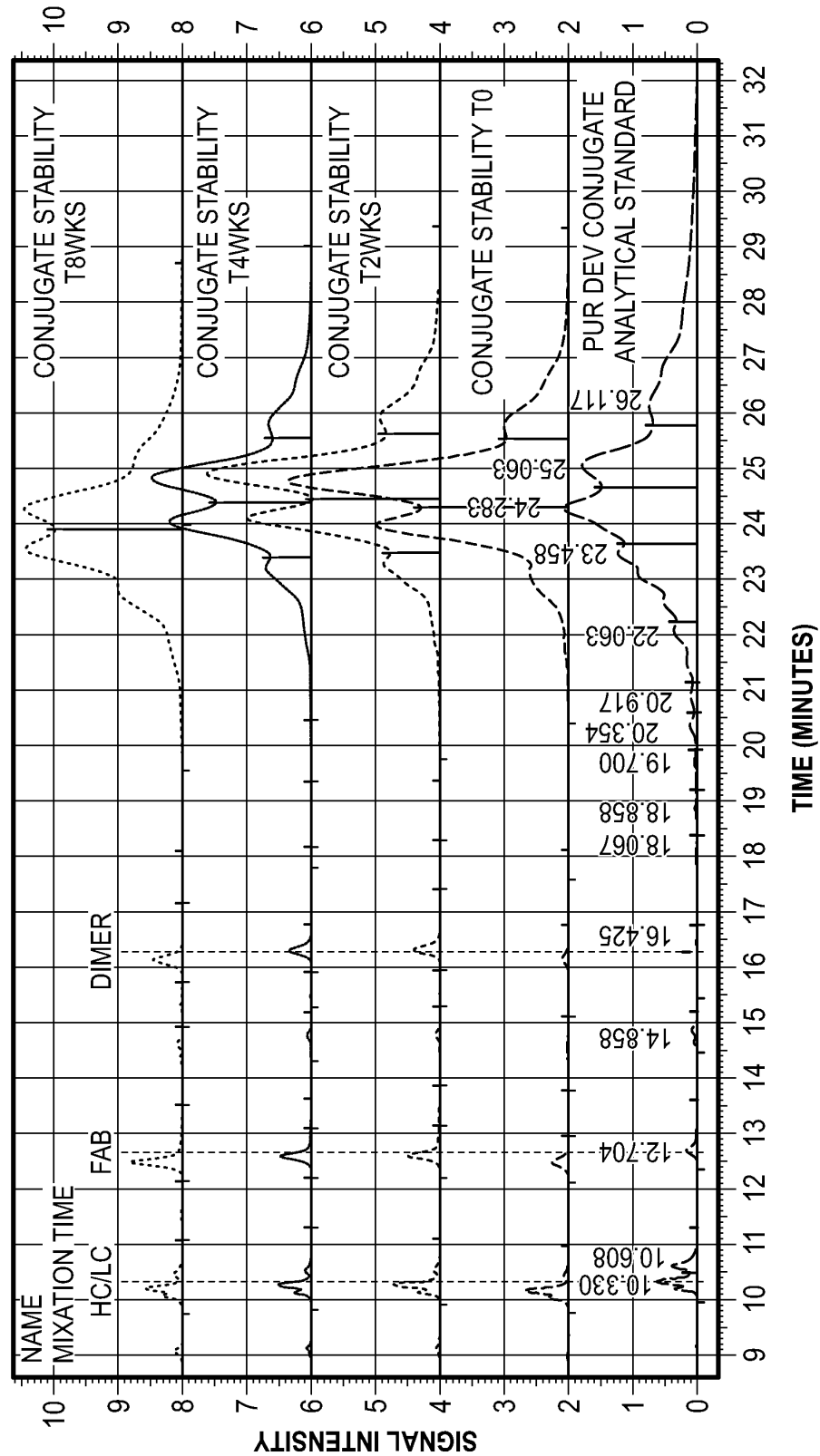


FIG. 27

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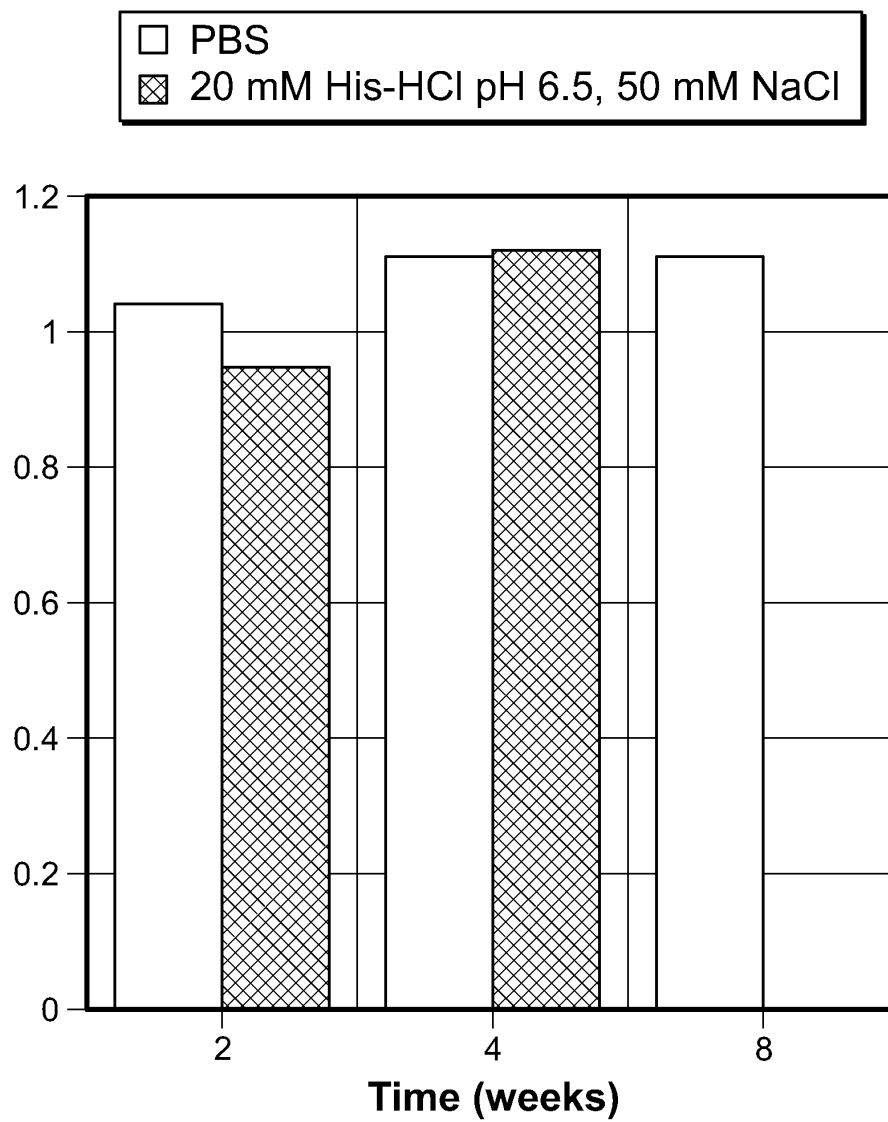


FIG. 28

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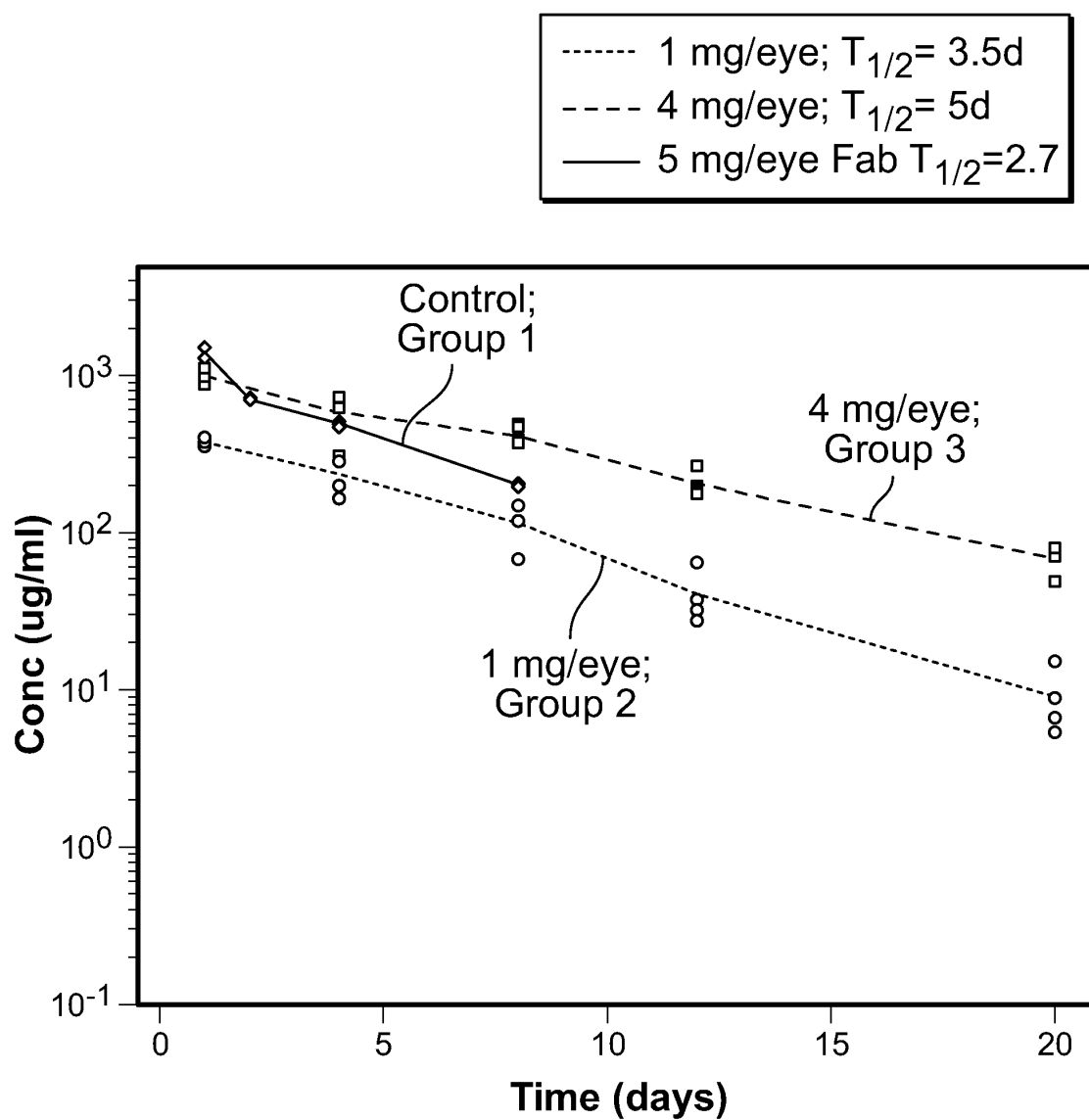


FIG. 29A

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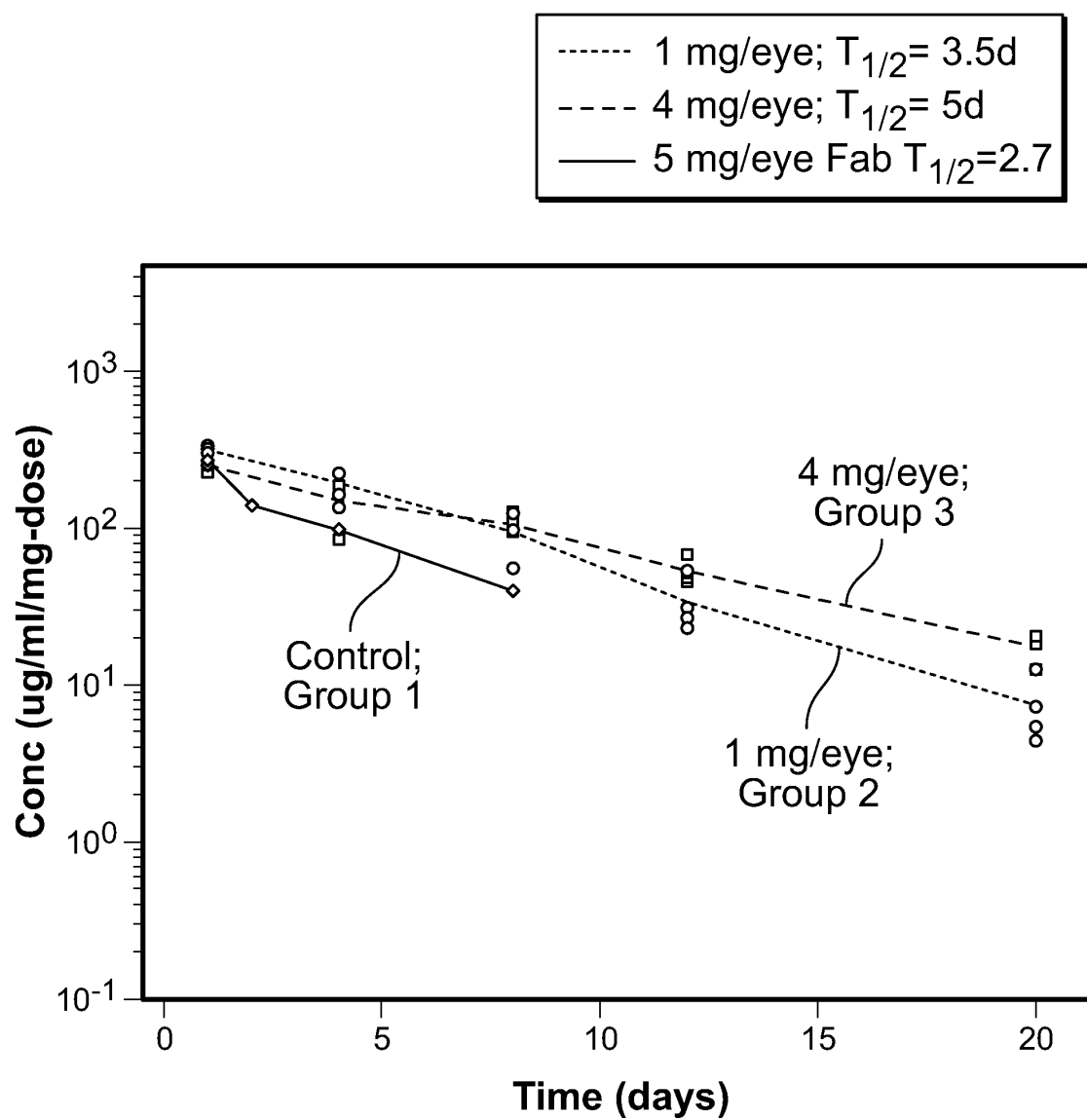


FIG. 29B

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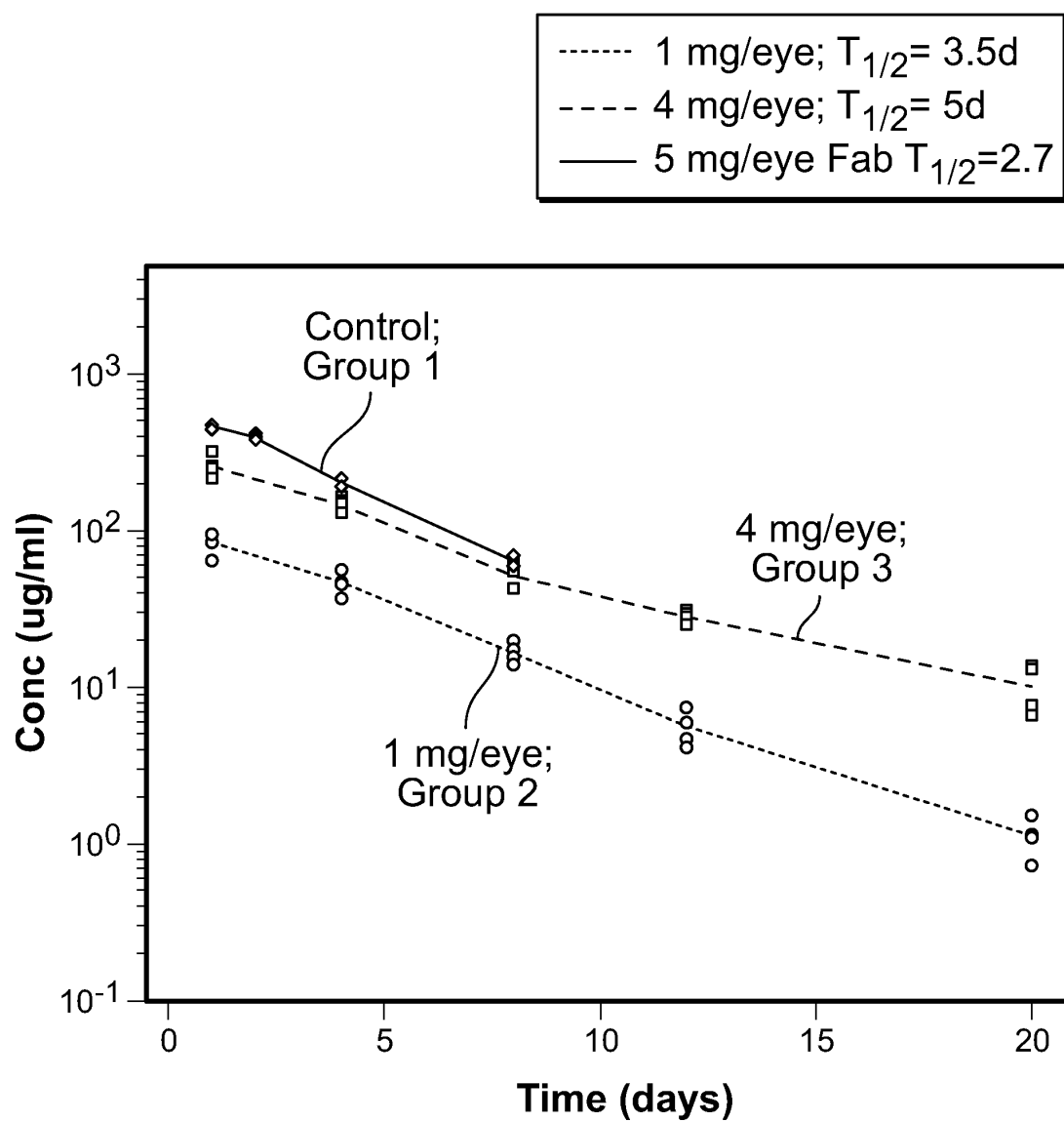


FIG. 30A

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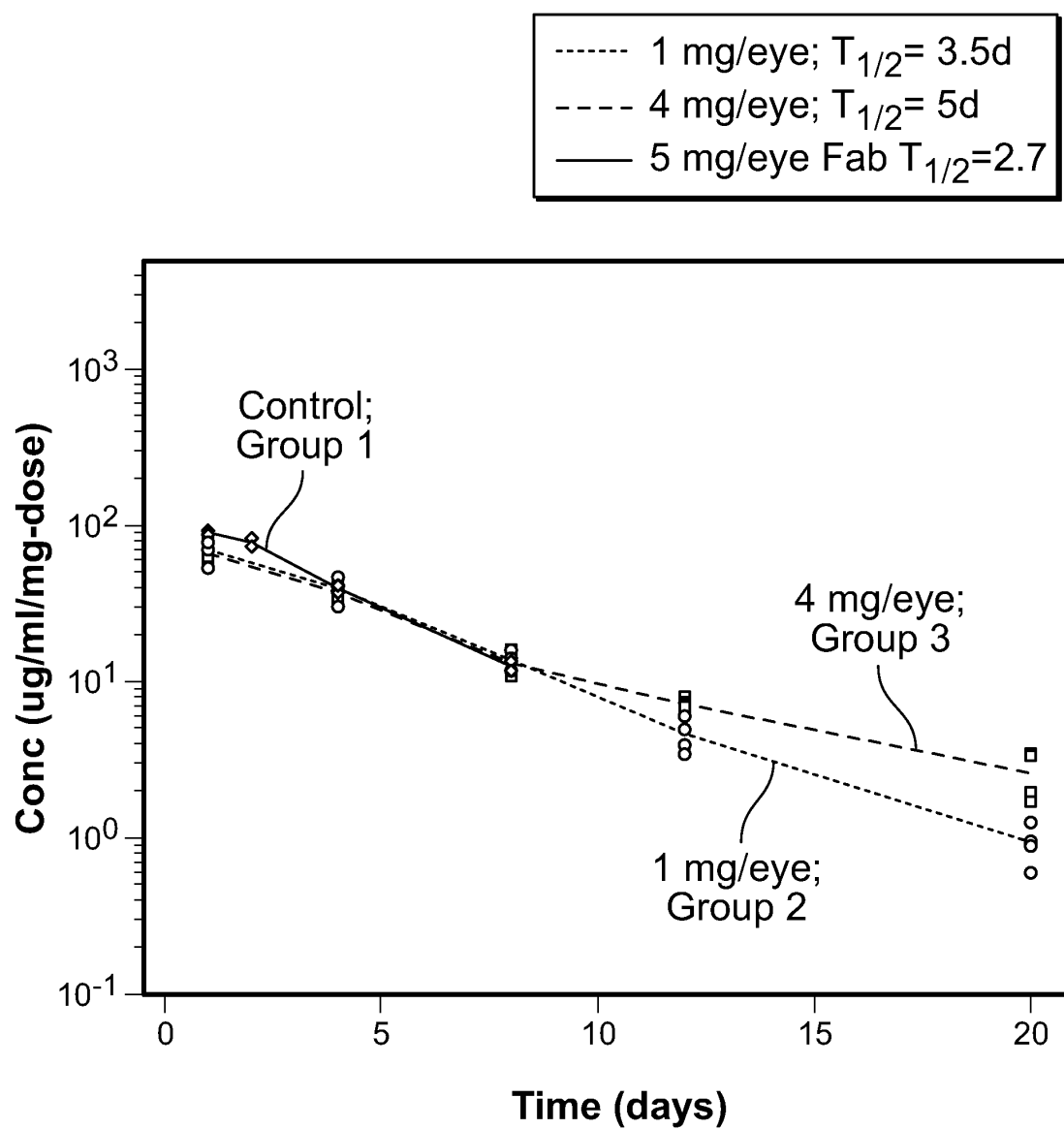


FIG. 30B

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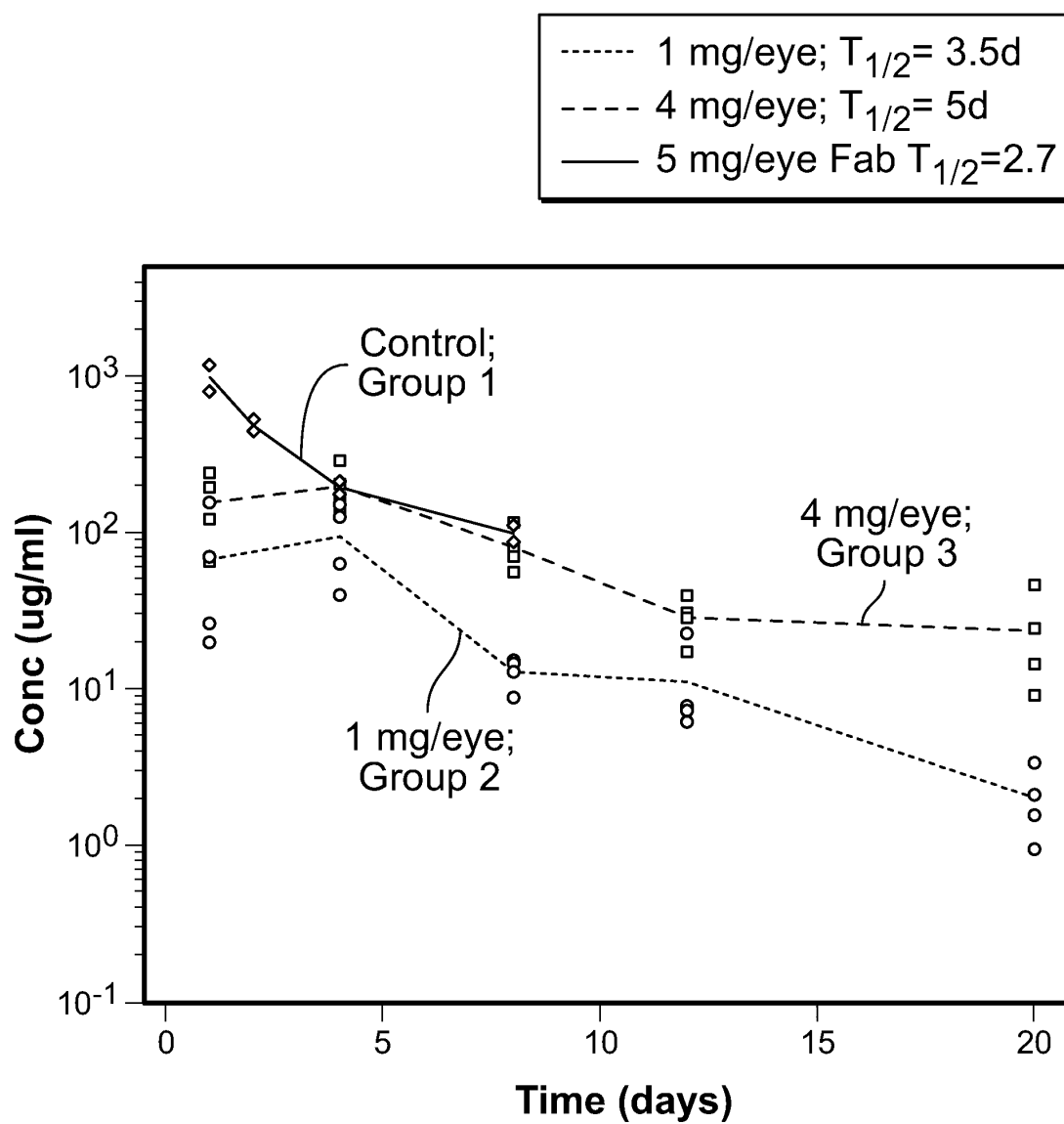


FIG. 31A

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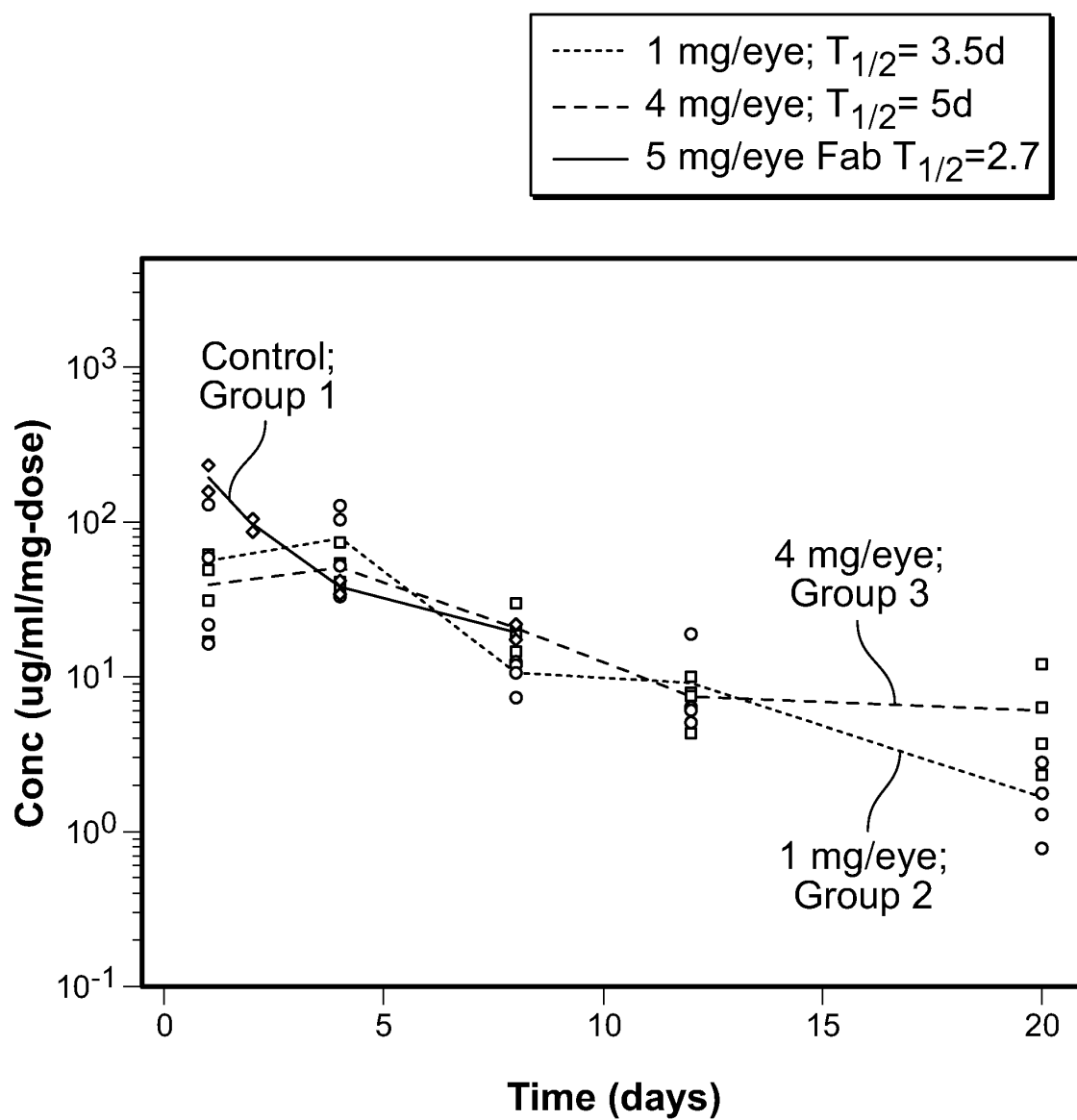


FIG. 31B

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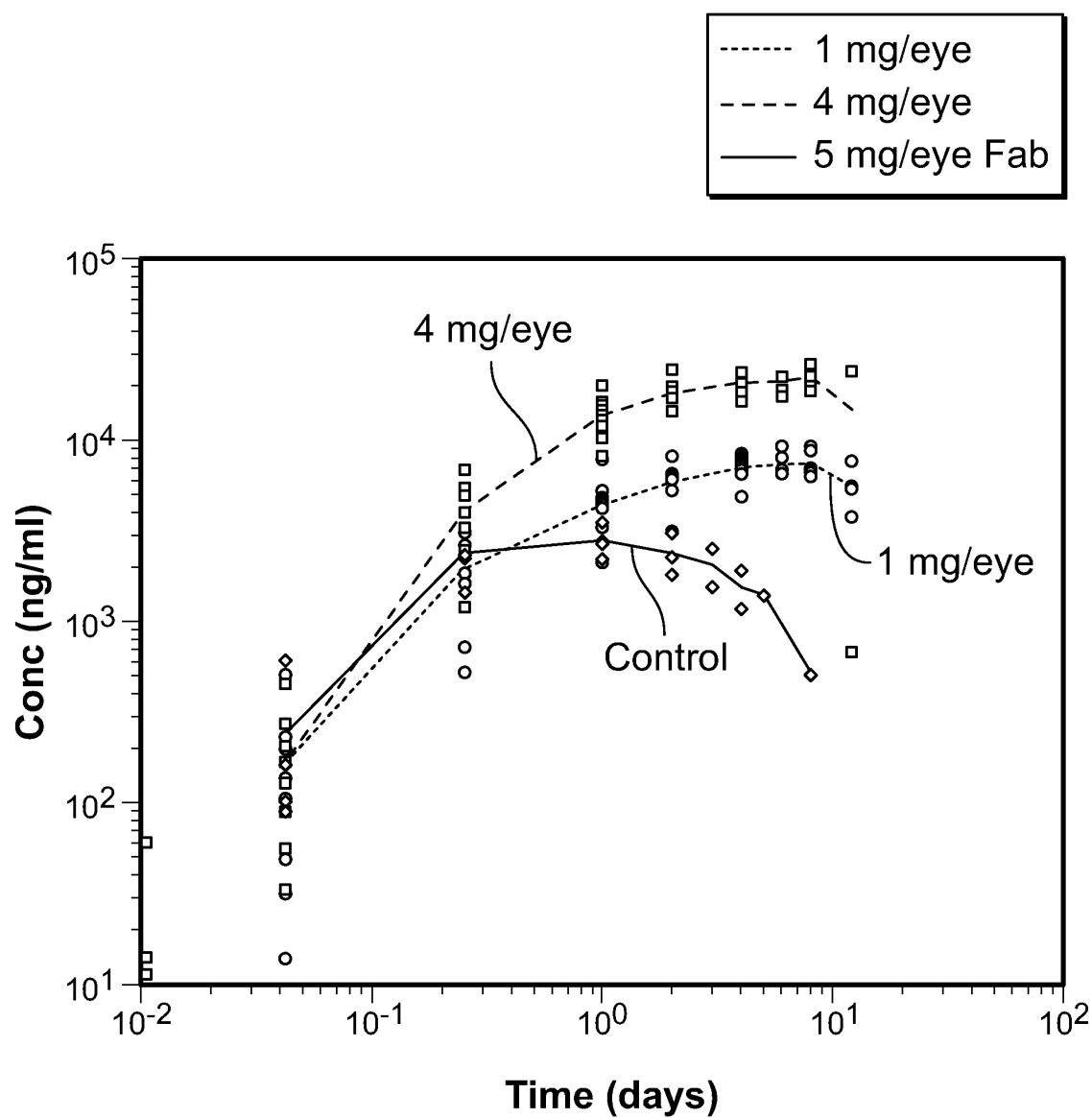


FIG. 32A

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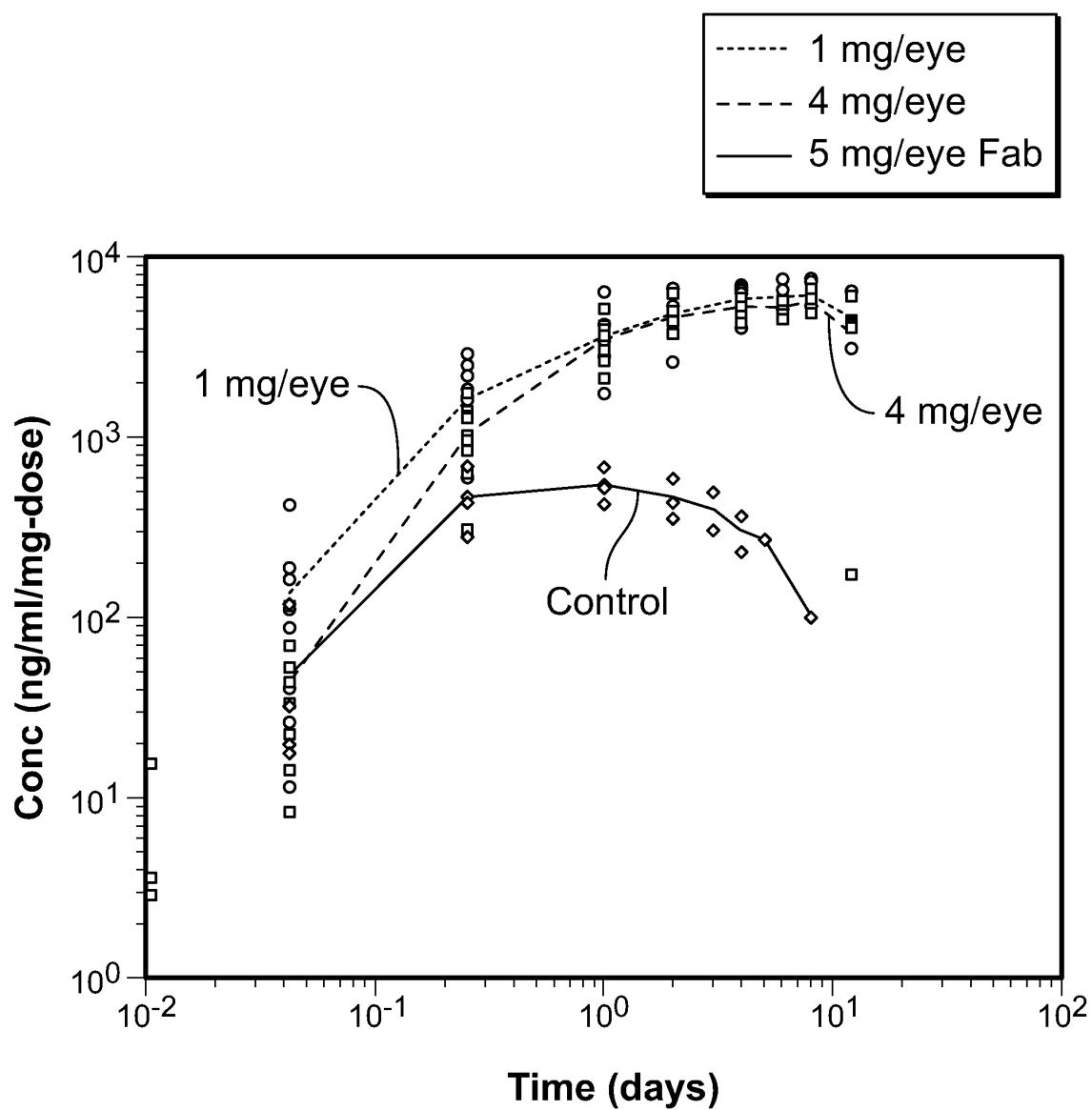


FIG. 32B

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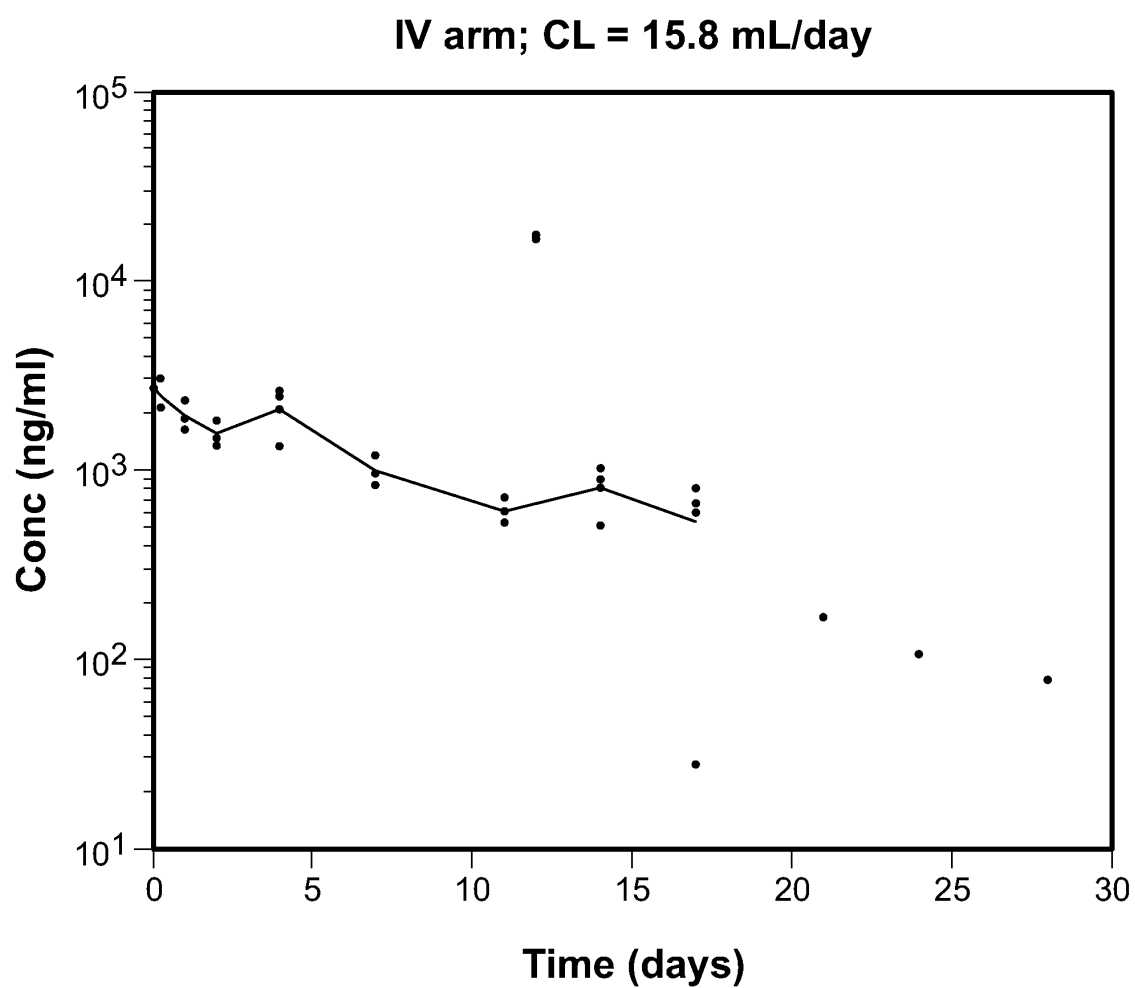


FIG. 32C

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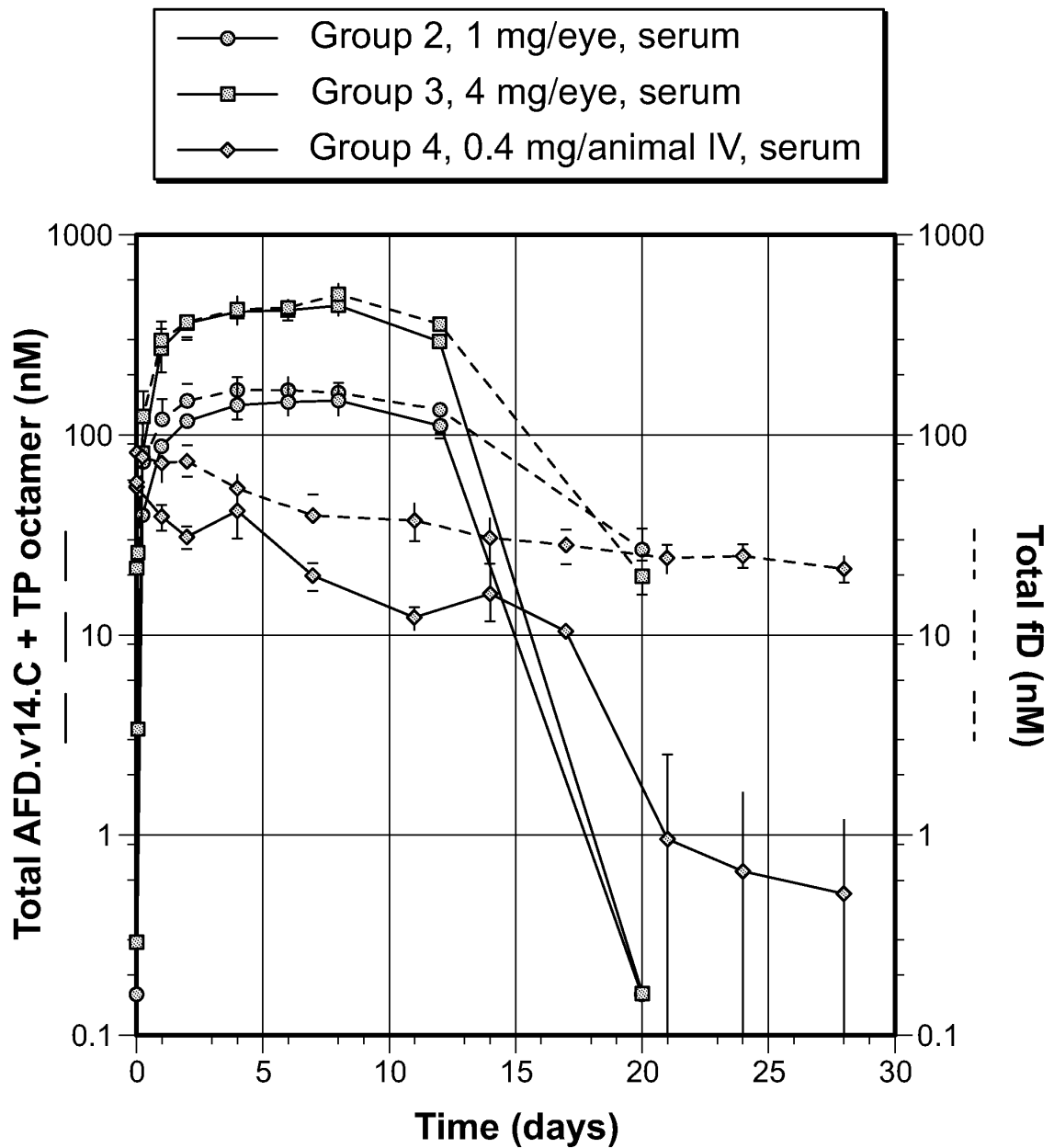


FIG. 33A

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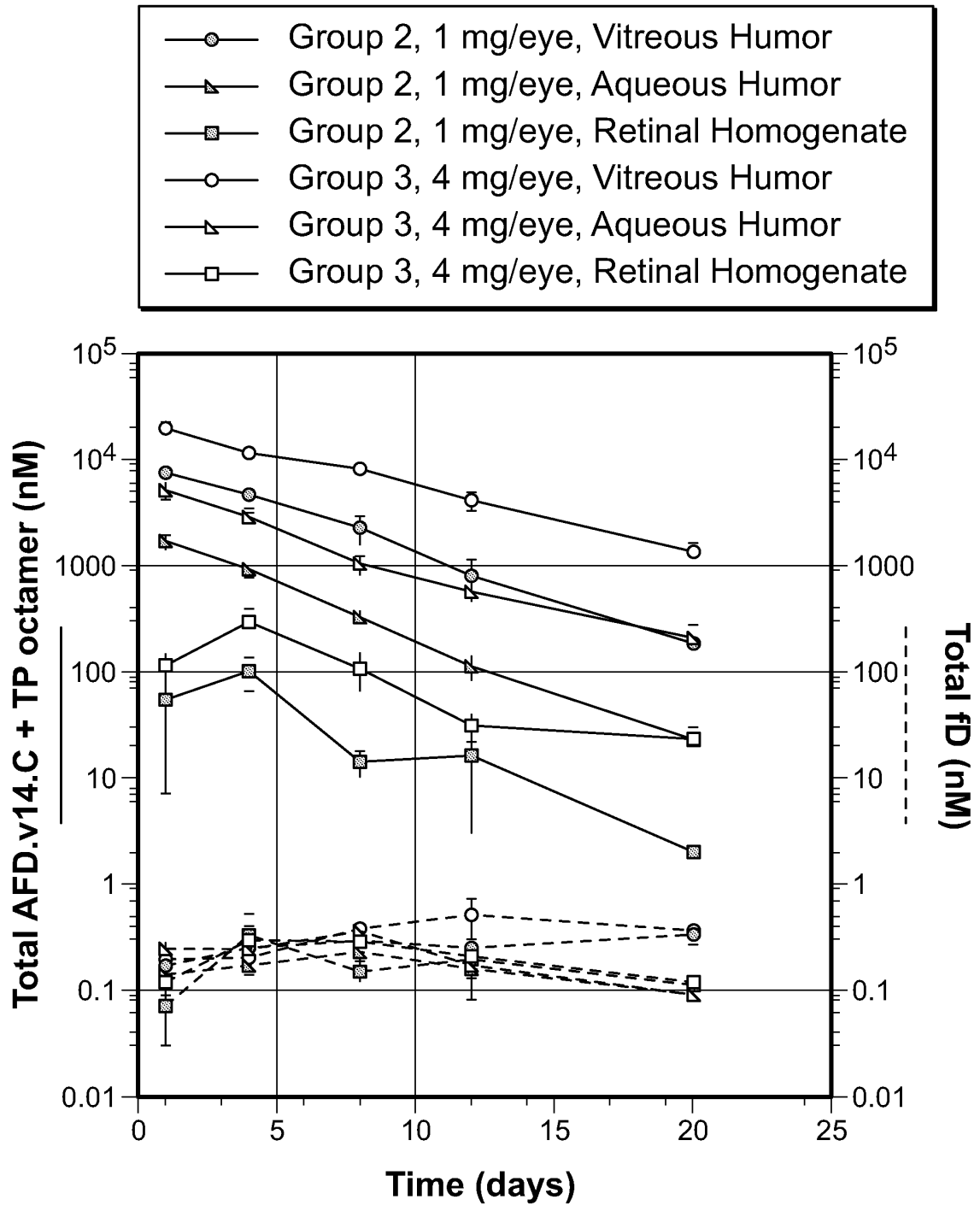


FIG. 33B

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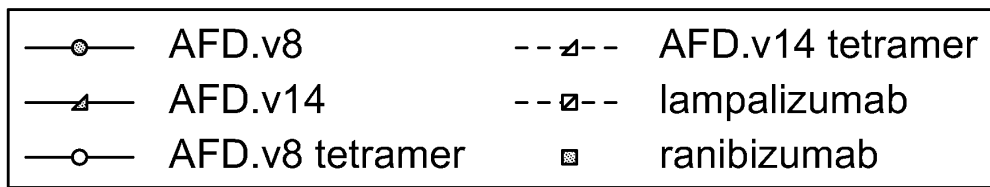
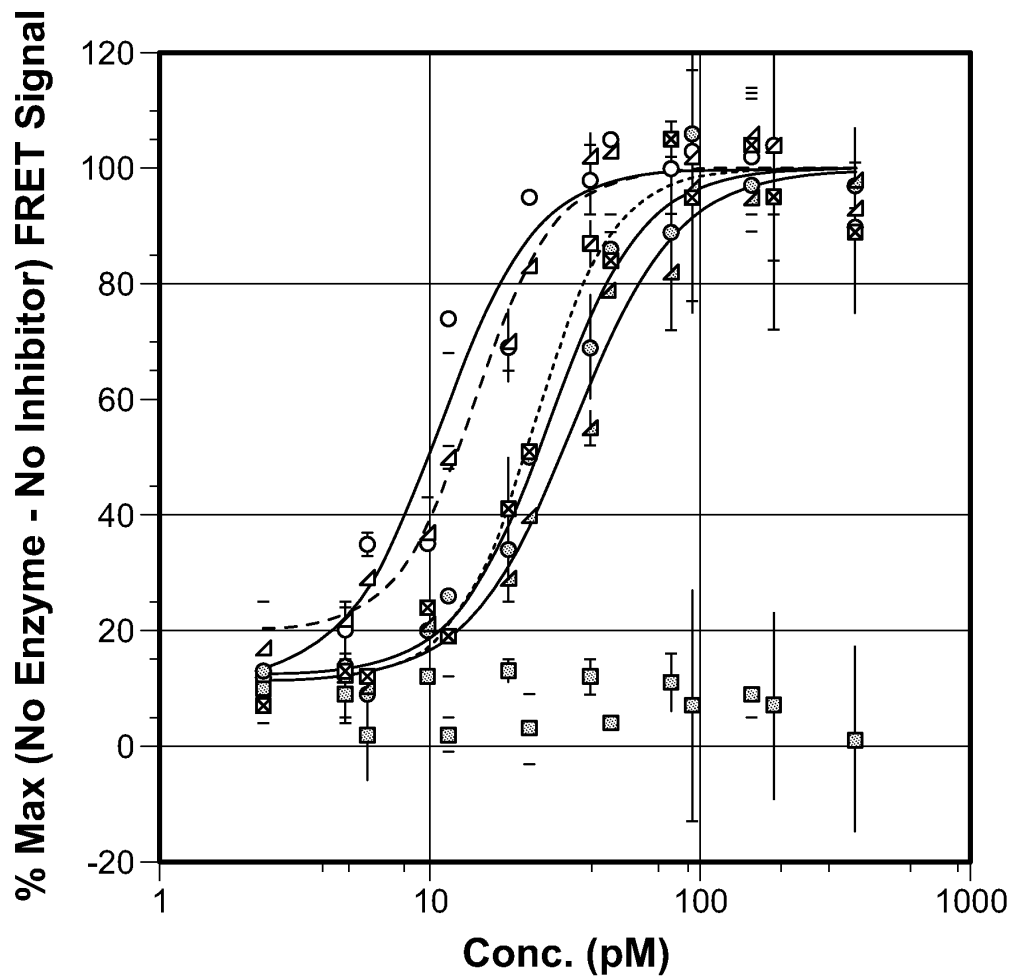
Factor D (50 pM) Cleavage of Factor B FRET

FIG. 34A

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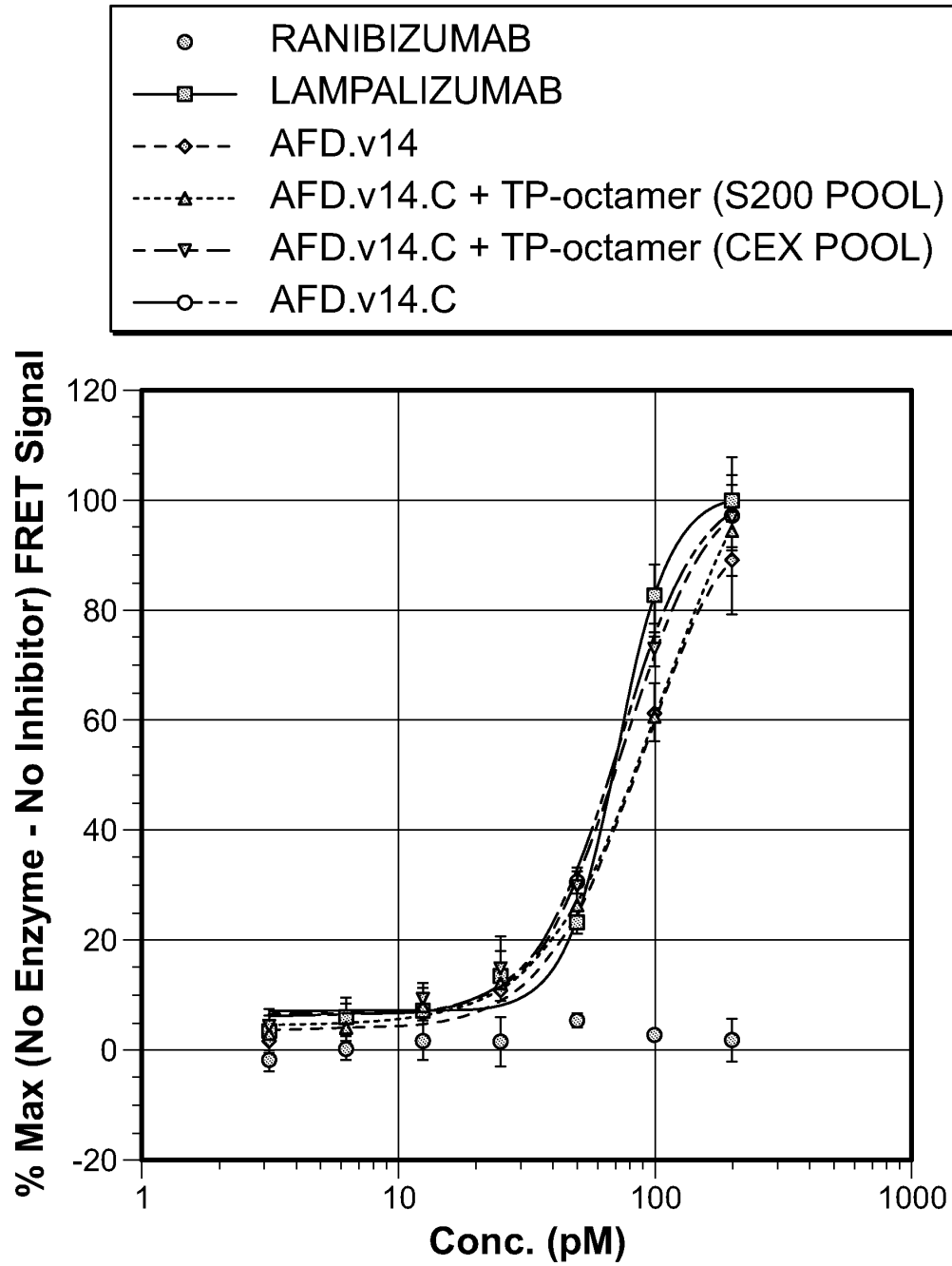


FIG. 34B

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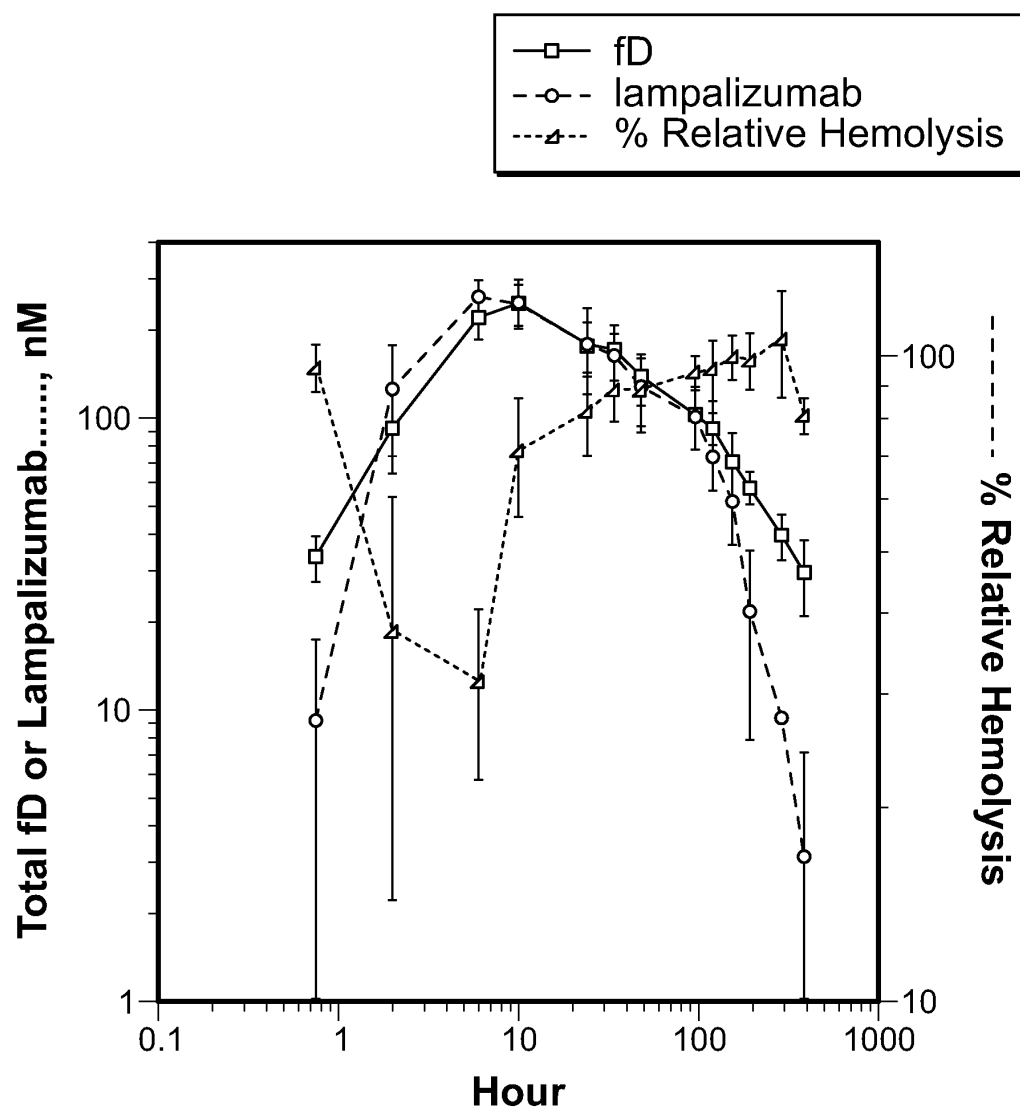


FIG. 35A

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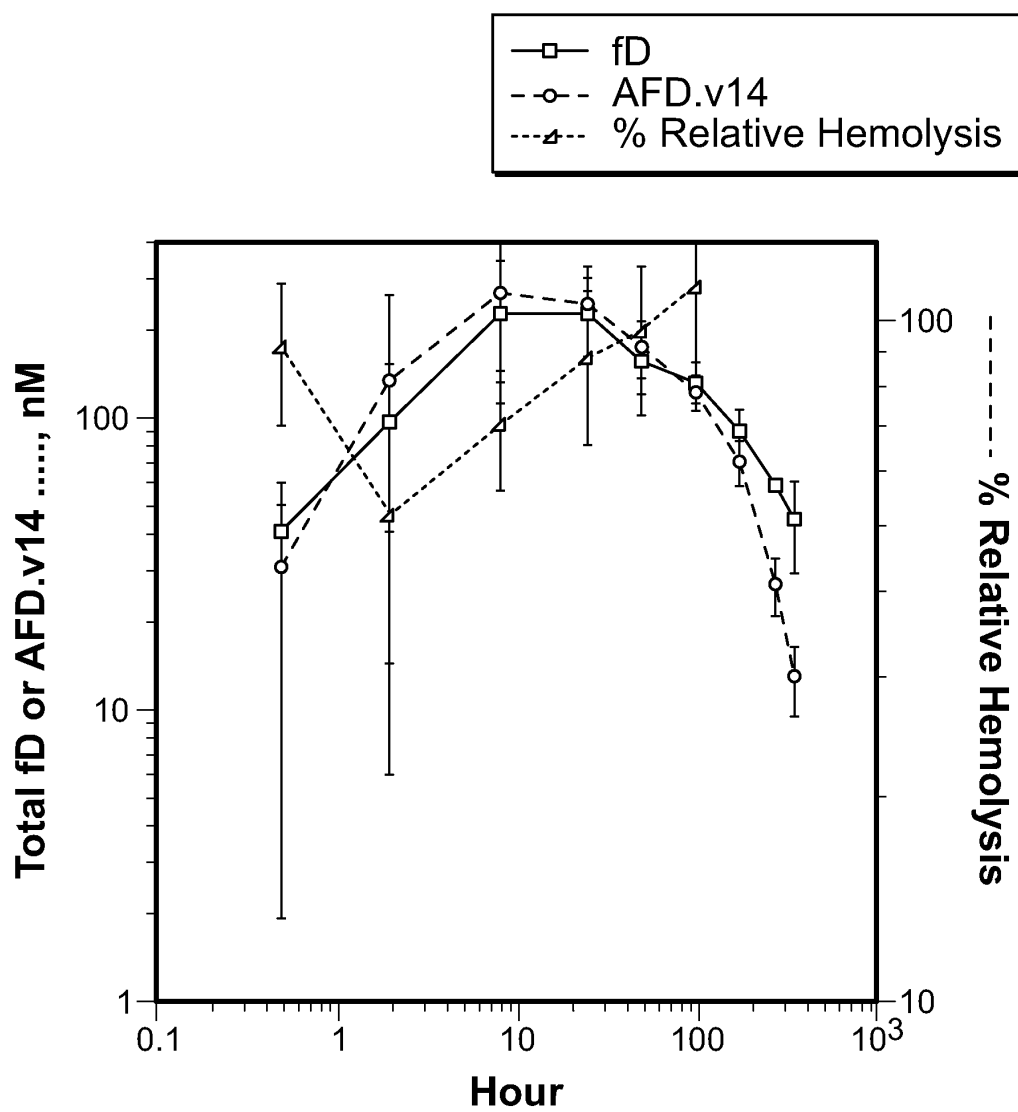


FIG. 35B

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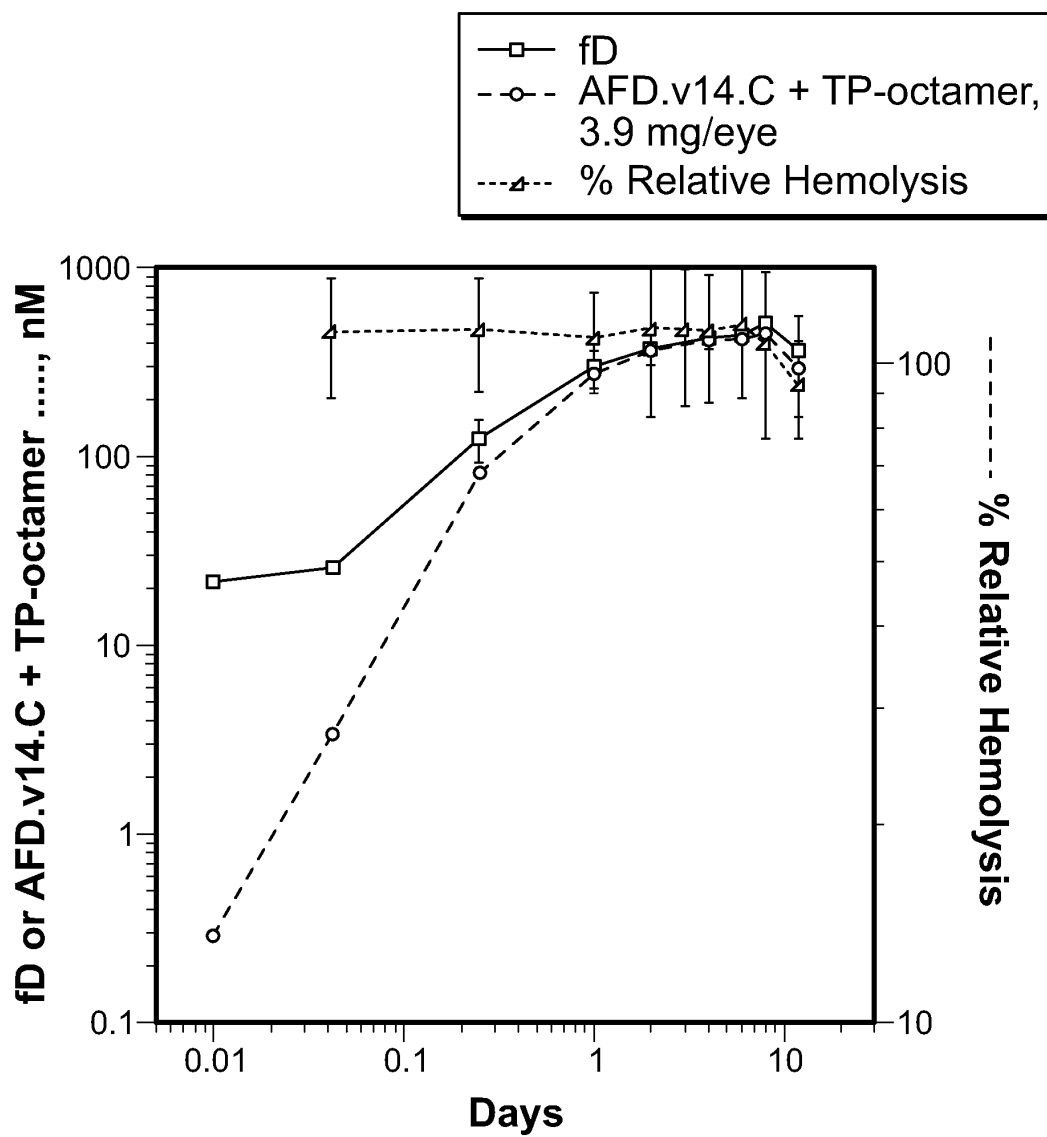


FIG. 35C

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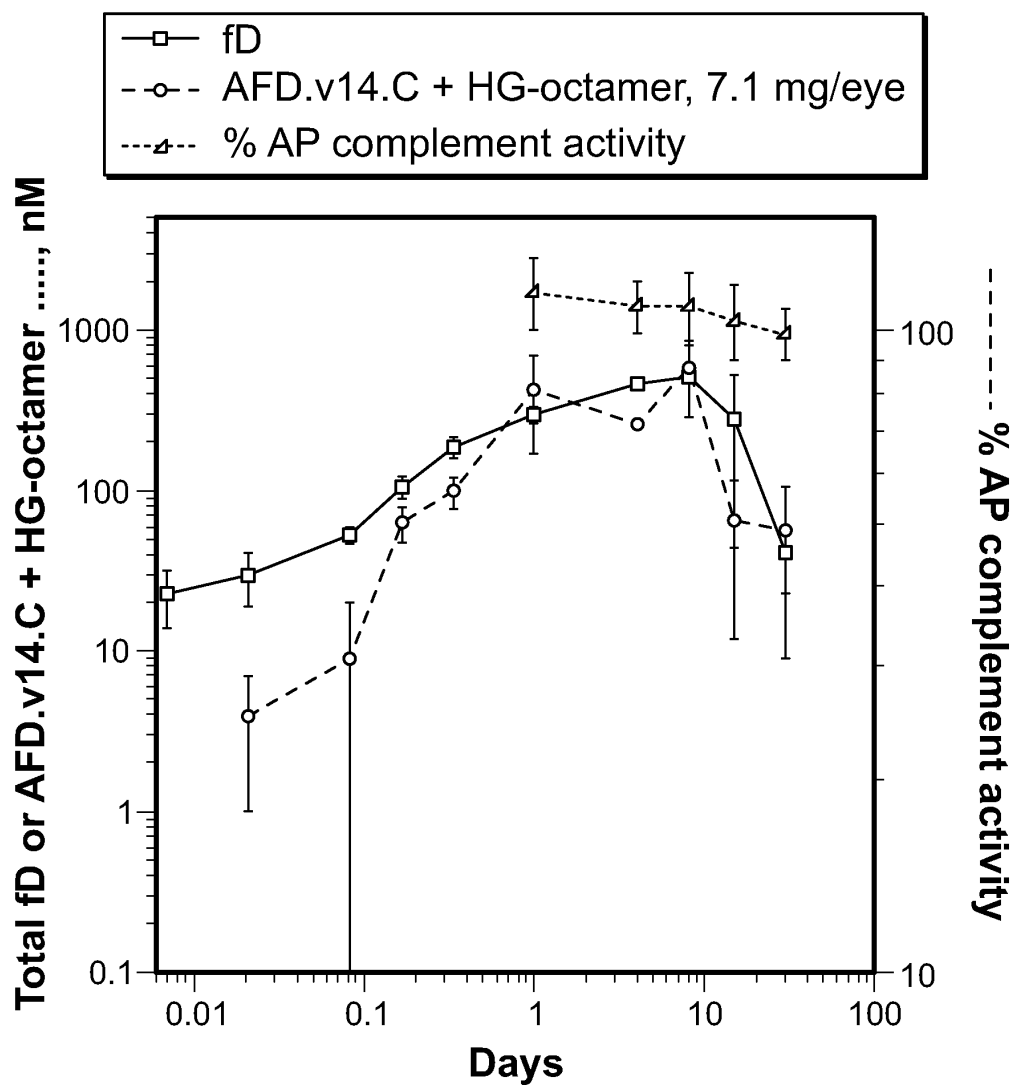


FIG. 35D

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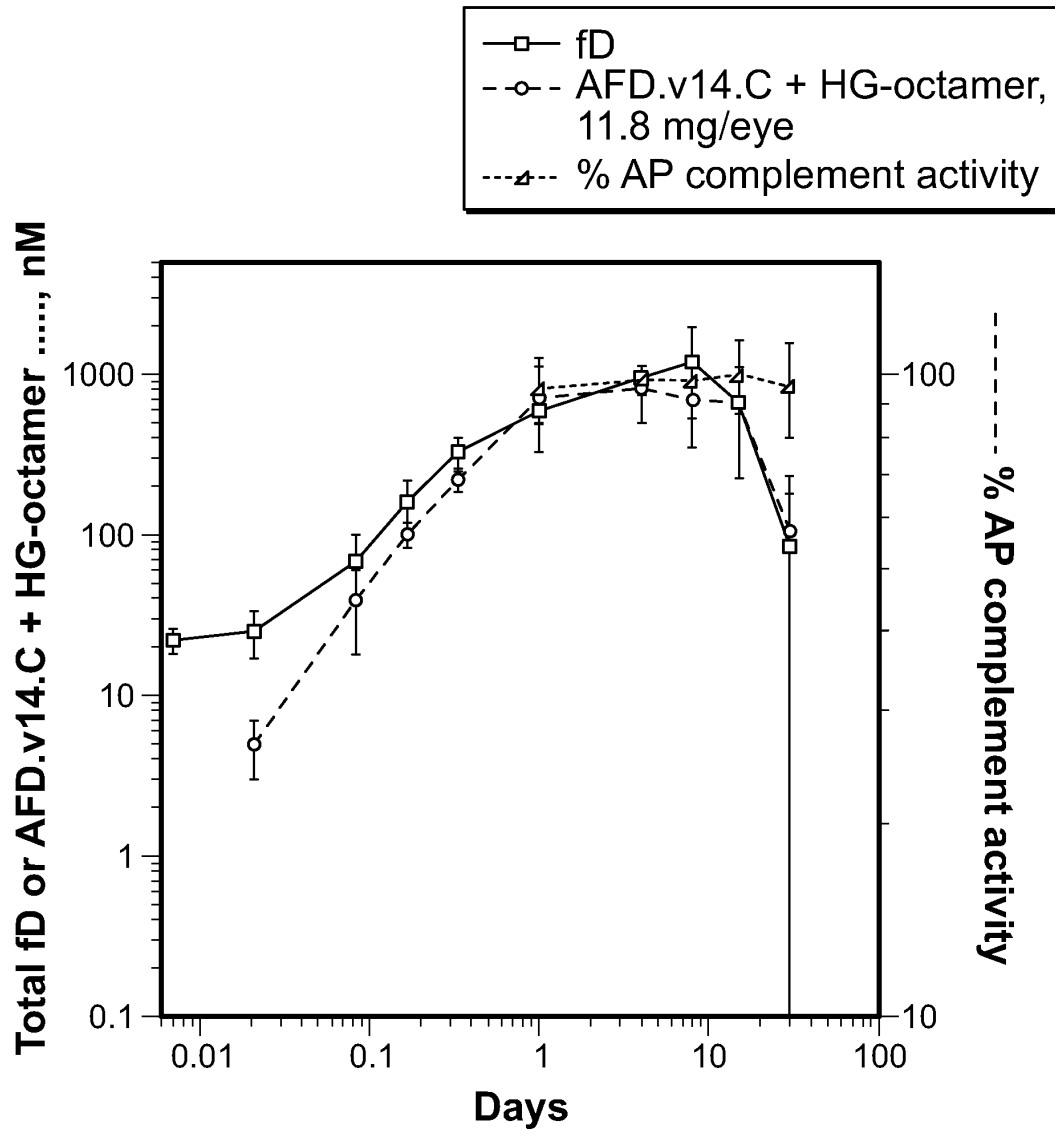


FIG. 35E

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2016/059179

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K47/60 A61P27/02
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, WPI Data, EMBASE, BIOSIS, Sequence Search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2009/134711 A1 (GENENTECH INC [US]; HUANG ARTHUR J [US]; KELLEY ROBERT F [US]; LOWMAN) 5 November 2009 (2009-11-05) paragraphs [0154], [0159]; claims 1-10; figures 4, 10; sequences 47, 63 -----	1-109
Y	RYAN S M ET AL: "Advances in PEGylation of important biotech molecules: Delivery aspects", EXPERT OPINION ON DRUG DELIVERY, INFORMA HEALTHCARE, GB, vol. 5, no. 4, 1 April 2008 (2008-04-01), pages 371-383, XP008106736, ISSN: 1742-5247, DOI: 10.1517/17425247.5.4.371 the whole document ----- -/--	1-109

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

17 January 2017

Date of mailing of the international search report

31/01/2017

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

Authorized officer

Langer, Miren

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2016/059179

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:
 - a. ☒ forming part of the international application as filed:
 - ☒ in the form of an Annex C/ST.25 text file.
 - ☐ on paper or in the form of an image file.
 - b. ☐ furnished together with the international application under PCT Rule 13~~ter~~.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.
 - c. ☐ furnished subsequent to the international filing date for the purposes of international search only:
 - ☐ in the form of an Annex C/ST.25 text file (Rule 13~~ter~~.1(a)).
 - ☐ on paper or in the form of an image file (Rule 13~~ter~~.1(b) and Administrative Instructions, Section 713).
2. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2016/059179

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 99/01556 A2 (GENENTECH INC [US]) 14 January 1999 (1999-01-14) -----	1-109
A	K. J. KATSCHKE ET AL: "Inhibiting Alternative Pathway Complement Activation by Targeting the Factor D Exosite", JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 287, no. 16, 13 April 2012 (2012-04-13), pages 12886-12892, XP055040644, ISSN: 0021-9258, DOI: 10.1074/jbc.M112.345082 -----	1-109
A	WO 2015/032776 A1 (HOFFMANN LA ROCHE [CH]; HOFFMANN LA ROCHE [US]) 12 March 2015 (2015-03-12) -----	1-109
A	WO 2008/055206 A2 (GENENTECH INC [US]; WU HERREN [US]; SINGH SANJAYA [US]; FUNG SEK CHUNG) 8 May 2008 (2008-05-08) -----	1-109
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Title of Invention

Methods for Treating Angiogenic Eye Disorders with High Doses of VEGF Receptor Fusion Proteins

Application Information

APPLICATION TYPE Utility - Nonprovisional Application
under 35 USC 111(a)

PATENT # -

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FILED BY Brandi Henley

PATENT CENTER # 65284919

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CUSTOMER # 147803

FIRST NAMED
INVENTOR Kenneth S. Graham

CORRESPONDENCE
ADDRESS -

AUTHORIZED BY Lance Termes

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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 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.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (not for submission under 37 CFR 1.99)	Application Number	17/384,070
	Filing Date	Jul-23-2021
	First Named Inventor	Kenneth S. Graham
	Art Unit	1647
	Confirmation Number	1061
	Examiner Name	Lockard, Jon McClelland
	Attorney Docket Number	125984-266215

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

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
	572	2021-0393738		12-23-2021	Ke	
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	568	2981145	CA	A1	10-06-2016	Seong Beom Kim et al.	
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	569	17/075252	WO	A1	05-04-2017	GENENTECH, INC.	
	571	19/108770	WO	A1	06-06-2019	Regeneron Pharmaceuticals, Inc.	

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Examiner Initial*	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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EXAMINER SIGNATURE			
Examiner Signature		Date Considered	
<p>*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.</p>			
<p>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.</p>			

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	Art Unit	1647
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	Examiner Name	Lockard, Jon McClelland
	Attorney Docket Number	125984-266215

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.			
☐ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.			
☒ None			
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	/Lance A. Termes/	Date (YYYY-MM-DD)	2024-04-29
Name/Print	Lance A. Termes	Registration Number	43184

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Kenneth S. Graham, et al. Application No.: 17/384,070 Filed: Jul-23-2021 For: HIGH CONCENTRATION VEGF RECEPTOR FUSION PROTEIN CONTAINING FORMULATIONS Customer No.: 147803	Confirmation No.: 1061 Examiner: Lockard, Jon McClelland Art Unit: 1647 SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR §1.97 and §1.98 Date of Transmission: April 29, 2024
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Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

The references cited on the attached IDS are being called to the attention of the Examiner. Copies of the references in compliance with the requirements of 37 CFR §1.98(a)(2) are submitted herewith. Cite Nos. 140, 162, 167, 180, 193, 201 and 218, previously considered by the Examiner as noted in the Notice of Allowance mailed January 31, 2024, are recited to include dates.

It is respectfully requested that the cited references be expressly considered during the prosecution of this application, and the references be made of record therein and appear among the “references cited” on any patent to issue therefrom.

The Examiner is encouraged to review the full prosecution history from related cases. Applicant understands that the prosecution history can be viewed electronically on PALM. Nevertheless, if the Examiner wishes Applicant to provide copies of any documents from related applications to the extent not already provided, he or she is requested to contact the undersigned.

Applicant cites the following applications, which are directed to related subject matter and are commonly owned or under an assignment obligation to be commonly owned:

Attorney Docket No.	Application No.	Filing Date	Publication No.	Status
125984-248591	62/669,506	05-10-2018	N/A	Expired
125984-248592	62/752,127	10-29-2018	N/A	Expired
125984-248593	62/769,876	11-20-2018	N/A	Expired
125984-248594	62/813,882	03-05-2019	N/A	Expired
125984-248595	16/409,631	05-10-2019	US 11,103,552	Issued
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Respectfully submitted,

/Lance A. Termes/

Lance A. Termes
Reg. No. 43184

Schwabe Williamson & Wyatt, PC
1211 SW 5th Avenue, Suite 1900
Portland, OR 97204
Tel: 503-222-9981



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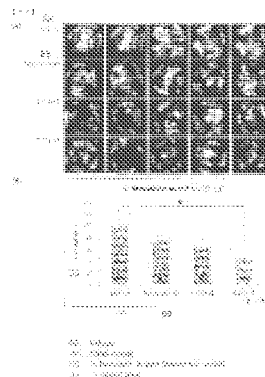
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(71) Demandeur/Applicant:
ILDONG PHARM CO., LTD., KR

(72) Inventeurs/Inventors:
KIM, SEONG BEOM, KR;
JUNG, HYEI YOON, KR;
YANG, SEOK WOO, KR;
KWON, HYUK SANG, KR;
KANG, JAE-HOON, KR

(74) Agent: MERIZZI RAMSBOTTOM & FORSTER

(54) Titre : COMPOSITION PHARMACEUTIQUE POUR PREVENIR ET TRAITER LES MALADIES OCULAIRES, CONTENANT COMME INGREDIENT ACTIF, UNE PROTEINE DE FUSION DANS LAQUELLE UN PEPTIDE DE TRANSLOCATION TISSULAIRE ET UNE PREPARATION ANTI-FACTEUR DE CROISSANCE ENDOTHELIALE VASCULAIRE SONT FUSIONNES
(54) Title: PHARMACEUTICAL COMPOSITION FOR PREVENTING AND TREATING EYE DISEASES, CONTAINING, AS ACTIVE INGREDIENT, FUSION PROTEIN IN WHICH TISSUE-PENETRATING PEPTIDE AND ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR PREPARATION ARE FUSED



(57) Abrégé/Abstract:

The present invention relates to a pharmaceutical composition for preventing and treating eye diseases, containing, as an active ingredient, a fusion protein in which a tissue-penetrating peptide and an anti-vascular endothelial growth factor (anti-VEGF) preparation are fused. More particularly, the present invention relates to: a pharmaceutical composition for preventing and treating eye diseases, containing, as an active ingredient, a fusion protein in which a tissue-penetrating peptide and an anti-VEGF preparation are fused, to a method for producing an anti-VEGF preparation, which overcomes resistance and has improved efficacy, the method comprising the steps of transforming a host cell with a recombinant vector containing a nucleic acid sequence coding for a fusion protein in which a tissue-penetrating peptide and an anti-VEGF preparation are fused, culturing the cell, and recovering a fusion protein from the cell; a method for treating eye diseases, comprising administering an effective dose of the fusion protein, according to the present invention, to a subject in need thereof; and a use for producing a preparation for treating eye diseases, containing the fusion protein, according to the present invention, as an active ingredient. Compared to conventional anti-VEGF preparations, the composition according to the present invention is considered to have improved efficacy and be able to be used for treating patients having drug resistance, by inhibiting various growth factors related to new blood vessels, besides VEGF, and by decreasing pericyte coverage. In addition, since drug delivery ability into the choroid tissue is improved when performing an intraocular injection, the composition can be developed into eye drops by reducing an administered dosage or extending an administration cycle, and by improving ocular penetrability.

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Abstract

The present invention relates to a pharmaceutical composition for preventing and treating eye diseases, comprising, as an active ingredient, a fusion protein in which a tissue-penetrating peptide and an anti-vascular endothelial growth factor (anti-VEGF) preparation are fused. More particularly, the present invention relates to: a pharmaceutical composition for preventing and treating eye diseases, comprising, as an active ingredient, a fusion protein in which a tissue-penetrating peptide and an anti-VEGF preparation are fused; a method for preparing an anti-VEGF preparation, which overcomes resistance and has an improved efficacy, the method comprising the steps of transforming a host cell with a recombinant vector comprising a nucleic acid sequence encoding a fusion protein in which a tissue-penetrating peptide and an anti-VEGF preparation are fused, culturing the cell, and recovering a fusion protein from the cell; a method for treating eye diseases, comprising administering an effective dose of the fusion protein according to the present invention to a subject in need thereof; and use of the fusion protein according to the present invention for preparing an agent for treating eye diseases. Compared to conventional anti-VEGF preparations, the composition according to the present invention is considered to have an improved efficacy and be able to be used for treating patients having drug resistance, by inhibiting various growth factors related to new blood vessels, besides VEGF, and by decreasing pericyte coverage. In addition, since drug delivery ability into the choroid tissue is improved when performing an intraocular injection, the composition can be developed as eye drops by reducing an administered dosage or extending an administration cycle, and by improving ocular penetrability.

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PHARMACEUTICAL COMPOSITION FOR PREVENTING AND TREATING
EYE DISEASES, CONTAINING, AS ACTIVE INGREDIENT, FUSION
PROTEIN IN WHICH TISSUE-PENETRATING PEPTIDE AND ANTI-
VASCULAR ENDOTHELIAL GROWTH FACTOR PREPARATION ARE FUSED

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Technical Field

This application claims the priority from and the
benefit of Korean Patent Application No. 10-2015-0045684
filed on March 31, 2015, which is hereby incorporated in its
entirety by reference.

The present invention relates to a pharmaceutical
composition for preventing and treating an eye disease, the
composition comprising, as an active ingredient, a fusion
protein in which a tissue-penetrating peptide is fused to an
anti-vascular endothelial growth factor (anti-VEGF) agent.
More specifically, the present invention relates to a
pharmaceutical composition for preventing and treating an
eye disease, the composition comprising, as an active
ingredient, a fusion protein in which a tissue-penetrating
peptide is fused to an anti-VEGF agent. The present
invention also relates to a method for preparing an anti-
VEGF agent with an improved efficacy and ability to overcome
resistance, the method comprising: transforming host cells
with a recombinant vector, the recombinant vector containing
a nucleic acid sequence encoding a fusion protein in which a
tissue-penetrating peptide is fused to an anti-VEGF agent;
culturing the cells; and collecting a fusion protein from
the cells. The present invention further relates to a method
for treating an eye disease, the method comprising
administering an effective amount of the fusion protein
according to the present invention to a subject in need
thereof; and to a use of the fusion protein according to the
present invention for preparing an eye disease therapeutic
agent comprising the fusion protein as an active ingredient.

Background Art

While macula lutea is a part of the retina of the eye in which visual cells are concentrated to receive light most clearly and accurately, and a disease that causes visual impairment by the degeneration of the macula lutea occurring due to various causes is called macular degeneration. The macular degeneration is one of the three causes of blindness, together with glaucoma and diabetic retinopathy. The greatest cause of macular degeneration is an increase in age, while family history, race, smoking, and the like are also known as causes of macular degeneration. Damage to the macula lutea will cause the loss of the ability to recognize details, such as small prints, facial features, or small objects. This macular degeneration has two types: non-exudative (dry) macular degeneration and exudative (wet) macular degeneration, while the prevalence of dry macular degeneration is 90%. In dry macular degeneration, wastes form yellow precipitates, called drusen, which may accumulate in the tissue below macular tissue. The presence of drusen interferes with blood flow to the retina, especially the macula lutea, and the reduced blood flow reduces the supply of nutrients to the macula lutea, stopping or constricting efficient actions of photosensitive cells. As for wet macular degeneration, new weak blood vessels grow in or under the retina, causing fluid and blood to leak into the space below the macula. Wet macular degeneration is sometimes described as choroidal neovascularization. The choroid is a vascular region below the macula lutea and neovascularization refers to the growth of new blood vessels in the tissue. As can be inferred from the name of the choroidal neovascularization, with respect to wet macular degeneration, blood vessels are newly formed to grow from the choroid to the macula lutea.

This macular degeneration was considered to be a disease for elderly people, but in recent years, patients in their 40s and 50s are known to be rapidly increasing. The main causes of this decrease in age at onset of macular
5 degeneration are westernization of eating habits, such as an increase in fat intake, and unfavorable habits, such as smoking, drinking, and exposure to ultraviolet rays.

Diabetic macular edema (DME) is explained by the
10 thickening of the retina and/or hard exudate within one disc diameter from the center of the retina. DME and diabetic retinopathy (DR) are microvascular complications occurring in diabetic patients, and weaken eyesight and eventually result in blindness. The patients with DR show a
15 progression of DME, and dilated hyperpermeable capillaries and microaneurysm leakage may cause DME after the breakdown of blood-retinal barriers. Similar to DR, DME is associated with choroidal neovascularization that penetrates damaged or tissue-destroyed Bruch's membranes.

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Meanwhile, examples of a typical medication that is used for the prevention or treatment of various eye diseases associated with neovascularization in eyes (such as the macular degeneration and diabetic macular edema) include
25 ranibizumab, bevacizumab, aflibercept, conbercept, and the like. Currently developed biopharmaceuticals, including the foregoing medications, for the treatment of major eye diseases, such as macular degeneration and diabetic retinopathy edema, are mainly used to treat diseases of
30 posterior eyeballs, including the retina, in the form of an intraocular injection. Recently, attempts have been made to develop a form of eye drops of ranibizumab, aflibercept and the like in order to solve such problems as reduced patient convenience, increased side effects, and psychological fear

of injections. However, as shown in the test results that ranibizumab reached the retinal tissue 3-7 days after a half-dose (250 µg) of ranibizumab is dropped in the eyes 6 times at 2 hour intervals in rabbits (Chen et al., 2011. Eye), ranibizumab has a poor ocular permeability and a difficulty in reaching the posterior part of the eyeball where the lesion is present, while a large amount of drug is lost due to aqueous outflow by eye blinking at the time of applying the eye drops, and thus, its pharmaceutical effect in the form of eye drops is difficult to achieve in the eyes. In addition, similar to aflibercept, conbercept (Chengdu Kanghong pharm.), which was approved as a therapeutic agent for macular degeneration in 2013, is a fusion protein in which the second domain of vascular endothelial growth factor receptor-1 (VEGFR-1) is linked to the third and fourth domains of VEGFR-2 via Fc, and is also being currently developed as an eye drop dosage form. However, according to the reports, conbercept has a bioavailability of less than about 5% at the time of applying its eye drops (Wang et al., 2013. PLOS ONE).

In addition, ranibizumab, which is marketed under the trade name Lucentis, has received attention since about 90% of patients with macular degeneration showed response at the time of development. However, only 30% of responding patients showed a therapeutic effect, such as eyesight improvement, and its continuous administration caused drug resistance (Syed et al., 2012. Nature Rev. Drug Discov.). In order to improve such shortcomings, aflibercept, which is an Fc fusion antibody designed to have a 100-fold increase in binding ability to VEGF-A and to be able to inhibit even VEGF-B and PlGF, had been released in 2011 and showed a significant commercial growth, but, actually, it has been confirmed that the two products have no difference in a

clinical efficacy.

About 10% of patients with macular degeneration are unresponsive to anti-VEGF agents, and thus, the therapeutic effect thereof to such patients cannot be expected. This is thought to be due to other growth factor-dependent neovascular bypass other than VEGF-A. In addition, it has been confirmed that repeated administrations caused resistance in about 45% of patients, and drug response decreases as the number of administration increases (Lux et al., 2007. Br. J. Ophthalmol.). This resistance is known to be caused by vascular strengthening resulting from increased pericyte coverage that contributes to stabilization of endothelial cells at the time of repeated administrations of anti-VEGF agent and pericyte-dependent VEGF production.

Therefore, the recent development trend of eye disease therapeutic agents is to develop a combination therapy using a PDGF inhibitor for inducing pericyte dissociation in order to overcome resistance and improve efficacy of anti-VEGF agents. Therefore, an eye disease therapeutic agent capable of: (i) adding a function of blocking VEGF-A and other neovascularization-related ligands; (ii) overcoming resistance to an anti-vascular endothelial growth factor agent; (iii) disrupting pericyte coverage to improve drug efficacy; (iv) improving the frequency of administration; and (v) being developed as eye drops.

Detailed Description of the Invention

30 Technical Problem

The present inventors have found that a fusion of an anti-vascular endothelial growth factor (anti-VEGF) agent and a tissue-penetrating peptide increases the tissue penetration of drug, disrupts pericyte coverage to exert its

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effect on even a patient showing resistance to drug, reduces the dose or improves the frequency of administration, and allows a development as eye drops, and then completed the present invention.

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Therefore, an aspect of the present invention is to provide a pharmaceutical composition for preventing and treating an eye disease, the composition comprising, as an active ingredient, a fusion protein in which a tissue-
10 penetrating peptide is fused to an anti-vascular endothelial growth factor (anti-VEGF) agent.

Another aspect of the present invention is to provide a method for preparing an anti-vascular endothelial growth
15 factor (anti-VEGF) agent with an improved efficacy and ability to overcome resistance, the method comprising: (a) transforming host cells with a recombinant vector, the recombinant vector including a nucleic acid sequence encoding a fusion protein in which a tissue-penetrating
20 peptide is fused to an anti-vascular endothelial growth factor (anti-VEGF) agent; (b) culturing the cells; and (c) collecting a fusion protein from the cells.

Still another aspect of the present invention is to
25 provide a method for treating an eye disease, the method comprising administering an effective amount of a fusion protein, in which a tissue-penetrating peptide is fused to an anti-vascular endothelial growth factor (anti-VEGF) agent, to a subject in need thereof.

30

Still another aspect of the present invention is to provide a use of a fusion protein in which a tissue-
penetrating peptide is fused to an anti-vascular endothelial growth factor (anti-VEGF) agent for preparing an eye disease

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therapeutic agent comprising the fusion protein as an active ingredient.

Technical Solution

5 In accordance with an aspect of the present invention, there is provided a pharmaceutical composition for preventing and treating an eye disease, the composition comprising, as an active ingredient, a fusion protein in which a tissue-penetrating peptide is fused to an anti-vascular endothelial growth factor (anti-VEGF) agent.

15 In accordance with another aspect of the present invention, there is provided a method for preparing an anti-vascular endothelial growth factor (anti-VEGF) agent with an improved efficacy and ability to overcome resistance, the method comprising: (a) transforming host cells with a recombinant vector, the recombinant vector including a nucleic acid sequence encoding a fusion protein in which a tissue-penetrating peptide is fused to an anti-vascular endothelial growth factor (anti-VEGF) agent; (b) culturing the cells; and (c) collecting a fusion protein from the cells.

25 In accordance with still another aspect of the present invention, there is provided a method for treating an eye disease, the method comprising administering an effective amount of a fusion protein, in which a tissue-penetrating peptide is fused to an anti-vascular endothelial growth factor (anti-VEGF) agent, to a subject in need thereof.

30 In accordance with still another aspect of the present invention, there is provided a use of a fusion protein in which a tissue-penetrating peptide is fused to an anti-vascular endothelial growth factor (anti-VEGF) agent for

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preparing an eye disease therapeutic agent comprising the fusion protein as an active ingredient.

Hereinafter, the present invention will be described in detail.

In accordance with an aspect of the present invention, there is provided a pharmaceutical composition for preventing and treating an eye disease, the composition comprising, as an active ingredient, a fusion protein in which a tissue-penetrating peptide is fused to an anti-vascular endothelial growth factor (anti-VEGF) agent.

Vascular endothelial growth factor-A (VEGF-A) among the proteins present in nature is well known to induce blood extravasation. This is also called a vascular permeability factor. This action is known to be due to its combination with a vascular endothelial growth factor receptor (VEGFR2), but interestingly, the mutation experiment of vascular endothelial growth factor-A showed that the vascular penetration of vascular endothelial growth factor-A was increased even though vascular endothelial growth factor-A did not bind to the vascular endothelial growth factor receptor. This suggested that there is another receptor for vascular endothelial growth factor-A (Stacker et al., 1999. J. Biol. Chem.). Other contemporary researchers established that this receptor is neuropilin (NRP) (Makinen et al., 1999. J. Biol. Chem.).

Neuropilin was first found in the *Xenopus* nervous system. Neuropilin is a transmembrane glycoprotein, and has two types: NRP1 and NRP2. Neuropilin acts as a coreceptor for VEGF receptors (VEGFRs) by VEGF family ligand binding. In particular, NRP1 binds to various VEGF ligands by acting

as a co-receptor for VEGFR1, VEGFR2, and VEGFR3. On the other hand, NRP2 contributes to lymphangiogenesis and cell adhesion by acting as a co-receptor for VEGFR2 and VEGFR3. In addition, NRP1/NRP2 (NRP1/2) act as a co-receptor for the
5 Plexin family receptors and bind to secreted class 3 semaphorin ligands (Sema3A, Sema3B, Sema3C, Sema3D, Sema3E, Sema3F and Sema3G).

As used herein, the term "tissue penetrating" or
10 "tissue penetration" means having any one characteristic of: specifically recognizing tissues overexpressing neuropilin to be accumulated in the tissues; widening the cell gap between vascular endothelial cells to promote drug extravasation; or promoting the drug distribution in the eye
15 by adjusting the gap between corneal cells, which are a tissue acting as a barrier against water-soluble molecules.

As used herein, the term "neuropilin (NRP)" refers to a transmembrane glycoprotein, and has two types: NRP1 and
20 NRP2. Neuropilin is largely composed of five domains. From the N-terminus, a1/a2 domains are classified as CUB domains which an Ig-like C2 type domain of semaphorin binds thereto. Especially, these domains form a complex with plexin to increase binding ability with semaphorin-plexin. The b1 and
25 b2 domains of neuropilin are classified as FV/VIII domains which the C-termini of VEGF family ligands or secreted class 3 semaphorin ligands (Sema3s) bind thereto. The VEGF ligands and class 3 semaphorin ligands have a recognition site (RXRR, Arg-X-Arg-Arg) of furin protease, and thus the ligands
30 commonly end with an arginine (Arg) amino acid residue at the C-terminus by furin processing (Adams et al., 1997. EMBO J.). It has been reported that the Arg residue at the C-terminus of the VEGF and Sema3s ligands is very important in the interaction of neuropilin b1b2 domains (Teesalu et al.,

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2009. Proc. Natl. Acad. Sci. USA). The tertiary structure of a complex between the VEGF ligand and the neuropilin blb2 domain has been revealed (Parker et al., 2012. J. Biol. Chem.), and accordingly, the amino acid sequence of VEGF, which is important in the binding to the neuropilin blb2 domain, can be recognized. However, it still has not been established which site of the C-terminus of Sema3A binding to NRPI specifically binds to NRP.

10 The anti-vascular endothelial growth factor agent includes a molecule that interferes with an interaction between VEGF and a natural VEGF receptor, for example, a molecule that binds to VEGF or a VEGF receptor to prevent or interfere with an interaction between VEGF and VEGF receptor. 15 Examples of the VEGF antagonist include anti-VEGF antibodies, anti-VEGF receptor antibodies, and VEGF receptor-based chimeric molecules.

As used herein, the term "fusion" refers to 20 integrating two molecules each possessing the same or different functions or structures, and may be a fusion by any physical, chemical, or biological method whereby a tissue-penetrating peptide can bind to an anti-vascular endothelial growth factor agent. The fusion may be 25 preferably by a linker peptide, while this linker peptide may bind to, for example, the C-terminus of Fab (antigen-binding fragment) or Fc fragment in an antibody.

The eye disease of the present invention preferably 30 means an eye disease by neovascularization. As used herein, the expression "eye disease by neovascularization" refers to any eye disease by vascular growth or proliferation, vascular leakage, or those associated therewith.

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The fusion protein according to the present invention increases the tissue penetration of drug by binding to a neuropilin receptor, disrupts pericyte coverage to exert its effect on even a patient showing resistance to drug, improves the frequency of administration, and allows its development as eye drops.

Specifically, according to an Example of the present invention, a ranibizumab mutant having a point mutation in which cysteine (C) is substituted with serine (S) in the amino acid sequence of ranibizumab significantly increased productivity, while a modified form in which a tissue-penetrating peptide (TPP) is fused to the ranibizumab mutant also maintained the increased productivity intact (Example 1).

According to another Example of the present invention, as a result of comparison of the affinity to neuropilin receptor and the disruption ability of tight junction between endothelial cells of a fusion protein in which a tissue-penetrating peptide was fused to the C-terminus of the ranibizumab mutant, it was confirmed that the fusion protein very favorably bound to neuropilin receptor NRP1 and Sema3A ligand at similar levels, and remarkably inhibited VE-cadherin, indicating its significantly excellent disruptive ability of tight junctions between endothelial cells (Example <1-3>).

According to another Example of the present invention, in order to investigate whether the fusion protein in which a tissue-penetrating peptide is fused to the C-terminus of a ranibizumab mutant can improve the penetration by binding with neuropilin receptors distributed widely in ocular endothelial cells, the extracted eyeballs were immersed in a

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solution comprising the fusion protein and a solution containing ranibizumab and then the penetration over time was compared therebetween (Example 4). The experiment results confirmed that an anti-vascular endothelial growth factor agent binding to the tissue penetrating peptide initiated the penetration from the corneal epithelial tissues from one hour after the experiment and showed a significantly high drug distribution in the eye within 2 hours compared with ranibizumab, and thus, confirmed the possibility of controlling the dose and increasing the interval of administration through the improvement of penetration.

That is, it could be verified that, compared with the previous study that the ocular penetration of ranibizumab was significantly low, the fusion protein according to the present invention penetrated the cornea, which serves as a barrier against water-soluble molecules, more rapidly than ranibizumab, and reached the inside of the eyeball. Thus, the fusion protein according to the present invention has a possibility of being developed as eye drops through the improvement of formulation in the future. The effect of increasing the ocular tissue penetration through the fusion with the tissue-penetrating peptide was similarly observed in the whole antibody form with a large molecular weight and a complicated protein structure, as well as in a Fab-type ranibizumab modified form. A fusion protein in which a tissue-penetrating peptide is fused to the Fc-terminus of immunoglobulin G (IgG) type bevacizumab also showed a significantly increased ocular penetration ability compared with bevacizumab, indicating that a bevacizumab modified form according to the present invention can also be developed as a drug with an increased therapeutic effect.

It can be predicted from the results of the present Examples that, similar to bevacizumab, aflibercept, conbercept and the like in a fusion protein form in which VEGF receptors (VEGFR1 and VEGFR2) are fused to an Fc fragment, if a tissue-penetrating peptide is fused to the Fc-terminus, can also be developed as drugs with a remarkably enhanced therapeutic effect, compared with existing Fc fusion proteins.

In another Example of the present invention, the neovascularization inhibitory effect and the neovascularization inhibitory effect in drug resistance models were compared and evaluated using various animal disease models between the fusion protein of the present invention and ranibizumab. As a result of experiment using corneal neovascularization models, the fusion protein of the present invention showed a significant neovascularization inhibitory effect of 50% or more compared with a control group and an equivalent effect to ranibizumab, confirming an improvement in efficacy by the tissue-penetrating peptide fused to the C-terminus (Example <5-1>). In addition, as for the neovascularization inhibitory effect in drug resistance models, the fusion protein of the present invention showed an excellent efficacy by two times or more compared with ranibizumab, while this value is similar to the results in a literature disclosing a co-administration of anti-VEGF aptamer and anti-PDGF antibody agent (Jo et al., 2006. Am. J. Pathol. 168), and thus, it can be predicted that the fusion protein of the present invention has a possibility of eyesight improvement in about 70% of the patients administered with ranibizumab, of which eyesight was only maintained without eyesight improvement (Example <5-2>). The excellent effect of inhibiting neovascularization in the eye disease by the fusion protein

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according to the present invention was also observed similarly in a choroidal neovascularization (CNV) model used as an actual macular degeneration efficacy model and an oxygen-induced retinopathy (OIR) used as a retinopathy efficacy model, and thus, it can be predicted that the fusion protein of the present invention has a clinically remarkably increased therapeutic effect, compared with ranibizumab (Example 6 and Example 7).

10 As used herein, the term "prevention" refers to all acts of suppressing an eye disease or delaying the progress of an eye disease by administering a composition of the present invention.

15 As used herein, the term "treatment" refers to all acts of improving or beneficially changing an eye disease by administering a composition of the present invention. More specifically, the term "treatment" refers comprehensively to ameliorating symptoms of an eye disease, which may encompass
20 healing, substantially preventing, or ameliorating the condition of an eye disease, and may encompass ameliorating, healing, or preventing one symptom or most of the symptoms resulting from an eye disease, but is not limited thereto.

25 In practicing the present invention, a person skilled in the art can determine an effective dose (effective amount), the number of administrations, and the route of administration in order to prevent or treat an eye disease, upon properly considering various factors, such as a type
30 and severity of the corresponding eye disease, the age, weight, health condition, sex, diet, and excretion rate of the subject in need of administration. The term "effective amount" comprehensively refers to an amount to improve symptoms of an eye disease when administered to a subject,

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and encompasses an amount to heal or substantially prevent an eye disease or ameliorate the condition of an eye disease. The term "subject" may be an animal, preferably a mammal, and especially, an animal including a human being, and may
5 include cells, tissues, organs, or the like which are derived from an animal. The subject may be a patient in need of treatment. The composition of the present invention may be administered to mammals including humans by any methods. For example, the composition of the present
10 invention may be administered orally or parenterally. The parental administration may be, but is not limited to, intravenous, intramuscular, intra-arterial, intramedullary, intradural, intracardiac, transdermal, subcutaneous, intraperitoneal, intranasal, intestinal, topical, sublingual,
15 or rectal administration. An immunogenic complex protein according to the present invention may be administered alone or in combination with a known compound having an effect of preventing and treating a target disease.

20 For example, the dose of the pharmaceutical composition of the present invention to the human body may vary depending on the age, weight, sex, dosage form, health condition, and disease severity of a patient. For ocular injection, the dose may be generally 0.001-10 mg/day per
25 eyeball, and preferably, 0.1-2 mg/day per eyeball. For eye drops, the dose may be 0.001-100 mg/day and preferably 0.01-10 mg/day per 1 ml of an eye drop solution. The composition may also be divisionally administered at predetermined intervals according to the determination of a physician or
30 pharmacist.

The composition of the present invention may further contain a pharmaceutically acceptable additive. Examples of the pharmaceutically acceptable additive may include starch,

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gelatinized starch, microcrystalline cellulose, lactose, povidone, colloidal silicon dioxide, calcium hydrogen phosphate, lactose, mannitol, taffy, Arabia rubber, pregelatinized starch, corn starch, cellulose powder, 5 hydroxypropyl cellulose, Opadry, sodium carboxymethyl starch, carunauba wax, synthetic aluminum silicate, stearic acid, magnesium stearate, aluminum stearate, calcium stearate, white sugar, dextrose, sorbitol, talc, etc. The pharmaceutically acceptable additive according to the 10 present invention is preferably contained in 0.1-90 weight part relative to the pharmaceutical composition.

In addition, the pharmaceutical composition may be in various forms suitable for any route of administration, 15 including, but not limited to, an injection, eye drops, eye ointment, and an intraocular dosage form. In cases where the pharmaceutical composition is formulated, diluents or excipients, such as a filler, an extender, a binder, a wetting agent, a disintegrant, or a surfactant, may be used. 20 The injection may include all of intravitreal injection and intraocular local injection including conjunctival injection, but is not limited thereto. The injection may contain conventional additives, such as a solubilizer, an isotonic agent, a suspending agent, an emulsifier, a stabilizer, and 25 a preservative.

Suitable carriers for the injection of the present invention include physiological saline, bacteriostatic water, Cremophor EL (EASE, Parsippany, NJ, USA) or phosphate 30 buffered saline (PBS). In all cases, the composition must be sterile and should be fluid to the extent that easy syringability exists. The composition must be stable under the conditions of manufacture and storage, and must be preserved against the contaminating action of microorganisms

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such as bacteria and fungi. The carrier may be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), and suitable mixtures thereof. The proper fluidity may be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of a dispersion, and by the use of surfactants. Prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In many cases, the composition will be preferable to contain isotonic agents, for example, sugars, polyalcohols, such as mannitol or sorbitol, or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate, hyaluronic acid, and gelatin.

The eye drops may be a water-soluble ophthalmic solution, a water-insoluble ophthalmic solution, or an ophthalmic emulsion. The eye drops of the present invention may contain, in addition to a fusion protein in which the above essential component, tissue-penetrating peptide, is fused to the anti-vascular endothelial cell growth factor (anti-VEGF) agent, any conventionally known component in the eye drops, for example, a buffer, a viscosity controlling agent, a stabilizer, an isotonic agent, a preservative, and the like, may be mixed with the fusion protein. Of these, examples of the buffer may include known buffers of citrate, phosphate, acetate, and amino acid salts. In addition, examples of the viscosity controlling agent may include polyvinyl alcohol, hydroxypropylcellulose, methylcellulose, povidone, hydroxypropyl methylcellulose, ethylcellulose,

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hydroxyethylcellulose, carmellose, polyethylene glycol, chondroitin, or salts thereof. Examples of the stabilizer may include: antioxidants, such as sodium nitrite, sodium hydrogen sulfite, and sodium metabisulfite; and
5 chelating agents, such as sodium edetate, cyclodextrin, citric acid, and citrate. In addition, examples of the isotonicizing agent may include: salts, such as sodium chloride and potassium chloride; polyhydric alcohols, such as glycerin and propylene glycol; sugars, such as glucose,
10 sucrose, and trehalose; sugar alcohols, such as xylitol and sorbitol; polyethers, such as polyethylene glycol; and amidosulfonic acids, such as taurine. In addition, examples of the preservative may include benzalkonium chloride, benzethonium chloride, chlorobutanol, paraoxybenzoic ester,
15 thimerosal, sorbic acid, sorbate, chlorhexidine gluconate, and the like. In the eye drops of the present invention, the pH at room temperature is preferably 4.5-8.5, more preferably 5.5-8, and particularly preferably 6-8. The pH is measured at room temperature using a pH meter (e.g.,
20 Accumet model 25 pH/Ion meter manufactured by Fisher Scientific).

Some ophthalmic drugs cannot be administered as eye drops since they have poor permeability through the eye
25 barrier. Therefore, ointment can be used to extend the contact time and increase the amount of drug absorbed. Examples of the water-insoluble polymer as a carrier component which can be used in eye drops may include ethyl cellulose, an ethylene-vinyl acetate copolymer, polymethyl
30 methacrylate, an ethyl acrylate-methyl methacrylate-trimethylammonium ethyl chloride methacrylate copolymer, and a methyl methacrylate-butyl methacrylate-dimethyl aminoethyl methacrylate copolymer, and the like. Examples of the biodegradable polymer may include polylactic acid, a

polylactic acid-glycolic acid copolymer, polycyanoacrylate, polyalkyl cyanoacrylate, poly-ε-caprolactone, and the like. Examples of the water-soluble polymer may include: cellulose derivatives, such as hydroxypropylmethyl cellulose phthalate, 5 carboxymethylethyl cellulose, and hydroxypropyl cellulose; calcium alginate, chitosan, albumin, gelatin, a methacrylic acid-methyl methacrylate copolymer, and the like. Examples of an oily component may include tripalmitine, cetyl alcohol, cholesterol, various phospholipids, cetyl palmitate, 10 cholesterol palmitate, and the like. These carrier components usually have an ability to sustained-release an active component comprising an active substance for ophthalmic therapy. A carrier component with high specific gravity that is usable without addition of any specific gravity modified form may be, for example, hydroxypropyl 15 methyl cellulose phthalate 200731 (specific gravity: 1.65), hydroxypropyl methyl cellulose phthalate 220824 (specific gravity: 1.82), carboxymethyl ethyl cellulose (specific gravity: 1.59) and the like. Nevertheless, even when such a 20 carrier component is used, it is preferable to add a specific gravity modified form to further increase the specific gravity. In the present invention, examples of the specific gravity modified form used for adjusting the specific gravity of carrier particles may include, but are 25 not limited to: insoluble components, such as titanium oxide (specific gravity: 4.17); hardly soluble components, such as tricalcium phosphate (specific gravity: 3.14), anhydrous calcium hydrogen phosphate (specific gravity: 2.89), and calcium hydrogen phosphate dehydrate (specific gravity: 30 2.30); water-soluble components, such as sodium chloride (specific gravity: 2.17), potassium chloride (specific gravity: 1.98), calcium chloride (specific gravity: 2.0), magnesium chloride (specific gravity: 2.41), sodium carbonate (specific gravity: 2.53), sodium dihydrogen

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phosphate (specific gravity: 1.95), sodium monohydrogen phosphate (specific gravity: 1.7), and potassium dihydrogen phosphate (specific gravity: 2.34).

5 An insert is generally similar to a soft contact lens placed in the cornea, except that the insert is placed in the upper cul-de-sac rather than attached to the open cornea, or less frequently in the lower conjunctival sac. The insert is typically manufactured of a biologically soluble
10 material that dissolves or disintegrates in the lachrymal fluid while releasing the drug.

 Solid preparations for oral administration may include a tablet, a pill, a powder, a granule, a capsule, and the
15 like. These solid preparations may be prepared by mixing tyrosol with at least one excipient, for example, starch, calcium carbonate, sucrose, lactose, gelatin, or the like. In addition to simple excipients, lubricants, such as magnesium stearate and talc, may be used. Liquid
20 preparations for oral administration include a suspension, a liquid for internal use, oil, syrup, and the like, and may also include, in addition to simple diluents, such as water and liquid paraffin, several excipients, for example, a wetting agent, a sweetener, an aroma, a preservative, and
25 the like.

 In addition, the therapeutic composition of the present invention may further contain any physiologically acceptable carrier, excipient, or stabilizer (Remington: The
30 Science and Practice of Pharmacy, 19th Edition, Alfonso, R., ed, Mack Publishing Co. (Easton, PA: 1995)). The acceptable carrier, excipient, or stabilizer is non-toxic to a user at used dose and concentration, and examples thereof include: buffers, for example, phosphoric acid, citric acid, and

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other organic acids; antioxidants including ascorbic acids; low-molecular weight (less than about 10 residues) polypeptides; proteins, for example, serum albumin, gelatin, or immunoglobulin; hydrophilic polymers, for example, polyvinyl pyrrolidone; amino acids, for example, glycine, glutamine, asparagine, arginine, or lysine; monosaccharides, disaccharides, and other carbohydrates, including glucose, mannose, or dextrin; chelating agents, for example, EDT; sugar alcohols, for example, mannitol or sorbitol; salt-forming counter ions, for example, sodium; and (or) non-ionic surfactants, for example, Tween, pluronics, or polyethylene glycol (PEG).

In accordance with another aspect of the present invention, there is provided the pharmaceutical composition wherein the tissue-penetrating peptide includes any one amino acid sequence selected from the group consisting of SEQ ID NOs: 1 to 7.

The tissue-penetrating peptide represented by an amino acid sequence selected from SEQ ID NOs: 1 to 7 is designed based on the fact that the amino acid sequence of a binding region of VEGF_A ligand, which binds to b1b2 domain of neuropilin, and the length of the amino acid sequence are analyzed, and the nucleotide sequences of furin C-terminus sequences of semaphorin 3A and semaphorin 3F, which are known to bind to neuropilin, are analyzed, and thus the sequences of the C-terminus thereof are similar to each other.

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According to another aspect of the present invention, the present invention provides a pharmaceutical composition wherein the anti-vascular endothelial growth factor agent includes: an agent used to prevent or treat an eye disease

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and selected from the group consisting of bevacizumab, ranibizumab, r84 (PLOS One. 2010 Aug 6;5(8)), aflibercept, conbercept, CT01 (WO2005056764A2), DOM15-10-11 (WO2008149147A2), DOM15-26-593 (WO2008149143A2), PRS-050
5 (Mross et al., 2013. PLOS One), CT-322 (Dineen et al., 2008. BMC Cancer), ESBA903 (Asmus et al., 2015. Eur J Pharm Biopharm.), and EPI-0030 (WO2011023130A1); biosimilars thereof, and mutants thereof. More preferably, the anti-vascular endothelial growth factor agent may be ranibizumab,
10 bevacizumab, aflibercept, or conbercept, but is not limited thereto.

As used herein, the term "biosimilar" refers to a copy medical product that is verified to have equivalence in
15 light of quality, efficacy, and safety by mimicking an off-patent original biological medical product that has already been developed/marketed by using biotechnology (such as gene recombination and cell culture technology).

20 In accordance with another aspect of the present invention, there is provided a pharmaceutical composition wherein the mutant may be one in which cysteine is deleted, or substituted with another amino acid residue including serine excluding cysteine in heavy chain constant domain and
25 light chain constant domain.

In an Example of the present invention, a ranibizumab mutant in which the last residue cysteine is substituted with serine in the nucleotide sequence of ranibizumab was
30 constructed by a protein engineering method using the conversion of the amino acid sequence of ranibizumab (Example <1-1>).

In accordance with another aspect of the present

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invention, there is provided the pharmaceutical composition, wherein the mutant is a ranibizumab mutant consisting of a light chain represented by SEQ ID NO: 8 and a heavy chain represented by SEQ ID NO: 10.

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The tissue-penetrating peptide according to an aspect of the present invention may further include a linker peptide. The linker peptide may be composed of 1 to 50 amino acids, preferably 4 to 20 amino acids, more preferably 4 to 15 amino acids. In addition, the linker peptide may be composed of glycine (G), serine (S) or alanine (A), while the sequence of the linker peptide may be preferably an amino acid sequence of $(GA)_n$ or $(GGGGS)_m$ (provided that n and m each are independently an integer of 1 to 20, and mean the number of repetition of the sequence in parentheses), and more preferably an amino acid sequence of GAGA or $(GGGGS)_3$.

In an Example of the present invention, a fusion protein in which a tissue-penetrating peptide (TPP) is fused to a ranibizumab mutant through the linker was constructed, and the effect thereof was investigated. The fusion protein may include a fusion protein (IDB0062) having a form in which TPP#2 is linked to the ranibizumab mutant (IDB0061) according to the present invention by a linker $((GGGGS)_3)$, and consisting of the amino acid sequences represented by SEQ ID NO: 12 and SEQ ID NO: 14; a fusion protein (IDB0064) having a form in which TPP#5 is linked to the ranibizumab mutant (IDB0061) according to the present invention by a linker $((GGGGS)_3)$, and consisting of the amino acid sequences represented by SEQ ID NO: 16 and SEQ ID NO: 18; and a fusion protein (IDB0072) having a form in which TPP#2 is linked to the heavy chain of bevacizumab by a linker $((GGGGS)_3)$, and consisting of the amino acid sequences

represented by SEQ ID NO: 20 and SEQ ID NO: 22.

The pharmaceutical composition of the present invention can be used to treat any eye disease by
5 neovascularization. As used herein, the expression "eye disease by neovascularization" refers to any eye disease by vascular growth or proliferation, vascular leakage, or those associated therewith.

10 The eye disease by neovascularization may be selected from the group consisting of proliferative vitreoretinopathy, macular degeneration, pigmentary retinopathy, diabetic retinopathy, choroidal neovascularization, neovascular glaucoma, ischemic optic neuropathy, retinopathy of
15 prematurity, retinopathy of immaturity, epidemic conjunctivitis, neovascular iris disease, retrolental fibroplasias, atopic keratitis, superior limbic keratitis, pterygium keratitis sicca, phlyctenular keratoconjunctivitis, scleritis, and diabetic macular edema, and more preferably,
20 examples thereof may be macular degeneration and diabetic macular edema, but are not limited thereto.

In accordance with another aspect of the present invention, there is provided a method for preparing an anti-
25 vascular endothelial growth factor (anti-VEGF) agent with an improved efficacy and ability to overcome resistance, the method comprising: (a) transforming host cells with a recombinant vector, the recombinant vector comprising a nucleic acid sequence encoding a fusion protein in which a
30 tissue-penetrating peptide is fused to an anti-vascular endothelial growth factor (anti-VEGF) agent; (b) culturing the cells; and (c) collecting a fusion protein from the cells.

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The nucleic acid sequence encoding the fusion protein may be selected from the group consisting of SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 17, SEQ ID NO: 19, SEQ ID NO: 21, and SEQ ID NO: 23. Specifically, the nucleic acids encoding the light and heavy chains of the ranibizumab modified form IDB0062 according to the present invention are described by the nucleotide sequences of SEQ ID NO: 13 and SEQ ID NO: 15; the nucleic acids encoding the light and heavy chains of the ranibizumab modified form IDB0064 according to the present invention are described by the nucleotide sequences of SEQ ID NO: 17 and SEQ ID NO: 19; and the nucleic acids encoding the light and heavy chains of the bevacizumab modified form IDB0072 according to the present invention are described by the nucleotide sequences of SEQ ID NO: 21 and SEQ ID NO: 23.

As used herein, the vector refers to an expression vector that is prepared by inserting the polynucleotide of the present invention into a vector by a method well known in the art to express the fusion protein of the present invention using appropriate transcription/translation regulatory sequences.

The polynucleotide sequence cloned according to the present invention may be operably linked to an appropriate expression control sequence, while the operably linked gene sequence and the expression control sequence may be contained in one expression vector having both a selection marker and a replication origin. The term "operably linked" means that the polynucleotide (nucleic acid) sequence is linked in a manner of enabling gene expression by an expression control sequence. The term "expression control sequence" refers to a DNA sequence that controls the expression of an operably linked polynucleotide sequence in

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a particular host cell. Such an expression control sequence may include at least one selected from the group consisting of a promoter for performing transcription, an operator sequence for controlling transcription, a sequence
5 for encoding a suitable mRNA ribosomal binding site, a sequence for controlling the termination of transcription and translation and the like.

The vector used as a parent vector of the expression
10 vector is not particularly limited, while any plasmid, virus, or other medium, which is commonly employed for expression in a microorganism used as a host cell in a technical field to which the present invention pertains, can be used. Examples of the plasmid may include *Escherichia coli*-derived
15 plasmids (pBR322, pBR325, pUC118, pUC119, and pET-22b (+)), *Bacillus subtilis*-derived plasmids (pUB110 and pTP5), and yeast-derived plasmids (YEpl3, YEpl24, and YCp50), but are not limited thereto. Examples of the virus may include animal viruses (such as retrovirus, adenovirus, and vaccinia
20 virus), insect viruses (such as baculovirus), and the like, but are not limited thereto.

The host cells may be selected from ones that can control the expression of an inserted sequence or produce a
25 target product from a gene in a preferable specific manner. Different host cells have their own characteristic and specific mechanisms for protein translation, post-translational processing, and transformation. A suitable cell line or host system may be selected from ones that
30 provide preferable transformation and processing of expressed heterologous proteins. The expression in yeasts can produce biologically active products. The expression in eukaryotic cells can increase the likelihood of "natural" folding.

Any host cell known in the art may be used as a host cell as long as it is capable of performing continuous cloning and expressing while stabilizing the vector of the present invention. For example, *E. coli* JM109, *E. coli* BL21DE, *E. coli* DH5, *E. coli* RR1, *E. coli* LE392, *E. coli* B, *E. coli* X 1776, and *E. coli* W3110. Also, *Agrobacterium* spp. strains (such as *Agrobacterium* A4), *Bacilli* spp. strains (such as *Bacillus subtilis*), other intestinal bacteria such as *Salmonella typhimurium* or *Serratia marcescens*, and various *Pseudomonas* spp. strains may be used as host cells.

In addition, in cases where the vector of the present invention is transfected into eukaryotic cells, yeast (*Saccharomyces cerevisiae*), and insect cells and human cells (e.g., CHO cell line (Chinese hamster ovary), W138, BHK, COS-7, 293, HepG2, 3T3, RIN, and MDCK cell lines) may be used as host cells.

Any known method whereby a vector is delivered into a host cell to transform the host cell may be used, but is not particularly limited. For example, *E. coli* can be transformed by heat shock or electroporation. When a producing cell line is constructed using animal cells, the cells can be transfected by calcium phosphate precipitation, a DEAE-dextran method, electroporation, direct microinjection, a DNA-loaded liposome method, a lipofectamine-DNA complex method, cell sonication, gene bombardment using high-velocity microprojectiles, a polycation method, and receptor-mediated transfection. Some of these techniques may be modified for use *in vivo* or *ex vivo*.

Transgenic cells are cultured under appropriate

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conditions allowing the expression of fusion proteins, while these conditions can be implemented according to methods well known to a person skilled in the art. Transgenic cells may be cultured in large quantities by a routine culturing method. A medium containing carbon sources, nitrogen sources, vitamins, and minerals may be used as a culture medium, of which one example is 2X YT medium. Cells can be cultured under conventional cell culture conditions. For instance, the cells may be cultured at a temperature range of 15-45°C for 10-40 hours. Centrifugation or filtration may be carried out to remove cells in the culture liquid and collect only the culture medium, and such a step may be carried out as needed by a person skilled in the art. The culture medium (filtrate) with the cells removed is refrigerated by a conventional method, so that the culture medium can be preserved for a short time so as not to lose its activity.

The fusion proteins expressed in transgenic cells (or transformants) can be purified in a conventional manner, and for example, the fusion proteins of the present invention can be purified by using salting out (e.g., ammonium sulfate precipitation or sodium phosphate precipitation), solvent precipitation (e.g., protein fraction precipitation using acetone, ethanol, and the like), dialysis, gel filtration, ion exchange, column chromatography (such as reverse-phase column chromatography, and affinity column chromatography) and ultra-filtration, alone or in combination (Maniatis et al, Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory, Cold Spring Harbor, N.Y.(1982); Sambrook et al, Molecular Cloning: A Laboratory Manual, 2d Ed., Cold Spring Harbor Laboratory Press(1989); Deutscher, M., Guide to Protein Purification Methods Enzymology, vol. 182. Academic Press. Inc., San Diego, CA(1990)).

Advantageous Effects

The pharmaceutical composition comprising , as an active ingredient, a fusion protein in which a tissue-
5 penetrating peptide is fused to an anti-vascular endothelial growth factor (anti-VEGF) agent, of the present invention, increases the tissue penetration of the anti-vascular endothelial growth factor agent and improves the ability of the drug transfer into the choroidal tissues at the time of
10 intraocular injection, thereby allowing its development in the form of eye drops as well as showing effects of treating drug-resistant patients, reducing the dose, and increasing the frequency of administration.

15 Brief Description of the Drawings

FIG. 1A is a schematic diagram of a fusion protein in which a tissue-penetrating peptide is fused to an anti-vascular endothelial growth factor antigen-binding fragment (Fab). FIG. 1B is a schematic diagram showing the binding
20 of a fusion protein, in which a tissue-penetrating peptide is fused to an anti-vascular endothelial growth factor, to VEGF and neuropilin receptor-1. FIG. 1C is a schematic diagram of modified forms in which a tissue-penetrating peptide binds to various vascular endothelial growth factor
25 inhibitor forms (Fab, whole IgG, and Fc fusion protein).

FIG. 2 shows the HPLC analysis results of major products by the production of ranibizumab and the fusion protein of the present invention (IDB0062: Fab fusion
30 protein in which tissue-penetrating peptide TPP#2 is fused to a ranibizumab mutant). AU means an arbitrary unit.

FIG. 3 shows the 12% non-reducing SDS-PAGE gel analysis results of primary purified products of the fusion

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proteins according to the present invention (IDB0062: Fab fusion protein in which tissue-penetrating peptide TPP#2 is fused to a ranibizumab mutant; IDB0064: Fab fusion protein in which tissue-penetrating peptide TPP#5 is fused to a ranibizumab mutant).

FIG. 4A shows the VEGF binding affinity analysis results of ranibizumab, a ranibizumab mutant, and a fusion protein according to the present invention. FIG. 4B shows the neuropilin receptor-1 binding ability analysis evaluation results of a tissue-penetrating peptide and a fusion protein according to the present invention (IDB0061: ranibizumab mutant; IDB0062: Fab fusion protein in which tissue-penetrating peptide TPP#2 is fused to a ranibizumab mutant; Fc-TPP#2: Fc fusion protein in which a tissue-penetrating peptide TPP#2 is fused to the Fc-terminus of IgG1).

FIG. 5A shows the evaluation results of stability by storage condition of a fusion protein according to the present invention. FIG. 5B shows the evaluation results of stability by repeated freezing/thawing of the fusion protein.

FIG. 6A shows the evaluation results of vascularization inhibitory effect of ranibizumab, a ranibizumab mutant, and a fusion protein according to the present invention in corneal neovascularization prevention models. FIG. 6B is a graph obtained by quantifying the results of FIG. 6A.

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FIG. 7A shows the evaluation results of vascularization inhibitory effect of ranibizumab and a fusion protein according to the present invention in corneal neovascularization resistance models. FIG. 7B is a graph

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obtained by quantifying the results of FIG. 7A. FIG. 7C shows the evaluation results of pericyte coverage reduction effect of ranibizumab and a fusion protein according to the present invention.

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FIG. 8A shows the optical microscopic evaluation results of ocular penetration of ranibizumab modified form IDB0062, which is a fusion protein according to the present invention. FIG. 8B is a graph obtained by quantifying the results of FIG. 8A. FIG. 8C shows the analysis results of distribution of FITC-conjugated protein in the ocular tissue section after reaction for 2 hours using a fluorescent microscope together with DAPI staining. FIG. 8D is a graph obtained by quantifying the results of FIG. 8C. FIG. 8E shows the analysis result of distribution of IDB0062 according to retinal penetration ability thereof by analyzing the retina tissue fragment through a confocal microscope.

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FIG. 9A shows the evaluation results of ocular penetration ability of bevacizumab modified form IDB0072, which is a fusion protein according to the present invention, using a fluorescent microscope. FIG. 9B is a graph obtained by quantifying the results of FIG. 9A.

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FIG. 10A shows an inhibitory aspect of choroidal neovascular proliferation by drug treatment of ranibizumab or a fusion protein according to the present invention in choroidal neovascularization (CNV) models. FIG. 10B is a graph obtained by quantifying the results of FIG. 10A.

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FIG. 11A shows the analysis results of the inhibition of leakage at vascular terminals by drug treatment of ranibizumab or a fusion protein according to the present

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invention in oxygen-induced retinopathy (OIR) models. FIG. 11B is a graph obtained by quantifying the results of FIG. 11A.

5 FIG. 12A shows the analysis results of the inhibition of the formation of neovascular and vascular tufts by drug treatment of ranibizumab or a fusion protein according to the present invention in oxygen-induced retinopathy (OIR) models using a fluorescent microscope after isolectin B4
10 staining. FIG. 12B is a graph obtained by quantifying the results of FIG. 12A.

FIG. 13 shows the western blot analysis results of the amount of drug present in retinal tissues according to the
15 time after the intraocular injection of IDB0062 and ranibizumab into rats.

Mode for Carrying Out the Invention

Hereinafter, the present invention will be described
20 in detail.

However, the following examples are merely for illustrating the present invention and are not intended to limit the scope of the present invention.

25 <Example 1>

Construction of ranibizumab modified form having fused tissue-penetrating peptide

30 <1-1> Construction of ranibizumab mutant IDB0061 with increased productivity

The low production yield of ranibizumab is due to a low culture yield of Fab fragments and a complicated post-treatment process by the polymorphism of produced proteins through periplasmic expression. To overcome this problem, a

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particular amino acid sequence of ranibizumab was converted through protein engineering (such as point mutation introduction) so that a producing cell line was optimized so as to export most of the produced proteins out of cells to increase the expression rate and to produce only uniform-shaped proteins, thereby producing ranibizumab mutant IDB0061. Accordingly, it was confirmed that the culture productivity was improved and the purification process was simplified, leading to a remarkable improvement in production yield.

Specifically, according to the protein engineering for conversion of the amino acid sequence of ranibizumab, a gene was synthesized by changing cysteine to serine at the terminus in the nucleotide sequence of ranibizumab. Thereafter, an expression test was conducted after transformation into producing cell line SUPEX5 (KCTC 12657BP).

The construction procedure of a light chain region of ranibizumab mutant IDB0061 is as follows: The nucleic acid sequence of ranibizumab was obtained from the related patent and subjected to codon optimization, on the basis of which a nucleic acid of Fab light chain variable region (VL) comprising a signal sequence was synthesized. The CL region of Fab was constructed by PCR using anti-albumin Fab SL335 vector as a template and primers (SEQ ID NOs: 24 and 25). The construction procedure of a heavy chain region of ranibizumab mutant IDB0061 is as follows: The nucleic acid sequence of ranibizumab was obtained from the related patent and subjected to codon optimization, on the basis of which a nucleic acid of Fab heavy chain variable region (VH) comprising a signal sequence (gIII) was synthesized. The CH1 region of Fab was constructed by PCR using anti-albumin

[Table 1]

Sequences of primers used for cloning (5'→3')	
SEQ ID NO: 24	tatgggtacaccatctgtgttccalc
SEQ ID NO: 25	aagctctcccclgattcaactcttttgax
SEQ ID NO: 26	cacaaagaacttcacacagcagagast
SEQ ID NO: 27	ctaacgaacgcagacaccttttttgtttt
SEQ ID NO: 28	algaaaaaacttcagcttccgatlccagst
SEQ ID NO: 29	gatgaasacagatgctcgacgccaca
SEQ ID NO: 30	zcxgafccatgaaaaaacttcacattcagatccagst
SEQ ID NO: 31	aggctcgaatttaacgacccagacaccttttttgtttt
SEQ ID NO: 32	acdtccaccaaaggccccatc
SEQ ID NO: 33	aaaagtatttcagctccaactttcttatccac
SEQ ID NO: 34	ctacacaaagaaacttcagcccaaatctt
SEQ ID NO: 35	ctaacgaacgcagacaccttttttgtttt
SEQ ID NO: 36	algaaaaaactgctgttcccgattccagc
SEQ ID NO: 37	cccttsscccltgatgaxx
SEQ ID NO: 38	agggcatctcacaaaaactgcttttcacgattccsc
SEQ ID NO: 39	gaxxaatttttaacgaacccagacaccttttttgtttt
SEQ ID NO: 40	cccgatctcalgaaaaaacttcacatttcagatccagst
SEQ ID NO: 41	cccgatctcalgaaaaaactgcttttcacgattccsc
SEQ ID NO: 42	acdtctcaccccccgaataactcfaaaccaacacacacaccaagccattlaactccaxx

The amino acid sequence of ranibizumab was subjected to point mutation using a method ordinarily used in a field of protein engineering. Specifically, cysteine was substituted with serine at the 214th amino acid residue in the light chain amino acid sequence of ranibizumab, while cysteine was substituted with serine at the 226th amino acid

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residue in the heavy chain amino acid sequence of ranibizumab. The amino acid sequences of the light chain and the heavy chain of the point-mutated ranibizumab mutant IDB0061 were indicated by SEQ ID NO: 8 and SEQ ID NO: 10, respectively, while the nucleic acid sequences encoding the amino acid sequences were indicated by SEQ ID NO: 9 and SEQ ID NO: 11, respectively.

The sequence of ranibizumab mutant IDB0061 finally completed through PCR was cloned in pHEKA vector, and transformed into SUPEX5 strain. Specifically, after 100 μ l of competent cells was added to a 1-mm cuvette, 3 μ l of the DNA was added thereto, and then gene introduction was carried out by electric shock at 1800 V, thereby completing the preparation of a producing cell line.

The producing cell lines of ranibizumab and IDB0061 were respectively inoculated at 1% (v/v) in 50 ml of 2 $\times$ YT media (100 mM potassium phosphate buffer, pH 7.2, 50 μ g/ml kanamycin), and pre-cultured at 220 rpm for 18 hours at 28°C. Then, 180 ml of 2 $\times$ YT media were added in 1L-baffled flask, and 20 ml of 1 M potassium phosphate (pH 7.2) and 50 μ g/ml kanamycin that were previously bacteriostatic were added to the sterilized main culture media, and then the pre-culture liquid was inoculated until OD₆₀₀ was about 0.15. Thereafter, the cells were cultured at 28°C and 220 rpm until OD₆₀₀ was 0.5-0.7, followed by addition of 0.1 mM IPTG, and then the temperature was lowered to 20°C to induce expression. After 21 hours of the expression induction, the culture liquid was centrifuged to collect a culture supernatant, which was then filtered by a depth filter and membrane sterile filter, and loaded on a protein L column, thereby purifying target proteins.

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As a result of productivity comparison between ranibizumab mutant IDB0061 according to the present invention and original ranibizumab, as shown in Table 2, it was verified that IDB0061 had higher productivity than ranibizumab through only batch culture using basal media, and purification at a purity of 95% or higher could be attained from the culture liquid without cell disruption through a one-step process using an adsorption column, thereby achieving process simplification.

[Table 2]

Comparison of productivity among ranibizumab, ranibizumab mutant and ranibizumab modified form according to the present invention

Drug name	cultivation	Productivity (mg/L)	Purification	Purity
Novartis ranibizumab	Flask batch culture	<1 ¹	Cell extraction & protein G	>98%
IDB0061		6-7	Affinity column(protein L)	>95%
IDB0062		4-5		>95%
IDB0064		2-4		>95%

1. Anti-VEGF antibody patent (PCT/US1998/006604, Genetech)
2. The purity of the final purified product is indicated for Novartis' ranibizumab, whereas the purity of primary purified product through Protein L column is indicated for IDB0061 and IDB0062.

<1-2> Fusion of ranibizumab mutant and tissue-penetrating peptide

In order to improve an efficacy of and overcome a resistance against ranibizumab as an anti-VEGF agent, the present inventors attempted to fuse a tissue-penetrating peptide (TPP), which is capable of binding to both neuropilin 1 (NRP1) and neuropilin 2 or only neuropilin 1, to the C-terminus of ranibizumab. The amino acid sequences

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of TPP are shown in Table 3 below. Among the sequence listings in Table 3, TPPs having the amino acid sequences of SEQ ID NOs: 1 to 4 can bind to both neuropilin 1 and 2, whereas TPPs having the amino acid sequence of SEQ ID NOs: 5 to 7 can bind specifically to neuropilin 1. A schematic diagram of a fusion protein in which TPP is fused to ranibizumab is shown in FIG. 1. Specifically, fusion proteins, in which various TPPs (peptides specifically binding to neuropilin receptors) described in Table 3 are fused to the C-terminus of ranibizumab mutant IDB0061 constructed in Example <1-1>, and cell lines producing the fusion proteins were constructed by APRILBIO.

Meanwhile, among TPPs shown in Table 3, TPP#2 having the amino acid sequence of SEQ ID NO: 2 was obtained by modifying the C-terminus regions of VEGF₁₆₅ as an intrinsic ligand of neuropilin and class 3 semaphorin ligands; and TPP#5 was obtained by isolating and identifying a peptide derived from a clone selectively binding to the b1 domain of neuropilin 1 using both blb2 domain protein of neuropilin 1 and blb2 domain protein of neuropilin 2 as competitors. Here, AVASTIN was fused thereto using a linker to act as a bivalent in the neuropilin receptor, so that these peptides were designed to have a tissue penetration while having a similar affinity to VEGF and Sema3A ligands.

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[Table 3]

Sequence information of tissue-penetrating peptide (TPP)

TPP#1 (SEQ ID NO: 1)	HTPGNCHKFKHLQENKKGNVSR
TPP#2 (SEQ ID NO: 2)	HTPGNSNRYKHLQENKKGRPRK
TPP#3 (SEQ ID NO: 3)	REAPGAPESPEPQDQYKPRIRK
TPP#4 (SEQ ID NO: 4)	REAPGAPESPEPQDQYKPRPRK
TPP#5 (SEQ ID NO: 5)	HTPGNSNRYKHLQENKKGRPRK
TPP#6 (SEQ ID NO: 6)	HTPGNSNRYKHLQENKKGRPRK
TPP#7 (SEQ ID NO: 7)	HTPGNATKPRK

5 The construction procedure of IDB0062 having a form in which TPP#2 peptide is linked to ranibizumab mutant IDB0061 without bound TPP (a form in which only point mutation is introduced into ranibizumab) by a linker is as follows.

Specifically, a light chain region of ranibizumab
10 mutant IDB0062 having fused TPP was constructed by obtaining the nucleic acid sequence of ranibizumab from the related patent, and performing codon optimization, on the basis of which a nucleic acid of a light chain variable region (VL) comprising a signal sequence was synthesized. Then, a
15 nucleic acid (CL'-linker-TPP#2) comprising a linker and the TPP#2 sequence in addition to a partial sequence in which cysteine is substituted with serine in the C-terminus of the light chain constant region (CL) was synthesized. The CL region of Fab was constructed by PCR using anti-albumin Fab
20 SL335 as a template and primers (SEQ ID NOs: 24 and 25), and CL'-linker-TPP#2 was constructed by PCR using the synthesized CL'-linker-TPP#2 nucleic acid as a template and primers (SEQ ID NOs: 26 and 27). These two products were linked through linking PCR to construct the CL-linker-TPP#2
25 oligonucleotide. VL was constructed using the synthesized

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VL nucleic acid as a template and primers (SEQ ID NOs: 28 and 29), and then assembly PCR was conducted using primers (SEQ ID NOs: 30 and 31, including BamHI and XhoI sequences) together with CL-linker-TPP#2 to complete the final VL-CL-linker-TPP#2 sequence.

A heavy chain region of ranibizumab mutant IDB0062 having fused TPP#2 was constructed by obtaining the nucleic acid sequence of ranibizumab from the related patent, and performing codon optimization, on the basis of which a nucleic acid of a heavy chain variable region (VH) comprising a signal sequence (gIII) was synthesized. Then, a nucleic acid (CH1'-linker-TPP#2) comprising a linker and the TPP#2 sequence in addition to a partial sequence in which cysteine is substituted with serine in the C-terminus of the heavy chain constant region (CH1) was synthesized. The CH1 region of Fab was constructed by PCR using anti-albumin Fab SL335 as a template and primers (SEQ ID NOs: 32 and 33), and CH1'-linker-TPP#2 was constructed by PCR using the synthesized CH1'-linker-TPP nucleic acid as a template and primers (SEQ ID NOs: 34 and 35). These two products were linked through linking PCR to construct the CH1-linker-TPP#2 oligonucleotide. VH was constructed using the synthesized VH nucleic acid as a template and primers (SEQ ID NOs: 36 and 37), and then assembly PCR was conducted using primers (SEQ ID NOs: 38 and 39, including EcoRI and HindIII sequences) together with CL-linker-TPP#2 to complete the final VH-CH1-linker-TPP#2 sequence. The light chain of the fragment finally completed through PCR was digested with BamHI and XhoI, and the heavy chain thereof was digested with EcoRI and HindIII, and these were cloned into pHEKA vector digested with the same restriction enzymes. The pHEKA vector comprising the IDB0062 sequence, which was completed by the foregoing method, was transformed into

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SUPEX5 strain. Specifically, after 100 μ l of competent cells was added to a 1-mm cuvette, 3 μ l of the DNA was added thereto, and then gene introduction was carried out by electric shock at 1800 V, thereby completing the preparation of a producing cell line.

The amino acid sequences of the light chain and the heavy chain of the constructed IDB0062 were indicated by SEQ ID NO: 12 and SEQ ID NO: 13, respectively, while the nucleic acid sequences encoding the amino acid sequences were indicated by SEQ ID NO: 13 and SEQ ID NO: 15, respectively

<1-3> Selection of ranibizumab modified form IDB0062

The affinity to a neuropilin receptor and the tight junction disruption ability between endothelial cells were compared for various ranibizumab modified form candidate proteins constructed in Example <1-2>.

First, the affinity to a neuropilin receptor was performed on neuropilin 1 (NRP 1). Specifically, surface plasmon resonance (SPR) was performed using Biacore 2000 (GE Healthcare) in order to investigate the binding ability of TPP to the neuropilin 1 domain. Specifically, each neuropilin 1 domain was diluted in 10 mM Na-acetate buffer (pH 4.0), and fixed on CM5 sensor chip (GE Healthcare, USA) at about 1,000 response units (RU). HBS-EP buffer (10 mM HEPES, 2 mM ethylenediaminetetraacetic acid, and 0.005% surfactant P20, pH 7.4, GE Healthcare) at a flow rate of 30 μ l/min was used for analysis, while VEGF165 was used for analysis at concentrations from 80 nM to 5 nM, semaphorin 3A from 1 μ M to 62.5 nM, and TPP from 25 μ M to 1.5625 μ M. After the association/dissociation analysis, the CM5 chip was regenerated by allowing buffer (20mM NaOH, 1M NaCl, pH 10.0) to flow at a flow rate of 30 μ l/min for 1 minute.

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Sensorgrams obtained from association for 3 minutes and dissociation for 3 minutes were subjected to normalization and subtraction in comparison with blank cells to calculate affinity.

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In addition, the disruption ability of tight junction between endothelial cells was evaluated by measuring the degree of inhibition of VE-cadherin and E-cadherin by the proteins. It has been known that the reduction in
10 expression of VE-cadherin and E-cadherin in endothelial cells results in the disruption of tight junction between endothelial cells, and as a result, the delivery power (or tissue penetrating power) of a drug into the choroidal tissue is increased upon the intraocular administration of
15 the drug. Specifically, for an experimental method for indirectly confirming the enhancement of vascular penetration of TPP, the change of VE-cadherin was investigated by Western blot. Specifically, for confirmation of the enhancement of vascular penetration,
20 HUVEC cells were seeded at a density of 3×10^5 cells/well in a 6-well plate, cultured for 24 hours, and treated with 1 μ M TPP for 10 minutes, followed by Western blot. The gels subjected to SDS-PAGE were transferred to PVDF membranes, and detection was carried out using primary antibodies
25 (SantaCruz) recognizing VE-cadherin and β -actin and HRC-conjugated secondary antibodies (SantaCruz). Analysis was performed using ImageQuant LAS4000 mini (GE Healthcare).

The experimental results, as shown in Table 4,
30 confirmed that TPP#2-fused Fc (Fc-TPP#2) bound to a neuropilin receptor (NRP 1) at a high level (similar level to Sema3A ligand), and remarkably inhibited VE-cadherin. TPP#5-fused Fc (Fc-TPP#5) was shown to have higher binding ability to NRP 1 than Sema3A and also have more excellent

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inhibitory effect on VE-cadherin. It was confirmed that IDB0062 binds to the neuropilin receptor (NRP 1) at a high level, and inhibits VE-cadherin at a similar level to Fc-TPP#2.

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[Table 4]

TPP candidate selection

Clone	Linker length/TPP length (number of amino acids)	Receptor (neuropilin)	Affinity, K_D (M)	VE-cadherin inhibition
VERFL ₁	-	NRP 1	$2.51 \pm 0.36 \times 10^{-7}$	++
2aaa5A	-	NRP 1	$2.79 \pm 0.14 \times 10^{-7}$	+
Fc-TPP#2	15/20	NRP 1	$6.3 \pm 0.21 \times 10^{-7}$	++
Fc-TPP#2	15/14	NRP 1	$1.7 \pm 0.2 \times 10^{-7}$	+++
IDB0062	15/22	NRP 1	$1.0 \pm 0.11 \times 10^{-7}$	++

<1-4> Confirmation of productivity of ranibizumab

10 modified form IDB0062

The productivity of IDB0062 was investigated by the same method as in Example <1-1>. As shown in Table 1, the results confirmed that IDB0062 in which TPP#2 was fused to IDB0061 also showed about 5 times or higher productivity

15 than ranibizumab.

In addition, the purity of the first purified product obtained by an adsorption column was analyzed by HPLC. HPLC analysis was carried out in the following manner. The first

20 purified product obtained by an adsorption column was concentrated using Amicon (Millipore, 10K), and then diluted to a final concentration of 0.5 mg/ml by exchange with a formulation buffer (10 mM histidine, 0.1% Tween20, 10% trehalose). Waters Alliance e2695 was used as an analytical

25 instrument, BioSuite 250 UHR SEC (4.6 × 300 mm, 4 μm, Waters) as a column, and 20mM potassium phosphate buffer

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(250 mM KCl, pH 6.2) as a mobile phase. For the analysis, 20 µl of the concentrated sample was injected, and analyzed at a flow rate of 0.35 ml/min for 20 minutes. Protein peaks were analyzed at a UV 280 nm wavelength.

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The experimental results confirmed that ranibizumab is a mixture of three main components, of which only the third component is an active ingredient, whereas IDB0062 was produced in a single form (FIG. 2).

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<1-5> Construction of ranibizumab modified form IDB0064 and confirmation of productivity thereof

Following ranibizumab modified form IDB0062, ranibizumab modified form IDB0064 was constructed by linking and fusing TPP#5, of which the VE-cadherin inhibitory effect was confirmed in Example <1-3>, thereto using a linker and then productivity thereof was investigated.

The detailed construction procedures of IDB0064 are as follows. For binding of TPP#5 as new TPP to IDB0061, gene cloning was carried out. In order to use IDB0062 as a template and replace the TPP of the C-terminus from TPP#2 to TPP#5, specific primers (SEQ ID NOs: 40, 41 and 42) were used. The primers were prepared by setting an annealing region in the anterior sequences of a part shared by TPP#2 and TPP#5 and then extending the sequences of TPP#5 therefrom, and cloning was carried out using the primers. PCR was performed for 30 cycles in the order of denaturation(95℃, 40 sec), annealing(65℃, 40 sec), extension (72℃, 1 min) to obtain Fab light chain-TPP#5 and Fab heavy chain-TPP#5 genes. The light chain of the PCR product was treated with BamHI and XhoI, while the heavy chain was treated with EcoRI and HindIII, followed by being ligated to pHEKA vector which was then transformed into the

producing cell line SUPEK5.

The amino acid sequences of the light chain and the heavy chain of the constructed IDB0064 were indicated by SEQ ID NO: 16 and SEQ ID NO: 18, respectively, while the nucleic acid sequences encoding the amino acid sequences were indicated by SEQ ID NO: 17 and SEQ ID NO: 19, respectively.

The productivity of the constructed IDB0064 in the producing cell line was investigated. The IDB0064 producing cell line was inoculated at 1% (v/v) in 50 ml of 2 × YT media (100 mM potassium phosphate buffer, pH 7.2, 50 µg/ml kanamycin), and pre-cultured at 220 rpm for 18 hours at 28°C. Then, 180 ml of 2× YT media were added in 1L-baffled flask, and 20 ml of 1 M potassium phosphate (pH 6.4) and 50 µg/ml kanamycin that were previously bacteriostatic were added to sterilized main culture media, and then the pre-culture liquid was inoculated such that OD₆₀₀ was about 0.15. Thereafter, the cells were cultured at 28°C and 220 rpm until OD₆₀₀ was 0.5-0.7, followed by addition of 0.05 mM IPTG, and then the temperature was lowered to 20°C to induce expression. After 21 hours of the expression induction, the culture liquid was centrifuged to collect a culture supernatant, which was then filtered by a depth filter and membrane sterile filter, and loaded on a protein L column, thereby purifying target proteins. As shown in Table 2 and FIG. 3, the purification results confirmed that even the linkage of the TPP#5 sequence constructed as an artificial nucleotide sequence to IDB0061_Fab favorably induced expression, so that a target protein with relatively high purity could be obtained at a productivity of about 3-4 mg/L through only primary purification.

<Example 2>

Confirmation of bivalent characteristics of
ranibizumab modified form IDB0062

5 The binding ability of ranibizumab modified form
IDB0062 to VEGF-A and neuropilin 1 receptor was investigated.

<2-1> SPR (Biacore2000) assay of binding ability to
neuropilin 1 receptor

10 For investigation of the binding ability of IDB0062
and IDB0072 to NRPI, SPR assay was performed. After the
Biacore CM5 chip was activated with EDC/NHS mixture, target
protein NRPI was diluted in a fixing buffer (10 mM sodium
acetate, pH 5.5), and fixed to final 79 Ru through
15 calculation at Rmax:200. IDB0062 and IDB0072 samples were
then diluted up to 12.5 nM to 400 nM in HBSEP buffer before
the assay. The analytical flow rate was 30 µl/min, and as a
result, sensorgrams were obtained based on the result graphs
to calculate Kd values.

20

As shown in Table 4, the binding ability of IDB0062 to
neuropilin 1 receptor was confirmed to be maintained at a
similar level to the binding activity of a control drug (Fc-
TPP#2). These results indicate that TPP#2 peptide fused to
25 the C-terminus of ranibizumab favorably binds to neuropilin
1 receptor.

<2-2> ELISA assay of binding ability to neuropilin 1
receptor

30 NRPI (self-produced) was diluted in carbonate coating
buffer (0.1 M NaHCO₃, pH 9.6) to a final concentration of 10
µg/ml, and the diluted NRPI was added at 100 µl/well in an
ELISA plate (SPL, Immunoplate Maxi binding), followed by
coating at 37°C for 2 hours. Then, the plate was washed

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three times, blocked (4% skim milk, pH 7.4) at 37°C for 1 hour, and washed three times. Then, each sample was diluted at appropriate folds, and was used to treat at 100 µl/well, followed by reaction at 37°C for 1 hour. Upon completion of the sample reaction, the plate was washed three times, and then Goat anti-human kappa light chain Ab-HRP (Sigma Aldrich, A7164) was diluted 5,000 times in blocking buffer, and was used to treat at 100 µl/well, followed by reaction at 37°C for 1 hour. The plate was washed five times, and treated with TMB substrate (Bethyl, E102) at 100 µl/well, followed by reaction for 2-3 minutes. Thereafter, the reaction was stopped with stop solution (1N HCl) at 100 µl/well and the absorbance at 450 nm was measured using ELISA plate reader.

The ELISA assay also confirmed that the binding ability of IDB0062 to neuropilin 1 receptor was equivalent to that of the control drug (Fc-TPP#2) (FIG. 4B). Therefore, it was again confirmed that the characteristics of TPP#2 peptide were maintained when fused to the C-terminus of ranibizumab.

<2-3> ELISA assay of binding ability to VEGF

VEGF (R&D system, 293-VE-500/CF) was diluted in the carbonate coating buffer (0.1 M NaHCO₃, pH 9.6) to a final concentration of 3 µg/ml, and the diluted VEGF was added at 100 µl/well in an ELISA plate (SPL, Immunoplate Maxi binding), followed by coating at 37°C for 2 hours. Then, the plate was washed three times, blocked (4% skim milk, pH 7.4) at 37°C for 1 hour, and washed three times, and then each sample was diluted to appropriate folds, and was used to treat at 100 µl/well, followed by 37°C for 1 hour. Upon completion of the sample reaction, the plate was washed three times, and then Goat anti-human kappa light chain Ab-HRP (Sigma Aldrich, A7164) was diluted 5,000 times in

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blocking buffer, and was used to treat at 100 µl/well, followed by 37°C for 30 minutes. The plate was washed seven times, and treated with TMB substrate (Bethyl, E102) at 100 µl/well, followed by reaction for 2-3 minutes. Thereafter, the reaction was stopped with stop solution (1N HCl) at 100 µl/well and the absorbance at 450 nm was measured using ELISA plate reader.

As shown in FIG, 4A, the ELISA assay results of IDB0062 confirmed that the binding ability of IDB0062 to VEGF-A was somewhat reduced compared with ranibizumab. The presumed reason is that the complementary-determining region (CDR) binding to VEGF-A is partially changed as the tertiary structure of IDB0062 was changed by an alteration of a specific amino acid on the sequence. However, since the binding ability of ranibizumab is significantly higher than general antibodies, it is considered that such a reduction in binding ability will not cause a substantial deterioration in its clinical efficacy.

<Example 3>

Evaluation of stability of ranibizumab modified form

IDB0062

It has been confirmed that the alteration of a specific amino acid on the sequence of IDB0062 caused its structural modification and thus the binding ability of IDB0062 to VEGF-A was somewhat reduced compared with ranibizumab. Therefore, in order to investigate how the alteration affects the stability of IDB0062, its stability according to the storage condition and repeated freezing/thawing was analyzed.

The first purified product, after being changed into a formulation buffer, was concentrated to a concentration (5

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mg/ml) used in an animal experiment, and then the stability experiment was carried out. For the stability experiment according to the storage condition, the sample was dispensed in 10 µl aliquots, and while being stored at 4°C and -80°C for 5 weeks, the sample was taken out on a weekly basis, thawed in ice, and analyzed by VEGF binding ELISA assay. While the procedure in which the sample was frozen at -80°C and thawed in ice was repeated five times, a partial sample was taken out and evaluated for repeated freezing/thawing stability through VEGF binding ELISA assay.

As a result, as shown in FIG. 5, the binding ability of IDB0062 to VEGF-A was stably maintained at 4°C and -80°C until five weeks after storage, and even physical impact through five times of repeated freezing/thawing did not affect its activity, and thus, it was determined that there was no deterioration in its stability due to an alteration of the amino acid sequence.

20 <Example 4>

Evaluation of ocular tissue penetration of anti-VEGF agent modified form

For analysis of ocular penetration of a ranibizumab modified form, an ex-vivo ocular penetration model was constructed and its efficacy was evaluated. In addition, in order to evaluate whether the tissue penetration was improved by the fusion of a tissue-penetrating peptide in an antibody with a large molecular weight and a more complicated tertiary structure (including Fc fusion protein), the ocular penetration of bevacizumab and its modified form IDB0072 was analyzed at the same time.

<4-1> Evaluation of tissue penetration of ranibizumab modified form IDB0062

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In order to investigate whether TEP fused to the C-terminus of IDB0062 can actually improve tissue penetration through the binding to a neuropilin receptor distributed widely in the ocular endothelial cells; the extracted
5 eyeballs were immersed in FITC-conjugated ranibizumab and IDB0062 solutions to compare the degree of penetration over time therebetween.

In order to increase conjugation efficiency of protein
10 and FITC, a protein sample was adjusted to a concentration of 1 mg/ml through an exchange with 100 mM sodium carbonate buffer (pH 9.0), and mixed with FITC (1 mg/ml in DMSO), followed by reaction at room temperature for 2 hours. Since
TEP#2 peptide has many free amine groups capable of binding
15 FITC, different moles of FITC per protein were applied for the reaction. Thereafter, while unconjugated FITC was removed using PD-10 desalting column, the buffer was changed with PBS, and then the purified product was quantified, and used as a sample for efficacy evaluation. The conjugation
20 results confirmed that the F/P ratios of ranibizumab and IDB0062 were 1.127 and 1.133, respectively, which indicates that almost the same number of moles of FITC bound to one molecule of protein. After the solutions of FITC-conjugated ranibizumab and IDB0062 were diluted to 0.3 mg/ml with PBS,
25 C57BL/6 mouse eyeballs were extracted, immersed therein at 37°C for 1 hour and 2 hours, and washed with PBS two times for 10 minutes each time, and then paraffin slides were prepared. The eyeballs were fixed at 4°C for 4 hours using Davidson's solution (glacial acetic acid: ethyl alcohol:
30 neutralized formalin: distilled water = 1: 3: 2: 3), and then the anterior tissue of the conjunctiva was partially cut with scissors, and the retinal metaplasia was minimized in a paraffin slide preparation step. After overnight fixation at 4°C using 10% (v / v) formalin solution, moisture

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was removed from the tissues by increasing the concentration of alcohol from low to high concentration using an automatic infiltration machine, followed by transparency with xylene and then paraffin penetration. The paraffin penetration-completed tissue was placed in a base mold to make a paraffin block, and 4 sections were prepared using a microtome. The paraffin sections were unfolded to be attached to slides pre-coated with albumin, poly-L-lysine, and saline in a floating constant-temperature water bath. The tissue slides were deparaffinized and then directly mounted, and then FITC was observed using a confocal microscope to investigate the ocular tissue penetration and distribution.

As shown in FIGS. 8A and 8B, it was confirmed that IDB0062 began to penetrate into the eyeball rapidly through the cornea and posterior eyeball from 1 hour after the experiment, and within 2 hours, the distribution amounts in the ocular tissue and vitreous body were significantly increased by about four times compared with ranibizumab as a control drug. While the ocular tissue can be clearly distinguished and analyzed through DAPI staining, it was confirmed that, unlike ranibizumab, IDB0062 was distributed in large quantity even inside of the cornea (FIG. 8C, white arrow), and the drug IDB0062 distribution in the eye was increased by about 10 times compared with ranibizumab (FIG. 8D). While the data of FIG. 8E shows a cross-section of the ocular retinal tissue, it was confirmed that the control drug ranibizumab was mostly present near the sclera, whereas IDB0062 has reached the retina through the retina pigment epithelial cell (RPE) layer. In conclusion, the linkage of a tissue-penetrating peptide to ranibizumab which has a poor intraocular tissue penetration ratio could increase the ocular penetration ratio of ranibizumab by about 4 times. It

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was verified that such a linkage leads to the possibilities of controlling the drug dose, increasing in the interval of drug administration, and being developed as eye drops through the improvement of dosage form, through
5 the improvement of drug penetration.

<4-2> Evaluation of tissue penetration of bevacizumab modified form IDB0072

The whole antibody proteins, such as bevacizumab, have
10 higher molecular weights and complex tertiary structures, compared with antibody fragments (Fabs), and thus, have unfavorable characteristics in view of tissue penetration. Despite this, in order to investigate whether the fusion of a tissue-penetrating peptide to the C-terminus of
15 bevacizumab overcame these physical limitations and improved its penetration, compared with control drug bevacizumab, the same experiment was conducted.

The construction procedures of bevacizumab modified
20 form IDB0072 are as follows. IDB0072 is a type of antibody fusion protein in which TPF is fused to the C-terminus of bevacizumab by a linker, while the amino acid sequence of TPP is as shown in Table 3 above. Among the sequence listings in Table 3, TPPs having the amino acid sequences of
25 SEQ ID NOs: 1 to 4 can bind to both neuropilin 1 and 2, and TPPs having the amino acid sequence of SEQ ID NOs: 5 to 7 can bind specifically to neuropilin 1. Meanwhile, among TPPs shown in Table 3, TPP#2 was obtained by modifying the C-terminus regions of VEGF₁₆₅ as an intrinsic ligand of
30 neuropilin and the class 3 semaphorin ligand; and TPP#5 was obtained by isolating and identifying a peptide derived from a clone selectively binding to b1b2 domain of neuropilin 1. Among these TPPs, TPP#2 was fused to bevacizumab using a linker to act as a bivalent against the neuropilin receptor,

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so that IDB0072 was designed to have tissue penetration while having similar affinity to VEGF and Sema3A.

Specifically, a cell line producing IDB0072 in which
5 TPP #2 having the amino acid sequence of SEQ ID NO: 2 was
fused to the C-terminus of bevacizumab was constructed.
IDB0072 was cloned into pcDNA3.4 vector. The amino acid
sequences of the light chain and the heavy chain of the
constructed IDB0072 were indicated by SEQ ID NO: 20 and SEQ
10 ID NO: 22, respectively, while the nucleic acid sequences
encoding the amino acid sequences were indicated by SEQ ID
NO: 21 and SEQ ID NO: 23, respectively. A plasmid encoding a
protein in which the NR1 binding peptide was fused to the
constructed antibody heavy chain constant region and a
15 plasmid encoding a light chain chain protein were
transfected into CHO DG44 cells using NeonTM electrophoresis,
and then the cells were seeded at 3×10^6 cells in T25 flask,
and cultured at 37°C. Stable cells were secured using a
selective marker, and then cultured in a floating state for
20 7 days under conditions of 100 rpm, 37°C, pH 7.2, 50% DO₂
using serum-free SFM4CHO (Hyclone) in a bioreactor. The
supernatant was separated from the cells by centrifugation,
and sterilized by the 0.22 filter.

25 The culture liquid of IDB0072 was collected, and each
protein was purified with reference to a standard protocol.
The culture liquid was subjected to a protein A column
(MabselectSure resin, GE healthcare), followed by washing
with PBS (pH 7.4). The antibody was eluted at pH 3.0 using
30 0.1 M glycine buffer, and then the sample was neutralized to
pH 7.0 using 1 M Tris buffer. The eluted antibody fractions
were concentrated using a MILLIPORE Amicon Ultra (30 MWCO)
centrifugal concentrator, followed by exchange with PBS (pH
7.4) buffer. The purified fusion protein in which a peptide

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specifically binding to selected NRPl was fused to the antibody heavy chain constant region was quantified using absorbance and absorption coefficient at a corrected wavelength of 280 nm.

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In order to increase conjugation efficiency of protein and FITC, bevacizumab and IDB0072 were adjusted to a concentration of 3 mg/ml after an exchange with 100 mM sodium carbonate buffer (pH 9.0), and mixed with FITC (1 mg/ml in DMSO), followed by reaction at room temperature for 2 hours. In order to reduce the conjugation difference by TFP#2 fusion, the mole number of FITC per protein for IDB0072 was differently applied for the reaction, unlike that for control drug bevacizumab. Thereafter, while unconjugated FITC was removed using PD-10 desalting column, the buffer was changed with PBS, and then the purified product was quantified, and used as a sample for efficacy evaluation. The conjugation results confirmed that the F/P ratios of bevacizumab and IDB0072 were 2.18 and 1.98, respectively, which indicates that almost the same number of moles of FITC was bound to one molecule of protein. After the solutions of FITC-conjugated bevacizumab and IDB0072 were diluted to 0.9 mg/ml with PBS, C57BL/6 mouse eyeballs were extracted, immersed therein at 37°C for 1 hour and 2 hours, and washed with PBS five times for 10 minutes each time, and then paraffin slides were prepared. The subsequent procedures were carried out in the same manner as in Example <4-1>.

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In order to evaluate the activity of bevacizumab modified form IDB0072 as prepared, the binding ability of IDB0072 to the neuropilin 1 receptor was investigated by SPR assay. As shown in Table 5, the binding ability of IDB0062 to neuropilin 1 receptor was confirmed to show a similar

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level, compared with the control drug (Fc-TPP#2) and ranibizumab modified form IDB0062. These results indicate that TPP#2 peptide fused to the C-terminus of bevacizumab favorably binds to the neuropilin 1 receptor.

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[Table 5]

Evaluation on activity of TPP-fused form against NRP1

Clone	Linker length/TPP length (number of amino acids)	Receptor (neuropilin)	Affinity, K_D (M)	VE-cadherin inhibition
Fc-TPP#2	15/22	NRP1	$6.8 \pm 0.2 \times 10^{-5}$	++
IDB0062	15/22	NRP1	$1.0 \pm 0.1 \times 10^{-5}$	++
IDB0072	15/22	NRP1	$3.1 \pm 0.15 \times 10^{-5}$	++

10 As shown in FIG. 9A, it was confirmed that IDB0072 also improved ocular penetration, compared with the control drug bevacizumab. It was confirmed that the intraocular distribution of IDB0072 was significantly increased by about 1.5 times, compared with that of bevacizumab at 1 hour and 2
15 hours (FIG. 9B). It was also confirmed that in spite of its large molecular weight and structure, IDB0072 diffused into the cornea through the conjunctiva, compared with bevacizumab. Therefore, it was verified that even an antibody having a high molecular weight and a complex
20 structure can significantly increase its tissue penetration by linking a tissue-penetrating peptide to the Fc C-terminus. These results indicate that various Fc fusion proteins including antibody proteins can also improve the ocular tissue penetration through the linkage to a tissue-
25 penetrating peptide.

<Example 5>

Evaluation of efficacy of ranibizumab modified form using corneal neovascularization models

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For evaluation of efficacy of IDB0062, corneal neovascularization models were constructed. Being divided into prevention models and resistance models, they were then used to compare the inhibition of vascularization and the reduction of neovessels between IDB0062 and ranibizumab.

<5-1> Prevention models

For comparison of neovascularization inhibitory effect between IDB0062 and ranibizumab, corneal neovascularization models induced by an alkaline burn were constructed as follows: Cellulose filter paper was cut into a circle with a diameter of 2 mm, and then immersed in a 1M NaOH solution. The 6-week old female C57BL/6 mice were used. After anesthesia (Zoletil 40 mg/kg + Rompun 5 mg/kg, IP), the NaOH filter paper was placed on the left eye cornea to induce an alkaline burn for 30 seconds, followed by sufficient washing with 40 ml of PBS, thereby constructing corneal neovascularization animal models. As for the prevention models, drug treatment was carried out on the same day at which the alkaline burn was induced. Each drug was administered through eye drops at a concentration of 5 mg/ml with 5 μ l each time, four times a day for 5 days. After the completion of the administration, the eyeballs were extracted, immersed and fixed in 4% paraformaldehyde solution for one hour, and washed with PBS, and then the cornea was isolated using a dissecting microscope. The isolated cornea was additionally fixed in a 4% paraformaldehyde solution for 12 hours. The fixed cornea was washed with PBS, and subjected to reaction in a blocking buffer (PBS, 0.3% BSA, 0.1% Triton X100) at room temperature for 2 hours. A primary antibody (BD Pharmingen) specific to PECAM-1 (CD31) as a vascular endothelial marker and a primary antibody (Millipore) specific to NG-2 as a pericyte marker were reacted overnight in a refrigerator, and

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secondary fluorescent antibodies (Alexa Fluor488, Alexa Fluor594, Life Technologies) were reacted at room temperature for 4 hours for tissue staining. Upon completion of the staining procedures, the cornea was transferred to a slide, and mounted on the slide while four cut lines were incised in four directions toward the center of the cornea using a dissecting microscope. Upon completion of the mounting procedures, the cornea slide was observed for aspects of vessels and pericytes by fluorescence microscopy/confocal microscopy.

As shown in FIG. 6, the prevention model experiment results confirmed that IDB0062 further inhibited neovascularization by 25-30% in comparison with ranibizumab, showing a significant preventive effect of 50% or more in comparison with vehicle, while IDB0061 also showed the equivalent efficacy in comparison with ranibizumab, indicating that the decrease in VEGF binding ability due to the structural change of ranibizumab did not substantially affect its neovascularization inhibitory efficacy and that the improvement of its efficacy could be attained by TPP fused to its C-terminus.

<5-2> Resistance models

The resistance models were constructed by inducing an alkaline burn in the same manner as in the Prevention models, and were left for 10 days so that the corneal vascularization protruded sufficiently. The concentration and cycle of administration were the same as in the Prevention models. The administration was carried out for 10 days from 10 days after the alkaline burning, and the reduction degree of generated neovessels was compared between IDB0062 and ranibizumab (thereafter, the preparation of the corneal slide was the same as in the Prevention

models).

As shown in FIG. 7A, the vessels were developed up to the cornea in the vehicle- and ranibizumab-treated groups, whereas the vessels were locally distributed only in the ocular limbus in the IDB0062-treated group, showing a reduction of neovessels in the IDB0062-treated group. In conclusion, IDB0062 showed a significant neovessel reducing activity of 30% or more compared with the vehicle, and showed two times or higher improvement in efficacy in comparison with ranibizumab which showed no significant efficacy (FIG. 7B). These results are similar to the results in the literature in which anti-VEGF aptamer and anti-PDGF antibody agent were co-administered (Jo et al., 2006. Am. J. Pathol.). Therefore, it was expected that IDB0062 is likely to induce eyesight improvement in about 70% of ranibizumab-administered patients of which eyesight had been maintained without eyesight improvement.

In addition, as shown in FIG. 7C, it was confirmed that the IDB0062-treated group showed a significant reduction in pericyte coverage by nearly 40% in comparison with the vehicle-treated group, and these results are similar to that of a PDGF inhibitor which is under development as a co-administering agent for the purpose of treating patients having resistance to existing drugs. Therefore, it is anticipated that IDB0062 can be applicable as a monotherapy for treating resistance which is known to occur in 45% of patients administered with anti-VEGF inhibitor.

<Example 6>

Evaluation of efficacy of ranibizumab modified form
using choroidal neovascularization models

5 Choroidal neovascularization (CNV), which corresponds
to a model of age-related macular degeneration, was induced
by laser-induced choroidal neovascularization, and the
therapeutic effect of ranibizumab modified form IDB0062 was
investigated.

10 Seven-week old male Brown Norway (BN) rats (SLC Japan,
Tokyo, Japan) were acclimated for one week, and then
anesthetized by peritoneal injection of pentobarbital sodium
(Banlim Pharm, 25 mg/kg). Thereafter, the pupil was dilated
with 1% tropicamide eye drops, and then six photocoagulation
15 spots were formed around the optic nerve head using a diode
laser (wavelength, 532 nm; diameter, 100 µm; power, 150 mW;
time period, 0.1 sec). The destruction of Bruch's membrane
was verified by the formation of characteristic bubbles.
The eyeballs with hemorrhage or no bubbles were excluded
from the subsequent experimental procedures. After the
20 photocoagulation treatment, the rats were randomly divided
into five groups (10 rats per group) as shown in Table 6.
Drugs were administered intraocularly at concentrations
appropriate for respective groups using Hamilton syringe
(Hamilton, USA). The same amount of vehicle was
25 administered to the CNV group, and 100 µg/eye of ranibizumab
was administered as control drug. Subjects with surgical
damage caused by drug administration or subjects with lens
opacities or the like were excluded from subsequent
experimental procedures.

30

[Table 6]

Choroidal neovascularization model experimental groups

Group	dose
Vehicle	Buffer only
Ranibizumab	100 µg/eye
JDB0062	10 µg/eye
	50 µg/eye
	100 µg/eye

The degree of choroidal neovascularization was
 5 evaluated 10 days after drug administration. The eyeball of
 each rat was extracted, and then incised at a region
 adjacent to the cornea and sclera under a microscope.
 Thereafter, the retina was taken off using posterior tissues
 of the eyeball, and then the conjunctival tissue comprising
 10 a subretinal region was isolated. The isolated tissue was
 fixed in 4% paraformaldehyde for 1 hour, washed with PBS,
 and then stirred in PBS comprising 5% Triton X-100 and 1%
 BSA for 3 hours. After washing again, isolectin B4 (Sigma),
 as an endothelial cell marker, dissolved at 1 mg/ml in PBS,
 15 was diluted 1:50, followed by reaction at 4°C overnight.
 After washing with PBS containing 0.05% Tween 20 for 2 hours,
 streptavidin TRITC was diluted 1: 500, followed by reaction
 at 37°C for 4 hours, and then, after washing with PBS for 30
 minutes, the tissue was observed under a fluorescent
 20 microscope (BX51, Olympus, Japan). The sizes of subretinal
 neovascular areas were analyzed using Image J software (NIH,
 USA).

As shown in FIG. 10A, it was detected that, in the

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vehicle group, a lot of neovessels labeled with black color were stretched out from the inside (choroid) to the outside (retina) of the laser-injured area. In the group administered with 100 µg of control drug ranibizumab, compared with the vehicle group, neovascularization tended to be somewhat inhibited but vessels still stretching out were observed in some subjects. Whereas, it was confirmed that IDB0062 tended to inhibit neovascularization in a concentration-dependent manner. It was verified that the group administered with 50 µg of IDB0062 had neovascularization inhibitory efficacy at a similar level to the group administered with 100 µg of control drug ranibizumab. In the group administered with 100 µg of IDB0062, only the laser-induced scarring remained in the retina, and most of the neovascularization was inhibited. As shown in FIG. 10B obtained from the quantification of the above results, it was confirmed that vascularization was inhibited by about 31% in the group administered with 100 µg of ranibizumab and the group administered with 50 µg of IDB0062 in comparison with the vehicle group, and neovascularization was inhibited by about 36% in the group administered with 100 µg of IDB0062. In conclusion, it was verified that IDB0062 exhibited the same neovascularization inhibitory efficacy as ranibizumab using a half the dose of ranibizumab.

<Example 7>

Evaluation of efficacy of ranibizumab modified form using oxygen-induced retinopathy models

For retinopathy of prematurity models, oxygen-induced retinopathy (OIR) was induced, and the effect of ranibizumab modified form IDB0062 was investigated.

Mice born by crossbreeding of 7- to 8-week old C57BL/6 purchased from Koatech were used as experimental animals.

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On day 7 after birth, mice (postnatal day 7, P7) were placed in an oxygen chamber, and the oxygen concentration in the chamber was adjusted and maintained at 75% (hyperoxia) for 5 days (P7 to P11). The illumination in the laboratory was turned on or off every 12 hours and the temperature was maintained at $24 \pm 2^\circ \text{C}$. The mice were fed with free access to feed and drinking water. After 5 days, the mice were exposed to inner air (normoxia) out of the chamber for 5 days (P12-P17) to induce retinal angiogenesis. For drug administration, the mice were randomly divided into five groups (10 mice per group) immediately after the exposure to normoxia on P12, as shown in Table 7. Drugs were administered intraocularly at concentrations appropriate for respective groups using Hamilton syringe (Hamilton, USA). The same amount of vehicle was administered to the OIR group, and 10 $\mu\text{g}/\text{eye}$ of ranibizumab was administered as control drug. Subjects with surgical damage caused by drug administration or subjects with lens opacities or the like were excluded from subsequent experiment procedures.

[Table 7]

oxygen-induced retinopathy (OIR)
model experimental groups

Group	dose
Vehicle	Buffer only
Ranibizumab	10 $\mu\text{g}/\text{eye}$
IDB0062	5 $\mu\text{g}/\text{eye}$
	10 $\mu\text{g}/\text{eye}$
	15 $\mu\text{g}/\text{eye}$

The degree of retinal edema was evaluated on day 17 after birth. The mice were anesthetized by peritoneal injection of pentobarbital sodium (Hanlim Pharm, 25 mg/kg). After the abdomen was opened, 10 μ l of dextran (FD40S-1G, Sigma; 50 mg/ml in PBS) was injected into the heart. After 10 minutes, eyeballs were extracted, and fixed in 4% paraformaldehyde for 10 minutes, and then the retina was isolated. Thereafter, flat-mounted retina slides were prepared, and observed under a fluorescent microscope (BX51, Olympus, Japan). The amount of fluorescence extravasated out of vessels was quantitatively analyzed using Image J.

As shown in FIG. 11A, it was detected that, in the vehicle group treated without drug, fluorescence extravasation due to leakage was increased in the optic nerve disc area at the center part and the vascular terminal area outside of the retina. In the group treated with 10 μ g of control drug ranibizumab, compared to the vehicle group, vascular leakage were somewhat reduced, but fluorescence extravasation due to leaked vessels was still somewhat present in the vascular terminal area. Whereas, it was detected that the group treated with IDB0062 showed a tendency of inhibiting vascular leakage in a concentration-dependent manner, and the groups administered with IDB0062 (at least 10 μ g, corresponding to the same dose of ranibizumab), although not statistically significant, had a possibility of inhibiting vascular leakage more effectively compared with ranibizumab (FIG. 11B). Especially, in the group administered with 15 μ g of IDB0062, the shape of vessels has a dense and stable structure and the leaked area was not shown at all.

In addition, the extent of neovascularization in the retina was also evaluated. The isolated retina was fixed in

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4% paraformaldehyde for 3 hour, washed with PBS, and then stirred in PBS containing 5% Triton X-100 and 1% BSA for 3 hours. After washing again, isolectin B4(L2140, sigma) dissolved at 1 mg/ml in PBS was diluted 1:50, followed by reaction at 4°C overnight. After washing with PBS containing 0.05% Tween 20 for 2 hours, streptavidin TRITC was diluted 1: 500, followed by reaction at 37°C for 4 hours, and then, after washing with PBS for 30 minutes, the tissue was observed under a fluorescent microscope (BX51, Olympus, Japan).

When P7 mice were in hyperoxia condition for 5 days and then transferred to normoxia, P7 mice were in a relative ischemia state. Here, excessive neovessels grew in the retina, and the features of the formed neovessels were that the vessels grew from the retina toward the vitreous body corresponding to an avascular area and a specific structure called tufts having a form of irregular vessels that is easy to leak was formed. The formation of such tufts may be used as a measure to quantify neovascularization. As can be confirmed in FIG. 12A, in the stained vessels of the vehicle group, the boundaries between the vessels are clearly distinguished from each other, and the vessels exhibit characteristics of normal retinal vessels with a relatively thin and stable structure, whereas many neovessels that form tufts through gathering of irregular and thick vessels were observed. It was confirmed that, similar to the vehicle group, many neovessels in a form of tufts were distributed in the group treated with 10 µg of control drug ranibizumab. Whereas, IDB0062 significantly reduced the distribution of tufts, defined as neovessels, in a concentration-dependent manner, and, in the groups administered with 10 µg or more, most vascular structures were clearly distinguished from each other, and dense and tough normal vascular forms were observed rather than a tuft form. It was confirmed from a

graph obtained by quantifying the results that all of the vehicle group, the group treated with 10 µg of ranibizumab, and the group administered with 5 µg of IDB0062 showed the same degree of neovascularization, but the group administered with 10 µg of IDB0062 inhibited neovascularization by about 40% in comparison with the above groups (FIG. 12B). In conclusion, it was confirmed that, in the OIR models, the treatment with rabinizumab did not show retinal neovascularization inhibitory efficacy, whereas IDB0062 could significantly inhibit OIR-induced neovascularization at the same dose as ranibizumab.

<Example 8>

Assay of distribution of drug after intraocular injection

In order to investigate the distribution of drug in the tissue when ranibizumab and IDB0062 were intraocularly injected, respectively, proteins were extracted from the retinal tissue and Western blot assay was performed.

The eye of each rat was extracted and then the retina was isolated 4 hours and 72 hours after the intraocular injection. The isolated retina was washed three times with PBS, and then transferred to lysis buffer (20mM Tris-Cl, 150 mM NaCl, 1 mM EDTA, 0.1% triton X-100), and the tissues were disrupted using a homogenizer. Thereafter, supernatant was collected by centrifugation (14,000 rpm, 4°C, 10 min), and the protein contents of lysate was measured by Bradford assay. For Western blot assay, 12% non-reducing SDS-PAGE gel was used. Protein sample was loaded at 40 µg per well, and run at 25 mA for 1 hour. After transferring to PVDF membrane, proteins were detected using anti-kappa antibody-BRP (Sigma, F3761), and each protein band was quantified using Bio-Rad Chemidoc system.

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Since the heavy chain and the light chain of ranibizumab are linked by a disulfide bond, one band was observed at about 48 kDa in non-reducing SDS-PAGE. Whereas IDB0062 does not have a disulfide bond between the heavy chain and the light chain, and thus, two bands (heavy chain and light chain) were observed at 28 kDa in SDS-PAGE analysis. As shown in FIG. 13, it was verified that, as for the amount of drug present in the retina after 4 hours of the intraocular injection, IDB0062 was about 3.6 times higher than ranibizumab. These results indicate that IDB0062 specifically binds to the NRP1-expressing tissue by TPP, showing that IDB0062 can target the retinal tissue, which is a disease site with respect to various diseases caused by retinal neovascularization. In the intraocular injection of drug, a drug binding to a lesion tissue rather than a drug spread in the vitreous body has an increased opportunity to remove VEGF, so that the drug is likely to exert the same efficacy with a smaller dose. These results are presumed to support superior efficacy of IDB0062 in the efficacy evaluation using choroidal neovascularization models and retinopathy models.

Industrial applicability

In comparison with existing anti-vascular endothelial growth factor agents, the pharmaceutical compositions according to the present invention comprising, as an active ingredient, a fusion protein in which a tissue-penetrating peptide is fused to an anti-vascular endothelial growth factor (anti-VEGF) agent can inhibit various growth factors related to neovascularization as well as endothelial growth factors, reduce pericyte coverage to improve efficacy, and treat even drug-resistant patients. In addition, the pharmaceutical compositions of the present invention are highly industrial applicable in that the delivery capability

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of drug into the choroidal tissue is improved at the
intraocular injection, so that the drug is highly likely to
be developed as eye drops through a reduction in dose, an
increase in the frequency of administration, and an
5 improvement in ocular penetration.

Claims

1. A pharmaceutical composition for preventing and treating an eye disease, the pharmaceutical composition comprising, as an active ingredient, a fusion protein in which a tissue-penetrating peptide is fused to an anti-vascular endothelial growth factor (anti-VEGF) agent.
2. The pharmaceutical composition of claim 1, wherein the tissue-penetrating peptide comprises any one amino acid sequence selected from the group consisting of SEQ ID NOs: 1 to 7.
3. The pharmaceutical composition of claim 1, wherein the anti-vascular endothelial growth factor (anti-VEGF) agent is any one selected from the group consisting of ranibizumab, bevacizumab, aflibercept, conbercept, and a biosimilar or a mutant thereof.
4. The pharmaceutical composition of claim 3, wherein the mutant is characterized in that in each of heavy chain constant domain 1 and light chain constant domain of the mutant, cysteine is deleted, or substituted with another amino acid residue including serine excluding cysteine.
5. The pharmaceutical composition of claim 3, wherein the mutant is a ranibizumab mutant consisting of a light chain represented by SEQ ID NO: 8 and a heavy chain represented by SEQ ID NO: 10.
6. The pharmaceutical composition of claim 1, wherein the fusion protein consists of an amino acid sequence represented by SEQ ID NO: 12 or 16; and an amino acid sequence represented by SEQ ID NO: 14 or 18.

7. The pharmaceutical composition of claim 1, wherein the fusion protein consists of an amino acid sequence represented by SEQ ID NO: 20 and an amino acid
5 sequence represented by SEQ ID NO: 22.

8. The pharmaceutical composition of claim 1, wherein the fusion is attained by a linker peptide.

10 9. The pharmaceutical composition of any one of claims 1 to 8, wherein the eye disease is selected from the group consisting of proliferative vitreoretinopathy, macular degeneration, pigmentary retinopathy, diabetic retinopathy, choroidal neovascularization, neovascular glaucoma, ischemic
15 optic neuropathy, retinopathy of prematurity, retinopathy of immaturity, epidemic conjunctivitis, neovascular iris disease, retrolental fibroplasias, atopic keratitis, superior limbic keratitis, pterygium keratitis sicca, phlyctenular keratoconjunctivitis, scleritis, and diabetic
20 macular edema.

10. A method for preparing an anti-vascular endothelial growth factor (anti-VEGF) agent with an improved efficacy and ability to overcome resistance, the method
25 comprising:

(a) transforming host cells with a recombinant vector, the recombinant vector comprising a nucleic acid sequence encoding a fusion protein in which a tissue-penetrating peptide is fused to an anti-vascular endothelial growth
30 factor (anti-VEGF) agent;
(b) culturing the cells; and
(c) collecting a fusion protein from the cells.

11. The method of claim 10, wherein the anti-

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vascular endothelial growth factor (anti-VEGF) agent is any one selected from the group consisting of ranibizumab, bevacizumab, aflibercept, conbercept, and a biosimilar or a mutant thereof.

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12. The method of claim 10, wherein the fusion is attained by a linker peptide.

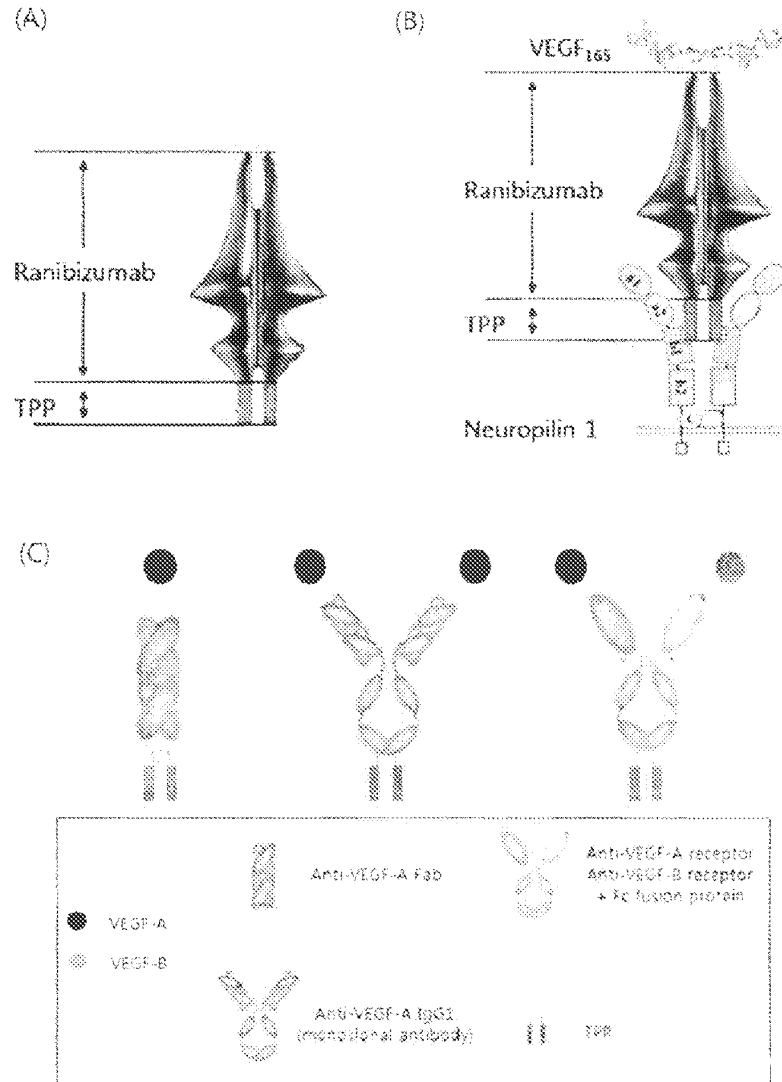
13. A method for treating an eye disease, the method comprising administering an effective amount of a fusion protein, in which a tissue-penetrating peptide is fused to an anti-vascular endothelial growth factor (anti-VEGF) agent, to a subject in need thereof.

14. Use of a fusion protein in which a tissue-penetrating peptide is fused to an anti-vascular endothelial growth factor (anti-VEGF) agent for preparing an eye disease therapeutic agent comprising the fusion protein as an active ingredient.

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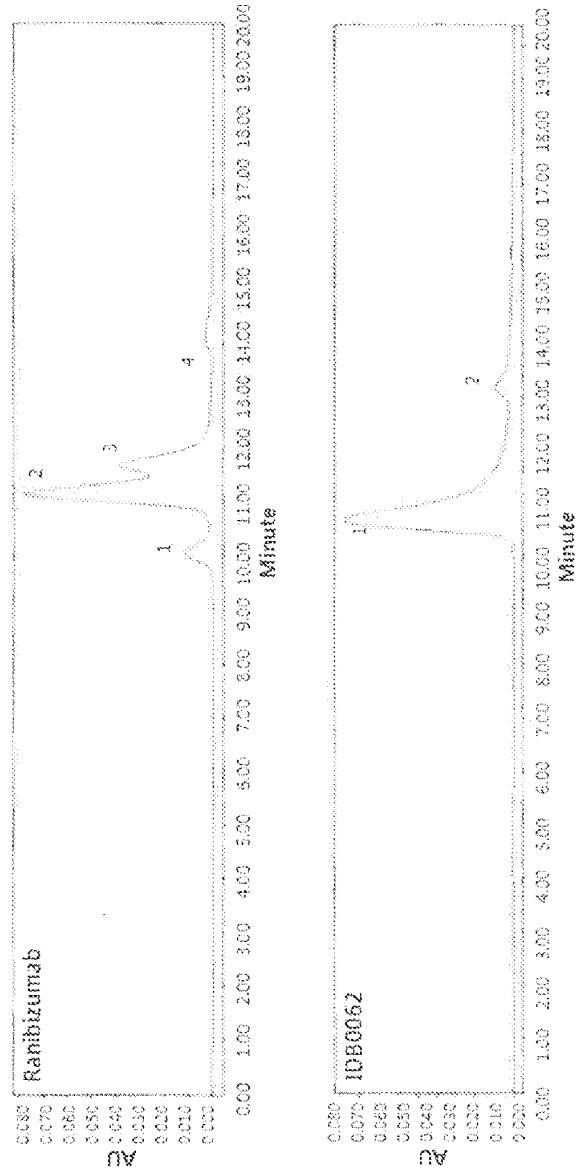
1/13

FIG. 1



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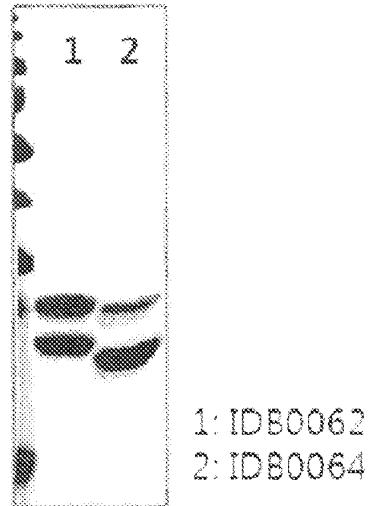
FIG. 2



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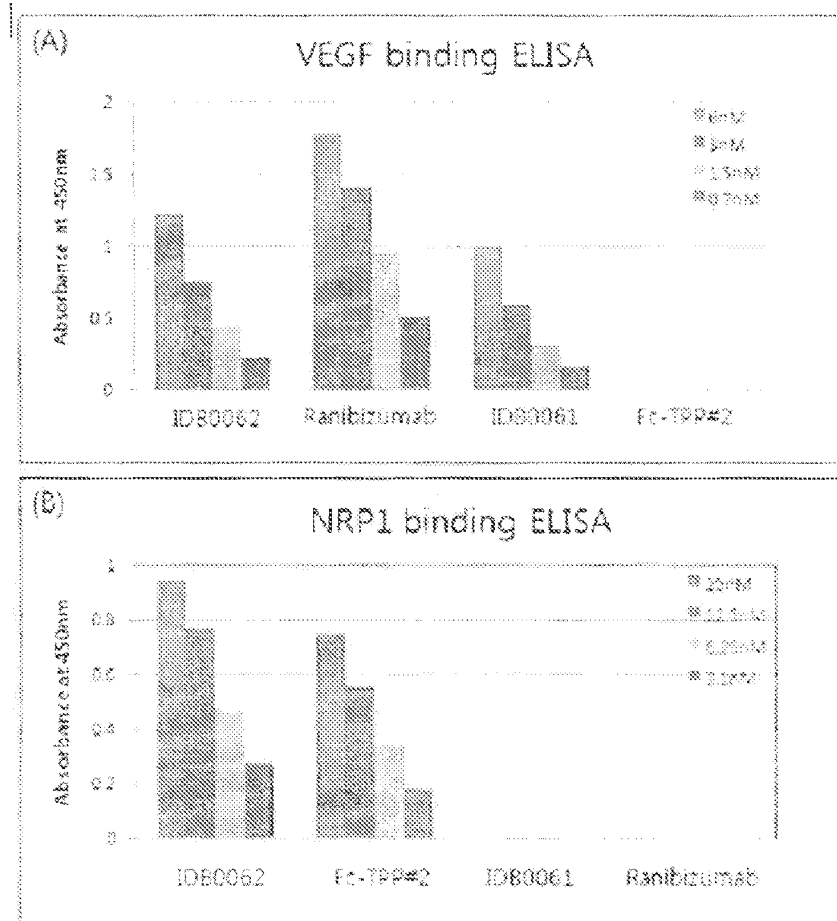
FIG. 3

Non-reducing SDS-PAGE(12%, 3ug)



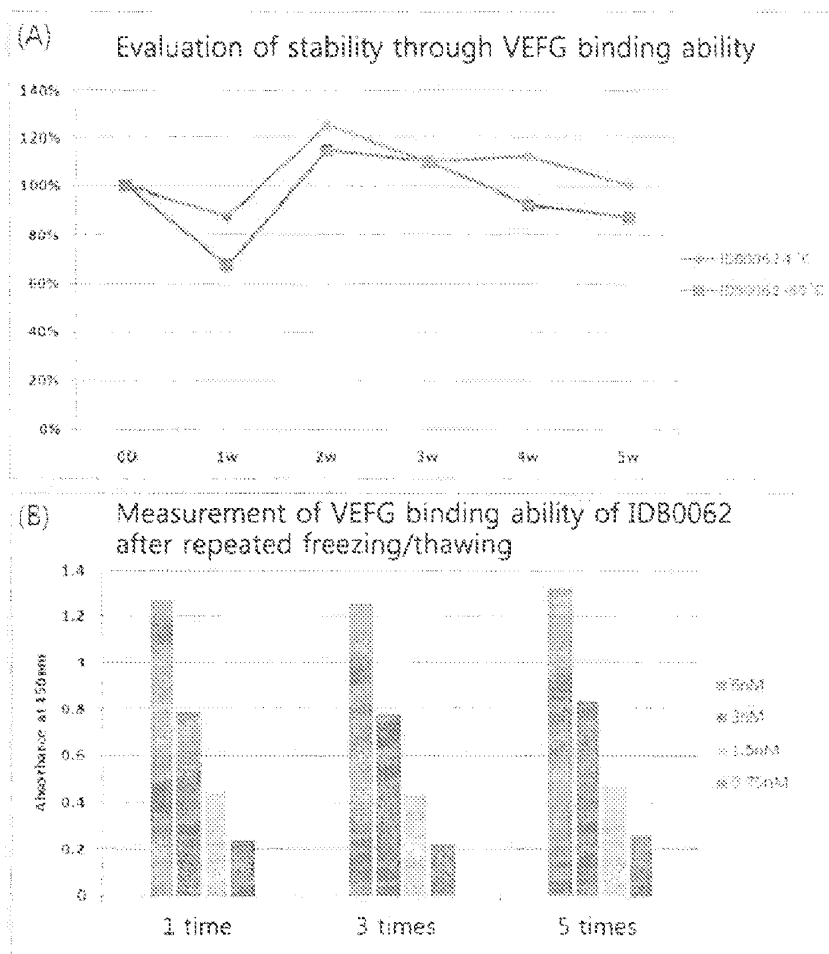
4/13

FIG. 4



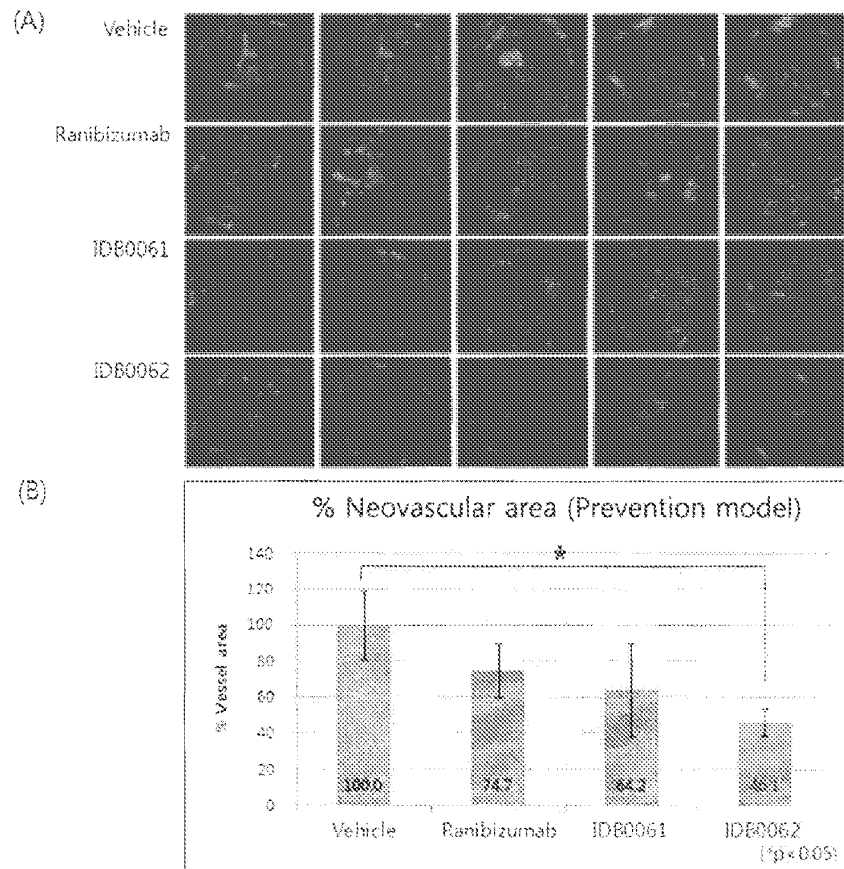
5/13

FIG. 5



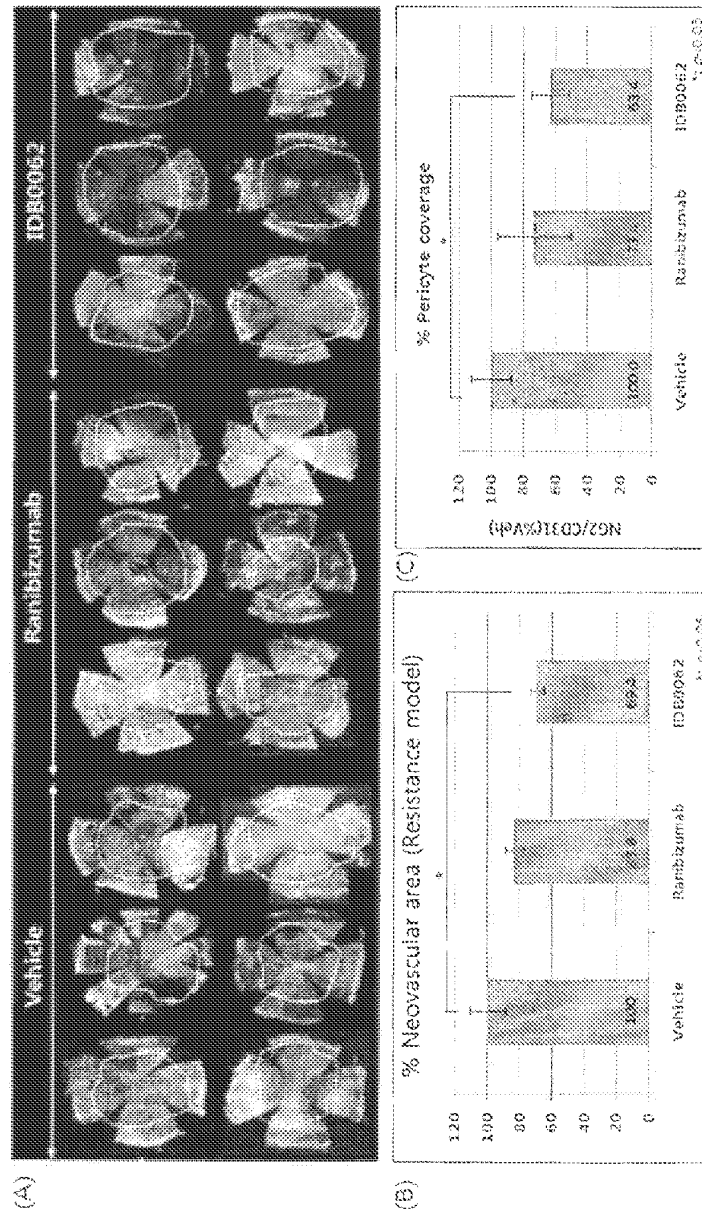
6/13

FIG. 6



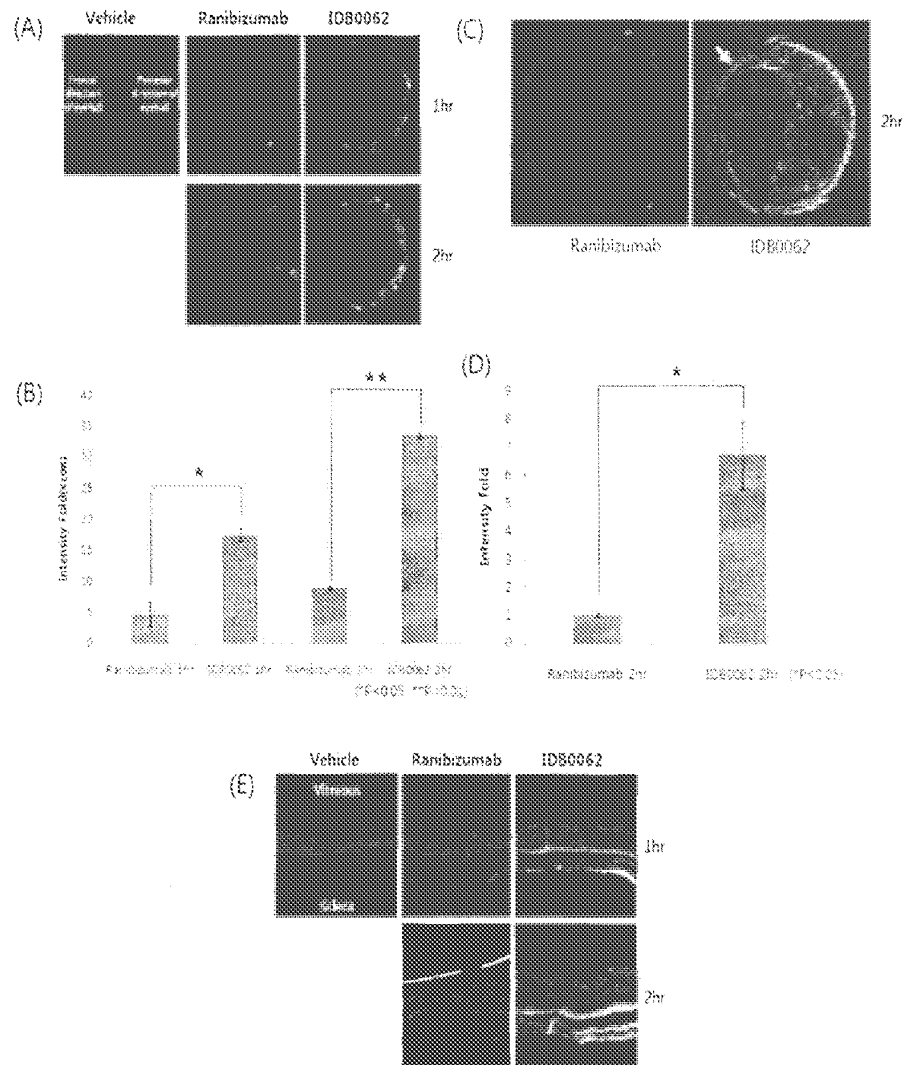
7/13

FIG. 7



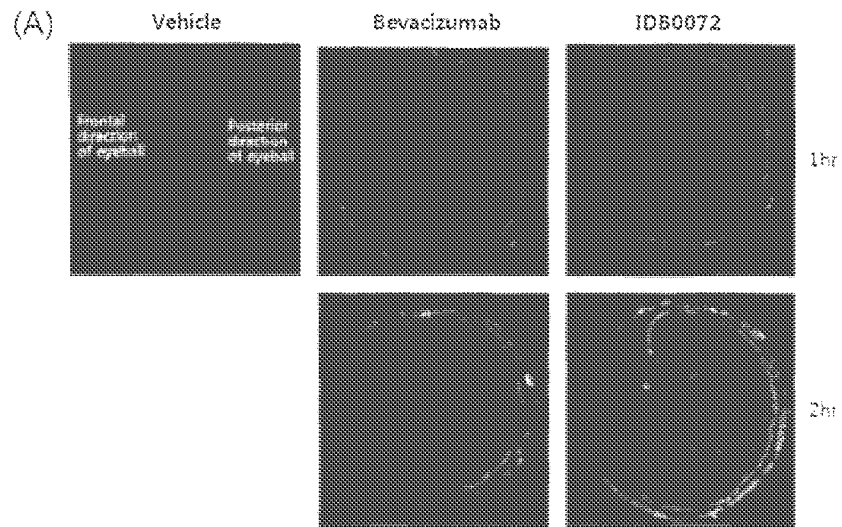
8/13

FIG. 8

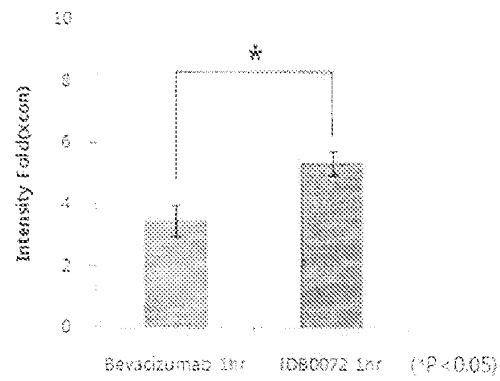


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FIG. 9

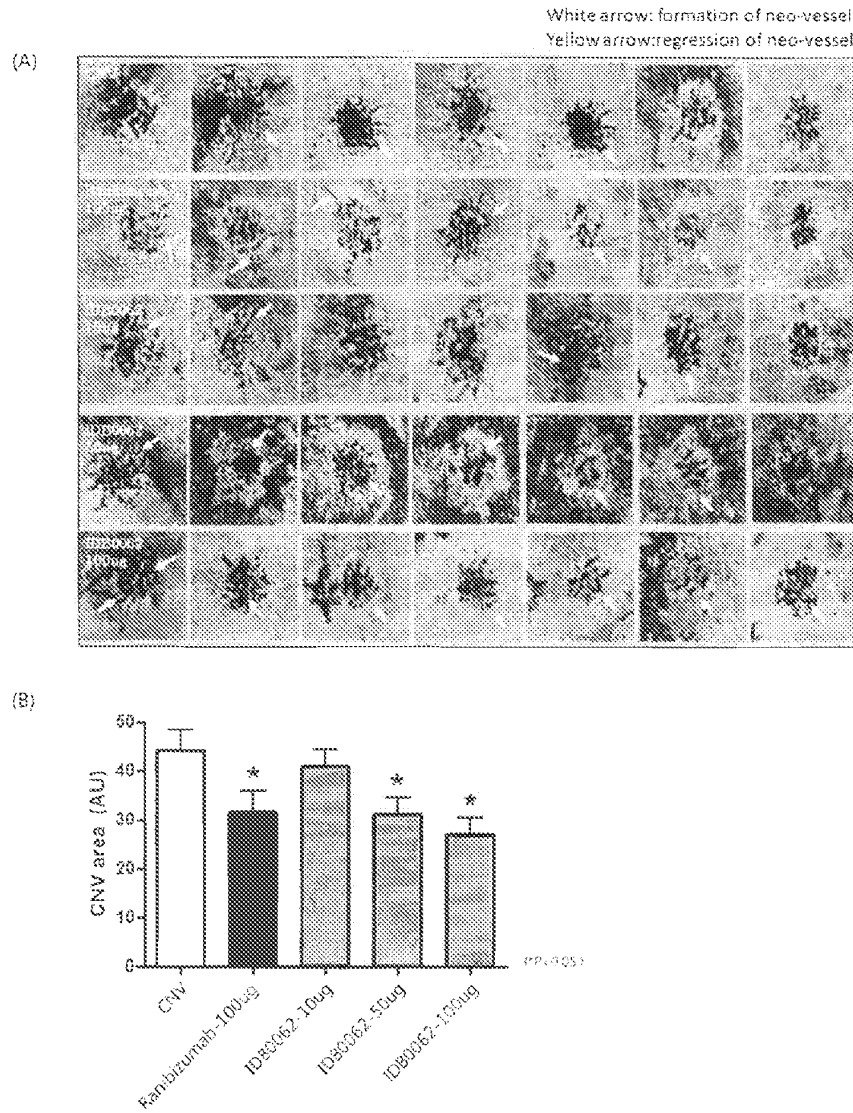


(B)



10/13

FIG. 10

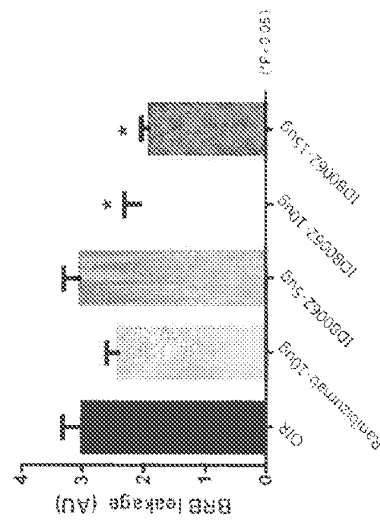


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FIG. 11



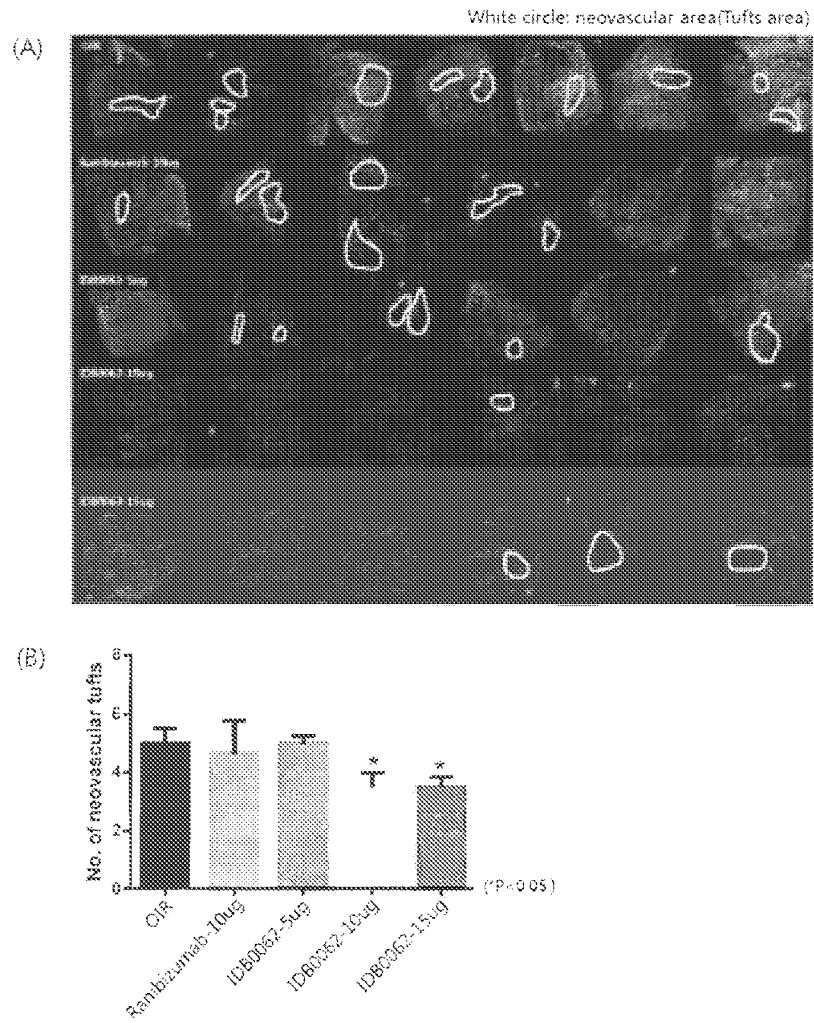
(A)



(B)

12/13

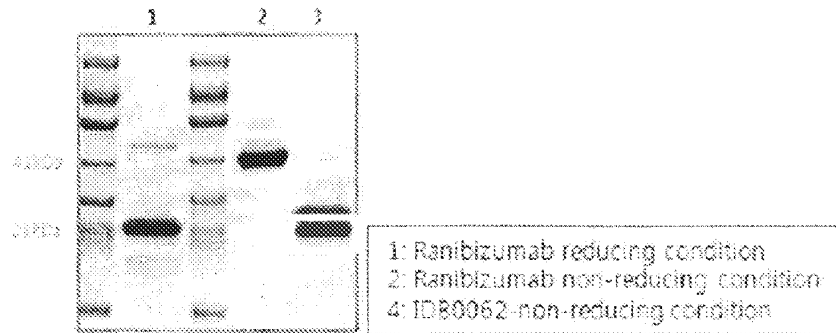
FIG. 12



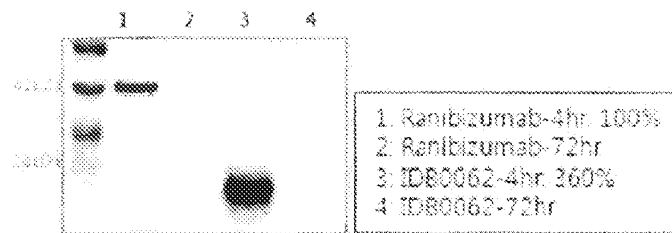
13/13

FIG. 13

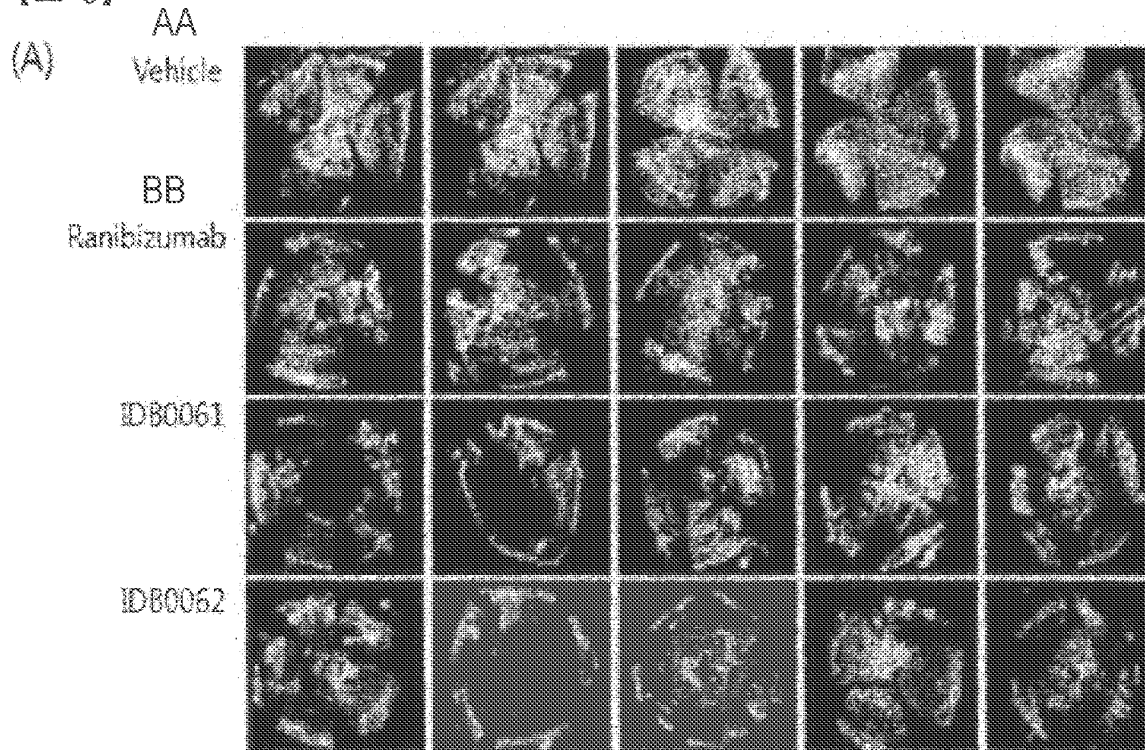
Non-reducing SDS-PAGE(12%, 3ug)



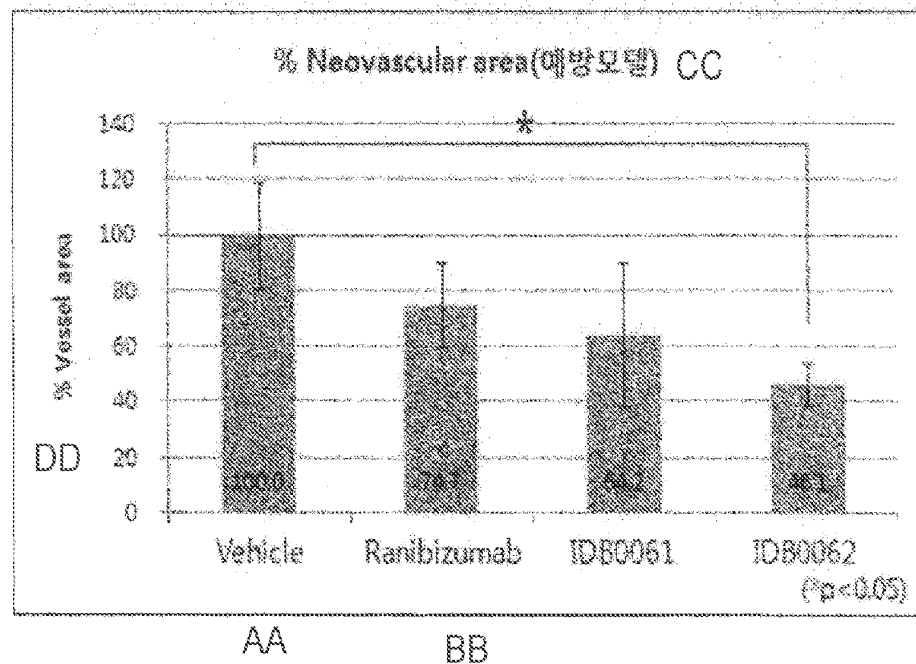
Western blot assay(12% non-reducing)



【도 6】



(B)



AA ... Vehicle

BB ... Ranibizumab

CC ... % Neovascular area (prevention model)

DD ... % Vessel area



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ELECTRONIC PAYMENT RECEIPT

APPLICATION # 17/384,070	RECEIPT DATE / TIME 04/29/2024 12:30:13 PM Z ET	ATTORNEY DOCKET # -
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Title of Invention

Methods for Treating Angiogenic Eye Disorders with High Doses of VEGF Receptor Fusion Proteins

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	1061	FILED BY	Lance Termes
PATENT CENTER #	65290229	AUTHORIZED BY	-
CUSTOMER #	147803	FILING DATE	07/23/2021
CORRESPONDENCE ADDRESS	-	FIRST NAMED INVENTOR	Kenneth S. Graham

Payment Information

PAYMENT METHOD DA / 500393	PAYMENT TRANSACTION ID E20244SC30428607	PAYMENT AUTHORIZED BY Lance Termes
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FEE CODE	DESCRIPTION	ITEM PRICE(\$)	QUANTITY	ITEM TOTAL(\$)
1820	REQUEST FOR CONTINUED EXAMINATION (RCE)- 2ND AND SUBSEQUENT REQUEST (SEE 37 CFR 1.114)	2000.00	1	2000.00
TOTAL AMOUNT:				\$2,000.00

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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If a new application is being filed and the application includes the necessary components for 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.

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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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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #
17/384,070

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Title of Invention

Methods for Treating Angiogenic Eye Disorders with High Doses of VEGF Receptor Fusion Proteins

Application Information

APPLICATION TYPE Utility - Nonprovisional Application
under 35 USC 111(a)

PATENT # -

CONFIRMATION # 1061

FILED BY Lance Termes

PATENT CENTER # 65290229

FILING DATE 07/23/2021

CUSTOMER # 147803

FIRST NAMED
INVENTOR Kenneth S. Graham

CORRESPONDENCE
ADDRESS -

AUTHORIZED BY -

Documents

TOTAL DOCUMENTS: 1

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
10430US02__RCE.pdf	1	Request for Continued Examination (RCE)	210 KB

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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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**Request
for
Continued Examination (RCE)
Transmittal**

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Alexandria, VA 22313-1450

Application Number	17/384,070
Filing Date	July 23, 2021
First Named Inventor	Kenneth S. Graham
Art Unit	1647
Examiner Name	Jon McClelland Lockard
Attorney Docket Number	125984-266215

This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. See Instruction Sheet for RCEs (not to be submitted to the USPTO) on page 2.

1. **Submission required under 37 CFR 1.114** Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).
- a. ☐ Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.
- i. ☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____
- ii. ☐ Other _____
- b. ☒ Enclosed
- i. ☐ Amendment/Reply
- iii. ☒ Information Disclosure Statement (IDS)
- ii. ☐ Affidavit(s)/ Declaration(s)
- iv. ☐ Other _____
2. **Miscellaneous**
- a. ☐ Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a period of _____ months. (Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)
- b. ☐ Other _____
3. **Fees** The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.
- a. ☒ The Director is hereby authorized to charge the following fees, any underpayment of fees, or credit any overpayments, to Deposit Account No. 500393.
- i. ☒ RCE fee required under 37 CFR 1.17(e)
- ii. ☐ Extension of time fee (37 CFR 1.136 and 1.17)
- iii. ☐ Other _____
- b. ☐ Check in the amount of \$ _____ enclosed
- c. ☐ Payment by credit card (Form PTO-2038 enclosed)
- d. ☒ Payment by USPTO patent electronic filing system.

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.

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

Signature	/Lance A. Termes/	Date	April 29, 2024
Name (Print/Type)	Lance A. Termes	Registration No.	43,184

CERTIFICATE OF MAILING OR TRANSMISSION

I hereby certify that this correspondence is transmitted by the USPTO patent electronic filing system, or by facsimile to (571) 273-8300, to the USPTO, or deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop RCE, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on the date shown below.

Signature	/Lance A. Termes/	Date	April 29, 2024
Name (Print/Type)	Lance A. Termes		

A Federal agency may not conduct or sponsor, and a person is not required to respond to, nor shall a person be subject to a penalty for failure to comply with an information collection subject to the requirements of the Paperwork Reduction Act of 1995, unless the information collection has a currently valid OMB Control Number. The OMB Control Number for this information collection is 0651-0031. Public burden for this form is estimated to average 12 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the information collection. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden to the Chief Administrative Officer, United States Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450 or email InformationCollection@uspto.gov. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. If filing this completed form by mail, 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.

TO: ipdocketing@schwabe.com,LTermes@schwabe.com
FROM: noreply@uspto.gov
CC: patentcenter_eofficeaction@uspto.gov
SUBJECT: USPTO: Patent Electronic System - e-Postcard Notification for Customer Number 147803

Wed Feb 07 05:39:13 EST 2024

Dear Patent Center Customer:

Correspondence Address:

Schwabe W&W PC / Regeneron Pharmaceuticals, Inc.
PacWest Center
1211 SW Fifth Avenue, Suite 1900
Portland, OREGON, 97204
UNITED STATES

An email notification regarding the correspondence was sent to the following email address(es) associated with customer number 147803:

ipdocketing@schwabe.com
LTermes@schwabe.com

This is a courtesy reminder that new correspondence is available for the application. If you have not done so already, please review the correspondence listed below. The official date of notification of the outgoing correspondence will be indicated on the form PTOL-90 accompanying the correspondence.

Application	Document	Mailroom Date	Attorney Docket No.
17384070	NOA	01/31/2024	
17384070	1449	01/31/2024	
17384070	1449	01/31/2024	
17384070	1449	01/31/2024	

To view your correspondence online, please sign in to [Patent Center](#) and then select Workbench/View correspondence. Or to update your email addresses, select Manage/Manage customer numbers.

If you have any questions, please contact the [Patent Electronic Business Center](#) (EBC) at ebc@uspto.gov or 866-217-9197 Monday – Friday, 6 a.m. to midnight ET.

Please do not reply to this email as it was sent from an unmonitored mailbox.

Sincerely,

The Patent Center Team



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

147803 7590 01/31/2024
Schwabe W&W, PC / Regeneron Pharmaceuticals, Inc.
PacWest Center
1211 SW Fifth Avenue, Suite 1900
Portland, OR 97204

EXAMINER	
LOCKARD, JON MCCLELLAND	
ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 01/31/2024

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/384,070	07/23/2021	Kenneth S. Graham		1061

TITLE OF INVENTION: Methods for Treating Angiogenic Eye Disorders with High Doses of VEGF Receptor Fusion Proteins

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	\$1200	\$0.00	\$1200.00	\$0	04/30/2024

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 40% the amount of undiscounted fees, and micro entity fees are 20% the amount of undiscounted 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. 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 the USPTO patent electronic filing system.

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 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. **Because electronic patent issuance may occur shortly after issue fee payment, any desired continuing application should preferably be filed prior to payment of this issue fee in order not to jeopardize copendency.**

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

147803 7590 01/31/2024
Schwabe W&W, PC / Regeneron Pharmaceuticals, Inc.
PacWest Center
1211 SW Fifth Avenue, Suite 1900
Portland, OR 97204

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 the USPTO patent electronic filing system 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.
17/384,070	07/23/2021	Kenneth S. Graham		1061

TITLE OF INVENTION: Methods for Treating Angiogenic Eye Disorders with High Doses of VEGF Receptor Fusion Proteins

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	\$1200	\$0.00	\$1200.00	\$0	04/30/2024

EXAMINER	ART UNIT	CLASS-SUBCLASS
LOCKARD, JON MCCLELLAND	1647	424-134100

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/AIA/122 or PTO/SB/122) attached.

☐ "Fee Address" indication (or "Fee Address" Indication form PTO/AIA/47 or 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 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)

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

☐ Electronic Payment via the USPTO patent electronic filing system ☐ 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. _____



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.
17/384,070	07/23/2021	Kenneth S. Graham		1061
147803	7590	01/31/2024		
Schwabe W&W, PC / Regeneron Pharmaceuticals, Inc.				
PacWest Center				
1211 SW Fifth Avenue, Suite 1900				
Portland, OR 97204				
			EXAMINER	
			LOCKARD, JON MCCLELLAND	
			ART UNIT	PAPER NUMBER
			1647	

DATE MAILED: 01/31/2024

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. The United States Patent and Trademark Office (USPTO) collects the information in this record under authority of 35 U.S.C. 2. The USPTO's system of records is used to manage all applicant and owner information including name, citizenship, residence, post office address, and other information with respect to inventors and their legal representatives pertaining to the applicant's/owner's activities in connection with the invention for which a patent is sought or has been granted. The applicable Privacy Act System of Records Notice for the information collected in this form is COMMERCE/PAT-TM-7 Patent Application Files, available in the Federal Register at 78 FR 19243 (March 29, 2013).

<https://www.govinfo.gov/content/pkg/FR-2013-03-29/pdf/2013-07341.pdf>

Routine uses of the information in this record may include disclosure to:

- 1) law enforcement, in the event that the system of records indicates a violation or potential violation of law;
- 2) a federal, state, local, or international agency, in response to its request;
- 3) a contractor of the USPTO having need for the information in order to perform a contract;
- 4) the Department of Justice for determination of whether the Freedom of Information Act (FOIA) requires disclosure of the record;
- 5) a Member of Congress submitting a request involving an individual to whom the record pertains, when the individual has requested the Member's assistance with respect to the subject matter of the record;
- 6) a court, magistrate, or administrative tribunal, in the course of presenting evidence, including disclosures to opposing counsel in the course of settlement negotiations;
- 7) the Administrator, General Services Administration (GSA), or their designee, during an inspection of records conducted by GSA under authority of 44 U.S.C. 2904 and 2906, in accordance with the GSA regulations and any other relevant (i.e., GSA or Commerce) directive, where such disclosure shall not be used to make determinations about individuals;
- 8) 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));
- 9) the Office of Personnel Management (OPM) for personnel research purposes; and
- 10) the Office of Management and Budget (OMB) for legislative coordination and clearance.

If you do not furnish the information requested on this form, the USPTO may not be able to process and/or examine your submission, which may result in termination of proceedings, abandonment of the application, and/or expiration of the patent.

Notice of Allowability	Application No. 17/384,070	Applicant(s) Graham et al.	
	Examiner JON M LOCKARD	Art Unit 1647	AIA (FITF) Status Yes

-- 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 the Request for Continued Examination filed 15 December 2023.
☐ 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 See Continuation Sheet . 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)	5. ☒ Examiner's Amendment/Comment
2. ☒ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____.	6. ☒ Examiner's Statement of Reasons for Allowance
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____.	7. ☐ Other _____.
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____.	

/J.L/ Examiner, Art Unit 1647	/CHRISTINE J SAOUD/ Primary Examiner, Art Unit 1645
----------------------------------	--

Continuation of 3. The allowed claim(s) is/are: 30-32 and 53-87)renumbered as claims 1-11,13-14,16,18,20,22,24,12,26,15,17,19,21,23,25 and 27-38, respectively)

Notice of Pre-AIA or AIA Status

1. The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

Continued Examination Under 37 CFR 1.114

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 allowance or after an Office action under *Ex Parte Quayle*, 25 USPQ 74, 453 O.G. 213 (Comm'r Pat. 1935). 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, prosecution in this application has been reopened pursuant to 37 CFR 1.114.

Applicant's submission filed on 15 December 2023 has been entered.

Information Disclosure Statement

3. The information disclosure statements (IDS) submitted on 15 December 2023 and 16 January 2024 have been considered by the examiner. Additionally, the IDS filed 03 December 2021, previously considered by the Examiner, is being provided to show that NPL references 140, 162, 167, 180, 193, 201 and 218 have been lined through. The references have been considered, but will not appear on the cover of the issued patent as they do not provide a date.

REASONS FOR ALLOWANCE

4. The following is an examiner's statement of reasons for allowance: The information disclosure statement (IDS) submitted on 15 December 2023 and 16 January 2024 have been

considered by the Examiner. After careful consideration, the Examiner has determined that none of the information contained therein raises new issues of patentability.

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."

Summary

6. Claims 30-32 and 53-87 are allowed.

Advisory Information

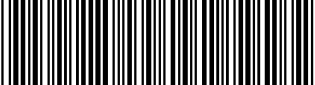
Any inquiry concerning this communication or earlier communications from the examiner should be directed to **JON M LOCKARD** whose telephone number is **(571) 272-2717**. The examiner can normally be reached M-F 9-6 EST.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at <http://www.uspto.gov/interviewpractice>. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joanne Hama** can be reached on **(571) 272-2911**. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of published or unpublished applications may be obtained from Patent Center. Unpublished application information in Patent Center is available to registered users. To file and manage patent submissions in Patent Center, visit: <https://patentcenter.uspto.gov>. Visit <https://www.uspto.gov/patents/apply/patent-center> for more information about Patent Center and <https://www.uspto.gov/patents/docx> for information about filing in DOCX format. For additional questions, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/J.L/
Examiner, Art Unit 1647
January 24, 2024

/Christine J Saoud/
Primary Examiner, Art Unit 1645

Issue Classification 	Application/Control No. 17/384,070	Applicant(s)/Patent Under Reexamination Graham et al.
	Examiner JON M LOCKARD	Art Unit 1647

CPC						
Symbol					Type	Version
A61K	/	38	/	179	F	2013-01-01
A61K	/	9	/	0048	I	2013-01-01
A61K	/	47	/	12	I	2013-01-01
A61P	/	27	/	02	I	2018-01-01
A61K	/	47	/	22	I	2013-01-01
A61K	/	47	/	26	I	2013-01-01
A61K	/	47	/	183	I	2013-01-01

CPC Combination Sets					
Symbol				Type	Set
	/		/		

/JON M LOCKARD/ Examiner, Art Unit 1647 (Assistant Examiner)	11 January 2024 (Date)	Total Claims Allowed: 38	
/CHRISTINE J SAOUD/ Primary Examiner, Art Unit 1645 (Primary Examiner)	12 January 2024 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure NONE

U.S. Patent and Trademark Office

Part of Paper No.: 20240111

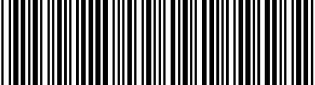
Issue Classification 	Application/Control No. 17/384,070	Applicant(s)/Patent Under Reexamination Graham et al.
	Examiner JON M LOCKARD	Art Unit 1647

INTERNATIONAL CLASSIFICATION			
CLAIMED			
A61K	/	38	/ 17
A61K	/	38	/ 18
C07K	/	14	/ 71
NON-CLAIMED			
	/		/

US ORIGINAL CLASSIFICATION	
CLASS	SUBCLASS

CROSS REFERENCES(S)						
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)					

/JON M LOCKARD/ Examiner, Art Unit 1647 (Assistant Examiner)	11 January 2024 (Date)	Total Claims Allowed: 38	
/CHRISTINE J SAUD/ Primary Examiner, Art Unit 1645 (Primary Examiner)	12 January 2024 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure NONE

Issue Classification 	Application/Control No. 17/384,070	Applicant(s)/Patent Under Reexamination Graham et al.
	Examiner JON M LOCKARD	Art Unit 1647

☐ 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
1	30	10	59	12	68	28	77	37	86						
2	31	11	60	26	69	29	78	38	87						
3	32	13	61	15	70	30	79								
4	53	14	62	17	71	31	80								
5	54	16	63	19	72	32	81								
6	55	18	64	21	73	33	82								
7	56	20	65	23	74	34	83								
8	57	22	66	25	75	35	84								
9	58	24	67	27	76	36	85								

/JON M LOCKARD/ Examiner, Art Unit 1647 (Assistant Examiner)	11 January 2024 (Date)	Total Claims Allowed: 38	
/CHRISTINE J SAOUD/ Primary Examiner, Art Unit 1645 (Primary Examiner)	12 January 2024 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure NONE

U.S. Patent and Trademark Office

Part of Paper No.: 20240111

<i>Search Notes</i> 	Application/Control No. 17/384,070	Applicant(s)/Patent Under Reexamination Graham et al.
	Examiner JON M LOCKARD	Art Unit 1647

CPC - Searched*		
Symbol	Date	Examiner

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner
NONE		03/16/2023	JML

* 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
PE2E Search (USPAT, US-PGPUB, EPO, DERWENT): See attached search history.	03/16/2023	JML
STN (MEDLINE, SCISEARCH, EMBASE, BIOSIS): See attached search history.	03/16/2023	JML
PALM: Inventor search.	03/16/2023	JML
PE2E Search (USPAT, US-PGPUB, EPO, DERWENT): See attached search history.	11/01/2023	JML

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<i>Search Notes</i> 	Application/Control No. 17/384,070	Applicant(s)/Patent Under Reexamination Graham et al.
	Examiner JON M LOCKARD	Art Unit 1647

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner
	PE2E Search (USPAT): See attached search history.	08/24/2023	JML
	DAV: Inventor search.	08/24/2023	JML
	PE2E Search (USPAT): See attached search history.	11/01/2023	JML
	DAV: Inventor search.	11/01/2023	JML
	PE2E Search (USPAT): See attached search history.	11/29/2023	JML
	DAV: Inventor search.	11/29/2023	JML
	PE2E Search (USPAT): See attached search history.	01/11/2024	JML
	DAV: Inventor search.	01/11/2024	JML

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PE2E SEARCH - Search History (Prior Art)

/J.L./

There are no Prior Art searches to show.

PE2E SEARCH - Search History (Interference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	British Equivalents	Time Stamp
N23	2661	vegf ADJ trap	(USPAT)	OR	ON	ON	2024/01/11 11:22 PM
N24	2745	aflibercept	(USPAT)	OR	ON	ON	2024/01/11 11:22 PM
N25	266	eylea	(USPAT)	OR	ON	ON	2024/01/11 11:23 PM
N26	113	vegf ADJ trap-eye	(USPAT)	OR	ON	ON	2024/01/11 11:23 PM
N27	417	(N23 N24 N25 N26) SAME formulation	(USPAT)	OR	ON	ON	2024/01/11 11:23 PM
N28	12	N27 SAME "high concentration"	(USPAT)	OR	ON	ON	2024/01/11 11:24 PM
N29	1	N27 AND (8mg OR "8 mg").clm.	(USPAT)	OR	ON	ON	2024/01/11 11:24 PM
N30	17	(graham-k-s-s\$ washawa-s\$).in.	(USPAT)	OR	ON	ON	2024/01/11 11:25 PM
N31	1	N28 AND N30	(USPAT)	OR	ON	ON	2024/01/11 11:25 PM

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	Filing Date	Jul-23-2021
	First Named Inventor	Kenneth S. Graham
	Art Unit	Not Yet Assigned 1647
	Confirmation Number	1061
	Examiner Name	Not Yet Assigned Jon Lockard
	Attorney Docket Number	125984-266215 / 10430US02

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	089	WHITAKER et al., "A Formulation Development Approach to Identify and Select Stable Ultra-High-Concentration Monoclonal Antibody Formulations With Reduced Viscosities," Journal of Pharmaceutical Sciences; Nov;106(11):3230-3241. doi: 10.1016/j.xphs.2017.06.017. (2017).	
	215	Wulff et al., Prevention of Thecal Angiogenesis, Antral Follicular Growth, and Ovulation in the Primate by Treatment with Vascular Endothelial Growth Factor Trap R1R2, Endocrinology, July 2002, 143(7): 2797- 2807	
	217	Wykoff et al., SAVE (Super-dose anti-VEGF) trial: 2.0 mg ranibizumab for recalcitrant neovascular age-related macular degeneration: 1-year results, Ophthalmic Surg Lasers Imaging Retina. 2013 Mar-Apr;44(2):121-6.	
	216	Wykoff et al., Two Year SAVE Outcomes: 2.0 mg ranibizumab for recalcitrant neovascular AMD, Ophthalmology 2013 Sep;120(9):1945-6	
	218	XOLAIR label	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT <small>(not for submission under 37 CFR 1.99)</small>	Application Number	17/384,070
	Filing Date	Jul-23-2021
	First Named Inventor	Kenneth S. Graham
	Art Unit	Not Yet Assigned
	Confirmation Number	1061
	Examiner Name	Not Yet Assigned
	Attorney Docket Number	125984-266215 / 10430US02

NON-PATENT LITERATURE DOCUMENTS			
Examiner Initial*	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
	219	You et al., High-Dose High-Frequency Aflibercept For Recalcitrant Neovascular Age-Related Macular Degeneration, Retina: June 2018 – 38(6): 1156-1165	
	085	ZALTRAP, "Injection for Intravenous Infusion Prescribing Information," Prescribing Information; 1-20, (2012). [http://products.sanofi.us/Zaltrap/Zaltrap.html]	
	220	Ziemssen et al., Safety of monoclonal antibodies and related therapeutic proteins for the treatment of neovascular macular degeneration: addressing outstanding issues, Expert Opin Drug Saf . 2016 Jan;15(1):75-87-Epub 2015 Dec 11	

EXAMINER SIGNATURE			
Examiner Signature	/JON M LOCKARD/		Date Considered 03/15/2023
<p>*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.</p>			
<p>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.</p>			

INFORMATION DISCLOSURE STATEMENT BY APPLICANT <small>(not for submission under 37 CFR 1.99)</small>	Application Number	17/384,070
	Filing Date	Jul-23-2021
	First Named Inventor	Kenneth S. Graham
	Art Unit	Not Yet Assigned
	Confirmation Number	1061
	Examiner Name	Not Yet Assigned
	Attorney Docket Number	125984-266215 / 10430US02

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.

- ☐ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

- ☒ None

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	/Lance A. Termes/	Date (YYYY-MM-DD)	2021-12-03
Name/Print	Lance A. Termes	Registration Number	43184

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (not for submission under 37 CFR 1.99)	Application Number	17/384,070
	Filing Date	Jul-23-2021
	First Named Inventor	Kenneth S. Graham
	Art Unit	1647
	Confirmation Number	1061
	Examiner Name	Lockard, Jon McClelland
	Attorney Docket Number	125984-266215

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
/J.L./	565	11,806,398		11-07-2023	Dix et al.	

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

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

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Receipt date: 01/16/2024

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (not for submission under 37 CFR 1.99)	Application Number	17/384,070
	Filing Date	Jul-23-2021
	First Named Inventor	Kenneth S. Graham
	Art Unit	1647
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	Examiner Name	Lockard, Jon McClelland
	Attorney Docket Number	125984-266215

EXAMINER SIGNATURE			
Examiner Signature	/JON M LOCKARD/	Date Considered	01/24/2024
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Signature	/Lance A. Termes/	Date (YYYY-MM-DD)	2024-01-16
Name/Print	Lance A. Termes	Registration Number	43184

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/J.L./	564	"ZHANG et al., "A Phase 1 Study of KH902, a Vascular Endothelial Growth Factor Receptor Decoy, for Exudative Age-Related Macular Degeneration," American Academy of Ophthalmology, pages 672-678, (2011). [doi:10.1016/j.ophtha.2010.08.008; ISSN 0161-6420/11/\$]."	

Receipt date: 12/15/2023

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (not for submission under 37 CFR 1.99)	Application Number	17/384,070
	Filing Date	Jul-23-2021
	First Named Inventor	Kenneth S. Graham
	Art Unit	1647
	Confirmation Number	1061
	Examiner Name	Lockard, Jon McClelland
	Attorney Docket Number	125984-266215

EXAMINER SIGNATURE			
Examiner Signature	/JON M LOCKARD/	Date Considered	01/11/2024
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	Filing Date	Jul-23-2021
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SIGNATURE			
<p>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.</p>			
Signature	/Lance A. Termes/	Date (YYYY-MM-DD)	2023-12-15
Name/Print	Lance A. Termes	Registration Number	43184

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Kenneth S. Graham, et al. Application No.: 17/384,070 Filed: Jul-23-2021 For: HIGH CONCENTRATION VEGF RECEPTOR FUSION PROTEIN CONTAINING FORMULATIONS Customer No.: 147803	Confirmation No.: 1061 Examiner: Lockard, Jon McClelland Art Unit: 1647 SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR §1.97 and §1.98 <u>Date of Transmission: January 16, 2024</u>
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Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

The reference cited on the attached IDS is being called to the attention of the Examiner.

It is respectfully requested that the cited reference be expressly considered during the prosecution of this application, and the reference be made of record therein and appear among the “references cited” on any patent to issue therefrom.

The Examiner is encouraged to review the full prosecution history from related cases. Applicant understands that the prosecution history can be viewed electronically on PALM. Nevertheless, if the Examiner wishes Applicant to provide copies of any documents

from related applications to the extent not already provided, he or she is requested to contact the undersigned.

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125984-248592	62/752,127	10-29-2018	N/A	Expired
125984-248593	62/769,876	11-20-2018	N/A	Expired
125984-248594	62/813,882	03-05-2019	N/A	Expired
125984-248595	16/409,631	05-10-2019	US 11,103,552	Issued
125984-248596	PCT/US2019/031879	05-10-2019	WO 2019/217927	Expired
125984-281135	18/367,444	09-12-2023		Pending

As provided for by 37 CFR §1.97(g) and (h), no inference should be made that the information and references cited are prior art merely because they are in this statement and no representation is being made that a search has been conducted or that this statement encompasses all the possible relevant information.

Applicant believes that no fee is required for submission of this statement.

However, if a fee is required in connection with this paper, the Commissioner is authorized to deduct such fee from the undersigned's Deposit Account No 500393.

Respectfully submitted,

/Lance A. Termes/

Lance A. Termes
Reg. No. 43184

Schwabe Williamson & Wyatt, PC
1211 SW 5th Avenue, Suite 1900
Portland, OR 97204
Tel: 503-222-9981

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (not for submission under 37 CFR 1.99)	Application Number	17/384,070
	Filing Date	Jul-23-2021
	First Named Inventor	Kenneth S. Graham
	Art Unit	1647
	Confirmation Number	1061
	Examiner Name	Lockard, Jon McClelland
	Attorney Docket Number	125984-266215

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
	565	11,806,398		11-07-2023	Dix et al.	

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

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
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NON-PATENT LITERATURE DOCUMENTS			
Examiner Initial*	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 <small>(not for submission under 37 CFR 1.99)</small>	Application Number	17/384,070
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	Art Unit	1647
	Confirmation Number	1061
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	Attorney Docket Number	125984-266215

EXAMINER SIGNATURE			
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CERTIFICATION STATEMENT			
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☐ See attached certification statement.			
☐ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.			
☒ None			
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	/Lance A. Termes/	Date (YYYY-MM-DD)	2024-01-16
Name/Print	Lance A. Termes	Registration Number	43184



UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #
17/384,070

RECEIPT DATE / TIME
01/16/2024 05:31:05 PM Z ET

ATTORNEY DOCKET #
-

Title of Invention

Methods for Treating Angiogenic Eye Disorders with High Doses of VEGF Receptor Fusion Proteins

Application Information

APPLICATION TYPE Utility - Nonprovisional Application
under 35 USC 111(a)

PATENT # -

CONFIRMATION # 1061

FILED BY Brandi Henley

PATENT CENTER # 63969760

FILING DATE 07/23/2021

CUSTOMER # 147803

FIRST NAMED
INVENTOR Kenneth S. Graham

CORRESPONDENCE
ADDRESS -

AUTHORIZED BY Lance Termes

Documents

TOTAL DOCUMENTS: 2

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
10430US02_IDS- Transmittal.pdf	2	Transmittal Letter	19 KB
10430US02_IDS-SB08.pdf	3	Information Disclosure Statement (IDS) Form (SB08)	52 KB

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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 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

In re application of: Kenneth S. Graham, et al. Application No.: 17/384,070 Filed: Jul-23-2021 For: METHODS FOR TREATING ANGIOGENIC EYE DISORDERS WITH HIGH DOSES OF VEGF RECEPTOR FUSION PROTEINS Customer No.: 147803	Confirmation No.: 1061 Examiner: Lockard, Jon McClelland Art Unit: 1647 SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR §1.97 and §1.98 <u>Date of Transmission: December 15, 2023</u>
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Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

The reference cited on the attached IDS is being called to the attention of the Examiner. A copy of the reference in compliance with the requirements of 37 CFR §1.98(a)(2) is submitted herewith.

It is respectfully requested that the cited reference be expressly considered during the prosecution of this application, and the reference be made of record therein and appear among the “references cited” on any patent to issue therefrom.

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Respectfully submitted,

/Lance A. Termes/

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Reg. No. 43184

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1211 SW 5th Avenue, Suite 1900
Portland, OR 97204
Tel: 503-222-9981



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564_NPL_Zhang2011.pdf	7	Non Patent Literature	605 KB

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DOCUMENT	MESSAGE DIGEST(SHA-512)
10430US02_IDS-Transmittal.pdf	492279F25E796FD78923FD42755F77110AFC6F0533BB4DC19A E6AA8BB57640A8026F3C541D8527BC854A8FF96C700F7569C 195E270C2B22B7DCB9AA06D809203
10430US02_IDS-SB08.pdf	A4C19474D5259DFD2C6DE9A69F3E34C1D1597740E5BCF65C C101EB9B287762BFD73470DEE7305B585530412F96AB7A46BF 5F6CD9E046A78917967C2F39842631
564_NPL_Zhang2011.pdf	8737A64C6C35B8F023AAE5CEAB24CC09990DF42994B601900 33C9A5F0ABEAEEAA55250E794308A1CFD83BEA73690E9F5EB FE6BC5ABE33CB1B900CAF0024CAFE9F

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 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.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (not for submission under 37 CFR 1.99)	Application Number	17/384,070
	Filing Date	Jul-23-2021
	First Named Inventor	Kenneth S. Graham
	Art Unit	1647
	Confirmation Number	1061
	Examiner Name	Lockard, Jon McClelland
	Attorney Docket Number	125984-266215

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

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

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

NON-PATENT LITERATURE DOCUMENTS			
Examiner Initial*	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
	564	"ZHANG et al., "A Phase 1 Study of KH902, a Vascular Endothelial Growth Factor Receptor Decoy, for Exudative Age-Related Macular Degeneration," American Academy of Ophthalmology, pages 672-678, (2011). [doi:10.1016/j.ophtha.2010.08.008; ISSN 0161-6420/11/\$]."	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT <small>(not for submission under 37 CFR 1.99)</small>	Application Number	17/384,070
	Filing Date	Jul-23-2021
	First Named Inventor	Kenneth S. Graham
	Art Unit	1647
	Confirmation Number	1061
	Examiner Name	Lockard, Jon McClelland
	Attorney Docket Number	125984-266215

EXAMINER SIGNATURE			
Examiner Signature		Date Considered	
<p>*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.</p>			
<p>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.</p>			

INFORMATION DISCLOSURE STATEMENT BY APPLICANT <small>(not for submission under 37 CFR 1.99)</small>	Application Number	17/384,070
	Filing Date	Jul-23-2021
	First Named Inventor	Kenneth S. Graham
	Art Unit	1647
	Confirmation Number	1061
	Examiner Name	Lockard, Jon McClelland
	Attorney Docket Number	125984-266215

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.			
☐ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.			
☒ None			
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	/Lance A. Termes/	Date (YYYY-MM-DD)	2023-12-15
Name/Print	Lance A. Termes	Registration Number	43184

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.

**Request
for
Continued Examination (RCE)
Transmittal**

Address to:
Mail Stop RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Application Number	17/384,070
Filing Date	July 23, 2021
First Named Inventor	Kenneth S. Graham
Art Unit	1647
Examiner Name	Jon McClelland Lockard
Attorney Docket Number	125984-266215

This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. See Instruction Sheet for RCEs (not to be submitted to the USPTO) on page 2.

1. **Submission required under 37 CFR 1.114** Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).
- a. ☐ Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.
- i. ☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____
- ii. ☐ Other _____
- b. ☒ Enclosed
- i. ☐ Amendment/Reply
- ii. ☐ Affidavit(s)/ Declaration(s)
- iii. ☒ Information Disclosure Statement (IDS)
- iv. ☐ Other _____
2. **Miscellaneous**
- a. ☐ Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a period of _____ months. (Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)
- b. ☐ Other _____
3. **Fees** The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.
- a. ☒ The Director is hereby authorized to charge the following fees, any underpayment of fees, or credit any overpayments, to Deposit Account No. 500393.
- i. ☒ RCE fee required under 37 CFR 1.17(e)
- ii. ☐ Extension of time fee (37 CFR 1.136 and 1.17)
- iii. ☐ Other _____
- b. ☐ Check in the amount of \$ _____ enclosed
- c. ☐ Payment by credit card (Form PTO-2038 enclosed)
- d. ☒ Payment by USPTO patent electronic filing system.

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.

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

Signature	/Lance A. Termes/	Date	December 15, 2023
Name (Print/Type)	Lance A. Termes	Registration No.	43,184

CERTIFICATE OF MAILING OR TRANSMISSION

I hereby certify that this correspondence is transmitted by the USPTO patent electronic filing system, or by facsimile to (571) 273-8300, to the USPTO, or deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop RCE, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on the date shown below.

Signature	/Lance A. Termes/	Date	December 15, 2023
Name (Print/Type)	Lance A. Termes	Date	December 15, 2023

A Federal agency may not conduct or sponsor, and a person is not required to respond to, nor shall a person be subject to a penalty for failure to comply with an information collection subject to the requirements of the Paperwork Reduction Act of 1995, unless the information collection has a currently valid OMB Control Number. The OMB Control Number for this information collection is 0651-0031. Public burden for this form is estimated to average 12 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the information collection. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden to the Chief Administrative Officer, United States Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450 or email InformationCollection@uspto.gov. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. If filing this completed form by mail, 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.



UNITED STATES
PATENT AND TRADEMARK OFFICE

Page 1 of 2
P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #
17/384,070

RECEIPT DATE / TIME
12/15/2023 12:33:00 PM Z ET

ATTORNEY DOCKET #
-

Title of Invention

Methods for Treating Angiogenic Eye Disorders with High Doses of VEGF Receptor Fusion Proteins

Application Information

APPLICATION TYPE Utility - Nonprovisional Application
under 35 USC 111(a)

PATENT # -

CONFIRMATION # 1061

FILED BY Lance Termes

PATENT CENTER # 63631142

FILING DATE 07/23/2021

CUSTOMER # 147803

FIRST NAMED
INVENTOR Kenneth S. Graham

CORRESPONDENCE
ADDRESS -

AUTHORIZED BY -

Documents

TOTAL DOCUMENTS: 1

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
10430US02__RCE.pdf	1	Request for Continued Examination (RCE)	210 KB

Warning: This is not a USPTO supplied RCE fillable form. Data in the form cannot be automatically loaded to other USPTO systems.

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
10430US02__RCE.pdf	2E97E43431B5CDFDDF788973E5863E67A17F0F6420700EE4E D1CB4CF4E47606A5B0219832A2370C9955D3FCE4586B781368

PGR2026-00039
Biocon Ex.1002
Page 598 of 4945

EA65735289AB6B3B53269473470AC

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 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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PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

ELECTRONIC PAYMENT RECEIPT

APPLICATION # 17/384,070	RECEIPT DATE / TIME 12/15/2023 12:33:00 PM Z ET	ATTORNEY DOCKET # -
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Title of Invention

Methods for Treating Angiogenic Eye Disorders with High Doses of VEGF Receptor Fusion Proteins

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	1061	FILED BY	Lance Termes
PATENT CENTER #	63631142	AUTHORIZED BY	-
CUSTOMER #	147803	FILING DATE	07/23/2021
CORRESPONDENCE ADDRESS	-	FIRST NAMED INVENTOR	Kenneth S. Graham

Payment Information

PAYMENT METHOD DA / 500393	PAYMENT TRANSACTION ID E2023BEC34385021	PAYMENT AUTHORIZED BY Lance Termes
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FEE CODE	DESCRIPTION	ITEM PRICE(\$)	QUANTITY	ITEM TOTAL(\$)
1820	REQUEST FOR CONTINUED EXAMINATION (RCE)- 2ND AND SUBSEQUENT REQUEST (SEE 37 CFR 1.114)	2000.00	1	2000.00
TOTAL AMOUNT:				\$2,000.00

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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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

147803 7590 12/06/2023
Schwabe W&W, PC / Regeneron Pharmaceuticals, Inc.
PacWest Center
1211 SW Fifth Avenue, Suite 1900
Portland, OR 97204

EXAMINER	
LOCKARD, JON MCCLELLAND	
ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 12/06/2023

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/384,070	07/23/2021	Kenneth S. Graham		1061

TITLE OF INVENTION: Methods for Treating Angiogenic Eye Disorders with High Doses of VEGF Receptor Fusion Proteins

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	\$1200	\$0.00	\$1200.00	\$0	03/06/2024

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 40% the amount of undiscounted fees, and micro entity fees are 20% the amount of undiscounted 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. 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 the USPTO patent electronic filing system.

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 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. **Because electronic patent issuance may occur shortly after issue fee payment, any desired continuing application should preferably be filed prior to payment of this issue fee in order not to jeopardize copendency.**

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

147803 7590 12/06/2023
Schwabe W&W, PC / Regeneron Pharmaceuticals, Inc.
PacWest Center
1211 SW Fifth Avenue, Suite 1900
Portland, OR 97204

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 the USPTO patent electronic filing system 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.
17/384,070	07/23/2021	Kenneth S. Graham		1061

TITLE OF INVENTION: Methods for Treating Angiogenic Eye Disorders with High Doses of VEGF Receptor Fusion Proteins

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	\$1200	\$0.00	\$1200.00	\$0	03/06/2024

EXAMINER	ART UNIT	CLASS-SUBCLASS
LOCKARD, JON MCCLELLAND	1647	424-134100

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/AIA/122 or PTO/SB/122) attached.

☐ "Fee Address" indication (or "Fee Address" Indication form PTO/AIA/47 or 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 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)

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

☐ Electronic Payment via the USPTO patent electronic filing system ☐ 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. _____



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.
17/384,070	07/23/2021	Kenneth S. Graham		1061
147803	7590	12/06/2023		
Schwabe W&W, PC / Regeneron Pharmaceuticals, Inc.				
PacWest Center				
1211 SW Fifth Avenue, Suite 1900				
Portland, OR 97204				
			EXAMINER	
			LOCKARD, JON MCCLELLAND	
			ART UNIT	PAPER NUMBER
			1647	

DATE MAILED: 12/06/2023

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. The United States Patent and Trademark Office (USPTO) collects the information in this record under authority of 35 U.S.C. 2. The USPTO's system of records is used to manage all applicant and owner information including name, citizenship, residence, post office address, and other information with respect to inventors and their legal representatives pertaining to the applicant's/owner's activities in connection with the invention for which a patent is sought or has been granted. The applicable Privacy Act System of Records Notice for the information collected in this form is COMMERCE/PAT-TM-7 Patent Application Files, available in the Federal Register at 78 FR 19243 (March 29, 2013).

<https://www.govinfo.gov/content/pkg/FR-2013-03-29/pdf/2013-07341.pdf>

Routine uses of the information in this record may include disclosure to:

- 1) law enforcement, in the event that the system of records indicates a violation or potential violation of law;
- 2) a federal, state, local, or international agency, in response to its request;
- 3) a contractor of the USPTO having need for the information in order to perform a contract;
- 4) the Department of Justice for determination of whether the Freedom of Information Act (FOIA) requires disclosure of the record;
- 5) a Member of Congress submitting a request involving an individual to whom the record pertains, when the individual has requested the Member's assistance with respect to the subject matter of the record;
- 6) a court, magistrate, or administrative tribunal, in the course of presenting evidence, including disclosures to opposing counsel in the course of settlement negotiations;
- 7) the Administrator, General Services Administration (GSA), or their designee, during an inspection of records conducted by GSA under authority of 44 U.S.C. 2904 and 2906, in accordance with the GSA regulations and any other relevant (i.e., GSA or Commerce) directive, where such disclosure shall not be used to make determinations about individuals;
- 8) 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));
- 9) the Office of Personnel Management (OPM) for personnel research purposes; and
- 10) the Office of Management and Budget (OMB) for legislative coordination and clearance.

If you do not furnish the information requested on this form, the USPTO may not be able to process and/or examine your submission, which may result in termination of proceedings, abandonment of the application, and/or expiration of the patent.

Notice of Allowability	Application No. 17/384,070	Applicant(s) Graham et al.	
	Examiner JON M LOCKARD	Art Unit 1647	AIA (FITF) Status Yes

-- 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 the Request for Continued Examination filed 22 November 2023.
☐ 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 See Continuation Sheet . 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)	5. ☒ Examiner's Amendment/Comment
2. ☒ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____.	6. ☒ Examiner's Statement of Reasons for Allowance
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____.	7. ☐ Other _____.
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____.	

/J.L/ Examiner, Art Unit 1647	/CHRISTINE J SAOUD/ Primary Examiner, Art Unit 1645
----------------------------------	--

Continuation of 3. The allowed claim(s) is/are: 30-32 and 53-87)renumbered as claims 1-11,13-14,16,18,20,22,24,12,26,15,17,19,21,23,25 and 27-38, respectively)

Notice of Pre-AIA or AIA Status

1. The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

Continued Examination Under 37 CFR 1.114

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 allowance or after an Office action under *Ex Parte Quayle*, 25 USPQ 74, 453 O.G. 213 (Comm'r Pat. 1935). 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, prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 22 November 2023 has been entered.

Information Disclosure Statement

3. The information disclosure statement (IDS) submitted on 22 November 2023 has been considered by the examiner.

REASONS FOR ALLOWANCE

4. The following is an examiner's statement of reasons for allowance: The information disclosure statement (IDS) submitted on 22 November 2023 has been considered by the Examiner. After careful consideration, the Examiner has determined that none of the information contained therein raises new issues of patentability.

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."

Summary

6. Claims 30-32 and 53-87 are allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **JON M LOCKARD** whose telephone number is **(571) 272-2717**. The examiner can normally be reached M-F 9-6 EST.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at <http://www.uspto.gov/interviewpractice>. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joanne Hama** can be reached on **(571) 272-2911**. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of published or unpublished applications may be obtained from Patent Center. Unpublished application information in Patent Center is available to registered users. To file and manage patent submissions in Patent Center, visit: <https://patentcenter.uspto.gov>. Visit <https://www.uspto.gov/patents/apply/patent-center> for more information about Patent Center and <https://www.uspto.gov/patents/docx> for information about filing in DOCX format. For additional questions, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Christine J Saoud/
Primary Examiner, Art Unit 1645

/J.L./
Examiner, Art Unit 1647
November 29, 2023

Search Notes 	Application/Control No. 17/384,070	Applicant(s)/Patent Under Reexamination Graham et al.
	Examiner JON M LOCKARD	Art Unit 1647

CPC - Searched*		
Symbol	Date	Examiner

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner
NONE		03/16/2023	JML

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

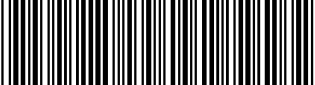
Search Notes		
Search Notes	Date	Examiner
PE2E Search (USPAT, US-PGPUB, EPO, DERWENT): See attached search history.	03/16/2023	JML
STN (MEDLINE, SCISEARCH, EMBASE, BIOSIS): See attached search history.	03/16/2023	JML
PALM: Inventor search.	03/16/2023	JML
PE2E Search (USPAT, US-PGPUB, EPO, DERWENT): See attached search history.	11/01/2023	JML

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<i>Search Notes</i> 	Application/Control No. 17/384,070	Applicant(s)/Patent Under Reexamination Graham et al.
	Examiner JON M LOCKARD	Art Unit 1647

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner
	PE2E Search (USPAT): See attached search history.	08/24/2023	JML
	DAV: Inventor search.	08/24/2023	JML
	PE2E Search (USPAT): See attached search history.	11/01/2023	JML
	DAV: Inventor search.	11/01/2023	JML
	PE2E Search (USPAT): See attached search history.	11/29/2023	JML
	DAV: Inventor search.	11/29/2023	JML

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Issue Classification 	Application/Control No. 17/384,070	Applicant(s)/Patent Under Reexamination Graham et al.
	Examiner JON M LOCKARD	Art Unit 1647

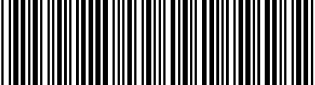
CPC						
Symbol					Type	Version
A61K	/	38	/	179	F	2013-01-01
A61K	/	9	/	0048	I	2013-01-01
A61K	/	47	/	12	I	2013-01-01
A61P	/	27	/	02	I	2018-01-01
A61K	/	47	/	22	I	2013-01-01
A61K	/	47	/	26	I	2013-01-01
A61K	/	47	/	183	I	2013-01-01

CPC Combination Sets							
Symbol				Type	Set	Ranking	Version
	/		/				

/JON M LOCKARD/ Examiner, Art Unit 1647 (Assistant Examiner)	29 November 2023 (Date)	Total Claims Allowed: 38	
/CHRISTINE J SAOUD/ Primary Examiner, Art Unit 1645 (Primary Examiner)	30 November 2023 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure NONE

U.S. Patent and Trademark Office

Part of Paper No.: 20231129

Issue Classification 	Application/Control No. 17/384,070	Applicant(s)/Patent Under Reexamination Graham et al.
	Examiner JON M LOCKARD	Art Unit 1647

INTERNATIONAL CLASSIFICATION			
CLAIMED			
A61K	/	38	/ 17
A61K	/	38	/ 18
C07K	/	14	/ 71
NON-CLAIMED			
	/		/

US ORIGINAL CLASSIFICATION	
CLASS	SUBCLASS

CROSS REFERENCES(S)						
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)					

/JON M LOCKARD/ Examiner, Art Unit 1647 (Assistant Examiner)	29 November 2023 (Date)	Total Claims Allowed: 38	
/CHRISTINE J SAOUD/ Primary Examiner, Art Unit 1645 (Primary Examiner)	30 November 2023 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure NONE

Issue Classification 	Application/Control No. 17/384,070	Applicant(s)/Patent Under Reexamination Graham et al.
	Examiner JON M LOCKARD	Art Unit 1647

☐ 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
1	30	10	59	12	68	28	77	37	86						
2	31	11	60	26	69	29	78	38	87						
3	32	13	61	15	70	30	79								
4	53	14	62	17	71	31	80								
5	54	16	63	19	72	32	81								
6	55	18	64	21	73	33	82								
7	56	20	65	23	74	34	83								
8	57	22	66	25	75	35	84								
9	58	24	67	27	76	36	85								

/JON M LOCKARD/ Examiner, Art Unit 1647 (Assistant Examiner)	29 November 2023 (Date)	Total Claims Allowed: 38	
/CHRISTINE J SAUD/ Primary Examiner, Art Unit 1645 (Primary Examiner)	30 November 2023 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure NONE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (not for submission under 37 CFR 1.99)	Application Number	17/384,070
	Filing Date	Jul-23-2021
	First Named Inventor	Kenneth S. Graham
	Art Unit	1647
	Confirmation Number	1061
	Examiner Name	Lockard, Jon McClelland
	Attorney Docket Number	125984-266215

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

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

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

NON-PATENT LITERATURE DOCUMENTS			
Examiner Initial*	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
/J.L./	560	AusPAR Eylea Afibercept Bayer Australia Ltd., PM-2010-03802-3-5 Final; 30 July 2012, pages 1-24.	
/J.L./	561	Eylea Assessment report; Committee for Medicinal Products for Human Use (CHMP), European Medicines Agency; EMA/646256/2012 corr; 20 September 2012, 1-83 pages.	
/J.L./	562	History of Changes for Study: NCT00383370, "To Access the Safety and Tolerability of Repeated Intravitreal Administration of VEGF Trap in Subjects With Wet AMD," Clinical Trials.gov archive, 1-33 pages; 20 April 2011.	

Receipt date: 11/22/2023

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (not for submission under 37 CFR 1.99)	Application Number	17/384,070
	Filing Date	Jul-23-2021
	First Named Inventor	Kenneth S. Graham
	Art Unit	1647
	Confirmation Number	1061
	Examiner Name	Lockard, Jon McClelland
	Attorney Docket Number	125984-266215

EXAMINER SIGNATURE			
Examiner Signature	/JON M LOCKARD/	Date Considered	11/29/2023
*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.			

PE2E SEARCH - Search History (Prior Art)

/J.L./

There are no Prior Art searches to show.
--

PE2E SEARCH - Search History (Interference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	British Equivalents	Time Stamp
N12	2626	L1	(USPAT)	OR	ON	ON	2023/11/29 10:27 PM
N13	2676	L2	(USPAT)	OR	ON	ON	2023/11/29 10:27 PM
N14	259	L3	(USPAT)	OR	ON	ON	2023/11/29 10:27 PM
N15	110	L4	(USPAT)	OR	ON	ON	2023/11/29 10:27 PM
N16	408	(N1 N2 N3 N4) SAME formulation	(USPAT)	OR	ON	ON	2023/11/29 10:27 PM
N17	12	N5 SAME "high concentration"	(USPAT)	OR	ON	ON	2023/11/29 10:27 PM
N18	25	N5 SAME (8mg OR "8 mg")	(USPAT)	OR	ON	ON	2023/11/29 10:27 PM
N19	1	N5 SAME (8mg OR "8 mg").clm.	(USPAT)	OR	ON	ON	2023/11/29 10:27 PM
N20	17	(graham-k\$-s\$ washawa-s\$).in.	(USPAT)	OR	ON	ON	2023/11/29 10:27 PM
N21	5	N5 AND N9	(USPAT)	OR	ON	ON	2023/11/29 10:27 PM
N22	3	"11730794".pn. "11732024".pn. "11103552".pn.	(US-PGPUB; USPAT)	OR	ON	ON	2023/11/29 10:27 PM

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (not for submission under 37 CFR 1.99)	Application Number	17/384,070
	Filing Date	Jul-23-2021
	First Named Inventor	Kenneth S. Graham
	Art Unit	1647
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	Examiner Name	Lockard, Jon McClelland
	Attorney Docket Number	125984-266215

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

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

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

NON-PATENT LITERATURE DOCUMENTS			
Examiner Initial*	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
	560	AusPAR Eylea Afibercept Bayer Australia Ltd., PM-2010-03802-3-5 Final; 30 July 2012, pages 1-24.	
	561	Eylea Assessment report; Committee for Medicinal Products for Human Use (CHMP), European Medicines Agency; EMA/646256/2012 corr; 20 September 2012, 1-83 pages.	
	562	History of Changes for Study: NCT00383370, "To Access the Safety and Tolerability of Repeated Intravitreal Administration of VEGF Trap in Subjects With Wet AMD," Clinical Trials.gov archive, 1-33 pages; 20 April 2011.	

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	Filing Date	Jul-23-2021
	First Named Inventor	Kenneth S. Graham
	Art Unit	1647
	Confirmation Number	1061
	Examiner Name	Lockard, Jon McClelland
	Attorney Docket Number	125984-266215

EXAMINER SIGNATURE			
Examiner Signature		Date Considered	
<p>*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.</p>			
<p>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.</p>			

INFORMATION DISCLOSURE STATEMENT BY APPLICANT <small>(not for submission under 37 CFR 1.99)</small>	Application Number	17/384,070
	Filing Date	Jul-23-2021
	First Named Inventor	Kenneth S. Graham
	Art Unit	1647
	Confirmation Number	1061
	Examiner Name	Lockard, Jon McClelland
	Attorney Docket Number	125984-266215

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.			
☐ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.			
☒ None			
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	/Lance A. Termes/	Date (YYYY-MM-DD)	2023-11-22
Name/Print	Lance A. Termes	Registration Number	43184

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Kenneth S. Graham, et al. Application No.: 17/384,070 Filed: Jul-23-2021 For: METHODS FOR TREATING ANGIOGENIC EYE DISORDERS WITH HIGH DOSES OF VEGF RECEPTOR FUSION PROTEINS Customer No.: 147803	Confirmation No.: 1061 Examiner: Lockard, Jon McClelland Art Unit: 1647 SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR §1.97 and §1.98 <u>Date of Transmission: November 22, 2023</u>
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Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

The references cited on the attached IDS are being called to the attention of the Examiner. Copies of the references in compliance with the requirements of 37 CFR §1.98(a)(2) are submitted herewith.

It is respectfully requested that the cited references be expressly considered during the prosecution of this application, and the references be made of record therein and appear among the “references cited” on any patent to issue therefrom.

The cited references may include office actions from related cases. The Examiner is encouraged to review the full prosecution history from related cases. Applicant understands

that the prosecution history can be viewed electronically on PALM. Nevertheless, if the Examiner wishes Applicant to provide copies of any documents from related applications to the extent not already provided, he or she is requested to contact the undersigned.

Applicant cites the following applications, which are directed to related subject matter and are commonly owned or under an assignment obligation to be commonly owned:

Attorney Docket No.	Application No.	Filing Date	Publication No.	Status
125984-248591	62/669,506	05-10-2018	N/A	Expired
125984-248592	62/752,127	10-29-2018	N/A	Expired
125984-248593	62/769,876	11-20-2018	N/A	Expired
125984-248594	62/813,882	03-05-2019	N/A	Expired
125984-248595	16/409,631	05-10-2019	US 11,103,552	Issued
125984-248596	PCT/US2019/031879	05-10-2019	WO 2019/217927	Expired
125984-281135	18/367,444	09-12-2023		Pending

As provided for by 37 CFR §1.97(g) and (h), no inference should be made that the information and references cited are prior art merely because they are in this statement and no representation is being made that a search has been conducted or that this statement encompasses all the possible relevant information.

Applicant believes that no fee is required for submission of this statement.

However, if a fee is required in connection with this paper, the Commissioner is authorized to deduct such fee from the undersigned's Deposit Account No. 500393.

Respectfully submitted,

/Lance A. Termes/

Lance A. Termes
Reg. No. 43184

Schwabe Williamson & Wyatt, PC
1211 SW 5th Avenue, Suite 1900
Portland, OR 97204
Tel: 503-222-9981



ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #
17/384,070

RECEIPT DATE / TIME
11/22/2023 11:49:00 AM Z ET

ATTORNEY DOCKET #
-

Title of Invention

Methods for Treating Angiogenic Eye Disorders with High Doses of VEGF Receptor Fusion Proteins

Application Information

APPLICATION TYPE Utility - Nonprovisional Application
under 35 USC 111(a)

PATENT # -

CONFIRMATION # 1061

FILED BY Brandi Henley

PATENT CENTER # 63355282

FILING DATE 07/23/2021

CUSTOMER # 147803

FIRST NAMED INVENTOR Kenneth S. Graham

CORRESPONDENCE ADDRESS -

AUTHORIZED BY Lance Termes

Documents

TOTAL DOCUMENTS: 8

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
10430US02_IDS-Transmittal.pdf	3	Transmittal Letter	20 KB
10430US02_IDS-SB08.pdf	3	Information Disclosure Statement (IDS) Form (SB08)	54 KB
Warning: This is not a USPTO supplied IDS fillable form. Data in the form cannot be automatically loaded to other USPTO systems.			
562_NPL_clearit1b.pdf	33	Non Patent Literature	723 KB
561_NPL_eylea-epar-public-assessment-report_en.pdf	83	Non Patent Literature	1125 KB

560_NPL_auspar-aflibercept-120730_pt4.pdf	33	Non Patent Literature	9605 KB
560_NPL_auspar-aflibercept-120730_pt2.pdf	25	Non Patent Literature	14952 KB
560_NPL_auspar-aflibercept-120730_pt1.pdf	24	Non Patent Literature	17106 KB
560_NPL_auspar-aflibercept-120730_pt3.pdf	30	Non Patent Literature	19687 KB

Digest

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560_NPL_auspar-aflibercept-
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02393818D73958E78619BEBB8880EB9B6E4E5DA5DAAD0DF77
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120730_pt3.pdf9D68F7FC77848EFC287E8C7C0332672420F54C824BEC204D7
973FF82894720B4538E23C66F047A74A5023112CDDDD9C980
C38BBB4795A4FD9BF3B84934CC6266

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 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/E0/903 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

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

ELECTRONIC PAYMENT RECEIPT

APPLICATION #
17/384,070

RECEIPT DATE / TIME
11/22/2023 11:18:32 AM Z ET

ATTORNEY DOCKET #
-

Title of Invention

Methods for Treating Angiogenic Eye Disorders with High Doses of VEGF Receptor Fusion Proteins

Application Information

APPLICATION TYPE Utility - Nonprovisional Application
under 35 USC 111(a)

PATENT # -

CONFIRMATION # 1061

FILED BY Lance Termes

PATENT CENTER # 63354251

AUTHORIZED BY -

CUSTOMER # 147803

FILING DATE 07/23/2021

CORRESPONDENCE ADDRESS -

FIRST NAMED INVENTOR Kenneth S. Graham

Payment Information

PAYMENT METHOD
DA / 500393

PAYMENT TRANSACTION ID
E2023ALB22445348

PAYMENT AUTHORIZED BY
Lance Termes

FEE CODE	DESCRIPTION	ITEM PRICE(\$)	QUANTITY	ITEM TOTAL(\$)
1820	REQUEST FOR CONTINUED EXAMINATION (RCE)- 2ND AND SUBSEQUENT REQUEST (SEE 37 CFR 1.114)	2000.00	1	2000.00
TOTAL AMOUNT:				\$2,000.00

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

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UNITED STATES
PATENT AND TRADEMARK OFFICE

ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #
17/384,070

RECEIPT DATE / TIME
11/22/2023 11:18:32 AM Z ET

ATTORNEY DOCKET #
-

Title of Invention

Methods for Treating Angiogenic Eye Disorders with High Doses of VEGF Receptor Fusion Proteins

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APPLICATION TYPE Utility - Nonprovisional Application
under 35 USC 111(a)

PATENT # -

CONFIRMATION # 1061

FILED BY Lance Termes

PATENT CENTER # 63354251

FILING DATE 07/23/2021

CUSTOMER # 147803

FIRST NAMED INVENTOR Kenneth S. Graham

CORRESPONDENCE ADDRESS -

AUTHORIZED BY -

Documents

TOTAL DOCUMENTS: 1

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
10430US02_RCE.pdf	1	Request for Continued Examination (RCE)	210 KB

Warning: This is not a USPTO supplied RCE fillable form. Data in the form cannot be automatically loaded to other USPTO systems.

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
10430US02_RCE.pdf	3B430BC6A1DEF8DFA00B59019114ACD49DA789D79CC11A94 2260DDFEB0721E082FCFA48BC783A3D1C8B4FCC548756CBA

8ED24C3804A6B9D51A364F5F010B8114

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 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

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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.

**Request
for
Continued Examination (RCE)
Transmittal**

Address to:
Mail Stop RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Application Number	17/384,070
Filing Date	July 23, 2021
First Named Inventor	Kenneth S. Graham
Art Unit	1647
Examiner Name	Jon McClelland Lockard
Attorney Docket Number	125984-266215

This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. See Instruction Sheet for RCEs (not to be submitted to the USPTO) on page 2.

1. **Submission required under 37 CFR 1.114** Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).
- a. ☐ Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.
- i. ☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____
- ii. ☐ Other _____
- b. ☒ Enclosed
- i. ☐ Amendment/Reply
- iii. ☒ Information Disclosure Statement (IDS)
- ii. ☐ Affidavit(s)/ Declaration(s)
- iv. ☐ Other _____
2. **Miscellaneous**
- a. ☐ Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a period of _____ months. (Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)
- b. ☐ Other _____
3. **Fees** The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.
- a. ☒ The Director is hereby authorized to charge the following fees, any underpayment of fees, or credit any overpayments, to Deposit Account No. 500393.
- i. ☒ RCE fee required under 37 CFR 1.17(e)
- ii. ☐ Extension of time fee (37 CFR 1.136 and 1.17)
- iii. ☐ Other _____
- b. ☐ Check in the amount of \$ _____ enclosed
- c. ☐ Payment by credit card (Form PTO-2038 enclosed)
- d. ☒ Payment by USPTO patent electronic filing system.

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.

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

Signature	/Lance A. Termes/	Date	November 22, 2023
Name (Print/Type)	Lance A. Termes	Registration No.	43,184

CERTIFICATE OF MAILING OR TRANSMISSION

I hereby certify that this correspondence is transmitted by the USPTO patent electronic filing system, or by facsimile to (571) 273-8300, to the USPTO, or deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop RCE, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on the date shown below.

Signature	/Lance A. Termes/	Date	November 22, 2023
Name (Print/Type)	Lance A. Termes	Date	November 22, 2023

A Federal agency may not conduct or sponsor, and a person is not required to respond to, nor shall a person be subject to a penalty for failure to comply with an information collection subject to the requirements of the Paperwork Reduction Act of 1995, unless the information collection has a currently valid OMB Control Number. The OMB Control Number for this information collection is 0651-0031. Public burden for this form is estimated to average 12 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the information collection. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden to the Chief Administrative Officer, United States Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450 or email InformationCollection@uspto.gov. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. If filing this completed form by mail, 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.



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

147803 7590 11/08/2023
Schwabe W&W, PC / Regeneron Pharmaceuticals, Inc.
PacWest Center
1211 SW Fifth Avenue, Suite 1900
Portland, OR 97204

EXAMINER

LOCKARD, JON MCCLELLAND

ART UNIT PAPER NUMBER

1647

DATE MAILED: 11/08/2023

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/384,070	07/23/2021	Kenneth S. Graham		1061

TITLE OF INVENTION: Methods for Treating Angiogenic Eye Disorders with High Doses of VEGF Receptor Fusion Proteins

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	\$1200	\$0.00	\$1200.00	\$0	02/08/2024

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 40% the amount of undiscounted fees, and micro entity fees are 20% the amount of undiscounted 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. 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 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. **Because electronic patent issuance may occur shortly after issue fee payment, any desired continuing application should preferably be filed prior to payment of this issue fee in order not to jeopardize copendency.**

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

147803 7590 11/08/2023
Schwabe W&W, PC / Regeneron Pharmaceuticals, Inc.
PacWest Center
1211 SW Fifth Avenue, Suite 1900
Portland, OR 97204

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.
17/384,070	07/23/2021	Kenneth S. Graham		1061

TITLE OF INVENTION: Methods for Treating Angiogenic Eye Disorders with High Doses of VEGF Receptor Fusion Proteins

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	\$1200	\$0.00	\$1200.00	\$0	02/08/2024

EXAMINER	ART UNIT	CLASS-SUBCLASS
LOCKARD, JON MCCLELLAND	1647	424-134100

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/AIA/122 or PTO/SB/122) attached.

☐ "Fee Address" indication (or "Fee Address" Indication form PTO/AIA/47 or 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 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)

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

☐ Electronic Payment via Patent Center or 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. _____



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.
17/384,070	07/23/2021	Kenneth S. Graham		1061
147803	7590	11/08/2023		
Schwabe W&W, PC / Regeneron Pharmaceuticals, Inc.				
PacWest Center				
1211 SW Fifth Avenue, Suite 1900				
Portland, OR 97204				
				EXAMINER
				LOCKARD, JON MCCLELLAND
			ART UNIT	PAPER NUMBER
			1647	

DATE MAILED: 11/08/2023

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.

Notice of Allowability	Application No. 17/384,070	Applicant(s) Graham et al.	
	Examiner JON M LOCKARD	Art Unit 1647	AIA (FITF) Status Yes

-- 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 the Request for Continued Examination filed 11 October 2023.
☐ 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 See Continuation Sheet . 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)	5. ☐ Examiner's Amendment/Comment
2. ☒ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date ____.	6. ☒ Examiner's Statement of Reasons for Allowance
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material ____.	7. ☐ Other ____.
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date ____.	

/J.L/ Examiner, Art Unit 1647	/CHRISTINE J SAOUD/ Primary Examiner, Art Unit 1645
----------------------------------	--

Continuation of 3. The allowed claim(s) is/are: 30-32 and 53-87 (renumbered as claims 1-11, 13-14, 16, 18, 20, 22, 24, 12, 26, 15, 17, 19, 21, 23, 25 and 27-38, respectively)

Notice of Pre-AIA or AIA Status

1. The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

Continued Examination Under 37 CFR 1.114

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 allowance or after an Office action under *Ex Parte Quayle*, 25 USPQ 74, 453 O.G. 213 (Comm'r Pat. 1935). 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, prosecution in this application has been reopened pursuant to 37 CFR 1.114.

Applicant's submission filed on 11 October 2023 has been entered.

Information Disclosure Statement

3. The information disclosure statements (IDS) submitted on 11 October 2023 and 16 October 2023 have been considered by the examiner.

REASONS FOR ALLOWANCE

4. The following is an examiner's statement of reasons for allowance: The information disclosure statements (IDS) submitted on 11 October 2023 and 16 October 2023 have been considered by the Examiner. After careful consideration, the Examiner has determined that none of the information contained therein raises new issues of patentability.

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."

Summary

6. Claims 30-32 and 53-87 are allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **JON M LOCKARD** whose telephone number is **(571) 272-2717**. The examiner can normally be reached M-F 9-6 EST.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at <http://www.uspto.gov/interviewpractice>. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joanne Hama** can be reached on **(571) 272-2911**. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of published or unpublished applications may be obtained from Patent Center. Unpublished application information in Patent Center is available to registered users. To file and manage patent submissions in Patent Center, visit: <https://patentcenter.uspto.gov>. Visit <https://www.uspto.gov/patents/apply/patent-center> for more information about Patent Center and <https://www.uspto.gov/patents/docx> for information about filing in DOCX format. For additional questions, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Christine J Saoud/
Primary Examiner, Art Unit 1645

/J.L./
Examiner, Art Unit 1647
November 1, 2023

<i>Search Notes</i> 	Application/Control No. 17/384,070	Applicant(s)/Patent Under Reexamination Graham et al.
	Examiner JON M LOCKARD	Art Unit 1647

CPC - Searched*		
Symbol	Date	Examiner

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner
NONE		03/16/2023	JML

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

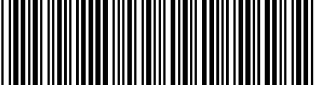
Search Notes		
Search Notes	Date	Examiner
PE2E Search (USPAT, US-PGPUB, EPO, DERWENT): See attached search history.	03/16/2023	JML
STN (MEDLINE, SCISEARCH, EMBASE, BIOSIS): See attached search history.	03/16/2023	JML
PALM: Inventor search.	03/16/2023	JML
PE2E Search (USPAT, US-PGPUB, EPO, DERWENT): See attached search history.	11/01/2023	JML

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<i>Search Notes</i> 	Application/Control No. 17/384,070	Applicant(s)/Patent Under Reexamination Graham et al.
	Examiner JON M LOCKARD	Art Unit 1647

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner
	PE2E Search (USPAT): See attached search history.	08/24/2023	JML
	DAV: Inventor search.	08/24/2023	JML
	PE2E Search (USPAT): See attached search history.	11/01/2023	JML
	DAV: Inventor search.	11/01/2023	JML

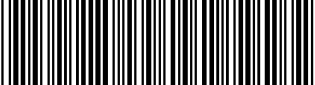
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Issue Classification 	Application/Control No. 17/384,070	Applicant(s)/Patent Under Reexamination Graham et al.
	Examiner JON M LOCKARD	Art Unit 1647

CPC						
Symbol					Type	Version
A61K	/	38	/	179	F	2013-01-01
A61K	/	9	/	0048	I	2013-01-01
A61K	/	47	/	12	I	2013-01-01
A61P	/	27	/	02	I	2018-01-01
A61K	/	47	/	22	I	2013-01-01
A61K	/	47	/	26	I	2013-01-01
A61K	/	47	/	183	I	2013-01-01

CPC Combination Sets							
Symbol				Type	Set	Ranking	Version
	/		/				

/JON M LOCKARD/ Examiner, Art Unit 1647 (Assistant Examiner)	01 November 2023 (Date)	Total Claims Allowed: 38	
/CHRISTINE J SAOUD/ Primary Examiner, Art Unit 1645 (Primary Examiner)	02 November 2023 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure NONE

Issue Classification 	Application/Control No. 17/384,070	Applicant(s)/Patent Under Reexamination Graham et al.
	Examiner JON M LOCKARD	Art Unit 1647

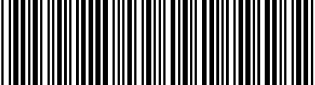
INTERNATIONAL CLASSIFICATION			
CLAIMED			
A61K	/	38	/ 17
A61K	/	38	/ 18
C07K	/	14	/ 71

NON-CLAIMED			
/		/	

US ORIGINAL CLASSIFICATION	
CLASS	SUBCLASS

CROSS REFERENCES(S)						
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)					

/JON M LOCKARD/ Examiner, Art Unit 1647 (Assistant Examiner)	01 November 2023 (Date)	Total Claims Allowed: 38	
/CHRISTINE J SAUD/ Primary Examiner, Art Unit 1645 (Primary Examiner)	02 November 2023 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure NONE

Issue Classification 	Application/Control No. 17/384,070	Applicant(s)/Patent Under Reexamination Graham et al.
	Examiner JON M LOCKARD	Art Unit 1647

☐ 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
1	30	10	59	12	68	28	77	37	86						
2	31	11	60	26	69	29	78	38	87						
3	32	13	61	15	70	30	79								
4	53	14	62	17	71	31	80								
5	54	16	63	19	72	32	81								
6	55	18	64	21	73	33	82								
7	56	20	65	23	74	34	83								
8	57	22	66	25	75	35	84								
9	58	24	67	27	76	36	85								

/JON M LOCKARD/ Examiner, Art Unit 1647 (Assistant Examiner)	01 November 2023 (Date)	Total Claims Allowed: 38	
/CHRISTINE J SAOUD/ Primary Examiner, Art Unit 1645 (Primary Examiner)	02 November 2023 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure NONE

U.S. Patent and Trademark Office

Part of Paper No.: 20231031

PE2E SEARCH - Search History (Prior Art)

/J.L./

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	British Equivalents	Time Stamp
L15	7	"11730794".pn. "11732024".pn. "11103552".pn.	(US-PGPUB; USPAT; EPO; DERWENT)	OR	ON	ON	2023/11/01 03:27 PM
L16	1	wo-2019217927-\$.did.	(US-PGPUB; USPAT; EPO; DERWENT)	OR	ON	ON	2023/11/01 03:27 PM
L17	2	wo-2019217927-\$.did.	(US-PGPUB; USPAT; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); EPO; DERWENT)	OR	ON	ON	2023/11/01 03:55 PM

PE2E SEARCH - Search History (Interference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	British Equivalents	Time Stamp
N11	3	"11730794".pn. "11732024".pn. "11103552".pn.	(US-PGPUB; USPAT)	OR	ON	ON	2023/11/01 04:04 PM

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (not for submission under 37 CFR 1.99)	Application Number	17/384,070
	Filing Date	Jul-23-2021
	First Named Inventor	Kenneth S. Graham
	Art Unit	1647
	Confirmation Number	1061
	Examiner Name	Lockard, Jon McClelland
	Attorney Docket Number	125984-266215

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

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

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

NON-PATENT LITERATURE DOCUMENTS			
Examiner Initial*	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
/J.L./	555	BAKRI et al., "Pharmacokinetics of Intravitreal Ranibizumab (Lucentis)," American Academy of Ophthalmology, Volume 114, Number 12: 2179-2182, (2007). [doi:10.1016/j.ophtha.2007.09.012].	
/J.L./	556	CHOI et al., "Normative Data of Ocular Biometry, Optical Coherence Tomography, and Electrophysiology Conducted for Cynomolgus Macaque Monkeys," Translational Vision Science & Technology, Volume 10 (No. 13) Article 14: 1-11, (2021). [Retrieved from the Internet 10/04/2023: https://doi.org/10.1167/tvst.10.13.14].	

Receipt date: 10/11/2023

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (not for submission under 37 CFR 1.99)	Application Number	17/384,070
	Filing Date	Jul-23-2021
	First Named Inventor	Kenneth S. Graham
	Art Unit	1647
	Confirmation Number	1061
	Examiner Name	Lockard, Jon McClelland
	Attorney Docket Number	125984-266215

EXAMINER SIGNATURE			
Examiner Signature	/JON M LOCKARD/	Date Considered	11/01/2023
*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.			
<p>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.</p>			

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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
/J.L./	557	11,730,794		08-22-2023	Yancopoulos	
/J.L./	558	11,732,024		08-22-2023	Furfine et al.	

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

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

NON-PATENT LITERATURE DOCUMENTS			
Examiner Initial*	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

Receipt date: 10/16/2023

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (not for submission under 37 CFR 1.99)	Application Number	17/384,070
	Filing Date	Jul-23-2021
	First Named Inventor	Kenneth S. Graham
	Art Unit	1647
	Confirmation Number	1061
	Examiner Name	Lockard, Jon McClelland
	Attorney Docket Number	125984-266215

EXAMINER SIGNATURE			
Examiner Signature	/JON M LOCKARD/	Date Considered	11/01/2023
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<p>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.</p>			



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Page 1 of 2

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #
17/384,070

RECEIPT DATE / TIME
10/16/2023 05:30:50 PM ET

ATTORNEY DOCKET #
-

Title of Invention

Methods for Treating Angiogenic Eye Disorders with High Doses of VEGF Receptor Fusion Proteins

Application Information

APPLICATION TYPE Utility - Nonprovisional Application
under 35 USC 111(a)

PATENT # -

CONFIRMATION # 1061

FILED BY Brandi Henley

PATENT CENTER # 63007181

FILING DATE 07/23/2021

CUSTOMER # 147803

FIRST NAMED
INVENTOR Kenneth S. Graham

CORRESPONDENCE
ADDRESS -

AUTHORIZED BY Lance Termes

Documents

TOTAL DOCUMENTS: 2

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
10430US02_IDS-SB08.pdf	3	Information Disclosure Statement (IDS) Form (SB08)	53 KB

Warning: This is not a USPTO supplied IDS fillable form. Data in the form cannot be automatically loaded to other USPTO systems.

10430US02_IDS- Transmittal.pdf	3	Transmittal Letter	20 KB
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Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
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PGR2026-00039
Biocon Ex.1002
Page 652 of 4945

10430US02_IDS-SB08.pdf	D75FFCDDD8CD599D129A960FCB7DEAAACBC66BDB0608D1 B46C0FD7F4E14E0CD679C86EDA244CA973BD94D63943C0A9 A75A1D48A7CF51D49376E051C0967089B8
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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 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.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (not for submission under 37 CFR 1.99)	Application Number	17/384,070
	Filing Date	Jul-23-2021
	First Named Inventor	Kenneth S. Graham
	Art Unit	1647
	Confirmation Number	1061
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	Attorney Docket Number	125984-266215

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
	557	11,730,794		08-22-2023	Yancopoulos	
	558	11,732,024		08-22-2023	Furfine et al.	

U.S. PATENT APPLICATION PUBLICATIONS						
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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

NON-PATENT LITERATURE DOCUMENTS			
Examiner Initial*	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	17/384,070
	Filing Date	Jul-23-2021
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	Art Unit	1647
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	Attorney Docket Number	125984-266215

EXAMINER SIGNATURE			
Examiner Signature		Date Considered	
<p>*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.</p>			
<p>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.</p>			

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	Filing Date	Jul-23-2021
	First Named Inventor	Kenneth S. Graham
	Art Unit	1647
	Confirmation Number	1061
	Examiner Name	Lockard, Jon McClelland
	Attorney Docket Number	125984-266215

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.			
☐ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.			
☒ None			
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	/Lance A. Termes/	Date (YYYY-MM-DD)	2023-10-16
Name/Print	Lance A. Termes	Registration Number	43184

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Kenneth S. Graham, et al. Application No.: 17/384,070 Filed: Jul-23-2021 For: METHODS FOR TREATING ANGIOGENIC EYE DISORDERS WITH HIGH DOSES OF VEGF RECEPTOR FUSION PROTEINS Customer No.: 147803	Confirmation No.: 1061 Examiner: Lockard, Jon McClelland Art Unit: 1647 SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR §1.97 and §1.98 <u>Date of Transmission: October 16, 2023</u>
---	--

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

Commissioner:

The references cited on the attached IDS are being called to the attention of the Examiner. Copies of the references in compliance with the requirements of 37 CFR §1.98(a)(2) are submitted herewith.

It is respectfully requested that the cited references be expressly considered during the prosecution of this application, and the references be made of record therein and appear among the “references cited” on any patent to issue therefrom.

The cited references may include office actions from related cases. The Examiner is encouraged to review the full prosecution history from related cases. Applicant understands

that the prosecution history can be viewed electronically on PALM. Nevertheless, if the Examiner wishes Applicant to provide copies of any documents from related applications to the extent not already provided, he or she is requested to contact the undersigned.

Applicant cites the following applications, which are directed to related subject matter and are commonly owned or under an assignment obligation to be commonly owned:

Attorney Docket No.	Application No.	Filing Date	Publication No.	Status
125984-248591	62/669,506	05-10-2018	N/A	Expired
125984-248592	62/752,127	10-29-2018	N/A	Expired
125984-248593	62/769,876	11-20-2018	N/A	Expired
125984-248594	62/813,882	03-05-2019	N/A	Expired
125984-248595	16/409,631	05-10-2019	US 11,103,552	Issued
125984-248596	PCT/US2019/031879	05-10-2019	WO 2019/217927	Expired
125984-281135	18/367,444	09-12-2023		Pending

As provided for by 37 CFR §1.97(g) and (h), no inference should be made that the information and references cited are prior art merely because they are in this statement and no representation is being made that a search has been conducted or that this statement encompasses all the possible relevant information.

Applicant believes that no fee is required for submission of this statement.

However, if a fee is required in connection with this paper, the Commissioner is authorized to deduct such fee from the undersigned's Deposit Account No. 500393.

Respectfully submitted,

/Lance A. Termes/

Lance A. Termes
Reg. No. 43184

Schwabe Williamson & Wyatt, PC
1211 SW 5th Avenue, Suite 1900
Portland, OR 97204
Tel: 503-222-9981

Doc Code: PET.AUTO Document Description: Petition automatically granted by EFS-Web		PTO/SB/140 U.S. Patent and Trademark Office Department of Commerce	
Electronic Petition Request	PETITION TO WITHDRAW AN APPLICATION FROM ISSUE AFTER PAYMENT OF THE ISSUE FEE UNDER 37 CFR 1.313(c)		
Application Number	17384070		
Filing Date	23-Jul-2021		
First Named Inventor	Kenneth Graham		
Art Unit	1647		
Examiner Name	JON LOCKARD		
Attorney Docket Number			
Title	Methods for Treating Angiogenic Eye Disorders with High Doses of VEGF Receptor Fusion Proteins		
<p>An application may be withdrawn from issue for further action upon petition by the applicant. To request that the Office withdraw an application from issue, applicant must file a petition under this section including the fee set forth in § 1.17(h) and a showing of good and sufficient reasons why withdrawal of the application from issue is necessary.</p> <p>APPLICANT HEREBY PETITIONS TO WITHDRAW THIS APPLICATION FROM ISSUE UNDER 37 CFR 1.313(c).</p> <p>A grantable petition requires the following items:</p> <p>(1) Petition fee; and</p> <p>(2) One of the following reasons:</p> <p>(a) Unpatentability of one or more claims, which must be accompanied by an unequivocal statement that one or more claims are unpatentable, an amendment to such claim or claims, and an explanation as to how the amendment causes such claim or claims to be patentable;</p> <p>(b) Consideration of a request for continued examination in compliance with § 1.114 (for a utility or plant application only); or</p> <p>(c) Express abandonment of the application. Such express abandonment may be in favor of a continuing application, but not a CPA under 37 CFR 1.53(d).</p>			
Petition Fee			
☐ Small Entity			
☐ Micro Entity			
☒ Regular Undiscounted			
Reason for withdrawal from issue			

☐ One or more claims are unpatentable ☒ Consideration of a request for continued examination (RCE) (List of Required Documents and Fees) ☐ Applicant hereby expressly abandons the instant application (any attorney/agent signing for this reason must have power of attorney pursuant to 37 CFR 1.32(b)).	
RCE request, submission, and fee. <div style="display: flex; align-items: flex-start;"> <div style="margin-right: 10px;"> ☒ I certify, in accordance with 37 CFR 1.4(d)(4) that : ☐ Are attached. </div> <div> The RCE request ,submission, and fee have already been filed in the above-identified application on 2023.10.11 </div> </div>	
THIS PORTION MUST BE COMPLETED BY THE SIGNATORY OR SIGNATORIES I certify, in accordance with 37 CFR 1.4(d)(4) that I am:	
☒ An attorney or agent registered to practice before the Patent and Trademark Office who has been given power of attorney in this application. ☐ An attorney or agent registered to practice before the Patent and Trademark Office, acting in a representative capacity. ☐ A sole inventor ☐ A joint inventor; I certify that I am authorized to sign this submission on behalf of all of the inventors as evidenced by the power of attorney in the application ☐ A joint inventor; all of whom are signing this e-petition	
Signature	/Lance A. Termes/
Name	Lance A. Termes
Registration Number	43184

Electronic Patent Application Fee Transmittal				
Application Number:		17384070		
Filing Date:		23-Jul-2021		
Title of Invention:		Methods for Treating Angiogenic Eye Disorders with High Doses of VEGF Receptor Fusion Proteins		
First Named Inventor/Applicant Name:		Kenneth S. Graham		
Filer:		Lance A. Termes		
Attorney Docket Number:				
Filed as Large Entity				
Filing Fees for Utility under 35 USC 111(a)				
Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Basic Filing:				
PETITION FEE- 37 CFR 1.17(H) (GROUP III)	1464	1	140	140
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Extension-of-Time:				
Miscellaneous:				
Total in USD (\$)				140



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

Decision Date : October 11, 2023

In re Application of :

Kenneth S. Graham

DECISION ON PETITION

UNDER CFR 1.313(c)(2)

Application No : 17384070

Filed : 23-Jul-2021

Attorney Docket No :

This is an electronic decision on the petition under 37 CFR 1.313(c)(2), filed October 11, 2023 , to withdraw the above-identified application from issue after payment of the issue fee.

The petition is **GRANTED**.

The above-identified application is withdrawn from issue for consideration of a submission under 37 CFR 1.114 (request for continued examination). See 37 CFR 1.313(c)(2).

Petitioner is advised that the issue fee paid in this application cannot be refunded. If, however, this application is again allowed, petitioner may request that it be applied towards the issue fee required by the new Notice of Allowance.

Telephone inquiries concerning this decision should be directed to the Patent Electronic Business Center (EBC) at 866-217-9197.

This application file is being referred to Technology Center AU 1647 for processing of the request for continuing examination under 37 CFR 1.114 .

Office of Petitions

Electronic Acknowledgement Receipt	
EFS ID:	48705903
Application Number:	17384070
International Application Number:	
Confirmation Number:	1061
Title of Invention:	Methods for Treating Angiogenic Eye Disorders with High Doses of VEGF Receptor Fusion Proteins
First Named Inventor/Applicant Name:	Kenneth S. Graham
Customer Number:	147803
Filer:	Lance A. Termes
Filer Authorized By:	
Attorney Docket Number:	
Receipt Date:	11-OCT-2023
Filing Date:	23-JUL-2021
Time Stamp:	13:04:40
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	\$140
RAM confirmation Number	E20230AD04398657
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	ePetition Request Form	petition-request.pdf	39967	no	2
			9711dc08264e2055b7baaea573c6898c166d0021		
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	38145	no	2
			a8ff2b547d5efd55f2b8c5b9395ff6c6e268163b		
Warnings:					
Information:					
Total Files Size (in bytes):			78112		
<p>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.</p> <p><u>New Applications Under 35 U.S.C. 111</u> 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.</p> <p><u>National Stage of an International Application under 35 U.S.C. 371</u> 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.</p> <p><u>New International Application Filed with the USPTO as a Receiving Office</u> 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.</p>					

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (not for submission under 37 CFR 1.99)	Application Number	17/384,070
	Filing Date	Jul-23-2021
	First Named Inventor	Kenneth S. Graham
	Art Unit	1647
	Confirmation Number	1061
	Examiner Name	Lockard, Jon McClelland
	Attorney Docket Number	125984-266215

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

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

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

NON-PATENT LITERATURE DOCUMENTS			
Examiner Initial*	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
	555	BAKRI et al., "Pharmacokinetics of Intravitreal Ranibizumab (Lucentis)," American Academy of Ophthalmology, Volume 114, Number 12: 2179-2182, (2007). [doi:10.1016/j.ophtha.2007.09.012].	
	556	CHOI et al., "Normative Data of Ocular Biometry, Optical Coherence Tomography, and Electrophysiology Conducted for Cynomolgus Macaque Monkeys," Translational Vision Science & Technology, Volume 10 (No. 13) Article 14: 1-11, (2021). [Retrieved from the Internet 10/04/2023: https://doi.org/10.1167/tvst.10.13.14].	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (not for submission under 37 CFR 1.99)	Application Number	17/384,070
	Filing Date	Jul-23-2021
	First Named Inventor	Kenneth S. Graham
	Art Unit	1647
	Confirmation Number	1061
	Examiner Name	Lockard, Jon McClelland
	Attorney Docket Number	125984-266215

EXAMINER SIGNATURE			
Examiner Signature		Date Considered	
<p>*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.</p>			
<p>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.</p>			

INFORMATION DISCLOSURE STATEMENT BY APPLICANT <small>(not for submission under 37 CFR 1.99)</small>	Application Number	17/384,070
	Filing Date	Jul-23-2021
	First Named Inventor	Kenneth S. Graham
	Art Unit	1647
	Confirmation Number	1061
	Examiner Name	Lockard, Jon McClelland
	Attorney Docket Number	125984-266215

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.			
☐ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.			
☒ None			
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	/Lance A. Termes/	Date (YYYY-MM-DD)	2023-10-11
Name/Print	Lance A. Termes	Registration Number	43184

Electronic Patent Application Fee Transmittal				
Application Number:		17384070		
Filing Date:		23-Jul-2021		
Title of Invention:		Methods for Treating Angiogenic Eye Disorders with High Doses of VEGF Receptor Fusion Proteins		
First Named Inventor/Applicant Name:		Kenneth S. Graham		
Filer:		Lance A. Termes		
Attorney Docket Number:				
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:				
RCE- 1ST REQUEST	1801	1	1360	1360
Total in USD (\$)				1360

Electronic Acknowledgement Receipt	
EFS ID:	48705868
Application Number:	17384070
International Application Number:	
Confirmation Number:	1061
Title of Invention:	Methods for Treating Angiogenic Eye Disorders with High Doses of VEGF Receptor Fusion Proteins
First Named Inventor/Applicant Name:	Kenneth S. Graham
Customer Number:	147803
Filer:	Lance A. Termes
Filer Authorized By:	
Attorney Docket Number:	
Receipt Date:	11-OCT-2023
Filing Date:	23-JUL-2021
Time Stamp:	12:57:37
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	\$1360
RAM confirmation Number	E20230AC58058533
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	Request for Continued Examination (RCE)	10430US02_RCE.pdf	199772	no	1
			f53dc62bd52cb03b6888f18548e4bf330c5652e8		
Warnings:					
This is not a USPTO supplied RCE SB30 form.					
Information:					
2	Transmittal Letter	10430US02_IDS-Transmittal.pdf	21307	no	3
			24fa9008e3c040237fc1c05f28b50fb7c15e3ea7		
Warnings:					
Information:					
3	Information Disclosure Statement (IDS) Form (SB08)	10430US02_IDS-SB08.pdf	55757	no	3
			adc935b715d5da0c9880b4bcf2ea18c030258b97		
Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
4	Non Patent Literature	555_NPL_bakri2007.pdf	119282	no	4
			a7c475dba121ecc4df80166b802eeb436dbbed31		
Warnings:					
Information:					
5	Non Patent Literature	556_NPL_Choi2021.pdf	1475662	no	11
			3eb3fb752bc26ddab48b99c041985a0332ed890b		
Warnings:					
Information:					
6	Fee Worksheet (SB06)	fee-info.pdf	37970	no	2
			8633f342c4002b928b78718d43a6c27514fe7f92		

Warnings:	
Information:	
Total Files Size (in bytes):	1909750
<p>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.</p> <p><u>New Applications Under 35 U.S.C. 111</u> 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.</p> <p><u>National Stage of an International Application under 35 U.S.C. 371</u> 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.</p> <p><u>New International Application Filed with the USPTO as a Receiving Office</u> 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.</p>	

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.

**Request
for
Continued Examination (RCE)
Transmittal**

Address to:
Mail Stop RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Application Number	17/384,070
Filing Date	July 23, 2021
First Named Inventor	Kenneth S. Graham
Art Unit	1647
Examiner Name	Jon McClelland Lockard
Attorney Docket Number	125984-266215

This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. See Instruction Sheet for RCEs (not to be submitted to the USPTO) on page 2.

1. **Submission required under 37 CFR 1.114** Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).
- a. ☐ Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.
- i. ☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____
- ii. ☐ Other _____
- b. ☒ Enclosed
- i. ☐ Amendment/Reply
- iii. ☒ Information Disclosure Statement (IDS)
- ii. ☐ Affidavit(s)/ Declaration(s)
- iv. ☐ Other _____
2. **Miscellaneous**
- a. ☐ Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a period of _____ months. (Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)
- b. ☐ Other _____
3. **Fees** The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.
- a. ☒ The Director is hereby authorized to charge the following fees, any underpayment of fees, or credit any overpayments, to Deposit Account No. 500393.
- i. ☒ RCE fee required under 37 CFR 1.17(e)
- ii. ☐ Extension of time fee (37 CFR 1.136 and 1.17)
- iii. ☐ Other _____
- b. ☐ Check in the amount of \$ _____ enclosed
- c. ☐ Payment by credit card (Form PTO-2038 enclosed)
- d. ☒ Payment by 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.

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

Signature	/Lance A. Termes/	Date	October 11, 2023
Name (Print/Type)	Lance A. Termes	Registration No.	43,184

CERTIFICATE OF MAILING OR TRANSMISSION

I hereby certify that this correspondence is being EFS-Web transmitted to the United States Patent and Trademark Office (USPTO), deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop RCE, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 or facsimile transmitted to the USPTO on the date shown below.

Signature	/Lance A. Termes/	Date	October 11, 2023
Name (Print/Type)	Lance A. Termes	Date	October 11, 2023

A Federal agency may not conduct or sponsor, and a person is not required to respond to, nor shall a person be subject to a penalty for failure to comply with an information collection subject to the requirements of the Paperwork Reduction Act of 1995, unless the information collection has a currently valid OMB Control Number. The OMB Control Number for this information collection is 0651-0031. Public burden for this form is estimated to average 12 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the information collection. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden to the Chief Administrative Officer, United States Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450 or email InformationCollection@uspto.gov. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. If filing this completed form by mail, 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.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Kenneth S. Graham, et al. Application No.: 17/384,070 Filed: Jul-23-2021 For: METHODS FOR TREATING ANGIOGENIC EYE DISORDERS WITH HIGH DOSES OF VEGF RECEPTOR FUSION PROTEINS Customer No.: 147803	Confirmation No.: 1061 Examiner: Lockard, Jon McClelland Art Unit: 1647 SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR §1.97 and §1.98 <u>Date of Transmission: October 11, 2023</u>
---	--

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

Commissioner:

The references cited on the attached IDS are being called to the attention of the Examiner. Copies of the references in compliance with the requirements of 37 CFR §1.98(a)(2) are submitted herewith.

It is respectfully requested that the cited references be expressly considered during the prosecution of this application, and the references be made of record therein and appear among the “references cited” on any patent to issue therefrom.

The cited references may include office actions from related cases. The Examiner is encouraged to review the full prosecution history from related cases. Applicant understands

that the prosecution history can be viewed electronically on PALM. Nevertheless, if the Examiner wishes Applicant to provide copies of any documents from related applications to the extent not already provided, he or she is requested to contact the undersigned.

Applicant cites the following applications, which are directed to related subject matter and are commonly owned or under an assignment obligation to be commonly owned:

Attorney Docket No.	Application No.	Filing Date	Publication No.	Status
125984-248591	62/669,506	05-10-2018	N/A	Expired
125984-248592	62/752,127	10-29-2018	N/A	Expired
125984-248593	62/769,876	11-20-2018	N/A	Expired
125984-248594	62/813,882	03-05-2019	N/A	Expired
125984-248595	16/409,631	05-10-2019	US 11,103,552	Issued
125984-248596	PCT/US2019/031879	05-10-2019	WO 2019/217927	Expired
125984-281135	18/367,444	09-12-2023		Pending

As provided for by 37 CFR §1.97(g) and (h), no inference should be made that the information and references cited are prior art merely because they are in this statement and no representation is being made that a search has been conducted or that this statement encompasses all the possible relevant information.

Applicant believes that no fee is required for submission of this statement.

However, if a fee is required in connection with this paper, the Commissioner is authorized to deduct such fee from the undersigned's Deposit Account No. 500393.

Respectfully submitted,

/Lance A. Termes/

Lance A. Termes
Reg. No. 43184

Schwabe Williamson & Wyatt, PC
1211 SW 5th Avenue, Suite 1900
Portland, OR 97204
Tel: 503-222-9981



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APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/384,070	10/17/2023	11786576		1061

147803 7590 09/27/2023
Schwabe W&W, PC / Regeneron Pharmaceuticals, Inc.
PacWest Center
1211 SW Fifth Avenue, Suite 1900
Portland, OR 97204

ISSUE NOTIFICATION

The projected patent number and issue date are specified above. The patent will issue electronically. The electronically issued patent is the official patent grant pursuant to 35 U.S.C. § 153. The patent may be accessed on or after the issue date through Patent Center at <https://patentcenter.uspto.gov/>. The patent will be available in both the public and the private sides of Patent Center. Further assistance in electronically accessing the patent, or about Patent Center, is available by calling the Patent Electronic Business Center at 1-888-217-9197.

The USPTO is implementing electronic patent issuance with a transition period, during which period the USPTO will mail a ceremonial paper copy of the electronic patent grant to the correspondence address of record. Additional copies of the patent (i.e., certified and presentation copies) may be ordered for a fee from the USPTO's Certified Copy Center at <https://certifiedcopycenter.uspto.gov/index.html>. The Certified Copy Center may be reached at (800)972-6382.

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 130 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 Center (<https://patentcenter.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 Patents Stakeholder Experience (OPSE), Stakeholder Support Division (SSD) at (571)-272-4200.

INVENTOR(s) (Please see PATENT CENTER site <https://patentcenter.uspto.gov> for additional inventors):

Kenneth S. Graham, Pleasant Valley, NY;
Saurabh WADHWA, Nanuet, NY;

APPLICANT(s) (Please see PATENT CENTER site <https://patentcenter.uspto.gov> for additional applicants):

Regeneron Pharmaceuticals, Inc., Tarrytown, NY;

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Receipt date: 12/03/2021

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (not for submission under 37 CFR 1.99)	Application Number	17/384,070
	Filing Date	Jul-23-2021
	First Named Inventor	Kenneth S. Graham
	Art Unit	Not Yet Assigned 1647
	Confirmation Number	1061
	Examiner Name	Not Yet Assigned Jon Lockard
	Attorney Docket Number	125984-266215 / 10430US02

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
	231	5,580,856		12-03-1996	Prestrelski et al.	
	232	6,136,346		10-24-2000	Eljamal et al.	
	101	6,171,586		01-09-2001	Lam et al.	
	102	6,267,958		07-31-2001	Andya et al.	
	233	6,358,530		03-19-2002	Eljamal et al.	
	234	6,582,729		06-24-2003	Eljamal et al.	
	235	6,586,574		07-01-2003	Hansen	
	236	6,652,875		11-25-2003	Bannister	
	103	6,685,940		02-03-2004	Andya et al.	
	034	6,833,349		12-21-2004	Xia et al.	
	237	6,875,432		04-05-2005	Liu et al.	
	035	7,070,959		07-04-2006	Papadopoulos et al.	
	036	7,087,411		08-08-2006	Daly et al.	
	104	7,060,268		06-13-2006	Andya et al.	
	037	7,279,159		10-09-2007	Daly et al.	
	051	7,303,746		12-04-2007	Wiegand et al.	
	056	7,303,747		12-04-2007	Wiegand et al.	
	054	7,306,799		12-11-2007	Wiegand et al.	
	053	7,374,757		05-20-2008	Papadopoulos et al.	
	052	7,374,758		05-20-2008	Papadopoulos et al.	
	055	7,396,664		07-08-2008	Daly et al.	
	045	7,399,612		07-15-2008	Daly et al.	
	046	7,521,049		04-21-2009	Wiegand et al.	
	048	7,524,499		04-28-2009	Papadopoulos et al.	
	064	7,608,261		10-27-2009	Furfine et al.	
	050	7,635,474		12-22-2009	Daly et al.	
	005	7,648,702		01-19-2010	Gombotz et al.	
	105	7,682,609		03-23-2010	Andya et al.	
	047	7,704,500		04-27-2010	Papadopoulos et al.	
	239	7,956,160		06-07-2010	Krishnan et al. 06/2011	
	065	7,807,164		10-05-2010	Furfine et al.	
	238	7,851,443		12-14-2010	Bissery et al.	
	040	7,964,377		06-21-2011	Papadopoulos et al.	

Change(s)
applied
to document,
/C.C.B./
9/13/2023

"FEE ADDRESS" INDICATION FORM

MAIL STOP M CORRESPONDENCE

Fax to: (571) 273-6500

Commissioner for Patents

P.O. Box 1450

Alexandria, VA 22313-1450

For the following listed patents, please recognize as the "Fee Address" under the provisions of 37 C.F.R. 1.363 the address associated with:

CUSTOMER NO. 26693

PATENT NUMBER (if known)	APPLICATION NUMBER
	17/384,070

Date: September 12, 2023

Signed: /Lance A. Termes/
Lance A. Termes

Attorney for Applicant, Registration No. 43,184

Address of signer:

Schwabe, Williamson & Wyatt PC

PacWest Center

1211 SW Fifth Avenue, Ste. 1900

Portland, OR 97204

Tel: Bend Office (541) 749-4044

Fax: Portland Office (503) 796-2900

Electronic Patent Application Fee Transmittal				
Application Number:		17384070		
Filing Date:		23-Jul-2021		
Title of Invention:		Methods for Treating Angiogenic Eye Disorders with High Doses of VEGF Receptor Fusion Proteins		
First Named Inventor/Applicant Name:		Kenneth S. Graham		
Filer:		Lance A. Termes		
Attorney Docket Number:				
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	1200	1200

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Extension-of-Time:				
Miscellaneous:				
Total in USD (\$)				1200

Electronic Acknowledgement Receipt	
EFS ID:	48577191
Application Number:	17384070
International Application Number:	
Confirmation Number:	1061
Title of Invention:	Methods for Treating Angiogenic Eye Disorders with High Doses of VEGF Receptor Fusion Proteins
First Named Inventor/Applicant Name:	Kenneth S. Graham
Customer Number:	147803
Filer:	Lance A. Termes
Filer Authorized By:	
Attorney Docket Number:	
Receipt Date:	12-SEP-2023
Filing Date:	23-JUL-2021
Time Stamp:	22:26:13
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	\$1200
RAM confirmation Number	E20239BM27108904
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)	10430US02_IF_Transmittal.pdf	206451	no	1
			04b56077ce231f8a3227fec177c6a6c51458403d3		
Warnings:					
Information:					
2	Maintenance Fee Address Change	10430US02_Fee_Address.pdf	17333	no	1
			b072f1bef443b188c0fe84fac0eb1be63df68a57		
Warnings:					
Information:					
3	Fee Worksheet (SB06)	fee-info.pdf	37824	no	2
			754bf312032aa6ce0a5091aa1a2f074512db1d5d		
Warnings:					
Information:					
Total Files Size (in bytes):			261608		
<p>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.</p> <p><u>New Applications Under 35 U.S.C. 111</u> 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.</p> <p><u>National Stage of an International Application under 35 U.S.C. 371</u> 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.</p> <p><u>New International Application Filed with the USPTO as a Receiving Office</u> 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.</p>					

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

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CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

147803 7590 09/01/2023
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PacWest Center
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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.

Lance A. Termes	(Typed or printed name)
/Lance A. Termes/	(Signature)
September 12, 2023	(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/384,070	07/23/2021	Kenneth S. Graham		1061

TITLE OF INVENTION: Methods for Treating Angiogenic Eye Disorders with High Doses of VEGF Receptor Fusion Proteins

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	\$1200	\$0.00	\$0.00	\$1200	12/01/2023

EXAMINER	ART UNIT	CLASS-SUBCLASS
LOCKARD, JON MCCLELLAND	1647	424-134100

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/AIA/122 or PTO/SB/122) attached.

☒ "Fee Address" indication (or "Fee Address" indication form PTO/AIA/47 or 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 Schwabe, Williamson & Wyatt PC

2 Thomas Triolo

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

Regeneron Pharmaceuticals, Inc.

(B) RESIDENCE: (CITY and STATE OR COUNTRY)

Tarrytown, NY

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)

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

☒ Electronic Payment via Patent Center or 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. 500393

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 /Lance A. Termes/

Date September 12, 2023

Typed or printed name Lance A. Termes

Registration No. 43,184



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NOTICE OF ALLOWANCE AND FEE(S) DUE

147803 7590 09/01/2023
Schwabe W&W, PC / Regeneron Pharmaceuticals, Inc.
PacWest Center
1211 SW Fifth Avenue, Suite 1900
Portland, OR 97204

EXAMINER

LOCKARD, JON MCCLELLAND

ART UNIT

PAPER NUMBER

1647

DATE MAILED: 09/01/2023

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/384,070	07/23/2021	Kenneth S. Graham		1061

TITLE OF INVENTION: Methods for Treating Angiogenic Eye Disorders with High Doses of VEGF Receptor Fusion Proteins

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	\$1200	\$0.00	\$0.00	\$1200	12/01/2023

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 40% the amount of undiscounted fees, and micro entity fees are 20% the amount of undiscounted 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. 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

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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 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. **Because electronic patent issuance may occur shortly after issue fee payment, any desired continuing application should preferably be filed prior to payment of this issue fee in order not to jeopardize copendency.**

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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.

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

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/384,070	07/23/2021	Kenneth S. Graham		1061

TITLE OF INVENTION: Methods for Treating Angiogenic Eye Disorders with High Doses of VEGF Receptor Fusion Proteins

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	\$1200	\$0.00	\$0.00	\$1200	12/01/2023

EXAMINER	ART UNIT	CLASS-SUBCLASS
LOCKARD, JON MCCLELLAND	1647	424-134100

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/AIA/122 or PTO/SB/122) attached.

☐ "Fee Address" indication (or "Fee Address" Indication form PTO/AIA/47 or 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,

1 _____

(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.

2 _____

3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

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(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)

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

☐ Electronic Payment via Patent Center or 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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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.
17/384,070	07/23/2021	Kenneth S. Graham		1061

147803 7590 09/01/2023
Schwabe W&W, PC / Regeneron Pharmaceuticals, Inc.
PacWest Center
1211 SW Fifth Avenue, Suite 1900
Portland, OR 97204

EXAMINER

LOCKARD, JON MCCLELLAND

ART UNIT	PAPER NUMBER
----------	--------------

1647

DATE MAILED: 09/01/2023

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.

Notice of Allowability	Application No. 17/384,070	Applicant(s) Graham et al.	
	Examiner JON M LOCKARD	Art Unit 1647	AIA (FITF) Status Yes

-- 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 the Amendment filed 01 August 2023.
☐ 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 See Continuation Sheet . 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)	5. ☒ Examiner's Amendment/Comment
2. ☒ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____.	6. ☐ Examiner's Statement of Reasons for Allowance
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____.	7. ☐ Other _____.
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____.	

/J.L/ Examiner, Art Unit 1647	/CHRISTINE J SAOUD/ Primary Examiner, Art Unit 1645
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Continuation of 3. The allowed claim(s) is/are: 30-32 and 53-87 (renumbered as claims 1-11, 13-14, 16, 18, 20, 22, 24, 12, 26, 15, 17, 19, 21, 23, 25 and 27-38, respectively)

Notice of Pre-AIA or AIA Status

1. The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

Terminal Disclaimer

2. The terminal disclaimer filed on 01 August 2023 has been reviewed and is accepted. The terminal disclaimer has been recorded.

Information Disclosure Statement

3. The information disclosure statements (IDS) submitted on 01 August 2023 and 11 August 2023 have been considered by the examiner.

Withdrawn Objections and/or Rejections

4. The objections to the Specification as set forth at pg. 2 of the previous Office action (mailed 22 March 2023) is withdrawn in view of Applicant's amendments to the Specification (filed 01 August 2023).
5. The objection to claim 35 as set forth at pg. 3 of the previous Office action (mailed 22 March 2023) is moot in view of Applicant's cancellation of said claim (filed 01 August 2023).
6. The rejection of claims 30-32, 35 and 39-52 under 35 U.S.C. 112(b) as set forth at pg. 3 of the previous Office action (mailed 22 March 2023) is withdrawn in view of Applicant's amendment to claim 30, the persuasive arguments presented at pg. 9 of the response which

points to a limiting definition in the Specification for the term “at least about”, and cancellation of claims 35 and 39-52 (filed 01 August 2023).

7. The rejection of claims 30-32, 35 and 39-52 under 35 U.S.C. 112(a) as set forth at pg. 3 of the previous Office action (mailed 22 March 2023) is withdrawn in view of Applicant’s amendment to claim 30, the persuasive arguments at pp. 9-10 of the Response, and cancellation of claims 35 and 39-52 (filed 01 August 2023).

8. The rejection of claims 30-32, 35 and 39-52 on the ground of nonstatutory double patenting as set forth at pp. 6-7 of the previous Office action (mailed 22 March 2023) is withdrawn in view of Applicant’s submission of a terminal disclaimer (filed 01 August 2023).

Summary

9. Claims 30-32 and 53-87 are allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **JON M LOCKARD** whose telephone number is **(571) 272-2717**. The examiner can normally be reached M-F 9-6 EST.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at <http://www.uspto.gov/interviewpractice>. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joanne Hama** can be reached on **(571) 272-2911**. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of published or unpublished applications may be obtained from Patent Center. Unpublished application information in Patent Center is available to registered users. To file and manage patent submissions in Patent Center, visit: <https://patentcenter.uspto.gov>. Visit <https://www.uspto.gov/patents/apply/patent-center> for more information about Patent Center and <https://www.uspto.gov/patents/docx> for information about filing in DOCX format. For additional questions, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Christine J Saoud/
Primary Examiner, Art Unit 1645

/J.L./
Examiner, Art Unit 1647
August 25, 2023

Search Notes 	Application/Control No. 17/384,070	Applicant(s)/Patent Under Reexamination Graham et al.
	Examiner JON M LOCKARD	Art Unit 1647

CPC - Searched*		
Symbol	Date	Examiner

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

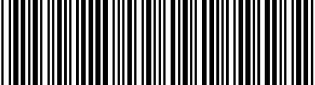
US Classification - Searched*			
Class	Subclass	Date	Examiner
NONE		03/16/2023	JML

* 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
PE2E Search (USPAT, US-PGPUB, EPO, DERWENT): See attached search history.	03/16/2023	JML
STN (MEDLINE, SCISEARCH, EMBASE, BIOSIS): See attached search history.	03/16/2023	JML
PALM: Inventor search.	03/16/2023	JML

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner
	PE2E Search (USPAT): See attached search history.	08/24/2023	JML
	DAV: Inventor search.	08/24/2023	JML

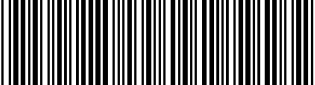
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Issue Classification 	Application/Control No. 17/384,070	Applicant(s)/Patent Under Reexamination Graham et al.
	Examiner JON M LOCKARD	Art Unit 1647

CPC						
Symbol					Type	Version
A61K	/	38	/	179	F	2013-01-01
A61P	/	27	/	02	I	2018-01-01
A61K	/	9	/	0048	I	2013-01-01
A61K	/	47	/	12	I	2013-01-01
A61K	/	47	/	183	I	2013-01-01
A61K	/	47	/	22	I	2013-01-01
A61K	/	47	/	26	I	2013-01-01

CPC Combination Sets							
Symbol				Type	Set	Ranking	Version
	/		/				

/JON M LOCKARD/ Examiner, Art Unit 1647 (Assistant Examiner)	25 August 2023 (Date)	Total Claims Allowed: 38	
/CHRISTINE J SAOUD/ Primary Examiner, Art Unit 1645 (Primary Examiner)	26 August 2023 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure NONE

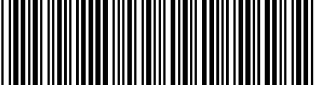
Issue Classification 	Application/Control No. 17/384,070	Applicant(s)/Patent Under Reexamination Graham et al.
	Examiner JON M LOCKARD	Art Unit 1647

INTERNATIONAL CLASSIFICATION			
CLAIMED			
A61K	/	38	/ 17
A61K	/	38	/ 18
C07K	/	14	/ 71
NON-CLAIMED			
	/		/

US ORIGINAL CLASSIFICATION	
CLASS	SUBCLASS

CROSS REFERENCES(S)						
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)					

/JON M LOCKARD/ Examiner, Art Unit 1647 (Assistant Examiner)	25 August 2023 (Date)	Total Claims Allowed: 38	
/CHRISTINE J SAUD/ Primary Examiner, Art Unit 1645 (Primary Examiner)	26 August 2023 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure NONE

Issue Classification 	Application/Control No. 17/384,070	Applicant(s)/Patent Under Reexamination Graham et al.
	Examiner JON M LOCKARD	Art Unit 1647

☐ 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
1	30	10	59	12	68	28	77	37	86						
2	31	11	60	26	69	29	78	38	87						
3	32	13	61	15	70	30	79								
4	53	14	62	17	71	31	80								
5	54	16	63	19	72	32	81								
6	55	18	64	21	73	33	82								
7	56	20	65	23	74	34	83								
8	57	22	66	25	75	35	84								
9	58	24	67	27	76	36	85								

/JON M LOCKARD/ Examiner, Art Unit 1647 (Assistant Examiner)	25 August 2023 (Date)	Total Claims Allowed: 38	
/CHRISTINE J SAOUD/ Primary Examiner, Art Unit 1645 (Primary Examiner)	26 August 2023 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure NONE

U.S. Patent and Trademark Office

Part of Paper No.: 20230824

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (not for submission under 37 CFR 1.99)	Application Number	17/384,070
	Filing Date	Jul-23-2021
	First Named Inventor	Kenneth S. Graham
	Art Unit	1647
	Confirmation Number	1061
	Examiner Name	Lockard, Jon McClelland
	Attorney Docket Number	125984-266215

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
	550	7,070,959		07-04-2006	Papadopoulos	
	524	11,505,593		11-22-2022	Wang et al.	
	525	11,534,396		12-27-2022	Blizzard et al.	
	526	11,542,317		01-03-2023	Wang et al.	
	527	11,559,564		01-24-2023	Yancopoulos	
	528	11,596,667		03-07-2023	Rezaei	
	529	11,666,632		06-06-2023	Brockmeyer et al.	
	530	11,667,702		06-06-2023	Liu et al.	
	531	11,692,027		07-04-2023	Kraft et al.	

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
	549	2005-0032699		02-10-2005	Holash et al.	
	551	2013-0295094		11-07-2013	Yancopoulos	
	532	2018-0298092		10-18-2018	Gekkiva et al.	
	534	2022-0356236		11-10-2022	Bigelow et al.	
	535	2023-0025418		01-26-2023	Wexler-Cohen et al.	
	536	2023-0063116		03-02-2023	Martin et al.	
	537	2023-0089914		03-23-2023	Kansara et al.	

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
	491	102380096	CN	N	04-30-2014	Chengdu Kanghong Biotechnologies Co Ltd.		x
	494	2663325	EP	A1	11-20-2013	Yancopoulos		
	495	3222285	EP	A1	09-27-2017	Yancopoulos		
	496	4147709	EP	A1	03-15-2023	Doyle et al.		

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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
	497	4190310	EP	A1	06-07-2023	Kim et al.		
	538	2019/199476	WO	A1	10-17-2019	AMGEN INC.		
	539	2019/217927	WO	A1	11-14-2019	Regeneron Pharmaceuticals, Inc.		
	540	2022/025660	WO	A1	02-03-2022	CELLTRION INC.		x
	541	2022/229932	WO	A1	11-03-2022	Stefansson		
	542	2022/232790	WO	A1	11-03-2022	ADVERUM BIOTECHNOLOGIES, INC.		
	543	2022/245739	WO	A1	11-24-2022	Regeneron Pharmaceuticals, Inc.		
	544	2023/001288	WO	A1	01-26-2023	BIOHERA SOLUTIONS, LTD.		x
	545	2023/023278	WO	A2	02-23-2023	UNIVERSITY OF UTAH RESEARCH FOUNDATION		
	546	2023/031478	WO	A1	03-09-2023	LEK PHARMACEUTICALS D.D.		
	547	2023/041569	WO	A1	03-23-2023	The Provost, Fellows, Foundation Scholars & the Other Members of Board, of the College of the Holy & Undiv. Trinity of Queen Elizabeth Near Dublin		
	548	2023/075506	WO	A1	05-04-2023	ALTEOGEN INC.		x

NON-PATENT LITERATURE DOCUMENTS					
Examiner Initial*	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
	466	Anonymous, Meeting Archive Titled “PA003 Eighteen-Month Results From an Extension Study of a Phase 2, Dose- and Interval-Ranging Study of VEGF Trap-Eye in Wet AMD,” presented by David S Boyer, MD at Moscone Center (October 2009)			
	467	Anonymous, Meeting Archive Titled “PA080 One-Year Results of a Phase 2 Study of Intravitreal VEGF Trap-Eye in Patients with Neovascular Age-Related Macular Degeneration,” presented by David S Boyer, MD at Georgia World Congress Center (November 2008)			

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NON-PATENT LITERATURE DOCUMENTS			
Examiner Initial*	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
	468	Anonymous, Meeting Archive Titled "PO259 OCT and Fluorescein Angiography Outcomes Through 1 Year for a Phase 2 Study of Intravitreal VEGF Trap-Eye in Neovascular AMD," presented by Peter K Kaiser, MD at Moscone Center (October 2009)	
	469	Anonymous, Meeting Archive Titled "PO260 VEGF Trap-Eye Vision-Specific Quality of Life Through 52 Weeks in Patients with Neovascular AMD in CLEAR-IT 2: A Phase 2 Clinical Trial," presented by Allen C Ho, MD at Moscone Center (October 2009)	
	470	Anonymous, Meeting Archive Titled "PO571 OCT and Fluorescein Angiographic Outcomes Through 1 Year for the Phase 2 Study of Intravitreal VEGF Trap-Eye in Neovascular AMD," presented by Quan Dong Nguyen, MD at Georgia World Congress Center (November 2008)	
	471	Benz et al., "CLEAR-IT-2: Interim Results Of The Phase II, Randomized, Controlled Dose-and Interval-ranging Study Of Repeated Intravitreal VEGF Trap Administration In Patients With Neovascular Age-related Macular Degeneration (AMD)," ARVO Annual Meeting Abstract (May 2007)	
	511	BROWN, "High-Dose Aflibercept - Rationale & Clinical Studies" Houston, TX 9 Feb 2020	
	472	ClinicalTrials.gov Archive, History of Changes for Study: NCT00320775, "Safety and Tolerability Study of Intravitreal VEGF-Trap Administration in Patients With Neovascular AMD," Version 01 (April 28, 2006)	
	473	ClinicalTrials.gov Archive, History of Changes for Study: NCT00320775, "Safety and Tolerability Study of Intravitreal VEGF-Trap Administration in Patients With Neovascular AMD," Version 02 (October 3, 2006)	
	474	ClinicalTrials.gov Archive, History of Changes for Study: NCT00320775, "Safety and Tolerability Study of Intravitreal VEGF-Trap Administration in Patients With Neovascular AMD," Version 03 (July 25, 2007)	
	475	ClinicalTrials.gov Archive, History of Changes for Study: NCT00320775, "Safety and Tolerability Study of Intravitreal VEGF-Trap Administration in Patients With Neovascular AMD," Version 04 (January 23, 2009)	
	476	ClinicalTrials.gov Archive, History of Changes for Study: NCT00320775, "Safety and Tolerability Study of Intravitreal VEGF-Trap Administration in Patients With Neovascular AMD," Version 05 (April 29, 2009)	
	477	ClinicalTrials.gov Archive, History of Changes for Study: NCT00320775, "Safety and Tolerability Study of Intravitreal VEGF-Trap Administration in Patients With Neovascular AMD," Version 06 (January 26, 2010)	
	478	ClinicalTrials.gov Archive, History of Changes for Study: NCT00320775, "Safety and Tolerability Study of Intravitreal VEGF-Trap Administration in Patients With Neovascular AMD," Version 07 (January 25, 2011)	
	479	ClinicalTrials.gov Archive, History of Changes for Study: NCT00320775, "Safety and Tolerability Study of Intravitreal VEGF-Trap Administration in Patients With Neovascular AMD," Version 08 (June 8, 2011)	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (not for submission under 37 CFR 1.99)	Application Number	17/384,070
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NON-PATENT LITERATURE DOCUMENTS			
Examiner Initial*	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
	480	ClinicalTrials.gov Archive, History of Changes for Study: NCT00320775, "Safety and Tolerability Study of Intravitreal VEGF-Trap Administration in Patients With Neovascular AMD," Version 09 (March 16, 2015)	
	481	ClinicalTrials.gov Archive, History of Changes for Study: NCT00320788, "Safety and Efficacy of Repeated Intravitreal Administration of Vascular Endothelial Growth Factor (VEGF) Trap in Patients With Wet Age-Related Macular Degeneration (AMD)," Version 01 (April 28, 2006)	
	482	ClinicalTrials.gov Archive, History of Changes for Study: NCT00320788, "Safety and Efficacy of Repeated Intravitreal Administration of Vascular Endothelial Growth Factor (VEGF) Trap in Patients With Wet Age-Related Macular Degeneration (AMD)," Version 02 (August 1, 2006)	
	483	ClinicalTrials.gov Archive, History of Changes for Study: NCT00320788, "Safety and Efficacy of Repeated Intravitreal Administration of Vascular Endothelial Growth Factor (VEGF) Trap in Patients With Wet Age-Related Macular Degeneration (AMD)," Version 03 (October 3, 2006)	
	484	ClinicalTrials.gov Archive, History of Changes for Study: NCT00320788, "Safety and Efficacy of Repeated Intravitreal Administration of Vascular Endothelial Growth Factor (VEGF) Trap in Patients With Wet Age-Related Macular Degeneration (AMD)," Version 04 (July 24, 2007)	
	485	ClinicalTrials.gov Archive, History of Changes for Study: NCT00320788, "Safety and Efficacy of Repeated Intravitreal Administration of Vascular Endothelial Growth Factor (VEGF) Trap in Patients With Wet Age-Related Macular Degeneration (AMD)," Version 05 (January 23, 2009)	
	486	ClinicalTrials.gov Archive, History of Changes for Study: NCT00320788, "Safety and Efficacy of Repeated Intravitreal Administration of Vascular Endothelial Growth Factor (VEGF) Trap in Patients With Wet Age-Related Macular Degeneration (AMD)," Version 06 (April 28, 2009).	
	487	ClinicalTrials.gov Archive, History of Changes for Study: NCT00320788, "Safety and Efficacy of Repeated Intravitreal Administration of Vascular Endothelial Growth Factor (VEGF) Trap in Patients With Wet Age-Related Macular Degeneration (AMD)," Version 07 (November 30, 2010)	
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (not for submission under 37 CFR 1.99)	Application Number	17/384,070
	Filing Date	Jul-23-2021
	First Named Inventor	Kenneth S. Graham
	Art Unit	1647
	Confirmation Number	1061
	Examiner Name	Lockard, Jon McClelland
	Attorney Docket Number	125984-266215

NON-PATENT LITERATURE DOCUMENTS			
Examiner Initial*	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
	498	Eylea, "Wet AMD: Dosing Flexibility," https://hcp.eylea.us/about/wet-amd-dosing/ (accessed January 5, 2022)	
	499	Eylea Label (revised March 2021), https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125387s069lbl.pdf (accessed September 26, 2022)	
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	Attorney Docket Number	125984-266215

NON-PATENT LITERATURE DOCUMENTS			
Examiner Initial*	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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	523	Tolentino et al., "One-year Results Of The Da Vinci Study of VEGF Trap-Eye In DME," ARVO Annual Meeting Abstract, Investigative Ophthalmology & Visual Science, 52:6646 (April 2011)	

Receipt date: 08/01/2023

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (not for submission under 37 CFR 1.99)	Application Number	17/384,070
	Filing Date	Jul-23-2021
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	Art Unit	1647
	Confirmation Number	1061
	Examiner Name	Lockard, Jon McClelland
	Attorney Docket Number	125984-266215

EXAMINER SIGNATURE			
Examiner Signature	/JON M LOCKARD/	Date Considered	08/24/2023
*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.			
<p>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.</p>			

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	Examiner Name	Jon McClelland Lockard
	Attorney Docket Number	125984-266215

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
/J.L./	553	11707506	B2	07-25-2023	Yancopoulos, George	

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

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
/J.L./	552	2014/005728	WO	A1	01-09-2014	Novartis AG	T ⁵

NON-PATENT LITERATURE DOCUMENTS			
Examiner Initial*	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

Receipt date: 08/11/2023

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (not for submission under 37 CFR 1.99)	Application Number	17/384,070
	Filing Date	Jul-23-2021
	First Named Inventor	Kenneth S. Graham
	Art Unit	1647
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	Examiner Name	Jon McClelland Lockard
	Attorney Docket Number	125984-266215

EXAMINER SIGNATURE		
Examiner Signature	/JON M LOCKARD/	Date Considered 08/24/2023
*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.		
<p>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.</p>		

PE2E SEARCH - Search History (Prior Art)

/J.L./

There are no Prior Art searches to show.
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PE2E SEARCH - Search History (Interference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	British Equivalents	Time Stamp
N1	2547	L1	(USPAT)	OR	ON	ON	2023/08/24 11:38 PM
N2	2551	L2	(USPAT)	OR	ON	ON	2023/08/24 11:38 PM
N3	249	L3	(USPAT)	OR	ON	ON	2023/08/24 11:38 PM
N4	106	L4	(USPAT)	OR	ON	ON	2023/08/24 11:38 PM
N5	393	(N1 N2 N3 N4) SAME formulation	(USPAT)	OR	ON	ON	2023/08/24 11:39 PM
N6	12	N5 SAME "high concentration"	(USPAT)	OR	ON	ON	2023/08/24 11:39 PM
N7	24	N5 SAME (8mg OR "8 mg")	(USPAT)	OR	ON	ON	2023/08/24 11:40 PM
N8	1	N5 SAME (8mg OR "8 mg").clm.	(USPAT)	OR	ON	ON	2023/08/24 11:40 PM
N9	17	(graham-k\$-s\$ washawa-s\$).in.	(USPAT)	OR	ON	ON	2023/08/24 11:41 PM
N10	5	N5 AND N9	(USPAT)	OR	ON	ON	2023/08/24 11:41 PM

Bibliographic Data

Application No: 17/384,070

Foreign Priority claimed: ☐ Yes ☒ No

35 USC 119 (a-d) conditions met: ☐ Yes ☒ No ☐ Met After Allowance

Verified and Acknowledged: /JON M LOCKARD/

Examiner's Signature

Initials

Title:

Methods for Treating Angiogenic Eye Disorders with High Doses of VEGF Receptor Fusion Proteins

FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
07/23/2021	424	1647	125984-266215
RULE			

APPLICANTS

Regeneron Pharmaceuticals, Inc., Tarrytown, NY,

INVENTORS

Kenneth S. Graham, Pleasant Valley, NY, UNITED STATES

Saurabh WADHWA, Nanuet, NY, UNITED STATES

CONTINUING DATA

This application is a CON of 16409631 05/10/2019 PAT 11103552

16409631 has PRO of 62813882 03/05/2019

16409631 has PRO of 62769876 11/20/2018

16409631 has PRO of 62752127 10/29/2018

16409631 has PRO of 62669506 05/10/2018

FOREIGN APPLICATIONS

IF REQUIRED, FOREIGN LICENSE GRANTED**

08/09/2021

STATE OR COUNTRY

UNITED STATES

ADDRESS

Schwabe W&W, PC / Regeneron Pharmaceuticals, Inc.

PacWest Center

1211 SW Fifth Avenue, Suite 1900

Portland, OR 97204

UNITED STATES

FILING FEE RECEIVED

\$1,820



UNITED STATES
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Alexandria, VA 22313 - 1450
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ELECTRONIC PAYMENT RECEIPT

APPLICATION #
17/384,070

RECEIPT DATE / TIME
08/11/2023 12:26:41 PM ET

ATTORNEY DOCKET #
125984-266215

Title of Invention

High Concentration VEGF Receptor Fusion Protein Containing Formulations

Application Information

APPLICATION TYPE Utility - Nonprovisional Application
under 35 USC 111(a)

PATENT # -

CONFIRMATION # 1061

FILED BY Aileen Lee

PATENT CENTER # 62602098

AUTHORIZED BY Lance Termes

CUSTOMER # 147803

FILING DATE 07/23/2021

CORRESPONDENCE ADDRESS -

FIRST NAMED INVENTOR Kenneth S. Graham

Payment Information

PAYMENT METHOD
DA / 500393

PAYMENT TRANSACTION ID
E20238AC27428540

PAYMENT AUTHORIZED BY
Aileen Lee

PRE-AUTHORIZED ACCOUNT
500393

PRE-AUTHORIZED CATEGORY
37 CFR 1.21 (Miscellaneous fees and charges)

FEE CODE	DESCRIPTION	ITEM PRICE(\$)	QUANTITY	ITEM TOTAL(\$)
1806	SUBMISSION OF AN INFORMATION DISCLOSURE STATEMENT	260.00	1	260.00
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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 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.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (not for submission under 37 CFR 1.99)	Application Number	17/384,070
	Filing Date	Jul-23-2021
	First Named Inventor	Kenneth S. Graham
	Art Unit	1647
	Confirmation Number	1061
	Examiner Name	Jon McClelland Lockard
	Attorney Docket Number	125984-266215

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
	553	11707506	B2	07-25-2023	Yancopoulos, George	

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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

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
	552	2014/005728	WO	A1	01-09-2014	Novartis AG		

NON-PATENT LITERATURE DOCUMENTS			
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Examiner Signature		Date Considered	
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<p>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.</p>			

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	Confirmation Number	1061
	Examiner Name	Jon McClelland Lockard
	Attorney Docket Number	125984-266215

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.			
☒ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.			
☐ None			
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	/Lance A. Termes/	Date (YYYY-MM-DD)	2023-08-11
Name/Print	Lance A. Termes	Registration Number	43184

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Kenneth S. Graham, et al.

Application No.: 17/384,070

Filed: Jul-23-2021

For: HIGH CONCENTRATION VEGF
RECEPTOR FUSION PROTEIN
CONTAINING FORMULATIONS

Customer No.: 147803

Confirmation No.: 1061

Examiner: Lockard, Jon McClelland

Art Unit: 1647

**SUPPLEMENTAL INFORMATION
DISCLOSURE STATEMENT UNDER
37 CFR §1.97 and §1.98**

Date of Transmission: August 11, 2023

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

Commissioner:

The references cited on the attached IDS are being called to the attention of the Examiner. Copies of the references in compliance with the requirements of 37 CFR §1.98(a)(2) are submitted herewith.

It is respectfully requested that the cited references be expressly considered during the prosecution of this application, and the references be made of record therein and appear among the “references cited” on any patent to issue therefrom.

The cited references may include office actions from related cases. The Examiner is encouraged to review the full prosecution history from related cases. Applicant understands

that the prosecution history can be viewed electronically on PALM. Nevertheless, if the Examiner wishes Applicant to provide copies of any documents from related applications to the extent not already provided, he or she is requested to contact the undersigned.

Applicant cites the following applications, which are directed to related subject matter and are commonly owned or under an assignment obligation to be commonly owned:

Attorney Docket No.	Application No.	Filing Date	Publication No.	Status
125984-248591	62/669,506	05-10-2018	N/A	Expired
125984-248592	62/752,127	10-29-2018	N/A	Expired
125984-248593	62/769,876	11-20-2018	N/A	Expired
125984-248594	62/813,882	03-05-2019	N/A	Expired
125984-248595	16/409,631	05-10-2019	US 11,103,552	Issued
125984-248596	PCT/US2019/031879	05-10-2019	WO 2019/217927	Expired

As provided for by 37 CFR §1.97(g) and (h), no inference should be made that the information and references cited are prior art merely because they are in this statement and no representation is being made that a search has been conducted or that this statement encompasses all the possible relevant information.

Please charge the IDS fee of \$260 to Deposit Account No. 500393. Please deduct any additional fees from, or credit any overpayment to, the above-noted Deposit Account in connection with this paper.

Respectfully submitted,

/Lance A. Termes/

Lance A. Termes
Reg. No. 43184

Schwabe Williamson & Wyatt, PC
1211 SW 5th Avenue, Suite 1900
Portland, OR 97204
Tel: 503-222-9981



UNITED STATES
PATENT AND TRADEMARK OFFICE

ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #
17/384,070

RECEIPT DATE / TIME
08/11/2023 12:26:41 PM ET

ATTORNEY DOCKET #
125984-266215

Title of Invention

High Concentration VEGF Receptor Fusion Protein Containing Formulations

Application Information

APPLICATION TYPE Utility - Nonprovisional Application
under 35 USC 111(a)

PATENT # -

CONFIRMATION # 1061

FILED BY Aileen Lee

PATENT CENTER # 62602098

FILING DATE 07/23/2021

CUSTOMER # 147803

FIRST NAMED INVENTOR Kenneth S. Graham

CORRESPONDENCE ADDRESS -

AUTHORIZED BY Lance Termes

Documents

TOTAL DOCUMENTS: 3

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
10430US02_IDS-Transmittal.pdf	3	Transmittal Letter	24 KB
10430US02_IDS-SB08.pdf	3	Information Disclosure Statement (IDS) Form (SB08)	54 KB
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New Applications Under 35 U.S.C. 111

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

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New International Application Filed with the USPTO as a Receiving Office

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(71) Applicant (for all designated States except US): **NO-VARTIS AG** [CH/CH]; Lichtstrasse 35, CH-4056 Basel (CH).

(72) Inventors; and

(71) Applicants (for US only): **SIGG, Juergen** [DE/CH]; Novartis Pharma AG, Postfach, CH-4002 Basel (CH). **ROY-ER, Christophe** [FR/DE]; Novartis Pharma AG, Postfach,

CH-4002 Basel (CH). **BRYANT, Andrew Mark** [GB/CH]; Novartis Pharma AG, Postfach, CH-4002 Basel (CH). **BUETTGEN, Heinrich Martin** [DE/CH]; Novartis Pharma AG, Postfach, CH-4002 Basel (CH). **PICCI, Marie** [FR/FR]; Novartis Pharma AG, Postfach, CH-4002 Basel (CH).

(74) Agent: **SPINNER, David Richard**; Novartis Pharma AG, Patent Department, CH-4002 Basel (CH).

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(54) Title: SYRINGE

(57) Abstract: The present invention relates to a syringe, particularly to a small volume syringe such as a syringe suitable for ophthalmic injections.

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SYRINGE

TECHNICAL FIELD

The present invention relates to a syringe, particularly to a small volume syringe such as a syringe suitable for ophthalmic injections.

5 BACKGROUND ART

Many medicaments are delivered to a patient in a syringe from which the user can dispense the medicament. If medicament is delivered to a patient in a syringe it is often to enable the patient, or a caregiver, to inject the medicament. It is important for patient safety and medicament integrity that the syringe and the contents of that syringe are sufficiently sterile to avoid
10 infection, or other, risks for patients. Sterilisation can be achieved by terminal sterilisation in which the assembled product, typically already in its associated packaging, is sterilised using heat or a sterilising gas.

For small volume syringes, for example those for injections into the eye in which it is intended that about 0.1ml or less of liquid is to be injected the sterilisation can pose difficulties that are
15 not necessarily associated with larger syringes. Changes in pressure, internal or external to the syringe, can cause parts of the syringe to move unpredictably, which may alter sealing characteristics and potentially compromise sterility. Incorrect handling of the syringe can also pose risks to product sterility.

Furthermore, certain therapeutics such as biologic molecules are particularly sensitive to
20 sterilisation, be it cold gas sterilisation, thermal sterilisation, or irradiation. Thus, a careful balancing act is required to ensure that while a suitable level of sterilisation is carried out, the syringe remains suitably sealed, such that the therapeutic is not compromised. Of course, the syringe must also remain easy to use, in that the force required to depress the plunger to administer the medicament must not be too high.

25 There is therefore a need for a new syringe construct which provides a robust seal for its content, but which maintains ease of use.

DISCLOSURE OF THE INVENTION

The present invention provides a pre-filled syringe, the syringe comprising a body, a stopper and a plunger, the body comprising an outlet at an outlet end and the stopper being arranged within
30 the body such that a front surface of the stopper and the body define a variable volume chamber

from which a fluid can be expelled through the outlet, the plunger comprising a plunger contact surface at a first end and a rod extending between the plunger contact surface and a rear portion, the plunger contact surface arranged to contact the stopper, such that the plunger can be used to force the stopper towards the outlet end of the body, reducing the volume of the variable volume chamber, characterised in that the fluid comprises an ophthalmic solution. In one embodiment, the ophthalmic solution comprises a VEGF-antagonist.

In one embodiment, the syringe is suitable for ophthalmic injections, more particularly intravitreal injections, and as such has a suitably small volume. The syringe may also be silicone oil free, or substantially silicone oil free, or may comprise a low level of silicone oil as lubricant. In one embodiment, despite the low silicone oil level, the stopper break loose and slide force is less than 20N.

For ophthalmic injections, it is particularly important for the ophthalmic solution to have particularly low particle content. In one embodiment, the syringe meets US Pharmacopeia standard 789 (USP789).

Syringe

The body of the syringe may be a substantially cylindrical shell, or may include a substantially cylindrical bore with a non circular outer shape. The outlet end of the body includes an outlet through which a fluid housed within the variable volume chamber can be expelled as the volume of said chamber is reduced. The outlet may comprise a projection from the outlet end through which extends a channel having a smaller diameter than that of the variable volume chamber. The outlet may be adapted, for example via a luer lock type connection, for connection to a needle or other accessory such as a sealing device which is able to seal the variable volume chamber, but can be operated, or removed, to unseal the variable volume chamber and allow connection of the syringe to another accessory, such as a needle. Such a connection may be made directly between the syringe and accessory, or via the sealing device. The body extends along a first axis from the outlet end to a rear end.

The body may be made from a plastic material (e.g. a cyclic olefin polymer) or from glass and may include indicia on a surface thereof to act as an injection guide. In one embodiment the body may comprise a priming mark. This allows the physician to align a pre-determined part of the stopper (such as the tip of the front surface or one of the circumferential ribs, discussed later) or plunger with the mark, thus expelling excess ophthalmic solution and any air bubbles from the

syringe. The priming process ensures that an exact, pre-determined dosage is administered to the patient.

The stopper may be made from rubber, silicone or other suitable resiliently deformable material. The stopper may be substantially cylindrical and the stopper may include one or more
5 circumferential ribs around an outer surface of the stopper, the stopper and ribs being dimensioned such that the ribs form a substantially fluid tight seal with an internal surface of the syringe body. The front surface of the stopper may be any suitable shape, for example substantially planar, substantially conical or of a domed shape. The rear surface of the stopper may include a substantially central recess. Such a central recess could be used to connect a
10 plunger to the stopper using a snap fit feature or thread connection in a known manner. The stopper may be substantially rotationally symmetric about an axis through the stopper.

The plunger comprises a plunger contact surface and extending from that a rod extends from the plunger contact surface to a rear portion. The rear portion may include a user contact portion adapted to be contacted by a user during an injection event. The user contact portion may
15 comprise a substantially disc shaped portion, the radius of the disc extending substantially perpendicular to the axis along which the rod extends. The user contact portion could be any suitable shape. The axis along which the rod extends may be the first axis, or may be substantially parallel with the first axis.

The syringe may include a backstop arranged at a rear portion of the body. The backstop may be
20 removable from the syringe. If the syringe body includes terminal flanges at the end opposite the outlet end the backstop may be configured to substantially sandwich terminal flanges of the body as this prevent movement of the backstop in a direction parallel to the first axis.

The rod may comprise at least one rod shoulder directed away from the outlet end and the backstop may include a backstop shoulder directed towards the outlet end to cooperate with the
25 rod shoulder to substantially prevent movement of the rod away from the outlet end when the backstop shoulder and rod shoulder are in contact. Restriction of the movement of the rod away from the outlet end can help to maintain sterility during terminal sterilisation operations, or other operations in which the pressure within the variable volume chamber or outside the chamber may change. During such operations any gas trapped within the variable volume chamber, or
30 bubbles that may form in a liquid therein, may change in volume and thereby cause the stopper to move. Movement of the stopper away from the outlet could result in the breaching of a sterility zone created by the stopper. This is particularly important for low volume syringes

where there are much lower tolerances in the component sizes and less flexibility in the stopper. The term sterility zone as used herein is used to refer to the area within the syringe that is sealed by the stopper from access from either end of the syringe. This may be the area between a seal of the stopper, for example a circumferential rib, closest to the outlet and a seal of the stopper, for example a circumferential rib, furthest from the outlet. The distance between these two seals defines the sterility zone of the stopper since the stopper is installed into the syringe barrel in a sterile environment.

To further assist in maintaining sterility during the operations noted above the stopper may comprise at a front circumferential rib and a rear circumferential rib and those ribs may be separated in a direction along the first axis by at least 3mm, by at least 3.5 mm, by at least 3.75mm or by 4mm or more. One or more additional ribs (for example 2, 3, 4 or 5 additional ribs, or between 1-10, 2-8, 3-6 or 4-5 additional ribs) may be arranged between the front and rear ribs. In one embodiment there are a total of three circumferential ribs.

A stopper with such an enhanced sterility zone can also provide protection for the injectable medicament during a terminal sterilisation process. More ribs on the stopper, or a greater distance between the front and rear ribs can reduce the potential exposure of the medicament to the sterilising agent. However, increasing the number of ribs can increase the friction between the stopper and syringe body, reducing ease of use. While this may be overcome by increasing the siliconisation of the syringe, such an increase in silicone oil levels is particularly undesirable for syringes for ophthalmic use.

The rod shoulder may be arranged within the external diameter of the rod, or may be arranged outside the external diameter of the rod. By providing a shoulder that extends beyond the external diameter of the rod, but still fits within the body, the shoulder can help to stabilise the movement of the rod within the body by reducing movement of the rod perpendicular to the first axis. The rod shoulder may comprise any suitable shoulder forming elements on the rod, but in one embodiment the rod shoulder comprises a substantially disc shaped portion on the rod.

In one embodiment of the syringe, when arranged with the plunger contact surface in contact with the stopper and the variable volume chamber is at its intended maximum volume there is a clearance of no more than about 2mm between the rod shoulder and backstop shoulder. In some embodiments there is a clearance of less than about 1.5 mm and in some less than about 1mm. This distance is selected to substantially limit or prevent excessive rearward (away from the outlet end) movement of the stopper.

In one embodiment the variable volume chamber has an internal diameter greater than 5mm or 6mm, or less than 3mm or 4mm. The internal diameter may be between 3mm and 6mm, or between 4mm and 5mm.

5 In another embodiment the syringe is dimensioned so as to have a nominal maximum fill volume of between about 0.1ml and about 1.5ml. In certain embodiments the nominal maximum fill volume is between about 0.5ml and about 1ml. In certain embodiments the nominal maximum fill volume is about 0.5ml or about 1ml, or about 1.5ml.

The length of the body of the syringe may be less than 70mm, less than 60mm or less than 50mm. In one embodiment the length of the syringe body is between 45mm and 50mm.

10 In one embodiment, the syringe is filled with between about 0.01ml and about 1.5ml (for example between about 0.05ml and about 1ml, between about 0.1ml and about 0.5ml, between about 0.15ml and about 0.175ml) of a VEGF antagonist solution. In one embodiment, the syringe is filled with 0.165ml of a VEGF antagonist solution. Of course, typically a syringe is filled with more than the desired dose to be administered to the patient, to take into account
15 wastage due to "dead space" within the syringe and needle. There may also be a certain amount of wastage when the syringe is primed by the physician, so that it is ready to inject the patient.

Thus, in one embodiment, the syringe is filled with a dosage volume (i.e. the volume of medicament intended for delivery to the patient) of between about 0.01ml and about 1.5ml (e.g. between about 0.05ml and about 1ml, between about 0.1ml and about 0.5ml) of a VEGF
20 antagonist solution. In one embodiment, the dosage volume is between about 0.03ml and about 0.05ml. For example, for Lucentis, the dosage volume is 0.05ml or 0.03ml (0.5mg or 0.3mg) of a 10mg/ml injectable medicament solution; for Eylea, the dosage volume is 0.05ml of a 40mg/ml injectable medicament solution. Although unapproved for ophthalmic indications, bevacizumab is used off-label in such ophthalmic indications at a concentration of 25mg/ml; typically at a
25 dosage volume of 0.05ml (1.25mg). In one embodiment, the extractable volume from the syringe (that is the amount of product obtainable from the syringe following filling, taking into account loss due to dead space in the syringe and needle) is about 0.09ml.

In one embodiment the length of the syringe body is between about 45mm and about 50mm, the internal diameter is between about 4mm and about 5mm, the fill volume is between about 0.12
30 and about 0.3ml and the dosage volume is between about 0.03ml and about 0.05ml.

As the syringe contains a medicament solution, the outlet may be reversibly sealed to maintain sterility of the medicament. This sealing may be achieved through the use of a sealing device as is known in the art. For example the OVSTM system which is available from Vetter Pharma International GmbH.

- 5 It is typical to siliconise the syringe in order to allow ease of use, i.e. to apply silicone oil to the inside of the barrel, which decreases the force required to move the stopper. However, for ophthalmic use, it is desirable to decrease the likelihood of silicone oil droplets being injected into the eye. With multiple injections, the amount of silicone droplets can build up in the eye, causing potential adverse effects, including “floaters” and an increase in intra-ocular pressure.
- 10 Furthermore, silicone oil can cause proteins to aggregate. A typical 1ml syringe comprises 100-800µg silicone oil in the barrel, though a survey of manufacturers reported that 500-1000µg was typically used in pre-filled syringes (Badkar *et al.* 2011, AAPS PharmaSciTech, 12(2):564-572). Thus, in one embodiment, a syringe according to the invention comprises less than about 800µg (i.e. about less than about 500µg, less than about 300µg, less than about 200µg, less than about
- 15 100µg, less than about 75µg, less than about 50µg, less than about 25µg, less than about 15µg, less than about 10µg) silicone oil in the barrel. If the syringe comprises a low level of silicone oil, this may be more than about 1µg, more than about 3µg, more than about 5µg, more than about 7µg or more than about 10µg silicone oil in the barrel. Thus, in one embodiment, the syringe may comprise about 1µg-about 500µg, about 3µg-about 200µg, about 5µg-about 100µg
- 20 or about 10µg-about 50µg silicone oil in the barrel. Methods for measuring the amount of silicone oil in such a syringe barrel are known in the art and include, for example, differential weighing methods and quantitation by infrared-spectroscopy of the oil diluted in a suitable solvent. Various types of silicone oil are available, but typically either DC360 (Dow Corning®; with a viscosity of 1000cP) or DC365 emulsion (Dow Corning®; DC360 oil with a viscosity of
- 25 350cP) are used for syringe siliconisation. In one embodiment, the pre-filled syringe of the invention comprises DC365 emulsion.

- During testing it was surprisingly found that, for syringes having small dimensions, such as those discussed above, and particularly those described in conjunction with the Figures below, the break loose and sliding forces for the stopper within the syringe are substantially unaffected by
- 30 reducing the siliconisation levels far below the current standard to the levels discussed here. This is in contrast to conventional thinking that would suggest that if you decrease the silicone oil level, the forces required would increase (see e.g. Schoenknecht, AAPS National Biotechnology Conference 2007 – Abstract no. NBC07-000488, which indicates that while 400µg silicone oil is

acceptable, usability improves when increased to 800 μ g). Having too great a force required to move the stopper can cause problems during use for some users, for example accurate dose setting or smooth dose delivery may be made more difficult if significant strength is required to move, and/or keep in motion, the stopper. Smooth administration is particularly important in sensitive tissues such as the eye, where movement of the syringe during administration could cause local tissue damage. Break loose and slide forces for pre-filled syringes known in the art are typically in the region of less than 20N, but where the pre-filled syringes contain about 100 μ g-about 800 μ g silicone oil. In one embodiment the glide/slide force for the stopper within the pre-filled syringe is less than about 11N or less than 9N, less than 7N, less than 5N or between about 3N to 5N. In one embodiment, the break loose force is less than about 11N or less than 9N, less than 7N, less than 5N or between about 2N to 5N. Note that such measurements are for a filled syringe, rather than an empty syringe. The forces are typically measured at a stopper travelling speed of 190mm/min. In one embodiment, the forces are measured with a 30G x 0.5 inch needle attached to the syringe. In one embodiment, the syringe has a nominal maximal fill volume of between about 0.5ml and 1ml, contains less than about 100 μ g silicone oil and has a break loose force between about 2N to 5N.

In one embodiment the syringe barrel has an internal coating of silicone oil that has an average thickness of about 450nm or less (i.e. 400nm or less, 350nm or less, 300nm or less, 200nm or less, 100nm or less, 50nm or less, 20nm or less). Methods to measure the thickness of silicone oil in a syringe are known in the art and include the rap.ID Layer Explorer® Application, which can also be used to measure the mass of silicone oil inside a syringe barrel.

In one embodiment, the syringe is silicone oil free, or substantially silicone oil free. Such low silicone oil levels can be achieved by using uncoated syringe barrels and/or by avoiding the use of silicone oil as a lubricant for product contacting machine parts, or pumps in the syringe assembly and fill line. A further way to reduce silicone oil and inorganic silica levels in a pre-filled syringe is to avoid the use of silicone tubing in filling lines, for example between storage tanks and pumps.

The syringe according to the invention may also meet certain requirements for particulate content. In one embodiment, the ophthalmic solution comprises no more than 2 particles $\geq 50\mu$ m in diameter per ml. In one embodiment, the ophthalmic solution comprises no more than 5 particles $\geq 25\mu$ m in diameter per ml. In one embodiment, the ophthalmic solution comprises no more than 50 particles $\geq 10\mu$ m in diameter per ml. In one embodiment, the ophthalmic solution

comprises no more than 2 particles $\geq 50\mu\text{m}$ in diameter per ml, no more than 5 particles $\geq 25\mu\text{m}$ in diameter per ml and no more than 50 particles $\geq 10\mu\text{m}$ in diameter per ml. In one embodiment, a syringe according to the invention meets USP789 (United States Pharmacopoeia: Particulate Matter in Ophthalmic Solutions). In one embodiment the syringe has low levels of silicone oil
 5 sufficient for the syringe to meet USP789.

VEGF Antagonists

Antibody VEGF antagonists

VEGF is a well-characterised signal protein which stimulates angiogenesis. Two antibody VEGF antagonists have been approved for human use, namely ranibizumab (Lucentis®) and
 10 bevacizumab (Avastin®).

Non-Antibody VEGF antagonists

In one aspect of the invention, the non-antibody VEGF antagonist is an immunoadhesin. One such immunoadhesin is aflibercept (Eylea®), which has recently been approved for human use and is also known as VEGF-trap (Holash *et al.* (2002) *PNAS USA* 99:11393-98; Riely & Miller
 15 (2007) *Clin Cancer Res* 13:4623-7s). Aflibercept is the preferred non-antibody VEGF antagonist for use with the invention. Aflibercept is a recombinant human soluble VEGF receptor fusion protein consisting of portions of human VEGF receptors 1 and 2 extracellular domains fused to the Fc portion of human IgG1. It is a dimeric glycoprotein with a protein molecular weight of 97 kilodaltons (kDa) and contains glycosylation, constituting an additional 15% of the total
 20 molecular mass, resulting in a total molecular weight of 115 kDa. It is conveniently produced as a glycoprotein by expression in recombinant CHO K1 cells. Each monomer can have the following amino acid sequence (SEQ ID NO: 1):

SDTGRPFVEMYSEIPEIIHMTGRELVIPCRVTSPNITVTLKKFPLDTLIPDGKRIIWDNRKGFIIISNATY
 KEIGLLTCEATVNGHLYKTNYLTHRQTNTIIDVVLSPSHGIELSVGEKLVNCTARTELVNGIDFNWEYPS
 25 SKHQHKKLVNRDLKTQSGSEMKKFLSTLTIDGVTRSDQGLYTCAASSGLMTKKNSTFVRVHEKDKTHTCP
 CPAPELLGGPSVFLFPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNST
 YRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVK
 GFYPSTDAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVVFSCSVMHEALHNHYTQKSL
 SLSPG

30 and disulfide bridges can be formed between residues 30-79, 124-185, 246-306 and 352-410 within each monomer, and between residues 211-211 and 214-214 between the monomers.

Another non-antibody VEGF antagonist immunoaderin currently in pre-clinical development is a recombinant human soluble VEGF receptor fusion protein similar to VEGF-trap containing extracellular ligand-binding domains 3 and 4 from VEGFR2/KDR, and domain 2 from VEGFR1/Flt-1; these domains are fused to a human IgG Fc protein fragment (Li et al., 2011 *Molecular Vision* 17:797-803). This antagonist binds to isoforms VEGF-A, VEGF-B and VEGF-C. The molecule is prepared using two different production processes resulting in different glycosylation patterns on the final proteins. The two glycoforms are referred to as KH902 (conbercept) and KH906. The fusion protein can have the following amino acid sequence (SEQ ID NO:2):

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10      MVS YWDTGVLLCALLSCLLLTGSSSGGRPFVEMYSEIPEIIHMTGRELVIPCRVTSFNITVTLKKFPLDT
      LIPDGKRIIWDSRKGFIISNATYKEIGLLTCEATVNGHLYKTNLYTHRQTNTIIDVVLSPSHGIELSVGEK
      LVLNCTARTELVNIGIDFNWEYPSSKHQHKLLVNRDLKTQSGSEMKKFLSTLTIDGVTRSDQGLYTCAASSG
      LMTKKNSTFVRVHEKPFVAFSGMESLVEATVGERVRLPAKYLGYPPPEIKWYKNGIPLSNHTIKAGHVL
      TIMEVSEKDTGNYTVILTNPISKEKQSHVSVLVVYVPPGPGDKTHTCPLCPAPELLGGPSVFLFPKPKDT
15      LMSIRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKC
      KVSNAKALPAIEKTIKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK
      ATPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGK

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and, like VEGF-trap, can be present as a dimer. This fusion protein and related molecules are further characterized in EP1767546.

Other non-antibody VEGF antagonists include antibody mimetics (e.g. Affibody® molecules, affilins, affitins, anticalins, avimers, Kunitz domain peptides, and monobodies) with VEGF antagonist activity. This includes recombinant binding proteins comprising an ankyrin repeat domain that binds VEGF-A and prevents it from binding to VEGFR-2. One example for such a molecule is DARPin® MP0112. The ankyrin binding domain may have the following amino acid sequence (SEQ ID NO: 3):

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      GSDLGKKLLEAARAGQDDEVRLMANGADVNTADSTGWTPLHLAVPWGHLEIVEVLLKYGADVNAKDFQGW
      TPLHLAAAGHGEIVEVLLKNGADVNAQDKFGKTAFDISIDNGNEDLAEILQKAA

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Recombinant binding proteins comprising an ankyrin repeat domain that binds VEGF-A and prevents it from binding to VEGFR-2 are described in more detail in WO2010/060748 and WO2011/135067.

Further specific antibody mimetics with VEGF antagonist activity are the 40 kD pegylated anticalin PRS-050 and the monobody angiocept (CT-322).

The afore-mentioned non-antibody VEGF antagonist may be modified to further improve their pharmacokinetic properties or bioavailability. For example, a non-antibody VEGF antagonist may be chemically modified (e.g., pegylated) to extend its *in vivo* half-life. Alternatively or in addition, it may be modified by glycosylation or the addition of further glycosylation sites not present in the protein sequence of the natural protein from which the VEGF antagonist was derived.

5 Variants of the above-specified VEGF antagonists that have improved characteristics for the desired application may be produced by the addition or deletion of amino acids. Ordinarily, these amino acid sequence variants will have an amino acid sequence having at least 60% amino acid sequence identity with the amino acid sequences of SEQ ID NO: 1, SEQ ID NO: 2 or SEQ ID NO: 3, preferably at least 80%, more preferably at least 85%, more preferably at least 90%, and most preferably at least 95%, including for example, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, and 100%. Identity or homology with respect to this sequence is defined herein as the percentage of amino acid residues in the candidate sequence that are identical with SEQ ID NO: 1, SEQ ID NO: 2 or SEQ ID NO: 3, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity, and not considering any conservative substitutions as part of the sequence identity.

Sequence identity can be determined by standard methods that are commonly used to compare the similarity in position of the amino acids of two polypeptides. Using a computer program such as BLAST or FASTA, two polypeptides are aligned for optimal matching of their respective amino acids (either along the full length of one or both sequences or along a predetermined portion of one or both sequences). The programs provide a default opening penalty and a default gap penalty, and a scoring matrix such as PAM 250 [a standard scoring matrix; see Dayhoff et al., in Atlas of Protein Sequence and Structure, vol. 5, supp. 3 (1978)] can be used in conjunction with the computer program. For example, the percent identity can then be calculated as: the total number of identical matches multiplied by 100 and then divided by the sum of the length of the longer sequence within the matched span and the number of gaps introduced into the longer sequences in order to align the two sequences.

30 Preferably, the non-antibody VEGF antagonist of the invention binds to VEGF via one or more protein domain(s) that are not derived from the antigen-binding domain of an antibody. The non-

antibody VEGF antagonist of the invention are preferably proteinaceous, but may include modifications that are non-proteinaceous (e.g., pegylation, glycosylation).

Therapy

The syringe of the invention may be used to treat an ocular disease, including but not limited to
5 choroidal neovascularisation, age-related macular degeneration (both wet and dry forms),
macular edema secondary to retinal vein occlusion (RVO) including both branch RVO (bRVO)
and central RVO (cRVO), choroidal neovascularisation secondary to pathologic myopia (PM),
diabetic macular edema (DME), diabetic retinopathy, and proliferative retinopathy.

Thus the invention provides a method of treating a patient suffering from of an ocular disease
10 selected from choroidal neovascularisation, wet age-related macular degeneration, macular
edema secondary to retinal vein occlusion (RVO) including both branch RVO (bRVO) and
central RVO (cRVO), choroidal neovascularisation secondary to pathologic myopia (PM),
diabetic macular edema (DME), diabetic retinopathy, and proliferative retinopathy, comprising
the step of administering an ophthalmic solution to the patient using a pre-filled syringe of the
15 invention. This method preferably further comprises an initial priming step in which the
physician depresses the plunger of the pre-filled syringe to align the pre-determined part of the
stopper with the priming mark.

In one embodiment, the invention provides a method of treating an ocular disease selected from
choroidal neovascularisation, wet age-related macular degeneration, macular edema secondary to
20 retinal vein occlusion (RVO) including both branch RVO (bRVO) and central RVO (cRVO),
choroidal neovascularisation secondary to pathologic myopia (PM), diabetic macular edema
(DME), diabetic retinopathy, and proliferative retinopathy, comprising administering a non-
antibody VEGF antagonist with a pre-filled syringe of the invention, wherein the patient has
previously received treatment with an antibody VEGF antagonist.

Kits

Also provided are kits comprising the pre-filled syringes of the invention. In one embodiment,
such a kit comprises a pre-filled syringe of the invention in a blister pack. The blister pack may
itself be sterile on the inside. In one embodiment, syringes according to the invention may be
placed inside such blister packs prior to undergoing sterilisation, for example terminal
30 sterilisation.

Such a kit may further comprise a needle for administration of the VEGF antagonist. If the VEGF antagonist is to be administered intravitreally, it is typical to use a 30-gauge x ½ inch needle, though 31-gauge and 32-gauge needles may be used. For intravitreal administration, 33-gauge or 34-gauge needles could alternatively be used. Such kits may further comprise instructions for use. In one embodiment, the invention provides a carton containing a pre-filled syringe according to the invention contained within a blister pack, a needle and optionally instructions for administration.

Sterilisation

As noted above, a terminal sterilisation process may be used to sterilise the syringe and such a process may use a known process such as an ethylene oxide (EtO) or a hydrogen peroxide (H₂O₂) sterilisation process. Needles to be used with the syringe may be sterilised by the same method, as may kits according to the invention.

The package is exposed to the sterilising gas until the outside of the syringe is sterile. Following such a process, the outer surface of the syringe may remain sterile (whilst in its blister pack) for up to 6 months, 9 months, 12 months, 15 months, 18 months, 24 months or longer. Thus, in one embodiment, a syringe according to the invention (whilst in its blister pack) may have a shelf life of up to 6 months, 9 months, 12 months, 15 months, 18 months, 24 months or longer. In one embodiment, less than one syringe in a million has detectable microbial presence on the outside of the syringe after 18 months of storage. In one embodiment, the pre-filled syringe has been sterilised using EtO with a Sterility Assurance Level of at least 10⁻⁶. In one embodiment, the pre-filled syringe has been sterilised using hydrogen peroxide with a Sterility Assurance Level of at least 10⁻⁶. Of course, it is a requirement that significant amounts of the sterilising gas should not enter the variable volume chamber of the syringe. The term "significant amounts" as used herein refers to an amount of gas that would cause unacceptable modification of the ophthalmic solution within the variable volume chamber. In one embodiment, the sterilisation process causes ≤10% (preferably ≤5%, ≤3%, ≤1%) alkylation of the VEGF antagonist. In one embodiment, the pre-filled syringe has been sterilised using EtO, but the outer surface of the syringe has ≤1ppm, preferably ≤0.2ppm EtO residue. In one embodiment, the pre-filled syringe has been sterilised using hydrogen peroxide, but the outer surface of the syringe has ≤1ppm, preferably ≤0.2ppm hydrogen peroxide residue. In another embodiment, the pre-filled syringe has been sterilised using EtO, and the total EtO residue found on the outside of the syringe and inside of the blister pack is ≤0.1mg. In another embodiment, the pre-filled syringe has been sterilised using hydrogen

peroxide, and the total hydrogen peroxide residue found on the outside of the syringe and inside of the blister pack is $\leq 0.1\text{mg}$.

General

The term “comprising” means “including” as well as “consisting” *e.g.* a composition
5 “comprising” X may consist exclusively of X or may include something additional *e.g.* X + Y.

The term “about” in relation to a numerical value *x* means, for example, $x \pm 10\%$.

References to a percentage sequence identity between two amino acid sequences means that, when aligned, that percentage of amino acids are the same in comparing the two sequences. This alignment and the percent homology or sequence identity can be determined using software
10 programs known in the art, for example those described in section 7.7.18 of *Current Protocols in Molecular Biology* (F.M. Ausubel *et al.*, eds., 1987) Supplement 30. A preferred alignment is determined by the Smith-Waterman homology search algorithm using an affine gap search with a gap open penalty of 12 and a gap extension penalty of 2, BLOSUM matrix of 62. The Smith-Waterman homology search algorithm is disclosed in Smith & Waterman (1981) *Adv. Appl.*
15 *Math.* 2: 482-489

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 shows a side view of a syringe

Figure 2 shows a cross section of a top down view of a syringe

20 Figure 3 shows a view of a plunger

Figure 4 shows a cross section through a plunger

Figure 5 shows a stopper

MODES FOR CARRYING OUT THE INVENTION

The invention will now be further described, by way of example only, with reference to the drawings.

Figure 1 shows a view from a side of a syringe 1 comprising a body 2, plunger 4, backstop 6 and a
5 sealing device 8.

Figure 2 shows a cross section through the syringe 1 of Figure 1 from above. The syringe 1 is suitable for use in an ophthalmic injection. The syringe 1 comprises a body 2, a stopper 10 and a plunger 4. The syringe 1 extends along a first axis A. The body 2 comprises an outlet 12 at an outlet end 14 and the stopper 10 is arranged within the body 2 such that a front surface 16 of the
10 stopper 10 and the body 2 define a variable volume chamber 18. The variable volume chamber 18 contains an injectable medicament 20 comprising an ophthalmic solution comprising a VEGF antagonist such as ranibizumab. The injectable fluid 20 can be expelled through the outlet 12 by movement of the stopper 10 towards the outlet end 14 thereby reducing the volume of the variable volume chamber 18. The plunger 4 comprises a plunger contact surface 22 at a first end 24 and a
15 rod 26 extending between the plunger contact surface 22 and a rear portion 25. The plunger contact surface 22 is arranged to contact the stopper 10, such that the plunger 4 can be used to move the stopper 10 towards the outlet end 14 of the body 2. Such movement reduces the volume of the variable volume chamber 18 and causes fluid therein to be expelled through the outlet.

The backstop 6 is attached to the body 2 by coupling to a terminal flange 28 of the body 2. The
20 backstop 6 includes sandwich portion 30 which is adapted to substantially sandwich at least some of the terminal flange 28 of the body 2. The backstop 6 is adapted to be coupled to the body 2 from the side by leaving one side of the backstop 6 open so that the backstop 6 can be fitted to the syringe 2.

The body 2 defines a substantially cylindrical bore 36 which has a bore radius. The rod 26
25 comprises a rod shoulder 32 directed away from the outlet end 14. The rod shoulder 32 extends from to a rod shoulder radius from the first axis A which is such that it is slightly less than the bore radius so that the shoulder fits within the bore 36. The backstop 6 includes a backstop shoulder 34 directed towards the outlet end 14. The shoulders 32, 34 are configured to cooperate to substantially prevent movement of the rod 26 away from the outlet end 14 when the backstop
30 shoulder 34 and rod shoulder 32 are in contact. The backstop shoulder 34 extends from outside the bore radius to a radius less than the rod shoulder radius so that the rod shoulder 32 cannot pass the

backstop shoulder 34 by moving along the first axis A. In this case the rod shoulder 32 is substantially disc, or ring, shaped and the backstop shoulder 34 includes an arc around a rear end 38 of the body 2.

5 The backstop 6 also includes two finger projections 40 which extend in opposite directions away from the body 2 substantially perpendicular to the first axis A to facilitate manual handling of the syringe 1 during use.

In this example the syringe comprises a 0.5ml body 2 filled with between about 0.1 and 0.3 ml of an injectable medicament 20 comprising a 10mg/ml injectable solution comprising ranibizumab. The syringe body 2 has an internal diameter of about between about 4.5mm and 4.8mm, a length of
10 between about 45mm and 50mm.

The plunger 4 and stopper 10 will be described in more detail with reference to later figures.

Figure 3 shows a perspective view of the plunger 4 of Figure 1 showing the plunger contact surface 22 at the first end 24 of the plunger 4. The rod 26 extends from the first end 24 to the rear portion 25. The rear portion 25 includes a disc shaped flange 42 to facilitate user handling of the device.
15 The flange 42 provides a larger surface area for contact by the user than a bare end of the rod 26.

Figure 4 shows a cross section through a syringe body 2 and rod 26. The rod 26 includes four longitudinal ribs 44 and the angle between the ribs is 90°.

Figure 5 shows a detailed view of a stopper 10 showing a conical shaped front surface 16 and three circumferential ribs 52,54,56 around a substantially cylindrical body 58. The axial gap between the
20 first rib 52 and the last rib 56 is about 3mm. The rear surface 60 of the stopper 10 includes a substantially central recess 62. The central recess 62 includes an initial bore 64 having a first diameter. The initial bore 64 leading from the rear surface 60 into the stopper 10 to an inner recess 66 having a second diameter, the second diameter being larger than the first diameter.

25 *Stopper movement forces*

0.5ml syringes siliconised with <100µg silicone oil, filled with Lucentis, comprising one of two different stopper designs were tested for maximal and average break out and slide force. Prior to testing, 30G x 0.5" needles were attached to the syringes. The testing was carried out at a stopper speed of 190mm/min over a travel length of 10.9mm. Stopper design 2 had a 45% increase in the
30 distance between the front circumferential rib and rear circumferential rib.

		Stopper design 1			Stopper design 2	
		Batch A	Batch B	Batch C	Batch D	Batch E
Break loose force of syringes	Average of 10 syringes	2.2N	2.3N	1.9N	2.1N	2.5N
	Max individual value	2.5N	2.5N	2.3N	2.6N	2.7N
Sliding force	Average of 10 syringes	3.1N	3.2N	3.1N	4.1N	4.6N
	Max individual value	3.5N	3.5N	3.6N	4.7N	4.8N

For both stopper designs, average and maximum break out force remained below 3N. For both stopper designs, average and maximum sliding force remained below 5N.

It will be understood that the invention has been described by way of example only and
5 modifications may be made whilst remaining within the scope and spirit of the invention.

CLAIMS

1. A pre-filled syringe, the syringe comprising a glass body, a stopper and a plunger, the body comprising an outlet at an outlet end and the stopper being arranged within the body such that a front surface of the stopper and the body define a variable volume chamber from which a fluid can be expelled through the outlet, the plunger comprising a plunger contact surface at a first end and a rod extending between the plunger contact surface and a rear portion, the plunger contact surface arranged to contact the stopper, such that the plunger can be used to force the stopper towards the outlet end of the body, reducing the volume of the variable volume chamber, characterised in that the fluid is an ophthalmic solution which comprises a VEGF-antagonist wherein:
- (a) the syringe has a nominal maximum fill volume of between about 0.5ml and about 1ml,
- (b) the syringe is filled a dosage volume of between about 0.03ml and about 0.05ml of said VEGF antagonist solution,
- (c) the syringe barrel comprises less than about 500µg silicone oil, and
- (d) the VEGF antagonist solution comprises no more than 2 particles $\geq 50\mu\text{m}$ in diameter per ml.
2. A pre-filled syringe according to claim 1, wherein the syringe is filled with between about 0.15ml and about 0.175ml of a VEGF antagonist solution.
3. A pre-filled syringe according to claim 1 or claim 2, wherein the syringe is filled with about 0.165ml of said VEGF antagonist solution.
4. A pre-filled syringe according to any previous claim, wherein the syringe is filled with dosage volume of about 0.05ml of a VEGF antagonist solution.
5. A pre-filled syringe according to any previous claim, in which the dosage volume is determined by the volume of the variable volume chamber when a predetermined part of the stopper is aligned with a priming mark on the syringe.
6. A pre-filled syringe according to any previous claim, wherein the syringe barrel has an internal coating of silicone oil that has an average thickness of about 450nm or less, preferably 400nm or less, preferably 350nm or less, preferably 300nm or less, preferably 200nm or less, preferably 100nm or less, preferably 50nm or less, preferably 20nm or less.

7. A pre-filled syringe according to any previous claim, wherein the syringe barrel has an internal coating of less than about 500µg silicone oil, preferably less than about 100µg silicone oil, preferably less than about 50µg silicone oil, preferably less than about 25µg silicone oil, preferably less than about 10µg silicone oil.
- 5 8. A pre-filled syringe according to any previous claim, wherein the syringe barrel has an internal coating of more than about 1µg, more than about 3µg, more than about 5µg, more than about 7µg or more than about 10µg silicone oil.
9. A pre-filled syringe according to any previous claim, wherein the syringe barrel has an internal coating of about 1µg-about 500µg, about 3µg-about 200µg, about 5µg-about 100µg or
10 about 10µg-about 50µg silicone oil.
10. A pre-filled syringe according to any previous claim, wherein the silicone oil is DC365 emulsion.
11. A pre-filled syringe according to any one of claims 1-5, wherein the syringe is silicone oil free.
- 15 12. A pre-filled syringe according to any previous claim, wherein the VEGF antagonist solution further comprises one or more of (i) no more than 5 particles $\geq 25\mu\text{m}$ in diameter per ml, and (ii) no more than 50 particles $\geq 10\mu\text{m}$ in diameter per ml.
13. A pre-filled syringe according to any previous claim, wherein the VEGF antagonist solution meets USP789.
- 20 14. A pre-filled syringe according to any previous claim, wherein the VEGF antagonist is an anti-VEGF antibody.
15. A pre-filled syringe according to claim 14, wherein the anti-VEGF antibody is ranibizumab.
16. A pre-filled syringe according to claim 15, wherein the ranibizumab is at a concentration of 10mg/ml.
- 25 17. A pre-filled syringe according to any one of claims 1-13 wherein the VEGF antagonist is a non-antibody VEGF antagonist.
18. A pre-filled syringe according to claim 17, wherein the non-antibody VEGF antagonist is aflibercept or conbercept.

19. A pre-filled syringe according to claim 18, wherein the non-antibody VEGF antagonist is aflibercept at a concentration of 40mg/ml.
20. A pre-filled syringe according to any previous claim, wherein the syringe has a stopper break loose force of less than about 11N.
- 5 21. A pre-filled syringe according to claim 20, wherein the syringe has a stopper break loose force of less than about 5N.
22. A pre-filled syringe according to any previous claim, wherein the syringe has a stopper slide force of less than about 11N.
23. A pre-filled syringe according to claim 22, wherein the syringe has a stopper slide force of
10 less than about 5N.
24. A pre-filled syringe according to any of claims 20-23, wherein the stopper break loose force or stopper slide force is measured using a filled syringe, at a stopper travelling speed of 190mm/min, with a 30G x 0.5 inch needle attached to the syringe.
25. A blister pack comprising a pre-filled syringe according to any previous claim, wherein the
15 syringe has been sterilised using H₂O₂ or EtO.
26. A blister pack comprising a pre-filled syringe according to claim 25, wherein the outer surface of the syringe has ≤ 1 ppm EtO or H₂O₂ residue.
27. A blister pack comprising a pre-filled syringe according to claim 25, wherein the syringe has been sterilised using EtO or H₂O₂ and the total EtO or H₂O₂ residue found on the outside of the
20 syringe and inside of the blister pack is ≤ 0.1 mg.
28. A blister pack comprising a pre-filled syringe according to any one of claims 25-27, wherein $\leq 5\%$ of the VEGF antagonist is alkylated.
29. A blister pack comprising a pre-filled syringe according to any of claims 25-28, wherein the syringe has been sterilised using EtO or H₂O₂ with a Sterility Assurance Level of at least 10⁻⁶.
- 25 30. A blister pack according to any of claims 25-29, wherein the pre-filled syringe has a shelf life of up to 6 months, 9 months, 12 months, 15 months, 18 months, 24 months or longer.

31. A kit comprising: (i) a pre-filled syringe according to any one of claims 1-24, or a blister pack comprising a pre-filled syringe according to any one of claims 25-30, (ii) a needle, and optionally (iii) instructions for administration.
32. A kit according to claim 31, wherein the needle is a 30-gauge x ½ inch needle.
- 5 33. A pre-filled syringe according to any one of claims 1-24 for use in therapy.
34. A pre-filled syringe according to any one of claims 1-24 for use in the treatment of an ocular disease selected from choroidal neovascularisation, wet age-related macular degeneration, macular edema secondary to retinal vein occlusion (RVO) including both branch RVO (bRVO) and central RVO (cRVO), choroidal neovascularisation secondary to pathologic myopia (PM),
10 diabetic macular edema (DME), diabetic retinopathy, and proliferative retinopathy.
35. A method of treating a patient suffering from of an ocular disease selected from choroidal neovascularisation, wet age-related macular degeneration, macular edema secondary to retinal vein occlusion (RVO) including both branch RVO (bRVO) and central RVO (cRVO), choroidal neovascularisation secondary to pathologic myopia (PM), diabetic macular edema (DME),
15 diabetic retinopathy, and proliferative retinopathy, comprising the step of administering an ophthalmic solution to the patient using a pre-filled syringe according to any one of claims 1-24.
36. The method of claim 35, further comprising an initial priming step in which the physician depresses the plunger of the pre-filled syringe to align the pre-determined part of the stopper with the priming mark.
- 20 37. A method according to claim 35 or 36, wherein the VEGF antagonist administered is a non-antibody VEGF antagonist and wherein the patient has previously received treatment with an antibody VEGF antagonist.

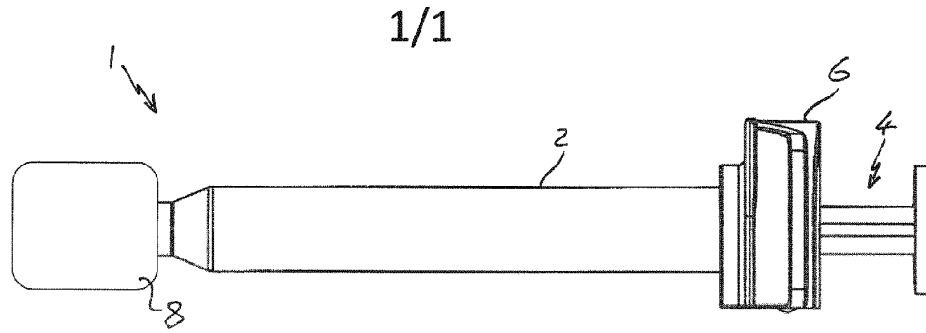


Fig 1

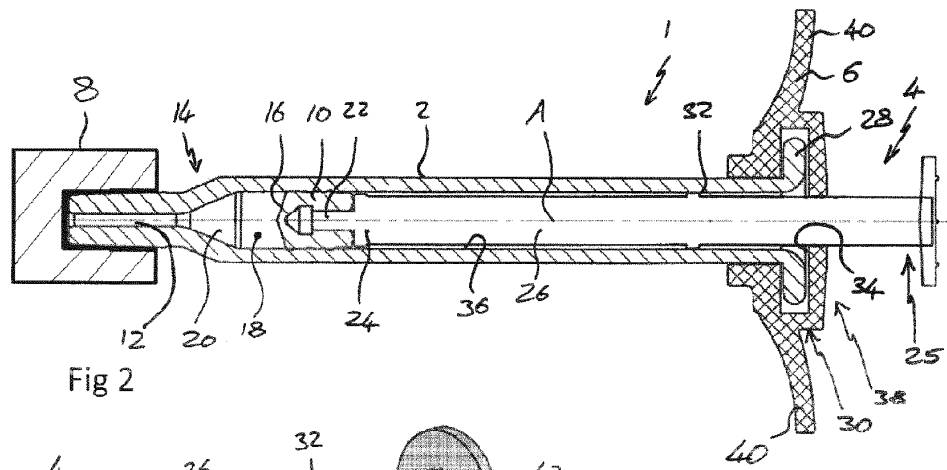


Fig 2

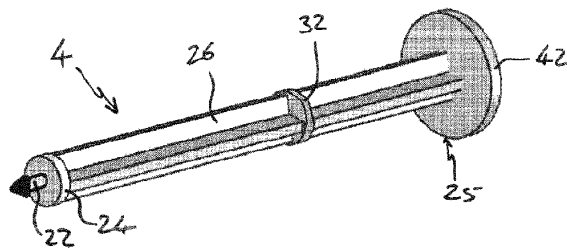


Fig 3

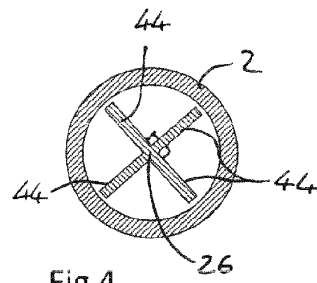


Fig 4

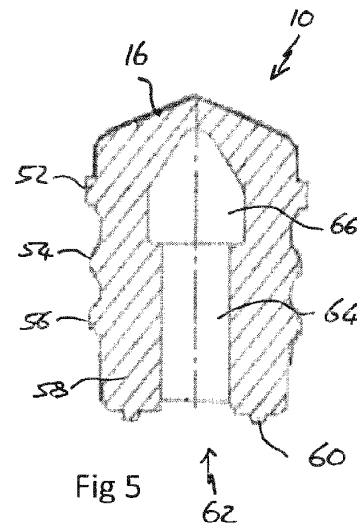


Fig 5

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2013/051491

A. CLASSIFICATION OF SUBJECT MATTER INV. A61K9/00 A61M5/28 A61M5/31 A61M5/315 ADD.				
According to International Patent Classification (IPC) or to both national classification and IPC				
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) A61M A61K				
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched				
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) EP0-Internal, WPI Data, EMBASE, BIOSIS				
C. DOCUMENTS CONSIDERED TO BE RELEVANT				
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.		
X	WO 2007/035621 A1 (OSI EYTECH INC [US]; SCYPINSKI STEPHEN [US]; CALIAS PERRY [US]; EVERE) 29 March 2007 (2007-03-29) page 1, lines 7-9 page 5, lines 10-18 page 6, lines 15,16 page 9, lines 12-20 page 10, line 3 - page 11, line 13 page 18, lines 6-12 page 18, line 21 - page 19, line 18 examples 1,2 figures 3-5	1-34		
X	----- US 2006/293270 A1 (ADAMIS ANTHONY P [US] ET AL) 28 December 2006 (2006-12-28) paragraphs [0002], [0026], [0043] - [0046], [0055] - [0065] examples ----- -/--	1-34		
☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.				
* Special categories of cited documents : <table border="0"> <tr> <td> "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed </td> <td> "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family </td> </tr> </table>			"A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family
"A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family			
Date of the actual completion of the international search		Date of mailing of the international search report		
8 April 2013		19/04/2013		
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016		Authorized officer López García, Mónica		

Form PCT/ISA/210 (second sheet) (April 2005)

page 1 of 2

PGR2026-00039
Biocon Ex.1002
Page 744 of 4945

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2013/051491

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2011/257601 A1 (FURFINE ERIC [US] ET AL) 20 October 2011 (2011-10-20) paragraphs [0003], [0008], [0009], [0039], [0050] claims 1-15 examples 4,6	1-34
A	<p>-----</p> <p>DE 10 2008 005938 A1 (VETTER & CO APOTHEKER [DE]) 30 July 2009 (2009-07-30) paragraphs [0002], [0005] figures 1-3</p> <p>-----</p>	1-34

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2013/051491

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 35-37
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (2)) (April 2005)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.1

Claims Nos.: 35-37

Independent claim 35 refers to " A method of treating a patient ... comprising the step of administering an ophthalmic solution to the patient using a pre-filled syringe according to any one of claims 1-24". Therefore, independent claim 35 and dependent claims 36 and 37 relate to a subject-matter considered by this Authority to be covered by the provision of rule 39.1(iv)/67.1(iv) PCT. Consequently, no examination will be carried out on the subject-matter of claims 35-37.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2013/051491

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2007035621 A1	29-03-2007	CA 2622573 A1 EP 1924309 A1 JP 2009508593 A WO 2007035621 A1	29-03-2007 28-05-2008 05-03-2009 29-03-2007
US 2006293270 A1	28-12-2006	NONE	
US 2011257601 A1	20-10-2011	AU 2007261536 A1 BR PI0713749 A2 CA 2654510 A1 CN 101478949 A EP 2029103 A2 EP 2364691 A1 JP 2009540001 A KR 20090018807 A RU 2009101226 A US 2007293432 A1 US 2010075903 A1 US 2011257601 A1 US 2012087929 A1 WO 2007149334 A2	27-12-2007 06-11-2012 27-12-2007 08-07-2009 04-03-2009 14-09-2011 19-11-2009 23-02-2009 27-07-2010 20-12-2007 25-03-2010 20-10-2011 12-04-2012 27-12-2007
DE 102008005938 A1	30-07-2009	NONE	

Form PCT/ISA/210 (patent family annex) (April 2005)

Doc Code: DIST.E.FILE Document Description: Electronic Terminal Disclaimer - Filed		PTO/SB/26 U.S. Patent and Trademark Office Department of Commerce
Electronic Petition Request	TERMINAL DISCLAIMER TO OBTAIN A DOUBLE PATENTING REJECTION OVER A "PRIOR" PATENT	
Application Number	17384070	
Filing Date	23-Jul-2021	
First Named Inventor	Kenneth Graham	
Attorney Docket Number	125984-266215	
Title of Invention	High Concentration VEGF Receptor Fusion Protein Containing Formulations	
☒ Filing of terminal disclaimer does not obviate requirement for response under 37 CFR 1.111 to outstanding Office Action ☒ This electronic Terminal Disclaimer is not being used for a Joint Research Agreement.		
Owner	Percent Interest	
Regeneron Pharmaceuticals, Inc.	100%	
<p>The owner(s) with percent interest listed above 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 number(s)</p> <p>11103552</p> <p>as the term of said prior patent is presently shortened by any terminal disclaimer. The owner 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.</p> <p>In making the above disclaimer, the owner 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:</p> <ul style="list-style-type: none"> - 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. <p>☒ Terminal disclaimer fee under 37 CFR 1.20(d) is included with Electronic Terminal Disclaimer request.</p>		

☐ I certify, in accordance with 37 CFR 1.4(d)(4), that the terminal disclaimer fee under 37 CFR 1.20(d) required for this terminal disclaimer has already been paid in the above-identified application.	
Applicant claims the following fee status:	
☐ Small Entity ☐ Micro Entity ☒ Regular Undiscounted	
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 any patent issued thereon.	
THIS PORTION MUST BE COMPLETED BY THE SIGNATORY OR SIGNATORIES	
I certify, in accordance with 37 CFR 1.4(d)(4) that I am:	
☒ An attorney or agent registered to practice before the Patent and Trademark Office who is of record in this application Registration Number <u>43184</u>	
☐ A sole inventor	
☐ A joint inventor; I certify that I am authorized to sign this submission on behalf of all of the inventors as evidenced by the power of attorney in the application	
☐ A joint inventor; all of whom are signing this request	
Signature	/Lance A. Termes/
Name	Lance A. Termes

*Statement under 37 CFR 3.73(b) is required if terminal disclaimer is signed by the assignee (owner).
 Form PTO/SB/96 may be used for making this certification. See MPEP § 324.

Electronic Patent Application Fee Transmittal				
Application Number:		17384070		
Filing Date:		23-Jul-2021		
Title of Invention:		High Concentration VEGF Receptor Fusion Protein Containing Formulations		
First Named Inventor/Applicant Name:		Kenneth S. Graham		
Filer:		Lance A. Termes		
Attorney Docket Number:		125984-266215		
Filed as Large Entity				
Filing Fees for Utility under 35 USC 111(a)				
Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Basic Filing:				
STATUTORY OR TERMINAL DISCLAIMER	1814	1	170	170
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Extension-of-Time:				
Miscellaneous:				
Total in USD (\$)				170

Doc Code: DISQ.E.FILE

Document Description: Electronic Terminal Disclaimer – Approved

Application No.: 17384070

Filing Date: 23-Jul-2021

Applicant/Patent under Reexamination: Graham

Electronic Terminal Disclaimer filed on August 1, 2023

☒ APPROVED

This patent is subject to a terminal disclaimer

☐ DISAPPROVED

Approved/Disapproved by: Electronic Terminal Disclaimer automatically approved by EFS-Web

U.S. Patent and Trademark Office

Electronic Acknowledgement Receipt	
EFS ID:	48381120
Application Number:	17384070
International Application Number:	
Confirmation Number:	1061
Title of Invention:	High Concentration VEGF Receptor Fusion Protein Containing Formulations
First Named Inventor/Applicant Name:	Kenneth S. Graham
Customer Number:	147803
Filer:	Lance A. Termes
Filer Authorized By:	
Attorney Docket Number:	125984-266215
Receipt Date:	01-AUG-2023
Filing Date:	23-JUL-2021
Time Stamp:	19:08:03
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	\$170
RAM confirmation Number	E202381J08027301
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	Terminal Disclaimer-Filed (Electronic)	eTerminal-Disclaimer.pdf	41251	no	2
			515fd98c0761a544dc749c95bb900492736ae940		
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	38079	no	2
			abf03ee9cee5bf8cdf737ce854aadf8e47f111d		
Warnings:					
Information:					
Total Files Size (in bytes):			79330		
<p>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.</p> <p><u>New Applications Under 35 U.S.C. 111</u> 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.</p> <p><u>National Stage of an International Application under 35 U.S.C. 371</u> 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.</p> <p><u>New International Application Filed with the USPTO as a Receiving Office</u> 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.</p>					

I hereby certify that this correspondence is being filed via
EFS-Web with the United States Patent and Trademark Office
on August 1, 2023.

PATENT
Attorney Docket No.: 125984-266215

SCHWABE, WILLIAMSON & WYATT PC

By: /Lance A. Termes/
Lance A. Termes

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Kenneth S. Graham et al.

Application No.: 17/384,070

Filed: July 23, 2021

For: **HIGH CONCENTRATION VEGF
RECEPTOR FUSION PROTEIN
CONTAINING FORMULATIONS**

Customer No.: 147803

Confirmation No. 1061

Examiner: Jon McClelland Lockard

Art Unit: 1647

RESPONSE TO NON-FINAL
OFFICE ACTION

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

Commissioner:

This paper is submitted in response to the non-final office action mailed March 22, 2023. A petition to extend the time for reply by two months is submitted herewith. Please enter the following amendments and remarks:

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/Arguments begin on page 8 of this paper.

Amendments to the Specification:

Please replace paragraph [001] with the following amended paragraph:

[001] This application is a continuation of U.S. Application No. 16/409,631, filed May 10, 2019, now U.S. Patent No. 11,103,552, which claims the benefit of U.S. Provisional Patent Application No. 62/813,882, filed March 5, 2019; U.S. Provisional Patent Application No. 62/769,876, filed November 20, 2018; U.S. Provisional Patent Application No. 62/752,127, filed October 29, 2018; and U.S. Provisional Patent Application No. 62/669,506, filed May 10, 2018; each of which is herein incorporated by reference in its entirety.

Please replace the title of the application with the following new title:

METHODS FOR TREATING ANGIOGENIC EYE DISORDERS WITH HIGH DOSES OF
VEGF RECEPTOR FUSION PROTEINS

Amendments to the Claims:

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

Listing of Claims:

1-29. (Canceled)

30. (Currently Amended) A method for treating an angiogenic eye disorder in a human ~~subject~~patient in need thereof comprising administering, intravitreally into an eye of the subject, in a volume of about 100 microliters or less, an intravitreal injection of at least about 8 mg of a VEGF receptor fusion protein comprising two polypeptides that comprise an immunoglobulin-like (Ig) domain 2 of VEGFR1, an Ig domain 3 of a VEGFR2, and a multimerizing component; wherein the VEGF receptor fusion protein is in an aqueous pharmaceutical formulation comprising at least 100 mg/ml of the VEGF receptor fusion protein and having a viscosity of about 5-15 centiPoise (cP) at 20°C, ~~to the eye of the patient.~~

31. (Currently Amended) The method of claim 30 wherein, following said intravitreal injection, the ~~subject~~patient maintains or achieves a reduction in central retinal thickness but does not experience a significant increase in blood pressure.

32. (Currently Amended) The method of claim 30 wherein, following said intravitreal injection, the ~~subject~~patient maintains or achieves an improvement in best corrected visual acuity but does not experience a significant increase in blood pressure.

33-52. (Canceled)

53. (New) The method of claim 30, wherein the viscosity is about 10-13 cP at 20°C.

54. (New) The method of claim 30, wherein the viscosity is about 11-12 cP at 20°C.

55. (New) The method of claim 30, wherein the viscosity is about 12-15 cP at 20°C.
56. (New) The method of claim 30, wherein the viscosity is about 5 cP at 20°C.
57. (New) The method of claim 30, wherein the viscosity is about 6 cP at 20°C.
58. (New) The method of claim 30, wherein the formulation comprises a sugar.
59. (New) The method of claim 30, wherein the formulation comprises sucrose, trehalose, sorbitol, mannitol, propane sulfonic acid or glycerol.
60. (New) The method of claim 30, wherein the formulation comprises an amino acid.
61. (New) The method of claim 30, wherein the angiogenic eye disorder is age-related macular degeneration (wet), macular edema, macular edema following retinal vein occlusion, retinal vein occlusion (RVO), central retinal vein occlusion (CRVO), branch retinal vein occlusion (BRVO), diabetic macular edema (DME), choroidal neovascularization (CNV), iris neovascularization, neovascular glaucoma, post-surgical fibrosis in glaucoma, proliferative vitreoretinopathy (PVR), optic disc neovascularization, corneal neovascularization, retinal neovascularization, vitreal neovascularization, pannus, pterygium, vascular retinopathy, diabetic retinopathy, non-proliferative diabetic retinopathy and/or proliferative diabetic retinopathy.
62. (New) The method of claim 61, wherein the angiogenic eye disorder is wet age-related macular degeneration.
63. (New) The method of claim 61, wherein the angiogenic eye disorder is diabetic macular edema.
64. (New) The method of claim 61, wherein the angiogenic eye disorder is diabetic retinopathy.

65. (New) The method of claim 61, wherein the angiogenic eye disorder is non-proliferative diabetic retinopathy.

66. (New) The method of claim 61, wherein the angiogenic eye disorder is proliferative diabetic retinopathy.

67. (New) The method of claim 61, wherein the angiogenic eye disorder is macular edema following retinal vein occlusion.

68. (New) The method of claim 30, wherein the VEGF receptor fusion protein is aflibercept.

69. (New) The method of claim 61, wherein the VEGF receptor fusion protein is aflibercept.

70. (New) The method of claim 62, wherein the VEGF receptor fusion protein is aflibercept.

71. (New) The method of claim 63, wherein the VEGF receptor fusion protein is aflibercept.

72. (New) The method of claim 64, wherein the VEGF receptor fusion protein is aflibercept.

73. (New) The method of claim 65, wherein the VEGF receptor fusion protein is aflibercept.

74. (New) The method of claim 66, wherein the VEGF receptor fusion protein is aflibercept.

75. (New) The method of claim 67, wherein the VEGF receptor fusion protein is aflibercept.

76. (New) The method of claim 30 for treating an angiogenic eye disorder in a human subject in need thereof comprising administering, intravitreally into an eye of the subject, in a volume of about 100 microliters or less, about 8 mg aflibercept; wherein the aflibercept is in an aqueous pharmaceutical formulation comprising at least 100 mg/ml of the aflibercept and having a viscosity of about 5-15 cP at 20°C.

77. (New) The method of claim 76, wherein the angiogenic eye disorder is wet age-related macular degeneration.

78. (New) The method of claim 76, wherein the angiogenic eye disorder is diabetic macular edema.

79. (New) The method of claim 76, wherein the angiogenic eye disorder is diabetic retinopathy.

80. (New) The method of claim 30 for treating an angiogenic eye disorder in a human subject in need thereof comprising administering, intravitreally into an eye of the subject, in a volume of about 70 microliters, about 8 mg aflibercept; wherein the aflibercept is in an aqueous pharmaceutical formulation comprising about 114.3 mg/ml of the aflibercept and having a viscosity of about 5-15 cP at 20°C.

81. (New) The method of claim 80, wherein the angiogenic eye disorder is wet age-related macular degeneration.

82. (New) The method of claim 80, wherein the angiogenic eye disorder is diabetic macular edema.

83. (New) The method of claim 80, wherein the angiogenic eye disorder is diabetic retinopathy.

84. (New) A method for treating an angiogenic eye disorder in a human subject in need thereof comprising administering, intravitreally into an eye of the subject, about 70

microliters of an aqueous pharmaceutical formulation comprising about 103-126 mg/ml of aflibercept and having a viscosity of about 5-15 cP at 20°C.

85. (New) The method of claim 84, wherein the angiogenic eye disorder is wet age-related macular degeneration.

86. (New) The method of claim 84, wherein the angiogenic eye disorder is diabetic macular edema.

87. (New) The method of claim 84, wherein the angiogenic eye disorder is diabetic retinopathy.

REMARKS/ARGUMENTS

Upon entry of the present amendment, claims 30-32 and 53-87 will be pending in the application. Claims 30-32 are hereby amended, former claims 35 and 39-52 are canceled, and new claims 53-87 are added.

Support for the amendments and new claims can be found in the specification at, *e.g.*, the following locations:

Claim 1 – paragraphs 0084, 0085 and 0095;
Claims 53-55 – paragraph 0021;
Claims 56 and 57 – paragraph 0095;
Claims 58 and 60 – paragraph 0090;
Claim 59 – paragraph 0091;
Claims 61-67, 77-79, 81-83 and 85-87 – paragraph 0027;
Claims 68-75 – paragraph 0019;
Claim 76 – paragraphs 0027, 0084 and 0095;
Claim 80 – paragraphs 0017, 0027, 0095 and 0213; and
Claim 84 – paragraphs 0027, 0095, 0194 and 0213.

No new matter is added.

No amendment or lack of comment on any specific remark should be construed as acquiescence to the validity of any ground of rejection or agreement therewith.

Objection to the Specification

The priority information in the specification has been updated. The title has been changed to: Methods for Treating Angiogenic Eye Disorders with High Doses of VEGF Receptor Fusion Proteins. Accordingly, Applicant respectfully requests withdrawal of this ground of objection.

Claim Objections

Claim 35 is canceled and a comma separates CRVO and branch retinal vein in new claim 61. Accordingly, Applicant respectfully requests withdrawal of this ground of objection.

Claim Rejections – 35 USC § 112(b) - Indefiniteness

Applicant disagrees that the term “at least about” is unclear. The specification discusses the term “about” in paragraph 0061 (pages 17-18). The meaning of the term “at least” is self-explanatory - the stated value or higher. Thus, the meaning of the term would be clear to a practitioner of ordinary skill in the art.

Claim Rejections – 35 USC § 112(a) – Written Description

Claims 30-32, 35 and 39-52 stand rejected as allegedly lacking sufficient written description support. The Examiner argued that the specification provides inadequate description for the breadth of formulations encompassed by the claims alleging that the claims do not specify the components that permit such use of a high concentration of VEGF receptor fusion protein. Applicant disagrees. The amended claims are fully described.

The formulation specified in the amended claims is optimal for delivery of at least 8 mg of VEGF receptor fusion protein to the vitreum in terms of several interrelated factors: protein concentration, injection volume and viscosity.

Volume. Intravitreal injection of a liquid formulation into the eye should be done in a volume of about 100 microliters or less. The vitreous chamber is a closed system having a typical volume of about 4-5 ml. The introduction of excess volume into the eye risks damaging increases in intraocular pressure.

Protein concentration. In order to inject the target amount of VEGF receptor fusion protein (8 mg) in an acceptably low volume (≤ 100 microliters), the concentration of the formulation must be relatively high, for example, greater than 100 mg/ml.

Viscosity. Formulations having high concentrations of VEGF receptor fusion protein, however, must have a viscosity suitable for injection via syringe. High viscosity formulations in a syringe would require excess pressure on the syringe plunger; possibly causing, for example, damaging shearing forces to the protein and difficulty for the clinician who delivers the injection. Acceptably low viscosities can be about 5-15 cP at 20°C. A major factor affecting viscosity of VEGF receptor fusion protein formulations is protein concentration. See *e.g.*, Figures 3C and 5. Lowering protein concentration to lower viscosity, however, presents a

challenge since delivery of ≥ 8 mg of VEGF receptor fusion protein to the eye would need to be done in a higher volume - thus, raising the possibility of causing an increase in intraocular pressure if 100 microliters is exceeded.

In spite of being constrained by these factors, Applicant successfully developed several formulations that meet these criteria. See for example, Figures 3B, 3C and 5 wherein the viscosities of several formulations including a variety of excipients were measured to be within the 5-15 cP range specified in the claims (Note: 1000 mPa-s=1000 cP). Thus, a representative number of species encompassed by the claims have been disclosed.

In view of the foregoing, Applicant submits that the amended claims are fully described and respectfully request withdrawal of this rejection.

Claim Rejections – Obviousness-Type Double Patenting

Claims 30-32, 35 and 39-52 stand rejected for allegedly being unpatentable on the ground of obviousness-type double patenting over claims 1-36 of US Patent No. 11,103,552.

Applicant thanks the Examiner for acknowledging that “[a] timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground. . . .” (numbered paragraph 21 of the Office Action) . Applicant submits herewith a terminal disclaimer over US Patent No. 11,103,552 in compliance with 37 C.F.R. § 1.321(c) and respectfully requests withdrawal of the double patenting rejection and allowance of the claims. Additionally, it is noted that the filing of a terminal disclaimer to obviate a rejection based on non-statutory double patenting is not an admission of the propriety of the rejection. See, e.g., *Quad Environmental Technologies Corp. v. Union Sanitary District*, 946 F.2d 870, 874 (Fed. Cir. 1991) (filing of a terminal disclaimer simply serves the statutory function of removing the rejection of double patenting, and raises neither a presumption nor estoppel on the merits of the rejection).

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 541-749-4085.

Appl. No. 17/384,070
Amdt. dated August 1, 2023
Reply to Office Action of March 22, 2023

PATENT

Please charge any fees or additional fees that may be due in connection with this paper, or credit any overpayment, to the undersigned's deposit account No. 500393.

Respectfully submitted,

/Lance A. Termes/

Lance A. Termes
Reg. No. 43,184

Customer No. 147803
Schwabe, Williamson & Wyatt PC
PacWest Center
1211 SW Fifth Avenue, Ste. 1900
Portland, OR 97204
Tel: Bend Office (541) 749-4044
Fax: Portland Office (503) 796-2900
LAT

PDX\125984\266215\LAT\37045567.1

Electronic Patent Application Fee Transmittal				
Application Number:		17384070		
Filing Date:		23-Jul-2021		
Title of Invention:		High Concentration VEGF Receptor Fusion Protein Containing Formulations		
First Named Inventor/Applicant Name:		Kenneth S. Graham		
Filer:		Lance A. Termes		
Attorney Docket Number:		125984-266215		
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:				
CLAIMS IN EXCESS OF 20	1202	18	100	1800
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Extension-of-Time:				
Extension - 2 months with \$0 paid	1252	1	640	640
Miscellaneous:				
Total in USD (\$)				2440

Electronic Acknowledgement Receipt	
EFS ID:	48381111
Application Number:	17384070
International Application Number:	
Confirmation Number:	1061
Title of Invention:	High Concentration VEGF Receptor Fusion Protein Containing Formulations
First Named Inventor/Applicant Name:	Kenneth S. Graham
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Filer Authorized By:	
Attorney Docket Number:	125984-266215
Receipt Date:	01-AUG-2023
Filing Date:	23-JUL-2021
Time Stamp:	19:02:52
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	\$2440
RAM confirmation Number	E202381J03397014
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	Extension of Time	10430US02_EOT.pdf	156942	no	1
			8b708b6e878423aa2236a74b960c4f329b6f2efb		
Warnings:					
Information:					
2		10430US02_Response.pdf	63862	yes	11
			99b4d5c5595899bd875b75f1a1ad1145b855260b		
	Multipart Description/PDF files in .zip description				
	Document Description		Start	End	
	Amendment/Request for Reconsideration-After Non-Final Rejection		1	1	
	Specification		2	2	
	Claims		3	7	
	Applicant Arguments/Remarks Made in an Amendment		8	11	
Warnings:					
Information:					
3	Fee Worksheet (SB06)	fee-info.pdf	40580	no	2
			047471544c0d67db8c10a113b807effd07e5728		
Warnings:					
Information:					
Total Files Size (in bytes):			261384		

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.

PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a)		Docket Number (Optional) 125984-266215																														
Application Number 17/384,070	Filed July 23, 2021																															
For High Concentration VEGF Receptor Fusion Protein Containing Formulations																																
Art Unit 1647	Examiner Jon McClelland Lockard																															
<p>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.</p> <p>The requested extension and fee are as follows (check time period desired and enter the appropriate fee below):</p> <table style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="text-align: left;"></th> <th style="text-align: center;"><u>Fee</u></th> <th style="text-align: center;"><u>Small Entity Fee</u></th> <th style="text-align: center;"><u>Micro Entity Fee</u></th> <th style="text-align: center;"></th> </tr> </thead> <tbody> <tr> <td>☐ One month (37 CFR 1.17(a)(1))</td> <td style="text-align: center;">\$220</td> <td style="text-align: center;">\$88</td> <td style="text-align: center;">\$44</td> <td style="text-align: center;">\$ _____</td> </tr> <tr> <td>☒ Two months (37 CFR 1.17(a)(2))</td> <td style="text-align: center;">\$640</td> <td style="text-align: center;">\$256</td> <td style="text-align: center;">\$128</td> <td style="text-align: center;">\$ <u>640</u></td> </tr> <tr> <td>☐ Three months (37 CFR 1.17(a)(3))</td> <td style="text-align: center;">\$1,480</td> <td style="text-align: center;">\$592</td> <td style="text-align: center;">\$296</td> <td style="text-align: center;">\$ _____</td> </tr> <tr> <td>☐ Four months (37 CFR 1.17(a)(4))</td> <td style="text-align: center;">\$2,320</td> <td style="text-align: center;">\$928</td> <td style="text-align: center;">\$464</td> <td style="text-align: center;">\$ _____</td> </tr> <tr> <td>☐ Five months (37 CFR 1.17(a)(5))</td> <td style="text-align: center;">\$3,160</td> <td style="text-align: center;">\$1,264</td> <td style="text-align: center;">\$632</td> <td style="text-align: center;">\$ _____</td> </tr> </tbody> </table> <p>☐ Applicant asserts small entity status. See 37 CFR 1.27.</p> <p>☐ 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.</p> <p>☐ A check in the amount of the fee is enclosed.</p> <p>☐ Payment by credit card. Form PTO-2038 is attached.</p> <p>☐ The Director has already been authorized to charge fees in this application to a Deposit Account.</p> <p>☒ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number <u>500393</u>.</p> <p>☒ Payment made via USPTO's patent electronic filing system (Patent Center or EFS-Web).</p> <p>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.</p> <p>I am the</p> <p>☐ applicant.</p> <p>☒ attorney or agent of record. Registration number <u>43,184</u></p> <p>☐ attorney or agent acting under 37 CFR 1.34. Registration number _____</p> <p><u>/Lance A. Termes/</u> <u>August 1, 2023</u></p> <p style="text-align: center;">Signature Date</p> <p><u>Lance A. Termes</u> <u>541-749-4085</u></p> <p style="text-align: center;">Typed or printed name Telephone Number</p> <p>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*.</p>				<u>Fee</u>	<u>Small Entity Fee</u>	<u>Micro Entity Fee</u>		☐ One month (37 CFR 1.17(a)(1))	\$220	\$88	\$44	\$ _____	☒ Two months (37 CFR 1.17(a)(2))	\$640	\$256	\$128	\$ <u>640</u>	☐ Three months (37 CFR 1.17(a)(3))	\$1,480	\$592	\$296	\$ _____	☐ Four months (37 CFR 1.17(a)(4))	\$2,320	\$928	\$464	\$ _____	☐ Five months (37 CFR 1.17(a)(5))	\$3,160	\$1,264	\$632	\$ _____
	<u>Fee</u>	<u>Small Entity Fee</u>	<u>Micro Entity Fee</u>																													
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FIRST NAMED INVENTOR Kenneth S. Graham

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(71) Applicant: **Celitrion, Inc.**
Incheon 22014 (KR)

(72) Inventors:

- **KIM, Su Jung**
Incheon 22014 (KR)
- **KIM, Kwang Woo**
Incheon 22014 (KR)

- **ROH, Ji Won**
Incheon 22014 (KR)
- **SHIN, Yeon Kyeong**
Incheon 22014 (KR)
- **OH, Jun Seok**
Incheon 22014 (KR)
- **LEE, Jae Bin**
Incheon 22014 (KR)
- **HAN, Won Yong**
Incheon 22014 (KR)

(74) Representative: **Cabinet Laurent & Charras**
Le Contemporain
50 Chemin de la Bruyère
69574 Dardilly Cedex (FR)

Remarks:

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(54) **STABLE PHARMACEUTICAL PREPARATION**

(57) A stable pharmaceutical formulation according to the present disclosure contains: a recombinant fusion protein; a surfactant; a sugar or a derivative thereof; a buffer; and an isotonic agent. The stable pharmaceutical formulation according to the present disclosure has low

viscosity while containing the recombinant fusion protein, may maintain excellent stability under long-term storage conditions, accelerated conditions and stress conditions, and may be administered intraocularly.

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Description**CROSS-REFERENCE TO RELATED APPLICATION(S)**

- 5 [0001] This application claims priority to Korean Patent Application No. 10-2020-0096434, filed on July 31, 2020, the disclosure of which is incorporated herein by reference in its entirety.

BACKGROUND10 **Technical Field**

[0002] The present disclosure relates to a pharmaceutical formulation, which is capable of stably preserving a drug capable of inhibiting vascular endothelial growth factor (VEGF) and may be intraocularly administered.

15 **Description of the Related Art**

[0003] Since release of vascular endothelial growth factor (VEGF) contributes to increased vascular permeability in the eye and inappropriate new blood vessel growth, it may cause neovascular (wet) age-related macular degeneration, visual impairment due to retinal vein occlusion (central retinal vein occlusion or branch retinal vein occlusion) macular edema, visual impairment due to diabetic macular edema, and visual impairment due to choroidal neovascularization caused by pathologic myopia. Thus, inhibiting VEGF is an effective method for treating ophthalmic diseases associated with angiogenesis.

20 [0004] The generic name for a VEGF inhibitor drug is aflibercept which is a recombinant fusion protein capable of inhibiting type A VEGF, type B VEGF, and placental growth factor (PlGF). A pharmaceutical formulation containing this drug should be administered by intraocular injection, and such administration should be performed directly by a qualified physician with experience in intraocular administration.

SUMMARY

30 [0005] For long-term storage of a VEGF inhibitor drug, the present inventors developed a formulation containing histidine, trehalose, and polysorbate 20 as stabilizers, and added sodium chloride as an isotonic agent to the formulation so as to have an osmotic pressure similar to that in the eye for the purpose of reducing pain during administration. However, the present inventors confirmed that the stability of the drug decreased in the presence of sodium chloride as an isotonic agent. To overcome this problem, the present inventors applied sodium chloride at a concentration capable of maintaining an appropriate osmotic pressure.

35 [0006] The formulation according to the present disclosure exhibited improved results in terms of drug stabilization compared to a liquid aflibercept formulation disclosed in Korean Patent Application Publication No. 10-2009-0018807, and the improved level was directly compared and evaluated through an experimental example (Experimental Example 1).

40 [0007] Therefore, the present inventors have finally confirmed the superiority of a stable pharmaceutical formulation containing the VEGF inhibitor drug aflibercept, which is the formulation of the present disclosure.

[0008] Accordingly, an object of the present disclosure is to provide a pharmaceutical formulation which is stable during long-term storage while containing the VEGF inhibitor drug aflibercept.

[0009] Another object of the present disclosure is to provide a pharmaceutical formulation having excellent long-term storage stability based on excellent stability under accelerated conditions and stress conditions.

45 [0010] Still another problem of the present disclosure is to provide a stable pharmaceutical formulation that may be administered intraocularly.

[0011] A stable pharmaceutical formulation according to one embodiment of the present disclosure contains: (A) a recombinant fusion protein; (B) a surfactant; (C) a sugar or a derivative thereof; and (D) a buffer.

[0012] In one embodiment of the present disclosure, the pharmaceutical formulation may be in a liquid form.

50 [0013] In one embodiment of the present disclosure, the recombinant fusion protein (A) may comprise a vascular endothelial growth factor (VEGF) antagonist.

[0014] In one embodiment of the present disclosure, the recombinant fusion protein (A) may comprise a human VEGF receptor extracellular domain.

55 [0015] In one embodiment of the present disclosure, the recombinant fusion protein (A) may comprise human VEGF receptor extracellular domain 1, 2, or a mixture thereof.

[0016] In one embodiment of the present disclosure, the recombinant fusion protein (A) may comprise an immunoglobulin G (IgG) Fc region, preferably a human immunoglobulin G (IgG) Fc region.

[0017] In one embodiment of the present disclosure, the recombinant fusion protein (A) may comprise: (1) a VEGF

receptor extracellular domain 1 component comprising amino acids 27 to 129 of SEQ ID NO: 2; (2) a VEGF receptor extracellular domain 2 component comprising amino acids 130 to 231 of SEQ ID NO: 2; and (3) an Fc region component comprising amino acids 232 to 457 of SEQ ID NO: 2. The amino acid sequence of SEQ ID NO: 2 may be encoded by the polynucleotide sequence of SEQ ID NO: 1.

- 5 [0018] In one embodiment of the present disclosure, the recombinant fusion protein (A) may comprise aflibercept.
- [0019] In one embodiment of the present disclosure, the concentration of the recombinant fusion protein (A) may be 5 to 100 mg/ml.
- [0020] In one embodiment of the present disclosure, the surfactant (B) may comprise polysorbate, poloxamer, or a mixture thereof.
- 10 [0021] In one embodiment of the present disclosure, the surfactant (B) may comprise polysorbate 20, polysorbate 40, polysorbate 60, polysorbate 80, or a mixture of two or more thereof.
- [0022] In one embodiment of the present disclosure, the surfactant (B) may comprise polysorbate 20.
- [0023] In one embodiment of the present disclosure, the concentration of the surfactant (B) may be 0.01 to 0.1% (w/v).
- [0024] In one embodiment of the present disclosure, the sugar (C) may comprise a monosaccharide, a disaccharide, an oligosaccharide, a polysaccharide, or a mixture of two or more thereof, and the derivative of the sugar (C) may comprise a sugar alcohol, a sugar acid, or a mixture thereof.
- 15 [0025] In one embodiment of the present disclosure, the sugar or derivative thereof (C) may comprise sorbitol, mannitol, trehalose, sucrose, or a mixture of two or more thereof.
- [0026] In one embodiment of the present disclosure, the sugar or derivative thereof (C) may comprise trehalose.
- 20 [0027] In one embodiment of the present disclosure, the concentration of the sugar or derivative thereof (C) may be 1 to 20% (w/v).
- [0028] In one embodiment of the present disclosure, the buffer (D) may comprise an amino acid.
- [0029] In one embodiment of the present disclosure, the buffer (D) may comprise a free amino acid, an amino acid salt, or a mixture thereof.
- 25 [0030] In one embodiment of the present disclosure, the buffer (D) may comprise histidine, histidine salt, or a mixture thereof.
- [0031] In one embodiment of the present disclosure, the concentration of the buffer (D) may be 1 to 20 mM.
- [0032] In one embodiment of the present disclosure, the stable pharmaceutical formulation of the present disclosure may be free of acetic acid, citric acid, phosphoric acid, or mixtures thereof.
- 30 [0033] In one embodiment of the present disclosure, the stable pharmaceutical formulation of the present disclosure may further contain (E) an isotonic agent.
- [0034] In one embodiment of the present disclosure, the isotonic agent (E) may comprise sodium chloride (NaCl), potassium chloride (KCl), calcium chloride (CaCl), or a mixture of two or more thereof.
- [0035] In one embodiment of the present disclosure, the concentration of the isotonic agent (E) may be 30 mM or less.
- 35 [0036] In one embodiment of the present disclosure, the formulation of the present disclosure may have a pH of 5.0 to 7.0.
- [0037] In one embodiment of the present disclosure, the formulation of the present disclosure may not contain NaF, KBr, NaBr, Na₂SO₄, NaSCN, K₂SO₄, or mixtures thereof.
- [0038] In one embodiment of the present disclosure, the formulation of the present disclosure may be free of a chelating agent.
- 40 [0039] A stable pharmaceutical formulation according to one embodiment of the present disclosure may contain: (A) 5 to 100 mg/ml of a recombinant fusion protein comprising (1) a VEGF receptor extracellular domain 1 component comprising amino acids 27 to 129 of SEQ ID NO: 2, (2) a VEGF receptor extracellular domain 2 component comprising amino acids 130 to 231 of SEQ ID NO: 2, and (3) an Fc region component comprising amino acids 232 to 457 of SEQ ID NO: 2; (B) 0.01 to 0.1% (w/v) of a surfactant; (C) 1 to 20% (w/v) of a sugar or a derivative thereof; (D) 1 to 20 mM of a buffer; and (E) 30 mM or less of an isotonic agent. The amino acid sequence of SEQ ID NO: 2 may be encoded by the polynucleotide sequence of SEQ ID NO: 1.
- 45 [0040] A stable pharmaceutical formulation according to one embodiment of the present disclosure may contain: (A) a vascular endothelial growth factor (VEGF) antagonist; (B) polysorbate; (C) a sugar or a derivative thereof; and (D) histidine.
- 50 [0041] The stable pharmaceutical formulation according to one embodiment of the present disclosure may further contain (E) sodium chloride.
- [0042] A stable pharmaceutical formulation according to one embodiment of the present disclosure may contain: (A) 5 to 100 mg/ml of a recombinant fusion protein comprising (1) a VEGF receptor extracellular domain 1 component comprising amino acids 27 to 129 of SEQ ID NO: 2, (2) a VEGF receptor extracellular domain 2 component comprising amino acids 130 to 231 of SEQ ID NO: 2, and (3) an Fc region component comprising amino acids 232 to 457 of SEQ ID NO: 2; (B) 0.01 to 0.1% (w/v) of polysorbate; (C) 1 to 20% (w/v) of a sugar or a derivative thereof; and (D) 1 to 20 mM of histidine.
- 55

[0043] The stable pharmaceutical formulation according to one embodiment of the present disclosure may further contain (E) 30 mM or less of sodium chloride.

[0044] In one embodiment of the present disclosure, the number of sub-visible particles having a particle diameter of equal to or more than 10.00 µm to less than 400.00 µm in the stable pharmaceutical formulation may be 50 or less as measured by HiAC after 9 months of storage at 563°C.

[0045] In one embodiment of the present disclosure, the stable pharmaceutical formulation may show a main component content of 98% or more after 10 days of storage at 563°C.

[0046] In one embodiment of the present disclosure, the stable pharmaceutical formulation may show a high-molecular-weight component content of 1% or less after 10 days of storage at 563°C.

[0047] In one embodiment of the present disclosure, the stable pharmaceutical formulation may show a low-molecular-weight component content of 0.05% or less after 10 days of storage at 563°C.

[0048] In one embodiment of the present disclosure, the stable pharmaceutical formulation may show a charge variant content of 87% or more after 9 months of storage at 563°C.

[0049] In one embodiment of the present disclosure, the stable pharmaceutical formulation may show a VEGF binding affinity of 90% or more after 9 months of storage at 563°C.

[0050] In one embodiment of the present disclosure, the stable pharmaceutical formulation may be for intravitreal administration, preferably intravitreal administration.

[0051] In one embodiment of the present disclosure, the stable pharmaceutical formulation may not be subjected to a reconstitution step, a dilution step, or both, before use.

[0052] A glass vial according to one embodiment of the present disclosure is filled with the stable pharmaceutical formulation.

[0053] A pre-filled syringe according to one embodiment of the present disclosure is filled with the stable pharmaceutical formulation.

DESCRIPTION OF SPECIFIC EMBODIMENTS

[Stable Pharmaceutical Formulation]

[0054] A stable pharmaceutical formulation according to the present disclosure contains: (A) a recombinant fusion protein; (B) a surfactant; (C) a sugar or a derivative thereof; and (D) a buffer.

[0055] As used herein, the term "free of" means that the pharmaceutical formulation does not contain the corresponding component. In addition, the term means that the pharmaceutical formulation does not substantially contain the corresponding component, that is, contains the corresponding component in an amount within a range that does not affect the activity of the fusion protein and the stability and viscosity of the pharmaceutical formulation, for example, contains the corresponding component in an amount of 0 to 1% (w/v), 0 to 1 ppm (w/v), or 0 to 1 ppb (w/v) based on the total weight of the pharmaceutical formulation. The pharmaceutical formulation may be in a liquid form, but is not limited thereto.

(A) Recombinant Fusion Protein

[0056] The recombinant fusion protein of the present disclosure may be a vascular endothelial growth factor (VEGF) antagonist. In addition, the recombinant fusion protein of the present disclosure may comprise: (1) a VEGF receptor extracellular domain 1 component comprising amino acids 27 to 129 of SEQ ID NO: 2; (2) a VEGF receptor extracellular domain 2 component comprising amino acids 130 to 231 of SEQ ID NO: 2; and (3) an Fc region component comprising amino acids 232 to 457 of SEQ ID NO: 2. The amino acid sequence of SEQ ID NO: 2 may be encoded by the polynucleotide sequence of SEQ ID NO: 1.

[0057] The recombinant fusion protein of the present disclosure may comprise a human VEGF receptor extracellular domain, and more specifically, may comprise a human VEGF receptor extracellular domain 1, 2, or a mixture thereof, but is not limited thereto.

[0058] The recombinant fusion protein may also comprise a human immunoglobulin G (IgG) Fc region, but is not limited thereto.

[0059] The recombinant fusion protein may comprise aflibercept, but is not limited thereto.

[0060] The concentration of the recombinant fusion protein of the present disclosure may be freely adjusted within a range that does not substantially adversely affect the stability and viscosity of the stable pharmaceutical formulation according to the present disclosure. In one embodiment of the present disclosure, the concentration of the recombinant fusion protein may be 5 to 100 mg/ml. In another embodiment of the present disclosure, the concentration of the recombinant fusion protein may be 5 to 95 mg/ml. In still another embodiment of the present disclosure, the concentration of the recombinant fusion protein may be 5 to 90 mg/ml. In still another embodiment of the present disclosure, the concentration of the recombinant fusion protein may be 5 to 85 mg/ml. In still another embodiment of the present disclosure,

the concentration of the recombinant fusion protein may be 5 to 80 mg/ml. In still another embodiment of the present disclosure, the concentration of the recombinant fusion protein may be 5 to 75 mg/ml. In still another embodiment of the present disclosure, the concentration of the recombinant fusion protein may be 5 to 70 mg/ml. In still another embodiment of the present disclosure, the concentration of the recombinant fusion protein may be 5 to 65 mg/ml. In still another embodiment of the present disclosure, the concentration of the recombinant fusion protein may be 5 to 60 mg/ml. In still another embodiment of the present disclosure, the concentration of the recombinant fusion protein may be 5 to 55 mg/ml. In still another embodiment of the present disclosure, the concentration of the recombinant fusion protein may be 5 to 50 mg/ml. In still another embodiment of the present disclosure, the concentration of the recombinant fusion protein may be 5 to 45 mg/ml. In still another embodiment of the present disclosure, the concentration of the recombinant fusion protein may be 5 to 40 mg/ml.

[0061] In addition, in another embodiment of the present disclosure, the concentration of the recombinant fusion protein may be 10 to 100 mg/ml. In still another embodiment of the present disclosure, the concentration of the recombinant fusion protein may be 10 to 90 mg/ml. In still another embodiment of the present disclosure, the concentration of the recombinant fusion protein may be 10 to 80 mg/ml. In still another embodiment of the present disclosure, the concentration of the recombinant fusion protein may be 10 to 70 mg/ml. In still another embodiment of the present disclosure, the concentration of the recombinant fusion protein may be 10 to 60 mg/ml. In still another embodiment of the present disclosure, the concentration of the recombinant fusion protein may be 10 to 50 mg/ml. In still another embodiment of the present disclosure, the concentration of the recombinant fusion protein may be 10 to 40 mg/ml.

[0062] Furthermore, in another embodiment of the present disclosure, the concentration of the recombinant fusion protein may be 20 to 100 mg/ml. In still another embodiment of the present disclosure, the concentration of the recombinant fusion protein may be 20 to 90 mg/ml. In still another embodiment of the present disclosure, the concentration of the recombinant fusion protein may be 20 to 80 mg/ml. In still another embodiment of the present disclosure, the concentration of the recombinant fusion protein may be 20 to 70 mg/ml. In still another embodiment of the present disclosure, the concentration of the recombinant fusion protein may be 20 to 60 mg/ml. In still another embodiment of the present disclosure, the concentration of the recombinant fusion protein may be 20 to 50 mg/ml. In still another embodiment of the present disclosure, the concentration of the recombinant fusion protein may be 20 to 40 mg/ml.

[0063] In addition, in another embodiment of the present disclosure, the concentration of the recombinant fusion protein may be 30 to 100 mg/ml. In still another embodiment of the present disclosure, the concentration of the recombinant fusion protein may be 30 to 90 mg/ml. In still another embodiment of the present disclosure, the concentration of the recombinant fusion protein may be 30 to 80 mg/ml. In still another embodiment of the present disclosure, the concentration of the recombinant fusion protein may be 30 to 70 mg/ml. In still another embodiment of the present disclosure, the concentration of the recombinant fusion protein may be 30 to 60 mg/ml. In still another embodiment of the present disclosure, the concentration of the recombinant fusion protein may be 30 to 50 mg/ml. In still another embodiment of the present disclosure, the concentration of the recombinant fusion protein may be 30 to 40 mg/ml.

(B) Surfactant

[0064] Examples of the surfactant include, but are not limited to, polyoxyethylene sorbitan fatty acid esters (e.g., polysorbate), polyoxyethylene alkyl ethers (e.g., Brij), alkylphenyl polyoxyethylene ethers (e.g., Triton-X), polyoxyethylene-polyoxypropylene copolymers (e.g., Poloxamer, Pluronic), sodium dodecyl sulfate (SDS), poloxamers, and mixtures thereof.

[0065] In one embodiment of the present disclosure, the surfactant may comprise polysorbate, poloxamer, or a mixture thereof, and specifically, comprise polyoxyethylene sorbitan fatty acid ester (polysorbate), poloxamer, or a mixture thereof. More specifically, the surfactant may comprise polysorbate 20, polysorbate 40, polysorbate 60, polysorbate 80, or a mixture of two or more thereof, but is not limited thereto. In another embodiment of the present disclosure, the polysorbate may comprise polysorbate 20, but is not limited thereto.

[0066] In one embodiment of the present disclosure, the concentration of the surfactant may be freely adjusted within a range that does not adversely affect the stability and viscosity of the stable pharmaceutical formulation according to the present disclosure. For example, the concentration of the surfactant may be 0.001 to 5% (w/v), or 0.005 to 2% (w/v), more preferably 0.01 to 1%, 0.01 to 0.5%, 0.01 to 0.1%, or 0.01 to 0.05% (w/v), but is not limited thereto.

(C) Sugar or Derivative of Sugar

[0067] The sugar may comprise a monosaccharide, a disaccharide, an oligosaccharide, a polysaccharide, or a mixture of two or more thereof. Examples of the monosaccharide include, but are not limited to, glucose, fructose, galactose, and the like. Examples of the disaccharide include, but are not limited to, sucrose, lactose, maltose, trehalose, and the like. Examples of the oligosaccharide include, but are not limited to, fructooligosaccharides, galactooligosaccharides, mannan oligosaccharides, and the like. Examples of the polysaccharide include, but are not limited to, starch, glycogen,

cellulose, chitin, pectin, and the like.

[0068] The derivative of the sugar may comprise a sugar alcohol, a sugar acid, or a mixture thereof. Examples of the sugar alcohol include, but are not limited to, glycerol, erythritol, threitol, arabitol, xylitol, ribitol, mannitol, sorbitol, galactitol, fucitol, iditol, inositol, volemitol, isomalt, maltitol, lactitol, maltotriitol, maltotetraitol, polyglycol, and the like. Examples of the sugar acid include, but are not limited to, aldonic acid (such as glyceric acid), ulosonic acid (such as neuramic acid), uronic acid (such as glucuronic acid), and aldonic acid (such as tartaric acid).

[0069] In one embodiment of the present disclosure, the sugar or derivative thereof may comprise sorbitol, mannitol, trehalose, sucrose, or a mixture of two or more thereof. In another embodiment of the present disclosure, the sugar or derivative thereof may comprise trehalose, but is not limited thereto.

[0070] In one embodiment of the present disclosure, the concentration of the sugar or derivative thereof may be freely adjusted within a range that does not substantially adversely affect the stability and viscosity of the pharmaceutical formulation according to the present disclosure. For example, the concentration of the sugar or derivative thereof may be 0.1 to 30% (w/v), or 0.5 to 25% (w/v), more preferably 1 to 20% (w/v). According to one embodiment of the present disclosure, the concentration of the sugar or derivative thereof may be 0.5 to 20% (w/v) or 1 to 25% (w/v). According to one embodiment of the present disclosure, the concentration of the sugar or derivative thereof may be 1 to 20% (w/v), 2 to 15% (w/v), 4 to 13% (w/v), or 8 to 12% (w/v).

(D) Buffer

[0071] The buffer is a neutralizing substance that minimizes the change in pH caused by acid or alkali. Examples of the buffer include phosphate, acetate, succinate, gluconate, citrate, as well as glutamate and histidine that are amino acids.

[0072] In one embodiment of the present disclosure, the buffer may comprise an amino acid, and more specifically, may comprise a free amino acid, an amino acid salt, or a mixture thereof, but is not limited thereto. In one embodiment of the present disclosure, the buffer may comprise histidine, histidine salt, or a mixture thereof, but is not limited thereto.

[0073] When a histidine salt is used as the buffer, the buffer may comprise, for example, histidine chloride, histidine acetate, histidine phosphate, histidine sulfate, or the like. The use of histidine as the buffer is preferable in terms of pH control and stability, but is not limited thereto. In addition, the pharmaceutical formulation may also contain other types of acids for pH adjustment, but according to one embodiment of the present disclosure, the pharmaceutical formulation may be free of acetic acid, citric acid, phosphoric acid, or mixtures thereof, but is not limited thereto.

[0074] In one embodiment of the present disclosure, the concentration of the buffer may be freely adjusted within a range that does not substantially adversely affect the stability and viscosity of the pharmaceutical formulation according to the present disclosure. In one embodiment of the present disclosure, the concentration of the buffer may be 1 to 20 mM or 1 to 10 mM. In one embodiment of the present disclosure, the concentration of the buffer may be 2 to 20 mM, or 2 to 10 mM. In one embodiment of the present disclosure, the concentration of the buffer may be 3 to 20 mM, or 3 to 10 mM. In one embodiment of the present disclosure, the concentration of the buffer may be 4 to 20 mM, or 4 to 10 mM. In one embodiment of the present disclosure, the concentration of the buffer may be 5 to 20 mM, or 5 to 10 mM. In one embodiment of the present disclosure, the concentration of the buffer may be 6 to 20 mM, or 6 to 10 mM. In one embodiment of the present disclosure, the concentration of the buffer may be 1 to 20 mM. In one embodiment of the present disclosure, the concentration of the buffer may be 6.4 to 9.6 mM, but is not limited thereto.

(E) Isotonic agent

[0075] In one embodiment of the present disclosure, the pharmaceutical formulation may further contain (E) an isotonic agent.

[0076] The isotonic agent may comprise sodium chloride, potassium chloride, calcium chloride, or a mixture of two or more thereof.

[0077] In one embodiment of the present disclosure, the concentration of the isotonic agent may be freely adjusted within a range that does not substantially adversely affect the stability and viscosity of the pharmaceutical formulation according to the present disclosure. In one embodiment of the present disclosure, the concentration of the isotonic agent may be 30 mM or less. In one embodiment of the present disclosure, the concentration of the isotonic agent may be 0.00001 to 30 mM, 0.0001 to 30 mM, 0.001 to 30 mM, 0.01 to 30 mM, 0.1 to 30 mM, or 1 to 30 mM. In one embodiment of the present disclosure, the concentration of the isotonic agent may be 0.00001 to 30 mM, 0.00001 to 25 mM, or 0.00001 to 20 mM. In one embodiment of the present disclosure, the concentration of the isotonic agent may be 0.0001 to 30 mM, 0.0001 to 25 mM, or 0.0001 to 20 mM. In one embodiment of the present disclosure, the concentration of the isotonic agent may be 0.001 to 30 mM, 0.001 to 25 mM, or 0.001 to 20 mM. In one embodiment of the present disclosure, the concentration of the isotonic agent may be 0.01 to 30 mM, 0.01 to 25 mM, or 0.01 to 20 mM. In one embodiment of the present disclosure, the concentration of the isotonic agent may be 0.1 to 30 mM, 0.1 to 25 mM, or 0.1 to 20 mM. In

one embodiment of the present disclosure, the concentration of the isotonic agent may be 1 to 30 mM, 1 to 25 mM, or 1 to 20 mM. In one embodiment of the present disclosure, the concentration of the isotonic agent may be 2 to 30 mM, 2 to 25 mM, or 2 to 20 mM. In one embodiment of the present disclosure, the concentration of the isotonic agent may be 3 to 30 mM, 3 to 25 mM, or 3 to 20 mM. In one embodiment of the present disclosure, the concentration of the isotonic agent may be 5 to 18 mM, 6 to 17 mM, or 7.2 to 15.6 mM, but is not limited thereto.

(F) pH

[0078] In one embodiment of the present disclosure, the pH of the stable pharmaceutical formulation may be 5.0 to 7.0, 5.0 to 6.5, 5.5 to 7.0, or 5.5 to 6.5. When the pH is within this range, the pharmaceutical formulation may exhibit excellent long-term stability and low viscosity. The pH of the pharmaceutical formulation may be adjusted using a buffer. In other words, when the pharmaceutical formulation contains a predetermined amount of a buffer, it may exhibit a pH within the above range without a separate pH-adjusting agent. In one embodiment of the present disclosure, the pharmaceutical formulation may be free of acetic acid, citric acid, phosphoric acid, or a mixture thereof. If acetic acid (acetate), citric acid (citrate), phosphoric acid, or a mixture thereof is used as a buffer, it may be difficult to show a pH within the above range. If the pharmaceutical formulation further contains an acid (e.g., hydrochloric acid) or a base (e.g., sodium hydroxide) as a separate pH-adjusting agent, the desired stability of the recombinant fusion protein may be reduced.

(G) Other Components

[0079] In one embodiment of the present disclosure, the stable pharmaceutical formulation may be free of a preservative. Examples of the preservative include octadecyldimethylbenzyl ammonium chloride, hexamethonium chloride, benzalkonium chloride, benzethonium chloride, phenol, butyl alcohol, benzyl alcohol, alkyl parabens, catechol, resorcinol, cyclohexanol, 3-pentanol, m-cresol, and the like. When the preservative is contained, it may not help improve the stability of the pharmaceutical formulation.

[0080] In one embodiment of the present disclosure, the stable pharmaceutical formulation may be free of NaF, KBr, NaBr, Na₂SO₄, NaSCN, K₂SO₄, or a mixture thereof, and may also be free of a chelating agent, but is not limited thereto.

(H) "Stable" Pharmaceutical Formulation

[0081] The term "stable" in the "stable" pharmaceutical formulation of the present disclosure means that the recombinant fusion protein according to the present disclosure essentially retains its physical stability and/or chemical stability and/or biological activity during production and/or storage thereof. Various analytical techniques for measuring antibody stability are readily available in the art. Stability may be measured for a selected period of time at a selected temperature.

[0082] Physical stability may be assessed by methods known in the art, which include measurement of a sample's apparent attenuation of light (absorbance, or optical density). This measurement of light attenuation is related to the turbidity of a formulation. In addition, for physical stability, the contents of high-molecular-weight components, the contents of low-molecular-weight components, the amounts of intact proteins, the number of sub-visible particles, and the like, may be measured.

[0083] Chemical stability can be assessed by, for example, detecting and quantifying chemically altered forms of the recombinant fusion protein. Chemical stability includes charge alteration (for example, occurring as a result of deamidation or oxidation) which can be evaluated by, for example, ion-exchange chromatography. For chemical stability, charge variants (acidic or basic peaks) may be measured.

[0084] Biological activity may be assessed by methods known in the art. For example, antigen binding affinity may be measured by ELISA.

[0085] In one embodiment of the present disclosure, the term "stable" pharmaceutical formulation means a pharmaceutical formulation satisfying one or more of the following criteria.

(H)-1 Turbidity

[0086]

- a pharmaceutical formulation having an absorbance A_{600} of 0 to 0.0700, or 0 to 0.0400, as measured by a spectrophotometer after 4 weeks of storage at a temperature of 56.3°C;

a pharmaceutical formulation having an absorbance A_{300} of 0 to 0.0700, or 0 to 0.0400, as measured by a spectrophotometer after 4 weeks of storage at a temperature of 10°C, 15°C, 20°C, 25°C, 30°C or 35°C under a closed condition;

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a pharmaceutical formulation having an absorbance A_{280} of 0 to 0.0700, or 0 to 0.0400, as measured by a spectrophotometer after 4 weeks of storage at a temperature of 4062°C and a relative humidity of 7565% under a closed condition;

5 (H)-2 Content of Main Component (Main Peak)

[0087]

- 10 - a pharmaceutical formulation in which the content of a main component after 9 months of storage at a temperature of 563°C is 98 to 99% as measured by SE-HPLC;
- a pharmaceutical formulation in which the content of a main component after 4 weeks of storage at a temperature of 4062°C and a relative humidity of 7565% under a closed condition is 89 to 92% as measured by SE-HPLC;

15 [0088] (H)-3 Content of High-Molecular-Weight Components (a peak whose retention time is earlier than that of the main peak (intact recombinant fusion protein))

- a pharmaceutical formulation in which the content of high-molecular-weight components after 9 months of storage at a temperature of 563°C is 98 to 100% as measured by SE-HPLC;

20 a pharmaceutical formulation in which the content of high-molecular-weight components after 4 weeks of storage at a temperature of 4062°C and a relative humidity of 7565% under a closed condition is 7 to 10% as measured by SE-HPLC;

[0089] (H)-4 Content of Low-Molecular-Weight Components (a peak whose retention time is later than that of the main peak (intact recombinant fusion protein))

25 a pharmaceutical formulation in which the content of low-molecular-weight components after 9 months of storage at a temperature of 563°C is 0.0 to 0.1% as measured by SE-HPLC;

a pharmaceutical formulation in which the content of low-molecular-weight components after 4 weeks of storage at a temperature of 4062°C and a relative humidity of 7565% under a closed condition is 0.0 to 1.2% as measured by SE-HPLC;

30 (H)-5 Content of one intact recombinant human VEGF receptor extracellular domain 1, one recombinant human VEGF receptor extracellular domain 2 and recombinant human IgG Fc region (1VEGF1 + 1VEGF2 + Fc)

[0090]

- 35 - a pharmaceutical formulation in which the content of one intact recombinant human VEGF receptor extracellular domain 1, one recombinant human VEGF receptor extracellular domain 2 and a recombinant human IgG Fc region (1VEGF1 + 1VEGF2 + Fc) after 9 months of storage at a temperature of 563°C is 96% to 98% as measured by reduced CE-SDS;
- 40 - a pharmaceutical formulation in which the content of one intact recombinant human VEGF receptor extracellular domain 1, one recombinant human VEGF receptor extracellular domain 2 and a recombinant human IgG Fc region (1VEGF1 + 1VEGF2 + Fc) after 4 weeks of storage at a temperature of 4062°C and a relative humidity of 7565% under a closed condition is 90% to 96% as measured by reduced CE-SDS;

45 (H)-6 Number of Sub-Visible Particles

[0091]

- 50 - a pharmaceutical formulation in which the number of sub-visible particles (≥ 2.00 mm, < 400.00 mm) after 9 months of storage at a temperature of 563°C is 0 to 100 as measured by HiAC;
- a pharmaceutical formulation in which the number of sub-visible particles (≥ 10.00 mm, < 400.00 mm) after 9 months of storage at a temperature of 563°C is 0 to 50 as measured by HiAC;
- a pharmaceutical formulation in which the number of sub-visible particles (≥ 25.00 mm, < 400.00 mm) after 9 months of storage at a temperature of 563°C is 0 to 5 as measured by HiAC;
- 55 - a pharmaceutical formulation in which the number of sub-visible particles (≥ 2.00 mm, < 400.00 mm) after 4 weeks of storage at a temperature of 4062°C and a relative humidity of 7565% under a closed condition is 0 to 100 as measured by HiAC;
- a pharmaceutical formulation in which the number of sub-visible particles (≥ 10.00 mm, < 400.00 mm) after 4 weeks

- of storage at a temperature of 4062°C and a relative humidity of 7565% under a closed condition is 0 to 50 as measured by HIAC;
- a pharmaceutical formulation in which the number of sub-visible particles (≥ 25.00 mm, < 400.00 mm) after 4 weeks of storage at a temperature of 4062°C and a relative humidity of 7565% under a closed condition is 0 to 5 as measured by HIAC;
- 5 - a pharmaceutical formulation in which the number of sub-visible particles (≥ 1.00 mm, < 400.00 mm) after 9 months of storage at a temperature of 563°C is 0 to 5,000 as measured by MFI;
- a pharmaceutical formulation in which the number of sub-visible particles (≥ 10.00 mm, < 400.00 mm) after 9 months of storage at a temperature of 563°C is 0 to 100 as measured by MFI;
- 10 - a pharmaceutical formulation in which the number of sub-visible particles (≥ 25.00 mm, < 400.00 mm) after 9 months of storage at a temperature of 563°C is 0 to 15 as measured by MFI;
- a pharmaceutical formulation in which the number of sub-visible particles (≥ 10.0 mm, < 100.00 mm) after 4 weeks of storage at a temperature of 563°C is 0 to 1,000 as measured by MFI;
- a pharmaceutical formulation in which the number of sub-visible particles (≥ 10.0 mm, < 100.00 mm) after 4 weeks of storage at a temperature of 563°C is 0 to 100 as measured by MFI;
- 15 - a pharmaceutical formulation in which the number of sub-visible particles (≥ 25.0 mm, < 100.00 mm) after 4 weeks of storage at a temperature of 563°C is 0 to 100 as measured by MFI;
- a pharmaceutical formulation in which the number of sub-visible particles (≥ 25.0 mm, < 100.00 mm) after 4 weeks of storage at a temperature of 563°C is 0 to 10 as measured by MFI;
- 20 - a pharmaceutical formulation in which the number of sub-visible particles (≥ 1.00 mm, < 100.00 mm) after 4 weeks of storage at a temperature of 4062°C is 0 to 5,000 as measured by MFI;
- a pharmaceutical formulation in which the number of sub-visible particles (≥ 1.00 mm, < 100.00 mm) after 4 weeks of storage at a temperature of 4062°C is 0 to 2,500 as measured by MFI;
- a pharmaceutical formulation in which the number of sub-visible particles (≥ 10.00 mm, < 100.00 mm) after 4 weeks of storage at a temperature of 4062°C is 0 to 1,000 as measured by MFI;
- 25 - a pharmaceutical formulation in which the number of sub-visible particles (≥ 10.00 mm, < 100.00 mm) after 4 weeks of storage at a temperature of 4062°C is 0 to 100 as measured by MFI;
- a pharmaceutical formulation in which the number of sub-visible particles (≥ 25.00 mm, < 100.00 mm) after 4 weeks of storage at a temperature of 4062°C is 0 to 100 as measured by MFI;
- 30 - a pharmaceutical formulation in which the number of sub-visible particles (≥ 25.00 mm, < 100.00 mm) after 4 weeks of storage at a temperature of 4062°C is 0 to 10 as measured by MFI;
- a pharmaceutical formulation in which the number of sub-visible particles (≥ 1.00 mm, < 400.00 mm) after 4 weeks of storage at a temperature of 4062°C at a relative humidity of 7565% under a closed condition is 0 to 20,000 as measured by MFI;
- 35 - a pharmaceutical formulation in which the number of sub-visible particles (≥ 10.00 mm, < 400.00 mm) after 4 weeks of storage at a temperature of 4062°C at a relative humidity of 7565% under a closed condition is 0 to 70 as measured by MFI;
- a pharmaceutical formulation in which the number of sub-visible particles (≥ 25.00 mm, < 400.00 mm) after 4 weeks of storage at a temperature of 4062°C at a relative humidity of 7565% under a closed condition is 0 to 15 as measured by MFI;
- 40

(H)-7 Oxidation Rate**[0092]**

- 45 - a pharmaceutical formulation in which the oxidation rate of heavy-chain Met 192 after 4 weeks of storage at a temperature of 563°C is 0% to 7% as measured by LC-MS;
- a pharmaceutical formulation in which the oxidation rate of heavy-chain Met 192 after 4 weeks of storage at a temperature of 4062°C and a relative humidity of 7565% under a closed condition is 0% to 6% as measured by LC-MS;
- 50

(H)-8 Charge Variants**[0093]**

- 55 - a pharmaceutical formulation in which the relative content of theoretical peak 4 to peak 11 is 89% to 91% as measured by cIEF after 4 weeks of storage at a temperature of 563°C;
- a pharmaceutical formulation in which the sum of theoretical peak 4 to peak 11 is 86% to 88% as measured by cIEF

- after 9 months of storage at a temperature of 563°C;
- a pharmaceutical formulation in which the sum of theoretical peak 4 to peak 11 is 86% to 88% as measured by cIEF after 4 weeks of storage at a temperature of 4062°C and a relative humidity of 7565% under a closed condition;
 - a pharmaceutical formulation in which the relative content of theoretical peak 4 to peak 11 is 86% to 88% as measured by cIEF after 4 weeks of storage at a temperature of 4062°C and a relative humidity of 7565% under a closed condition;

(H)-9 VEGF Binding Affinity

[0094]

- a pharmaceutical formulation having a VEGF binding affinity of 75% to 95% as measured by ELISA after 9 months of storage at a temperature of 563°C; and
- a pharmaceutical formulation having a VEGF binding affinity of 60% to 75% as measured by ELISA after 4 weeks of storage at a temperature of 4062°C and a relative humidity of 7565% under a closed condition.

[Method for Preparing Stable Pharmaceutical Formulation]

[0095] The stable pharmaceutical formulation of the present disclosure may be prepared using any known method which is not limited to a particular method. For example, the stable pharmaceutical formulation may be prepared by adding a buffer to a solution containing a surfactant, a sugar or a derivative thereof and an isotonic agent while adjusting the pH of the solution, and then adding a recombinant fusion protein to the mixed solution. Alternatively, the pharmaceutical formulation may be prepared by preparing a solution containing some excipients in the final step of a purification process, and then adding the remaining component to the solution. For example, the pharmaceutical formulation may be prepared by preparing a solution containing a recombinant fusion protein, a buffer, a sugar or a derivative thereof and an isotonic agent in the final step of a purification process, and then adding a surfactant to the solution.

[0096] In addition, the method for preparing the formulation may not comprise a freeze-drying step.

[0097] When the preparation method does not comprise the freeze-drying step, for example, the pharmaceutical formulation prepared according to the present disclosure may be treated by sterilization, and then immediately placed in a sealed container, such as a glass vial or pre-filled syringe, which is a primary packaging material.

[Method of Use of Stable Pharmaceutical Formulation]

[0098] The stable pharmaceutical formulation according to the present disclosure may be used to treat diseases caused by release of VEGF. Examples of diseases caused by release of VEGF include, but are not limited to, neovascular (wet) age-related macular degeneration, visual impairment due to retinal vein occlusion (central retinal vein occlusion or branch retinal vein occlusion) macular edema, visual impairment due to diabetic macular edema, and visual impairment due to choroidal neovascularization caused by pathologic myopia.

[0099] The stable pharmaceutical formulation according to the present disclosure may be used in a single-dosage form or a multiple-dosage form, and should be administered by a qualified physician with experience in intraocular administration (injection).

[0100] The concentrations of other components, including the recombinant fusion protein, in the pharmaceutical formulation, are as described above, and the total volume of the pharmaceutical formulation may be 0.05 to 3 mL.

[0101] The dosage and timing of administration of the pharmaceutical formulation may vary depending on the kind of disease, the severity and course of the disease, the patient's health and response to treatment, and the judgment of the treating physician, and the recommended dosage thereof is limited to 2 mg (equivalent to about 50 microliters), but intervals and timing of administration thereof are not limited. For example, a single product comprising the pharmaceutical formulation may be administered into one eye at a dose of 2 mg (as the concentration of the recombinant fusion protein), and then the same dose may be administered at intervals of 2 weeks to 2 months. Dosage intervals longer than 16 weeks have not been studied.

[0102] In one embodiment of the present disclosure, the stable pharmaceutical formulation may not be subjected to a reconstitution step, a dilution step, or both, before use.

[Treatment Method and Stabilization Method]

[0103] The present disclosure also provides a method for treating a patient, who has a disease caused by VEGF release, by using a stable pharmaceutical formulation containing: (A) a recombinant fusion protein; (B) a surfactant; (C) a sugar or a derivative thereof; and (D) a buffer.

[0104] The present disclosure also provides a method of stabilizing a stable pharmaceutical formulation containing: (A) a recombinant fusion protein; (B) a surfactant; (C) a sugar or a derivative thereof; and (D) a buffer, by providing pharmaceutical formulation conditions for stabilizing the recombinant fusion protein.

5 [0105] In one embodiment of the treating method or the stabilizing method, the pharmaceutical formulation may be in a liquid form.

[0106] In one embodiment of the treating method or the stabilizing method, the recombinant fusion protein (A) may comprise a vascular endothelial growth factor (VEGF) antagonist.

[0107] In one embodiment of the treating method or the stabilizing method, the recombinant fusion protein (A) may comprise a human VEGF receptor extracellular domain.

10 [0108] In one embodiment of the treating method or the stabilizing method, the recombinant fusion protein (A) may comprise human VEGF receptor extracellular domain 1, 2, or a mixture thereof.

[0109] In one embodiment of the treating method or the stabilizing method, the recombinant fusion protein (A) may comprise an immunoglobulin G (IgG) Fc region, preferably a human immunoglobulin G (IgG) Fc region.

15 [0110] In one embodiment of the treating method or the stabilizing method, the recombinant fusion protein (A) may comprise: (1) a VEGF receptor extracellular domain 1 component comprising amino acids 27 to 129 of SEQ ID NO: 2; (2) a VEGF receptor extracellular domain 2 component comprising amino acids 130 to 231 of SEQ ID NO: 2; and (3) an Fc region component comprising amino acids 232 to 457 of SEQ ID NO: 2.

[0111] In one embodiment of the treating method or the stabilizing method, the recombinant fusion protein (A) may comprise aflibercept.

20 [0112] In one embodiment of the treating method or the stabilizing method, the concentration of the recombinant fusion protein (A) may be 5 to 100 mg/ml.

[0113] In one embodiment of the treating method or the stabilizing method, the surfactant (B) may comprise polysorbate, poloxamer, or a mixture thereof.

25 [0114] In one embodiment of the treating method or the stabilizing method, the surfactant (B) may comprise polysorbate 20, polysorbate 40, polysorbate 60, polysorbate 80, or a mixture of two or more thereof.

[0115] In one embodiment of the treating method or the stabilizing method, the surfactant (B) may comprise polysorbate 20.

[0116] In one embodiment of the treating method or the stabilizing method, the concentration of the surfactant (B) may be 0.01 to 0.1% (w/v).

30 [0117] In one embodiment of the treating method or the stabilizing method, the sugar (C) may comprise a monosaccharide, a disaccharide, an oligosaccharide, a polysaccharide, or a mixture of two or more thereof, and the derivative of the sugar (C) may comprise a sugar alcohol, a sugar acid, or a mixture thereof.

[0118] In one embodiment of the treating method or the stabilizing method, the sugar or derivative thereof (C) may comprise sorbitol, mannitol, trehalose, sucrose, or a mixture of two or more thereof.

35 [0119] In one embodiment of the treating method or the stabilizing method, the sugar or derivative thereof (C) may comprise trehalose.

[0120] In one embodiment of the treating method or the stabilizing method, the concentration of the sugar or derivative thereof (C) may be 1 to 20% (w/v).

[0121] In one embodiment of the treating method or the stabilizing method, the buffer (D) may comprise an amino acid.

40 [0122] In one embodiment of the treating method or the stabilizing method, the buffer (D) may comprise a free amino acid, an amino acid salt, or a mixture thereof.

[0123] In one embodiment of the treating method or the stabilizing method, the buffer (D) may comprise histidine, histidine salt, or a mixture thereof.

45 [0124] In one embodiment of the treating method or the stabilizing method, the concentration of the buffer (D) may be 1 to 20 mM.

[0125] In one embodiment of the treating method or the stabilizing method, the stable pharmaceutical formulation of the present disclosure may be free of acetic acid, citric acid, phosphoric acid, or a mixture thereof.

[0126] In one embodiment of the treating method or the stabilizing method, the stable pharmaceutical formulation of the present disclosure may further contain (E) an isotonic agent.

50 [0127] The isotonic agent (E) may comprise sodium chloride (NaCl), potassium chloride (KCl), calcium chloride (CaCl₂), or a mixture of two or more thereof.

[0128] In one embodiment of the treating method or the stabilizing method, the content of the isotonic agent (E) may be 30 mM or less.

55 [0129] In one embodiment of the treating method or the stabilizing method, the formulation of the present disclosure may have a pH of 5.0 to 7.0.

[0130] In one embodiment of the treating method or the stabilizing method, the formulation of the present disclosure may be free of NaF, KBr, NaBr, Na₂SO₄, NaSCN, K₂SO₄, or a mixture thereof.

[0131] In one embodiment of the present disclosure, the formulation of the present disclosure may be free of a chelating

agent.

[0132] The stable pharmaceutical formulation according to one embodiment of the treating method or the stabilizing method may contain: (A) 5 to 100 mg/ml of a recombinant fusion protein comprising (1) a VEGF receptor extracellular domain 1 component comprising amino acids 27 to 129 of SEQ ID NO: 2, (2) a VEGF receptor extracellular domain 2 component comprising amino acids 130 to 231 of SEQ ID NO: 2, and (3) an Fc region component comprising amino acids 232 to 457 of SEQ ID NO: 2; (B) 0.01 to 0.1% (w/v) of a surfactant; (C) 1 to 20% (w/v) of a sugar or a derivative thereof; and (D) 1 to 20 mM of a buffer. The pharmaceutical formulation according to one embodiment of the treating method or the stabilizing method may further contain (E) 30 mM or less of an isotonic agent.

[0133] The stable pharmaceutical formulation according to one embodiment of the treating method or the stabilizing method may contain: (A) a vascular endothelial growth factor (VEGF) antagonist; (B) polysorbate; (C) a sugar or a derivative thereof; and (D) histidine. The stable pharmaceutical formulation according to one embodiment of the treating method or the stabilizing method may further contain (E) sodium chloride.

[0134] The stable pharmaceutical formulation according to one embodiment of the treating method or the stabilizing method may contain: (A) 5 to 100 mg/ml of a recombinant fusion protein comprising (1) a VEGF receptor extracellular domain 1 component comprising amino acids 27 to 129 of SEQ ID NO: 2, (2) a VEGF receptor extracellular domain 2 component comprising amino acids 130 to 231 of SEQ ID NO: 2, and (3) an Fc region component comprising amino acids 232 to 457 of SEQ ID NO: 2; (B) 0.01 to 0.1% (w/v) of polysorbate; (C) 1 to 20% (w/v) of a sugar or a derivative thereof; and (D) 1 to 20 mM of histidine. The stable pharmaceutical formulation according to one embodiment of the treating method or the stabilizing method may further contain (E) 30 mM or less of sodium chloride.

[0135] The number of sub-visible particles having a particle diameter of equal to or more than 10.00 µm to less than 400.00 µm in the stable pharmaceutical formulation according to one embodiment of the treating method or the stabilizing method may be 50 or less as measured by HIAc after 9 months of storage at 563°C.

[0136] The stable pharmaceutical formulation according to one embodiment of the treating method or the stabilizing method may show a main component content of 98% or more after 10 days of storage at 563°C.

[0137] The stable pharmaceutical formulation according to one embodiment of the treating method or the stabilizing method may show a high-molecular-weight component content of 1% or less after 10 days of storage at 563°C.

[0138] The stable pharmaceutical formulation according to one embodiment of the treating method or the stabilizing method may show a low-molecular-weight component content of 0.05% or less after 10 days of storage at 563°C.

[0139] The stable pharmaceutical formulation according to one embodiment of the treating method or the stabilizing method may show a charge variant content of 87% or more after 9 months of storage at 563°C.

[0140] The stable pharmaceutical formulation according to one embodiment of the treating method or the stabilizing method may show a VEGF binding affinity of 90% or more after 9 months of storage at 563°C.

[0141] In one embodiment of the treating method or the stabilizing method, the stable pharmaceutical formulation may be for intraocular administration, preferably intravitreal administration.

[0142] In one embodiment of the treating method or the stabilizing method, the stable pharmaceutical formulation may not be subjected to a reconstitution step, a dilution step, or both, before use.

[0143] A glass vial according to one embodiment of the treating method or the stabilizing method may be filled with the stable pharmaceutical formulation.

[0144] A pre-filled syringe according to one embodiment of the treating method or the stabilizing method may be filled with the stable pharmaceutical formulation.

[Product]

[0145] The present disclosure also provides a product comprising: the stable pharmaceutical formulation; and a container receiving the stable pharmaceutical formulation in a sealed state.

[0146] The stable pharmaceutical formulation is as described above.

[0147] In one embodiment of the present disclosure, the container may be formed of a material such as glass, a polymer (plastic), a metal or the like, but is not limited thereto. In one embodiment of the present disclosure, the container is a bottle, a vial, a cartridge, a syringe (pre-filled syringe), or a tube, but is not limited thereto. In one embodiment of the present disclosure, the container may be a glass or polymer vial, or a glass or polymer pre-filled syringe.

[0148] Specific product forms of the above-described vial, cartridge, pre-filled syringe, and methods of filling the stable pharmaceutical formulation into the vial, cartridge, pre-filled syringe, may be readily available or implemented by any person skilled in the technical field to which the present disclosure pertains. For example, U.S. Pat. Nos. 4,881,335 and 6,331,174, etc., disclose the specific product form of a pre-filled syringe and a filling method. The above-described vial, cartridge, pre-filled syringe may be a commercially available product or may be a product separately manufactured considering the physical properties of the stable pharmaceutical formulation, an area to which the formulation is to be administered, the dose of the formulation, and the like.

[0149] In one embodiment of the present disclosure, the product may further comprise instructions providing a method

of using the stable pharmaceutical formulation, a method of storing the formulation, or both. The method of using the formulation includes a method for treating a disease caused by VEGF release, and may include the route of administration, the dose of the formulation, and the timing of administration.

[0150] In one embodiment of the present disclosure, the product may comprise other required utensils (e.g., a needle, a syringe, etc.) from a commercial viewpoint and a user viewpoint.

[0151] Hereinafter, the present disclosure will be described in detail with reference to examples. However, the following examples serve merely to illustrate the present disclosure, and the scope of the present disclosure is not limited to the following examples.

Examples

[0152] The recombinant fusion protein used in the following experimental examples was affibercept incubated and purified at the Celtrion Research Institute.

[0153] The physical stability, chemical stability and biological activity of pharmaceutical formulations used in the following experimental examples were measured using the following methods.

- Turbidity

[0154] The absorbance at 600 nm was measured using a UV-Vis spectrophotometer.

- Content of Main Component

[0155] The main component content (main peak %) was measured using size exclusion high-performance liquid chromatography (SE-HPLC).

- Content of High-Molecular-Weight Components

[0156] The content of high-molecular-weight components (pre-peak %) was measured using size exclusion high-performance liquid chromatography (SE-HPLC).

- Content of Low-Molecular-Weight Components

[0157] The content of low-molecular-weight components (post-peak %) was measured using size exclusion high-performance liquid chromatography (SE-HPLC).

- Content of one recombinant human VEGF receptor extracellular domain 1, one recombinant human VEGF receptor extracellular domain 2 and recombinant human IgG Fc region (1VEGF1 + 1VEGF2 + Fc)

[0158] The content (%) of one intact recombinant human VEGF receptor extracellular domain 1, one recombinant human VEGF receptor extracellular domain 2 and a recombinant human IgG Fc region (1VEGF1 + 1VEGF2 + Fc) was measured using reduced capillary electrophoresis-sodium dodecyl sulfate (R CE-SDS).

- Number of Sub-Visible Particles

[0159] The number of sub-visible particles was measured using Micro Flow Imaging (MFI) and a light-shielding particle counter (model: HIAC 9703).

- Oxidation

[0160] The oxidation (%) of heavy-chain Met 192 was measured by peptide mapping using liquid chromatography-mass spectrometry (LC-MS).

- Charge Variants (relative content of peak 4 to peak 11 in a total of 12 peaks)

[0161] Acidic and basic peaks (%) were measured by Capillary Iso-Electric Focusing (cIEF).

- VEGF Binding Affinity

[0162] VEGF binding affinity (%) was measured by Enzyme-Linked ImmunoSorbent Assay (ELISA).

5 **Experimental Example 1: Comparison at Different Concentrations of Histidine Buffer; Comparison at pH 5.5 and pH 6.5; Comparison at Different Concentrations of Sodium Chloride Isotonic Agent; Comparison at Different Concentrations of Trehalose; and Confirmation of Superiority of the Formulation of the Present Disclosure**

10 [0163] For preparation of pharmaceutical formulations to be used in Experimental Example 1, each buffer was prepared so as to have a predetermined pH, and trehalose and sodium chloride was added thereto. Then, a recombinant fusion protein was added thereto and a surfactant was added, thereby preparing the samples shown in Table 1 below. The specific content of each component is shown in Table 1 below. Examples 1 to 9 and Comparative Example 1 were samples to which aflibercept purified at the Celltrion Research Institute was added, and Comparative Example 2 was a sample prepared by adding Regeneron's Eylea (aflibercept) to the same pharmaceutical formulation as that of Comparative Example 1. The target volume of each sample for filling a glass vial was 0.276 ml.

15 [0164] The pharmaceutical formulations prepared according to Examples 1 to 9 and Comparative Examples 1 and 2 were stored at a temperature of 563°C and at a temperature of 4062°C and a relative humidity of 7565%, and measured for their stabilities after 0 week, 2 weeks and 4 weeks at a temperature of 563°C, and for their stabilities after 2 weeks and 4 weeks at a temperature of 4062°C and a relative humidity of 7565%. The results of the measurement are shown in Tables 2 to 15 below.

[Table 1] Constitution of Experimental Example 1

	Buffer	pH	Sugar	Isotonic agent	Surfactant	Protein concentration
Example 1	8.0 mM histidine	5.5	10% (w/v) trehalose	13.0 mM sodium chloride	0.03% (w/v) polysorbate 20	40 mg/mL
Example 2	8.0 mM histidine	6.0	10% (w/v) trehalose	13.0 mM sodium chloride	0.03% (w/v) polysorbate 20	40 mg/mL
Example 3	8.0 mM histidine	6.5	10% (w/v) trehalose	13.0 mM sodium chloride	0.03% (w/v) polysorbate 20	40 mg/mL
Example 4	6.4 mM histidine	6.0	10% (w/v) trehalose	13.0 mM sodium chloride	0.03% (w/v) polysorbate 20	40 mg/mL
Example 5	9.6 mM histidine	6.0	10% (w/v) trehalose	13.0 mM sodium chloride	0.03% (w/v) polysorbate 20	40 mg/mL
Example 6	8.0 mM histidine	6.0	10% (w/v) trehalose	10.4 mM sodium chloride	0.03% (w/v) polysorbate 20	40 mg/mL
Example 7	8.0 mM histidine	6.0	10% (w/v) trehalose	15.6 mM sodium chloride	0.03% (w/v) polysorbate 20	40 mg/mL
Example 8	8.0 mM histidine	6.0	8% (w/v) trehalose	13.0 mM sodium chloride	0.03% (w/v) polysorbate 20	40 mg/mL
Example 9	8.0 mM histidine	6.0	12% (w/v) trehalose	13.0 mM sodium chloride	0.03% (w/v) polysorbate 20	40 mg/mL

(continued)

	Buffer	pH	Sugar	Isotonic agent	Surfactant	Protein concentration
Comparative Example 1	10 mM sodium phosphate	6.2	5% (w/v) sucrose	40.0 mM sodium chloride	0.03% (w/v) polysorbate 20	40 mg/mL
Comparative Example 2	10 mM sodium phosphate	6.2	5% (w/v) sucrose	40.0 mM sodium chloride	0.03% (w/v) polysorbate 20	40 mg/mL

[Table 2] Turbidity

	After 0 week at 563°C	After 2 weeks at 563°C	After 4 weeks at 563°C	After 2 weeks at 4062°C and 7565%	After 4 weeks at 4062°C and 7565%
Example 1	0.0154	0.0163	0.0275	0.0181	0.0143
Example 2	0.0230	0.0196	0.0252	0.0186	0.0258
Example 3	0.0214	0.0214	0.0207	0.0212	0.0203
Example 4	0.0200	0.0192	0.0164	0.0283	0.0350
Example 5	0.0156	0.0172	0.0206	0.0385	0.0245
Example 6	0.0150	0.0163	0.0240	0.0153	0.0190
Example 7	0.0124	0.0165	0.0162	0.0229	0.0191
Example 8	0.0157	0.0259	0.0176	0.0194	0.0210
Example 9	0.0126	0.0212	0.0394	0.0153	0.0379
Comparative Example 1	0.0203	0.0197	0.0207	0.0240	0.0191
Comparative Example 2	0.0105	0.0178	0.0170	0.0197	0.0181

[0165] Referring to Table 2 above, it can be seen that the formulations of Examples 1 to 9 satisfying the ranges specified in the present disclosure showed very low turbidities even after 4 weeks at a temperature of 563°C, suggesting that they were transparent pharmaceutical formulations. In particular, it can be seen that these formulations showed an absorbance of 0.0400 or lower even after 4 weeks at a temperature of 4062°C and a relative humidity of 7565%. It can be seen that these results are similar to those obtained for the conventional formulations (Comparative Examples 1 and 2).

[Table 3] Intact main component content (main peak %)

	After 0 week at 563°C	After 2 weeks at 563°C	After 4 weeks at 563°C	After 2 weeks at 4062°C and 7565%	After 4 weeks at 4062°C and 7565%
Example 1	99.33	99.32	99.18	94.52	89.41
Example 2	99.04	98.96	98.84	94.85	91.13
Example 3	98.89	98.76	98.61	94.96	91.47
Example 4	98.98	98.89	98.88	95.11	91.31
Example 5	99.08	98.94	98.95	95.11	91.27
Example 6	99.14	99.04	98.86	95.17	91.89
Example 7	98.91	98.92	98.95	95.20	91.27
Example 8	99.06	99.03	98.88	94.49	89.88

(continued)

	After 0 week at 563°C	After 2 weeks at 563°C	After 4 weeks at 563°C	After 2 weeks at 4062°C and 7565%	After 4 weeks at 4062°C and 7565%
Example 9	99.01	99.04	98.94	95.63	92.22
Comparative Example 1	98.90	98.61	98.79	92.00	8607
Comparative Example 2	98.09	97.95	97.98	92.97	89.34

[0166] Referring to Table 3 above, it can be seen that, after 4 weeks at a temperature of 563°C, the main component contents of the pharmaceutical formulations of all Examples 1 to 9 satisfying the ranges specified in the present disclosure were similar to those of Comparative Examples 1 and 2. However, it can be seen that, after 4 weeks at a temperature of 4062°C and a relative humidity of 7565%, the main component contents of the pharmaceutical formulations of Examples 1 to 9 were higher than those of Comparative Examples 1 and 2, suggesting that the formulation of the present disclosure is an improved pharmaceutical formulation capable of more stably storing a desired recombinant fusion protein.

[Table 4] Content (%) of high-molecular-weight components

	After 0 week at 563°C	After 2 weeks at 563°C	After 4 weeks at 563°C	After 2 weeks at 4062°C and 7565%	After 4 weeks at 4062°C and 7565%
Example 1	0.66	0.68	0.82	4.70	9.44
Example 2	0.96	1.03	1.15	4.69	8.24
Example 3	1.10	1.23	1.35	4.97	8.43
Example 4	1.02	1.08	1.10	4.47	8.10
Example 5	0.90	1.06	1.01	4.41	8.12
Example 6	0.86	0.94	1.13	4.35	7.56
Example 7	1.07	1.06	1.04	4.36	8.12
Example 8	0.88	0.96	1.10	5.07	9.47
Example 9	0.98	0.94	0.93	3.94	7.15
Comparative Example 1	1.10	1.38	1.19	7.45	13.29
Comparative Example 2	1.89	2.01	1.99	6.94	10.53

[0167] Referring to Table 4 above, it can be seen that, after 4 weeks at a temperature of 563°C, the high-molecular-weight component contents of the pharmaceutical formulations of all Examples 1 to 9 satisfying the ranges specified in the present disclosure were similar to those of Comparative Examples 1 and 2. However, it can be seen that, after 4 weeks at a temperature of 4062°C and a relative humidity of 7565%, the high-molecular-weight component contents of the pharmaceutical formulations of Examples 1 to 9 were lower than those of Comparative Examples 1 and 2, suggesting that the formulation of the present disclosure is an improved pharmaceutical formulation capable of more stably storing a desired recombinant fusion protein.

[Table 5] Content (%) of low-molecular-weight components

	After 0 week at 563°C	After 2 weeks at 563°C	After 4 weeks at 563°C	After 2 weeks at 4062°C and 7565%	After 4 weeks at 4062°C and 7565%
Example 1	0.02	0.00	0.01	0.77	1.15
Example 2	0.00	0.01	0.01	0.47	0.64
Example 3	0.01	0.01	0.04	0.08	0.10

(continued)

	After 0 week at 563°C	After 2 weeks at 563°C	After 4 weeks at 563°C	After 2 weeks at 4062°C and 7565%	After 4 weeks at 4062°C and 7565%
Example 4	0.00	0.03	0.02	0.42	0.59
Example 5	0.02	0.00	0.03	0.48	0.62
Example 6	0.00	0.01	0.00	0.48	0.55
Example 7	0.01	0.02	0.01	0.43	0.61
Example 8	0.06	0.02	0.02	0.44	0.65
Example 9	0.01	0.01	0.13	0.43	0.63
Comparative Example 1	0.00	0.01	0.02	0.54	0.64
Comparative Example 2	0.02	0.04	0.03	0.09	0.13

[0168] Referring to Table 5 above, it can be seen that, after 4 weeks at a temperature of 563°C, the low-molecular-weight component contents of the pharmaceutical formulations of all Examples 1 to 9 satisfying the ranges specified in the present disclosure were similar to those of Comparative Examples 1 and 2. In addition, it can be seen that, after 4 weeks at a temperature of 4062°C and a relative humidity of 7565%, the low-molecular-weight component contents of the pharmaceutical formulations of Examples 2 to 9 were similar to that of Comparative Example 1. However, it was confirmed that, at pH 5.5, the content of low-molecular-weight components in Example 1 was somewhat disadvantageous compared to those in Comparative Examples 1 to 2, and thus it was necessary to adjust the target pH and pH range to slightly increased values. The experimental results of adjusting the pH range are included in Experimental Example 2.

[Table 6] Content (%) of one recombinant human VEGF receptor extracellular domain 1, one recombinant human VEGF receptor extracellular domain 2 and recombinant human IgG Fc region (1VEGF1 + 1VEGF2 + Fc)

	After 0 week at 563°C	After 2 weeks at 563°C	After 4 weeks at 563°C	After 2 weeks at 4062°C and 7565%	After 4 weeks at 4062°C and 7565%
Example 1	95.43	95.97	98.30	95.18	90.60
Example 2	97.33	97.65	98.30	95.23	93.80
Example 3	97.57	98.04	98.30	97.32	96.20
Example 4	97.53	97.45	98.30	95.98	94.00
Example 5	97.45	97.83	98.30	95.69	93.80
Example 6	97.41	97.27	98.30	95.67	94.10
Example 7	96.65	98.35	97.70	95.74	93.80
Example 8	97.58	97.43	98.20	96.42	93.80
Example 9	97.52	96.33	97.90	95.71	93.90
Comparative Example 1	97.57	97.27	98.40	96.35	93.60
Comparative Example 2	97.89	97.15	98.30	96.74	96.40

[0169] Referring to Table 6 above, it can be seen that, after 4 weeks at a temperature of 563°C, the contents of one recombinant human VEGF receptor extracellular domain 1, one recombinant human VEGF receptor extracellular domain 2 and a recombinant human IgG Fc region (1VEGF1 + 1VEGF2 + Fc) in the pharmaceutical formulations of all Examples 1 to 9 satisfying the ranges specified in the present disclosure were similar to those in Comparative Examples 1 and 2. In addition, it can be seen that, after 4 weeks at a temperature of 4062°C and a relative humidity of 7565%, the contents

of one recombinant human VEGF receptor extracellular domain 1, one recombinant human VEGF receptor extracellular domain 2 and a recombinant human IgG Fc region (1VEGF1 + 1VEGF2 + Fc) in the pharmaceutical formulations of Examples 2 to 9 were similar to those in Comparative Examples 1 and 2. However, it was confirmed that, at pH 5.5, the content of one recombinant human VEGF receptor extracellular domain 1, one recombinant human VEGF receptor extracellular domain 2 and a recombinant human IgG Fc region (1VEGF1 + 1VEGF2 + Fc) in Example 1 was somewhat disadvantageous compared to those in Comparative Examples 1 to 2, and thus it was necessary to adjust the target pH and pH range to slightly increased values. The experimental results of adjusting the target pH and the pH range are included in Experimental Example 2.

[Table 7] Number of sub-visible particles (≥ 2.00 mm, < 400.00 mm, particles/mL) measured by HIAC

	After 0 week at 563°C	After 2 weeks at 563°C	After 4 weeks at 563°C	After 2 weeks at 4062°C and 7565%	After 4 weeks at 4062°C and 7565%
Example 1	18	170	115	112	77
Example 2	68	150	53	62	70
Example 3	30	20	13	15	78
Example 4	15	25	12	43	20
Example 5	105	28	12	60	87
Example 6	53	42	7	38	52
Example 7	33	28	7	53	55
Example 8	8	40	7	28	68
Example 9	33	68	13	142	73
Comparative Example 1	53	72	12	57	48
Comparative Example 2	-	-	-	-	-

[0170] Referring to Table 7 above, it can be seen that, after 4 weeks at a temperature of 563°C, the numbers of sub-visible particles (≥ 2.00 mm, < 400.00 mm) measured by HIAC in the pharmaceutical formulations of all Examples 1 to 9 satisfying the ranges specified in the present disclosure were similar to that in Comparative Example 1, suggesting that these formulations were very clean pharmaceutical formulations. In addition, it can be seen that, even after 4 weeks at a temperature of 4062°C and a relative humidity of 7565%, the numbers of sub-visible particles (≥ 2.00 mm, < 400.00 mm) measured by HIAC in the pharmaceutical formulations of Examples 1 to 9 were similar to that in Comparative Example 1.

[Table 8] Number of sub-visible particles (≥ 10.00 mm, < 400.00 mm, particles/mL) measured by HIAC

	After 0 week at 563°C	After 2 weeks at 563°C	After 4 weeks at 563°C	After 2 weeks at 4062°C and 7565%	After 4 weeks at 4062°C and 7565%
Example 1	5	10	3	23	8
Example 2	5	23	13	7	2
Example 3	7	2	0	3	15
Example 4	2	2	0	17	3
Example 5	7	7	0	10	10
Example 6	10	7	0	10	20
Example 7	25	2	0	13	3
Example 8	0	8	0	5	3

(continued)

	After 0 week at 563°C	After 2 weeks at 563°C	After 4 weeks at 563°C	After 2 weeks at 4062°C and 7565%	After 4 weeks at 4062°C and 7565%
Example 9	5	7	0	13	2
Comparative Example 1	3	12	0	8	3
Comparative Example 2	-	-	-	-	-

[0171] Referring to Table 8 above, it can be seen that, after 4 weeks at a temperature of 563°C, the numbers of sub-visible particles (≥ 10.00 mm, <400.00 mm) measured by HiAC in the pharmaceutical formulations of all Examples 1 to 9 satisfying the ranges specified in the present disclosure were similar to that in Comparative Example 1, suggesting that these formulations were very clean pharmaceutical formulations. In addition, it can be seen that, even after 4 weeks at a temperature of 4062°C and a relative humidity of 7565%, the numbers of sub-visible particles (≥ 10.00 mm, <400.00 mm) measured by HiAC in the pharmaceutical formulations of Examples 1 to 9 were similar to that in Comparative Example 1.

[Table 9] Number of sub-visible particles (≥ 25.00 mm, <400.00 mm, particles/mL) measured by HiAC

	After 0 week at 563°C	After 2 weeks at 563°C	After 4 weeks at 563°C	After 2 weeks at 4062°C and 7565%	After 4 weeks at 4062°C and 7565%
Example 1	2	0	0	2	0
Example 2	0	5	0	0	0
Example 3	0	0	0	2	0
Example 4	0	0	0	2	0
Example 5	0	3	0	0	0
Example 6	3	0	0	0	2
Example 7	5	0	0	2	0
Example 8	0	2	0	0	0
Example 9	0	3	0	0	0
Comparative Example 1	0	0	0	0	0
Comparative Example 2	-	-	-	-	-

[0172] Referring to Table 9 above, it can be seen that, after 4 weeks at a temperature of 563°C, the numbers of sub-visible particles (≥ 25.00 mm, <400.00 mm) measured by HiAC in the pharmaceutical formulations of all Examples 1 to 9 satisfying the ranges specified in the present disclosure were similar to that in Comparative Example 1, suggesting that these formulations were very clean pharmaceutical formulations. In addition, it can be seen that, even after 4 weeks at a temperature of 4062°C and a relative humidity of 7565%, the numbers of sub-visible particles (≥ 25.00 mm, <400.00 mm) measured by HiAC in the pharmaceutical formulations of Examples 1 to 9 were similar to that in Comparative Example 1.

[Table 10] Number of sub-visible particles (≥ 1.00 mm, <100.00 mm, particles/mL) measured by MFI

	After 0 week at 563°C	After 2 weeks at 563°C	After 4 weeks at 563°C	After 2 weeks at 4062°C and 7565%	After 4 weeks at 4062°C and 7565%
Example 1	-	2596	-	2885	6418

(continued)

	After 0 week at 563°C	After 2 weeks at 563°C	After 4 weeks at 563°C	After 2 weeks at 4062°C and 7565%	After 4 weeks at 4062°C and 7565%
Example 2	8406	1116	1996	1208	6484
Example 3	5255	7519	2436	1678	3768
Example 4	14701	-	3744	514	8558
Example 5	16433	1367	3819	1438	3190
Example 6	5135	990	4996	1979	2812
Example 7	6262	566	3459	1666	18324
Example 8	7976	5378	4145	1559	4109
Example 9	8554	672	4055	1609	11022
Comparative Example 1	6996	371	3197	496	3999
Comparative Example 2	-	-	-	-	-

[0173] Referring to Table 10 above, it can be seen that, after 4 weeks at a temperature of 563°C, the numbers of sub-visible particles (≥ 1.00 mm, <100.00 mm) measured by MFI in the pharmaceutical formulations of all Examples 1 to 9 satisfying the ranges specified in the present disclosure were similar to that in Comparative Example 1, suggesting that these formulations were very clean pharmaceutical formulations. In addition, it can be seen that, even after 4 weeks at a temperature of 4062°C and a relative humidity of 7565%, the numbers of sub-visible particles (≥ 1.00 mm, <100.00 mm) measured by MFI in the pharmaceutical formulations of Examples 1 to 9 were similar to that in Comparative Example 1.

[Table 11] Number of sub-visible particles (≥ 10.00 mm, <100.00 mm, particles/mL) measured by MFI

	After 0 week at 563°C	After 2 weeks at 563°C	After 4 weeks at 563°C	After 2 weeks at 4062°C and 7565%	After 4 weeks at 4062°C and 7565%
Example 1	-	126	-	31	35
Example 2	22	5	22	10	51
Example 3	51	27	14	20	33
Example 4	13	-	26	8	48
Example 5	17	9	19	15	18
Example 6	19	26	40	31	51
Example 7	19	7	18	22	40
Example 8	26	17	34	20	21
Example 9	22	18	30	96	68
Comparative Example 1	9	13	31	4	19
Comparative Example 2	-	-	-	-	-

[0174] Referring to Table 11 above, it can be seen that, after 4 weeks at a temperature of 563°C, the numbers of sub-visible particles (≥ 10.00 mm, <100.00 mm) measured by MFI in the pharmaceutical formulations of all Examples 1 to 9 satisfying the ranges specified in the present disclosure were similar to that in Comparative Example 1, suggesting that these formulations were very clean pharmaceutical formulations. In addition, it can be seen that, even after 4 weeks at

a temperature of 4062°C and a relative humidity of 7565%, the numbers of sub-visible particles (≥ 10.00 mm, <100.00 mm) measured by MFI in the pharmaceutical formulations of Examples 1 to 9 were similar to that in Comparative Example 1.

5 [Table 12] Number of sub-visible particles (≥ 25.00 mm, <100.00 mm, particles/mL) measured by MFI

	After 0 week at 563°C	After 2 weeks at 563°C	After 4 weeks at 563°C	After 2 weeks at 4062°C and 7565%	After 4 weeks at 4062°C and 7565%
10 Example 1	-	5	-	11	0
Example 2	4	0	0	0	9
Example 3	26	3	4	3	9
15 Example 4	0	-	11	4	8
Example 5	3	0	2	2	2
Example 6	3	6	2	4	15
Example 7	0	0	4	7	7
20 Example 8	5	2	4	0	0
Example 9	7	4	6	7	6
Comparative Example 1	0	3	2	0	0
25 Comparative Example 2	-	-	-	-	-

30 [0175] Referring to Table 12 above, it can be seen that, after 4 weeks at a temperature of 563°C, the numbers of sub-visible particles (≥ 25.00 mm, <100.00 mm) measured by MFI in the pharmaceutical formulations of all Examples 1 to 9 satisfying the ranges specified in the present disclosure were similar to that in Comparative Example 1, suggesting that these formulation were very clean pharmaceutical formulations. In addition, it can be seen that, even after 4 weeks at a temperature of 4062°C and a relative humidity of 7565%, the numbers of sub-visible particles (≥ 25.00 mm, <100.00 mm) measured by MFI in the pharmaceutical formulations of Examples 1 to 9 were similar to that in Comparative Example 1.

35 [Table 13] Oxidation rate (Met192, %)

	After 0 week at 563°C	After 2 weeks at 563°C	After 4 weeks at 563°C	After 2 weeks at 4062°C and 7565%	After 4 weeks at 4062°C and 7565%
40 Example 1	4.9	3.5	5.1	4.0	6.1
Example 2	5.6	4.0	4.9	4.0	4.9
Example 3	3.8	4.6	4.1	4.1	4.9
45 Example 4	4.7	4.3	6.5	4.4	4.5
Example 5	4.4	3.8	4.4	4.6	4.6
Example 6	4.9	3.7	3.8	5.5	5.1
Example 7	5.2	4.7	3.7	6.6	4.7
50 Example 8	4.2	5.5	5.3	4.2	4.6
Example 9	4.1	4.7	5.3	4.5	3.9
Comparative Example 1	4.2	3.8	4.3	4.3	5.8
55 Comparative Example 2	4.6	3.2	3.7	4.0	4.4

[0176] Referring to Table 13 above, it can be seen that, after 4 weeks at a temperature of 563°C, the oxidation rates (Met192) of the pharmaceutical formulations of all Examples 1 to 9 satisfying the ranges specified in the present disclosure were similar to those of Comparative Examples 1 and 2. In addition, it can be seen that, even after 4 weeks at a temperature of 4062°C and a relative humidity of 7565%, the oxidation rates (Met192) of the pharmaceutical formulations of Examples 1 to 9 were similar to those of Comparative Examples 1 and 2.

[Table 14] Charge variants (relative content (%) of peak 4 to peak 11 in a total of 12 peaks)

	After 0 week at 563°C	After 2 weeks at 563°C	After 4 weeks at 563°C	After 2 weeks at 4062°C and 7565%	After 4 weeks at 4062°C and 7565%
Example 1	87.3	86.4	87.1	86.3	88.3
Example 2	90.7	87.0	87.0	86.4	86.4
Example 3	87.4	87.1	87.3	86.0	85.3
Example 4	89.6	86.9	87.2	86.6	87.1
Example 5	87.9	86.8	86.7	86.6	86.8
Example 6	87.7	86.7	86.9	86.5	85.4
Example 7	88.8	86.8	87.2	86.7	86.6
Example 8	86.6	86.9	87.0	86.9	87.2
Example 9	88.7	86.7	87.3	86.8	86.5
Comparative Example 1	88.9	87.0	86.6	86.7	86.2
Comparative Example 2	87.5	91.0	91.3	91.3	89.9

[0177] Referring to Table 14 above, it can be seen that, after 4 weeks at a temperature of 563°C, charge variants (the relative content of peak 4 to peak 11 in a total of 12 peaks) in the pharmaceutical formulations of all Examples 1 to 9 satisfying the ranges specified in the present disclosure were similar to those in Comparative Examples 1 and 2. In addition, it can be seen that, even after 4 weeks at a temperature of 4062°C and a relative humidity of 7565%, charge variants (the relative content of peak 4 to peak 11 in a total of 12 peaks) in the pharmaceutical formulations of Examples 1 to 9 were similar to those in Comparative Examples 1 and 2.

[Table 15] VEGF binding affinity (%)

	After 0 week at 563°C	After 2 weeks at 563°C	After 4 weeks at 563°C	After 2 weeks at 4062°C and 7565%	After 4 weeks at 4062°C and 7565%
Example 1	82	-	86	82	59
Example 2	89	-	78	70	73
Example 3	91	-	79	70	74
Example 4	98	-	72	70	69
Example 5	90	-	82	75	75
Example 6	95	-	81	84	74
Example 7	89	-	83	76	63
Example 8	99	-	73	68	59
Example 9	96	-	81	82	60
Comparative Example 1	99	-	89	78	78

(continued)

	After 0 week at 563°C	After 2 weeks at 563°C	After 4 weeks at 563°C	After 2 weeks at 4062°C and 7565%	After 4 weeks at 4062°C and 7565%
Comparative Example 2	97	-	92	79	78

[0179] Referring to Table 15 above, it can be seen that, after 4 weeks at a temperature of 563°C, the VEGF binding affinities of the pharmaceutical formulations of all Examples 1 to 9 satisfying the ranges specified in the present disclosure were similar to those of Comparative Examples 1 and 2. In addition, it can be seen that, even after 4 weeks at a temperature of 4062°C and a relative humidity of 7565%, the VEGF binding affinities of the pharmaceutical formulations of Examples 1 to 9 were similar to those of Comparative Examples 1 and 2.

Experimental Example 2: Adjustment of Target pH and pH Range for Improving Low-Molecular-Weight Components Content

[0179] For preparation of pharmaceutical formulations to be used in Experimental Example 2, each buffer was prepared so as to have a predetermined pH, and trehalose and sodium chloride were added thereto. Then, a recombinant fusion protein was added thereto and a surfactant was added, thereby preparing the samples shown in Table 16 below. The specific content of each component is shown in Table 16. The following Examples were samples to which aflibercept purified at the Celltrion Research Institute was added, and Comparative Example 1 was a sample to which Regeneron's Eylea (aflibercept) was added. The difference between Example 2 and Example 10 was the protein concentration, and the difference between Examples 10 to 14 was pH. The target volume of each sample for filling a glass vial was 0.278 ml.

[0180] The pharmaceutical formulations prepared according to Examples 2 and 10 to 14 and Comparative Example 1 were stored at a temperature of 563°C and at a temperature of 5062°C, and measured for their stabilities after 0 day and 10 days at a temperature of 563°C, and for their stabilities after 5 days and 10 days at a temperature of 5062°C. The results of the measurement are shown in Tables 17 to 30 below.

[Table 16] Constitution of Experimental Example 2

	Buffer	pH	Sugar	Isotonic agent	Surfactant	Protein concentration
Example 2	8.0 mM histidine	6.0	10% (w/v) trehalose	13.0 mM sodium chloride	0.03% (w/v) polysorbate 20	40 mg/mL
Example 10	8.0 mM histidine	6.0	10% (w/v) trehalose	13.0 mM sodium chloride	0.03% (w/v) polysorbate 20	30 mg/mL
Example 11	8.0 mM histidine	5.5	10% (w/v) trehalose	13.0 mM sodium chloride	0.03% (w/v) polysorbate 20	30 mg/mL
Example 12	8.0 mM histidine	5.9	10% (w/v) trehalose	13.0 mM sodium chloride	0.03% (w/v) polysorbate 20	30 mg/mL
Example 13	8.0 mM histidine	6.2	10% (w/v) trehalose	13.0 mM sodium chloride	0.03% (w/v) polysorbate 20	30 mg/mL
Example 14	8.0 mM histidine	6.5	10% (w/v) trehalose	13.0 mM sodium chloride	0.03% (w/v) polysorbate 20	30 mg/mL
Comparative Example 1	10 mM sodium phosphate	6.2	5% (w/v) sucrose	40.0 mM sodium chloride	0.03% (w/v) polysorbate 20	40 mg/mL

[Table 17] Intact main component content (main peak %)

	After 0 day at 563°C	After 10 days at 563°C	After 5 days at 5062°C	After 10 days at 5062°C
Example 2	99.13	99.05	49.23	28.78
Example 10	99.15	99.08	54.71	34.78
Example 11	99.16	99.05	53.66	34.20
Example 12	99.16	98.97	51.06	32.47
Example 13	97.26	98.98	53.02	34.74
Example 14	99.12	98.99	51.82	33.02
Comparative Example 1	98.00	97.82	36.13	21.64

[0181] Referring to Table 17 above, it can be seen that, after 10 days at a temperature of 563°C, the main component contents of the pharmaceutical formulations of Examples 2 and 10 to 14 satisfying the ranges specified in the present disclosure were similar to that of Comparative Example 1. However, it can be seen that, after 10 days at a temperature of 5062°C, the main component contents of the pharmaceutical formulations of Examples 2 and 10 to 14 were higher than that of Comparative Example 1, suggesting that the formulation of the present disclosure is an improved pharmaceutical formulation capable of more stably storing a desired recombinant fusion protein.

[Table 18] Content (%) of high-molecular-weight components

	After 0 day at 563°C	After 10 days at 563°C	After 5 days at 5062°C	After 10 days at 5062°C
Example 2	0.84	0.92	44.81	64.84
Example 10	0.75	0.90	39.99	59.85
Example 11	0.81	0.90	39.27	57.98
Example 12	0.83	0.99	43.80	62.17
Example 13	2.70	0.98	42.91	61.49
Example 14	0.86	0.99	45.23	63.92
Comparative Example 1	1.98	2.15	61.70	76.09

[0182] Referring to Table 18 above, it can be seen that, after 10 days at a temperature of 563°C, the high-molecular-weight component contents of the pharmaceutical formulations of Examples 2 and 10 to 14 satisfying the ranges specified in the present disclosure were lower than to that of Comparative Example 1. In addition, it can be seen that, even after 10 days at a temperature of 5062°C, the high-molecular-weight component contents of the pharmaceutical formulations of Examples 2 and 10 to 14 were lower than to that of Comparative Example 1, suggesting that the formulation of the present disclosure is an improved pharmaceutical formulation capable of more stably storing a desired recombinant fusion protein.

[Table 19] Content (%) of low-molecular-weight components

	After 0 day at 563°C	After 10 days at 563°C	After 5 days at 5062°C	After 10 days at 5062°C
Example 2	0.04	0.03	5.96	6.38
Example 10	0.10	0.02	5.29	5.38
Example 11	0.03	0.05	7.06	7.82
Example 12	0.01	0.04	5.14	5.36

(continued)

	After 0 day at 563°C	After 10 days at 563°C	After 5 days at 5062°C	After 10 days at 5062°C
Example 13	0.03	0.04	4.07	3.77
Example 14	0.02	0.02	2.95	3.06
Comparative Example 1	0.02	0.02	2.17	2.28

[0183] Referring to Table 19 above, it can be seen that, after 10 days at a temperature of 563°C, the low-molecular-weight component contents of the pharmaceutical formulations of Examples 2 and 10 to 14 satisfying the ranges specified in the present disclosure were similar to that of Comparative Example 1. However, it can be seen that, after 10 days at a temperature of 5062°C, the low-molecular-weight component contents of the pharmaceutical formulations of Examples 2 and 10 to 14 were somewhat higher than that of Comparative Example 1. It can be seen that the low-molecular-weight component contents of Examples 11 to 14 were higher as the pH was lower, and the low-molecular-weight component content of Example 11 at pH 5.5 rapidly increased by about 4% or more beyond the acceptable fluctuation level compared to that of Example 13 which is a pharmaceutical formulation having a target pH. Therefore, it can be seen that the pH range of the formulation of the present disclosure is more preferably set to 5.9 to 6.5.

[Table 20] Content (%) of one recombinant human VEGF receptor extracellular domain 1, one recombinant human VEGF receptor extracellular domain 2 and recombinant human IgG Fc region (1VEGF1 + 1VEGF2 + Fc)

	After 0 day at 563°C	After 10 days at 563°C	After 5 days at 5062°C	After 10 days at 5062°C
Example 2	96.58	96.32	88.31	82.11
Example 10	96.66	96.62	88.58	84.32
Example 11	96.01	96.14	86.38	81.27
Example 12	96.17	96.18	89.43	85.43
Example 13	96.52	96.35	92.50	91.52
Example 14	96.48	96.34	95.90	92.85
Comparative Example 1	97.37	96.11	95.77	94.11

[0184] Referring to Table 20 above, it can be seen that, after 10 days at a temperature of 563°C, the contents of one recombinant human VEGF receptor extracellular domain 1, one recombinant human VEGF receptor extracellular domain 2 and a recombinant human IgG Fc region (1VEGF1 + 1VEGF2 + Fc) in the pharmaceutical formulations of Examples 2, and 10 to 14 satisfying the ranges specified in the present disclosure were similar to that in Comparative Example 1. However, it can be seen that, after 10 days at a temperature of 5062°C, the contents of one recombinant human VEGF receptor extracellular domain 1, one recombinant human VEGF receptor extracellular domain 2 and a recombinant human IgG Fc region (1VEGF1 + 1VEGF2 + Fc) in the pharmaceutical formulations of Examples 2, and 10 to 14 were somewhat lower than that in Comparative Example 1. It can be seen that the contents of one recombinant human VEGF receptor extracellular domain 1, one recombinant human VEGF receptor extracellular domain 2 and a recombinant human IgG Fc region (1VEGF1 + 1VEGF2 + Fc) in the pharmaceutical formulations of Examples 11 to 14 decreased as the pH decreased. And the low-molecular-weight component content of Example 11 at pH 5.5 rapidly increased by about 10% or more beyond the acceptable fluctuation level compared to that of Example 13 which is a pharmaceutical formulation having a target pH. Therefore, it can be seen that the pH range of the formulation of the present disclosure is more preferably set to 5.9 to 6.5.

[Table 21] Number of Sub-visible particles ($\geq 1.00 \mu\text{m}$, $<100.00 \mu\text{m}$, particles/mL) measured by MFI

	After 0 day at 563°C	After 10 days at 563°C	After 5 days at 5062°C	After 10 days at 5062°C
Example 2	222	530	324	1201

(continued)

	After 0 day at 563°C	After 10 days at 563°C	After 5 days at 5062°C	After 10 days at 5062°C
Example 10	546	84	234	430
Example 11	198	245	1112	704
Example 12	146	234	153	290
Example 13	198	143	125	14709
Example 14	157	205	231	430
Comparative Example 1	-	-	-	-

[0185] Referring to Table 21 above, it can be seen that, after 10 days at a temperature of 563°C, the numbers of sub-visible particles (≥ 1.00 mm, <100.00 mm) measured by MFI in the pharmaceutical formulations of Examples 2, and 10 to 14 satisfying the ranges specified in the present disclosure were absolutely low, suggesting that these formulations were very clean pharmaceutical formulations. In addition, it can be seen that, even after 10 days at a temperature of 5062°C, the numbers of sub-visible particles (≥ 1.00 mm, <100.00 mm) measured by MFI in the pharmaceutical formulations of Examples 2, and 10 to 14 were absolutely low, suggesting that these formulations were very clean pharmaceutical formulations.

[Table 22] Number of Sub-visible particles (≥ 10.00 mm, <100.00 mm, particles/mL) measured by MFI

	After 0 day at 563°C	After 10 days at 563°C	After 5 days at 5062°C	After 10 days at 5062°C
Example 2	0	26	2	4
Example 10	4	4	9	7
Example 11	0	6	10	29
Example 12	6	6	4	2
Example 13	0	6	5	97
Example 14	11	37	4	14
Comparative Example 1	-	-	-	-

[0186] Referring to Table 22 above, it can be seen that, after 10 days at a temperature of 563°C, the numbers of sub-visible particles (≥ 10.00 mm, <100.00 mm) measured by MFI in the pharmaceutical formulations of Examples 2, and 10 to 14 satisfying the ranges specified in the present disclosure were absolutely low, suggesting that these formulations were very clean pharmaceutical formulations. In addition, it can be seen that, even after 10 days at a temperature of 5062°C, the numbers of sub-visible particles (≥ 10.00 mm, <100.00 mm) measured by MFI in the pharmaceutical formulations of Examples 2, and 10 to 14 were absolutely low, suggesting that these formulations were very clean pharmaceutical formulations.

[Table 23] Number of Sub-visible particles (≥ 25.00 mm, <100.00 mm, particles/mL) measured by MFI

	After 0 day at 563°C	After 10 days at 563°C	After 5 days at 5062°C	After 10 days at 5062°C
Example 2	0	2	0	0
Example 10	0	0	0	6
Example 11	0	4	2	8
Example 12	4	0	0	0
Example 13	0	0	0	10

(continued)

	After 0 day at 563°C	After 10 days at 563°C	After 5 days at 5062°C	After 10 days at 5062°C
Example 14	3	12	2	0
Comparative Example 1	-	-	-	-

[0187] Referring to Table 23 above, it can be seen that, after 10 days at a temperature of 563°C, the numbers of sub-visible particles (≥ 25.00 mm, < 100.00 mm) measured by MFI in the pharmaceutical formulations of Examples 2, and 10 to 14 satisfying the ranges specified in the present disclosure were absolutely low, suggesting that these formulations were very clean pharmaceutical formulations. In addition, it can be seen that, even after 10 days at a temperature of 5062°C, the numbers of sub-visible particles (≥ 25.00 mm, < 100.00 mm) measured by MFI in the pharmaceutical formulations of Examples 2, and 10 to 14 were absolutely low, suggesting that these formulations were very clean pharmaceutical formulations.

[Table 24] VEGF binding affinity (%)

	After 0 day at 563°C	After 10 days at 563°C	After 5 days at 5062°C	After 10 days at 5062°C
Example 2	94	106	45	31
Example 10	104	110	56	34
Example 11	103	98	38	20
Example 12	102	91	67	39
Example 13	99	117	66	58
Example 14	113	83	78	59
Comparative Example 1	110	86	73	55

[0188] Referring to Table 24 above, it can be seen that, after 10 days at a temperature of 563°C, the VEGF binding affinities of the pharmaceutical formulations of Examples 2, and 10 to 14 satisfying the ranges specified in the present disclosure were similar to that of Comparative Example 1. However, it can be seen that, after 10 days at a temperature of 5062°C, the VEGF binding affinities of some of Examples 2, and 10 to 14 were somewhat higher than that of Comparative Example 1. It can be seen that the VEGF binding affinities of Examples 11 to 14 decreased as the pH decreased. In addition, it can be seen that the VEGF binding affinity of the formulation of Example 11 at pH 5.5 rapidly decreased by about 38% or more beyond the acceptable fluctuation level compared to that of Example 13 which is a pharmaceutical formulation having a target pH. Therefore, it can be seen that the pH range of the formulation of the present disclosure is more preferably set to 5.9 to 6.5.

Experimental Example 3: Additional Comparison for Determining the Concentration Range of Sodium Chloride Isotonic Agent and Confirmation of Superiority of the Formulation of the Present Disclosure

[0189] For preparation of pharmaceutical formulations to be used in Experimental Example 3, each buffer was prepared according to each concentration of sodium chloride, and then a recombinant fusion protein was added thereto and a surfactant was added, thereby preparing the samples shown in Table 25 below. The specific content of each component is shown in Table 25. Examples 15 and 16 and Comparative Example 1 were samples to which aflibercept purified at the Celltrion Research Institute was added. The target volume of each sample for filling a glass vial was 0.278 ml.

[0190] The pharmaceutical formulations prepared according to Examples 15 and 16 and Comparative Example 1 were stored at a temperature of 563°C and at a temperature of 4062°C and a relative humidity of 7565%, and measured for their stabilities after 4 weeks at a temperature of 563°C, and for their stabilities after 2 weeks and 4 weeks at a temperature of 4062°C and a relative humidity of 7565%. The results of the measurement are shown in Tables 26 to 31 below.

[Table 25] Constitution of Experimental Example 3

	Buffer	pH	Sugar	Isotonic agent	Surfactant	Protein concentration
Example 15	8.0 mM histidine	6.2	10% (w/v) trehalose	0.0 mM sodium chloride	0.03% (w/v) polysorbate 20	40 mg/mL
Example 16	8.0 mM histidine	6.2	10% (w/v) trehalose	7.2 mM sodium chloride	0.03% (w/v) polysorbate 20	40 mg/mL
Comparative Example 1	10 mM sodium phosphate	6.2	5% (w/v) sucrose	40.0 mM sodium chloride	0.03 % (w/v) polysorbate 20	40 mg/mL

[Table 26] Turbidity

	After 4 weeks at 563°C	After 2 weeks at 4062°C and 7565%	After 4 weeks at 4062°C and 7565%
Example 15	0.0048	0.0065	0.0052
Example 16	0.0034	0.0064	0.0127
Comparative Example 1	0.0078	0.0095	0.0103

[0191] Referring to Table 26 above, it can be seen that, even after 4 weeks at a temperature of 563°C, Examples 15 and 16 containing a low concentration of sodium chloride showed a very low turbidity, suggesting that they were transparent pharmaceutical formulations. In particular, it can be seen that Examples 15 and 16 showed an absorbance of 0.0400 or less even after 4 weeks of storage at a temperature of 4062°C and a relative humidity of 7565%. It can be seen that the turbidities of Examples 15 and 16 were similar to that of the conventional formulation (Comparative Example 1).

[Table 27] Charge variants (the relative content (%) of peak 4 to peak 11 in a total of 12 peaks)

	After 4 weeks at 563°C	After 2 weeks at 4062°C and 7565%	After 4 weeks at 4062°C and 7565%
Example 15	89.9	-	86.9
Example 16	89.6	-	87.7
Comparative Example 1	90.3	-	86.2

[0192] Referring to Table 27 above, it can be seen that, after 4 weeks at a temperature of 563°C, charge variants (the relative content of peak 4 to peak 11 in a total of 12 peaks) in the pharmaceutical formulations of Examples 15 and 16 containing a low concentration of sodium chloride were similar to those in Comparative Example 1. In addition, it can be seen that, even after 4 weeks at a temperature of 4062°C and a relative humidity of 7565%, charge variants (the relative content of peak 4 to peak 11 in a total of 12 peaks) in the pharmaceutical formulations of Examples 15 and 16 were similar to those in Comparative Example 1.

[Table 28] Number of sub-visible particles ($\geq 1.00\mu\text{m}$, $<100.00\mu\text{m}$, particles/mL) measured by MFI

	After 4 weeks at 563°C	After 2 weeks at 4062°C and 7565%	After 4 weeks at 4062°C and 7565%
Example 15	2770	1935	2184

(continued)

	After 4 weeks at 563°C	After 2 weeks at 4062°C and 7565%	After 4 weeks at 4062°C and 7565%
Example 16	2504	985	1355
Comparative Example 1	1399	6004	9586

[0193] Referring to Table 28 above, it can be seen that, after 4 weeks at a temperature of 563°C, the numbers of sub-visible particles (≥ 1.00 mm, <100.00 mm) measured by MFI in the formulations of Examples 15 and 16 containing a low concentration of sodium chloride were similar to that in Comparative Example 1, suggesting that these formulations were very clean pharmaceutical formulations. In addition, it can be seen that, even after 4 weeks at a temperature of 4062°C and a relative humidity of 7565%, the numbers of sub-visible particles (≥ 1.00 mm, <100.00 mm) measured by MFI in the formulations of Examples 15 and 16 were absolutely smaller than that in Comparative Example 1, suggesting that these formulations were very clean pharmaceutical formulations.

[Table 29] Number of sub-visible particles (≥ 10.00 mm, <100.00 mm, particles/mL) measured by MFI

	After 4 weeks at 563°C	After 2 weeks at 4062°C and 7565%	After 4 weeks at 4062°C and 7565%
Example 15	77	28	61
Example 16	64	0	22
Comparative Example 1	24	216	731

[0194] Referring to Table 29 above, it can be seen that, after 4 weeks at a temperature of 563°C, the numbers of sub-visible particles (≥ 10.00 mm, <100.00 mm) measured by MFI in the formulations of Examples 15 and 16 containing a low concentration of sodium chloride were similar to that in Comparative Example 1, suggesting that these formulations were very clean pharmaceutical formulations. In addition, it can be seen that, even after 4 weeks at a temperature of 4062°C and a relative humidity of 7565%, the numbers of sub-visible particles (≥ 10.00 mm, <100.00 mm) measured by MFI in the formulations of Examples 15 and 16 were absolutely smaller than that in Comparative Example 1, suggesting that these formulations were very clean pharmaceutical formulations.

[Table 30] Number of sub-visible particles (≥ 25.00 mm, <100.00 mm, particles/mL) measured by MFI

	After 4 weeks at 563°C	After 2 weeks at 4062°C and 7565%	After 4 weeks at 4062°C and 7565%
Example 15	9	7	8
Example 16	6	0	0
Comparative Example 1	2	4	7

[0195] Referring to Table 30 above, it can be seen that, after 4 weeks at a temperature of 563°C, the numbers of sub-visible particles (≥ 25.00 mm, <100.00 mm) measured by MFI in the formulations of Examples 15 and 16 containing a low concentration of sodium chloride were similar to that in Comparative Example 1, suggesting that these formulations were very clean pharmaceutical formulations. In addition, it can be seen that, even after 4 weeks at a temperature of 4062°C and a relative humidity of 7565%, the numbers of sub-visible particles (≥ 25.00 mm, <100.00 mm) measured by MFI in the formulations of Examples 15 and 16 were similar to that in Comparative Example 1, suggesting that these formulations were very clean pharmaceutical formulations.

[Table 31] VEGF binding affinity (%)

	After 4 weeks at 563°C	After 2 weeks at 4062°C and 7565%	After 4 weeks at 4062°C and 7565%
Example 15	105	95	87
Example 16	101	96	68
Comparative Example 1	99	85	72

[0196] Referring to Table 31 above, it can be seen that, after 4 weeks at a temperature of 563°C, the VEGF binding affinities of the pharmaceutical formulations of Examples 15 and 16 containing a low concentration of sodium chloride were similar to that of Comparative Example 1. In addition, it can be seen that, even after 4 weeks after a temperature of 4062°C and a relative humidity of 7565%, the VEGF binding affinities of the pharmaceutical formulations of Examples 15 and 16 containing a low concentration of sodium chloride were similar to that of Comparative Example 1.

Experimental Example 4: Confirmation of Superiority of the Formulation of the Present Disclosure by Evaluation of Long-Term Stability of Example 13

[0197] Evaluation of the long-term stability of Example 13 was performed according to the guideline (Guideline Q5C Quality of Biotechnological Products: Stability Testing of Biotechnological or Biological Products and ICH Guideline Q1A (R2): Stability Testing of New Drug Substances and Drug Products) provided by the International Conference on Harmonisation (ICH).

[0198] 0.278 mL of the stable liquid pharmaceutical formulation of Example 13 prepared by the method of Experimental Example 1 was stored in a sealed container at 563°C/ambient relative humidity. The stabilities of the pharmaceutical formulation were measured after 0 month, 3 months, 6 months and 9 months at the above temperature and humidity. Here, the protein concentration was set to 40 mg/mL.

[0199] To evaluate the long-term stability of Example 13, appearance analysis, measurement of the protein concentration using SoloVPE, measurement of the main component, high-molecular-weight component and low-molecular-weight component contents using SEC-HPLC, measurement of the content of one recombinant human VEGF receptor extracellular domain 1, one recombinant human VEGF receptor extracellular domain 2 and a recombinant human IgG Fc region (1VEGF + 1VEGF2 + Fc) by reduced CE-SDS, measurement of charge variants (the relative content of peak 4 to peak 11 in a total of 12 peaks) using cIEF, measurement of VEGF binding affinity, and the number of sub-visible particles were performed, and the results are shown in Tables 32 to 41 below.

[Table 32] Appearance

	0 month at 563°C	After 3 months at 563°C	After 6 months at 563°C	After 9 months at 563°C
Example 13	Ivory white	Ivory white	Ivory white	Ivory white

[0200] Referring to Table 32 above, it can be seen that the appearance of Example 13 did not change even after 9 months under the long-term storage temperature condition, suggesting that Example 13 was a stable pharmaceutical formulation.

[Table 33] Protein concentration (mg/ml)

	0 month at 563°C	After 3 months at 563°C	After 6 months at 563°C	After 9 months at 563°C
Example 13	39.1	39.9	39.7	42.4

[0201] Referring to Table 33 above, it can be seen that the protein concentration of Example 13 did not change even after 9 months under the long-term storage temperature condition, suggesting that Example 13 was a stable pharmaceutical formulation.

[Table 34] High-molecular-weight component content (%)

	0 month at 563°C	After 3 months at 563°C	After 6 months at 563°C	After 9 months at 563°C
Example 13	0.42	0.72	0.48	0.63

[0202] Referring to Table 34 above, it can be seen that the high-molecular-weight component content of Example 13 did not change even after 9 months under the long-term storage temperature condition, suggesting that Example 13 is a stable pharmaceutical formulation.

[Table 35] Low-molecular-weight component content (%)

	0 month at 563°C	After 3 months at 563°C	After 6 months at 563°C	After 9 months at 563°C
Example 13	0.24	0.00	0.00	0.00

[0203] Referring to Table 35 above, it can be seen that the low-molecular-weight component content of Example 13 did not change even after 9 months under the long-term storage temperature condition, suggesting that Example 13 was a stable pharmaceutical formulation.

[Table 36] Content (%) of one recombinant human VEGF receptor extracellular domain 1, one recombinant human VEGF receptor extracellular domain 2 and recombinant human IgG Fc region (1VEGF1 + 1VEGF2 + Fc)

	0 month at 563°C	After 3 months at 563°C	After 6 months at 563°C	After 9 months at 563°C
Example 13	97.42	97.48	97.40	97.37

[0204] Referring to Table 36 above, it can be seen that the content (%) of one recombinant human VEGF receptor extracellular domain 1, one recombinant human VEGF receptor extracellular domain 2 and a recombinant human IgG Fc region (1VEGF1 + 1VEGF2 + Fc) in Example 13 did not change even after 9 months under the long-term storage temperature condition, suggesting that Example 13 was a stable pharmaceutical formulation.

[Table 37] Number of sub-visible particles (≥ 2.00 mm, < 400.00 mm, particles/mL) measured by HIAC

	0 month at 563°C	After 3 months at 563°C	After 6 months at 563°C	After 9 months at 563°C
Example 13	-	185	172	297

[0205] Referring to Table 37 above, it can be seen that the number of sub-visible particles (≥ 2.00 mm, < 400.00 mm) in Example 13 was small even after 9 months under the long-term storage temperature condition, suggesting that Example 13 was a very clean pharmaceutical formulation.

[Table 38] Number of sub-visible particles (≥ 10.00 mm, < 400.00 mm, particles/mL) measured by HIAC

	0 month at 563°C	After 3 months at 563°C	After 6 months at 563°C	After 9 months at 563°C
Example 13	8	3	8	33

[0206] Referring to Table 38 above, it can be seen that the number of sub-visible particles (≥ 10.00 mm, < 400.00 mm) in Example 13 was small even after 9 months under the long-term storage temperature condition, suggesting that Example 13 was a very clean pharmaceutical formulation.

[Table 39] Number of sub-visible particles (≥ 25.00 mm, < 400.00 mm, particles/mL) measured by HIAC

	0 month at 563°C	After 3 months at 563°C	After 6 months at 563°C	After 9 months at 563°C
Example 13	0	0	0	5

[0207] Referring to Table 39 above, it can be seen that the number of sub-visible particles (≥ 25.00 mm, < 400.00 mm) in Example 13 was small even after 9 months under the long-term storage temperature condition, suggesting that Example 13 was a very clean pharmaceutical formulation.

[Table 40] Charge variants (the relative content (%) of peak 4 to peak 11 in a total of 12 peaks)

	0 month at 563°C	After 3 months at 563°C	After 6 months at 563°C	After 9 months at 563°C
Example 13	87.9	87.6	88.0	87.5

[0208] Referring to Table 40 above, it can be seen that charge variants (the relative content (%) of peak 4 to peak 11 in a total of 12 peaks) in Example 13 did not change even after 9 months under the long-term storage temperature condition, suggesting that Example 13 was a stable pharmaceutical formulation.

[Table 41] VEGF binding affinity (%)

	0 month at 563°C	After 3 months at 563°C	After 6 months at 563°C	After 9 months at 563°C
Example 13	112	106	98	92

[0209] Referring to Table 41 above, it can be seen that VEGF binding affinity of Example 13 did not change even after 9 months under the long-term storage temperature condition, suggesting that Example 13 was a stable pharmaceutical formulation.

[0210] As described above, the stable pharmaceutical formulation according to the present disclosure has low viscosity while containing a recombinant fusion protein, may maintain excellent stability under long-term storage conditions, accelerated conditions and stress conditions, and may be administered intraocularly.

Claims

1. A stable pharmaceutical formulation containing:

- (A) a recombinant fusion protein;
- (B) a surfactant;
- (C) a sugar or a derivative thereof, and
- (D) a buffer.

2. The stable pharmaceutical formulation of claim 1, wherein the stable pharmaceutical formulation is in a liquid form.

3. The stable pharmaceutical formulation of claim 1, wherein the recombinant fusion protein (A) comprises a vascular endothelial growth factor (VEGF) antagonist.

4. The stable pharmaceutical formulation of claim 1, wherein the recombinant fusion protein (A) comprises a human VEGF receptor extracellular domain.

5. The stable pharmaceutical formulation of claim 1, wherein the recombinant fusion protein (A) comprises human VEGF receptor extracellular domain 1, human VEGF receptor extracellular domain 2, or a mixture thereof.

6. The stable pharmaceutical formulation of claim 4 or 5, wherein the recombinant fusion protein (A) comprises a human immunoglobulin G (IgG) Fc region.

7. The stable pharmaceutical formulation of claim 1, wherein the recombinant fusion protein (A) comprise:

- (1) a VEGF receptor extracellular domain 1 component comprising amino acids 27 to 129 of SEQ ID NO: 2;
- (2) a VEGF receptor extracellular domain 2 component comprising amino acids 130 to 231 of SEQ ID NO: 2; and
- (3) an Fc region component comprising amino acids 232 to 457 of SEQ ID NO: 2.

8. The stable pharmaceutical formulation of claim 1, wherein the recombinant fusion protein (A) comprise aflibercept.

9. The stable pharmaceutical formulation of claim 1, wherein the recombinant fusion protein (A) is contained at a concentration of 5 to 100 mg/ml.

10. The stable pharmaceutical formulation of claim 1, wherein the surfactant (B) comprises polysorbate, poloxamer, or a mixture thereof.
11. The stable pharmaceutical formulation of claim 10, wherein the surfactant (B) comprises polysorbate 20, polysorbate 40, polysorbate 60, polysorbate 80, or a mixture of two or more thereof.
12. The stable pharmaceutical formulation of claim 11, wherein the surfactant (B) comprises polysorbate 20.
13. The stable pharmaceutical formulation of claim 1, wherein the surfactant (B) is contained at a concentration of 0.01 to 0.1% (w/v).
14. The stable pharmaceutical formulation of claim 1, wherein the sugar (C) comprises a monosaccharide, a disaccharide, an oligosaccharide, a polysaccharide, or a mixture of two or more thereof, and the derivative of the sugar (C) comprises a sugar alcohol, a sugar acid, or a mixture thereof.
15. The stable pharmaceutical formulation of claim 1, wherein the sugar or the derivative thereof (C) comprises sorbitol, mannitol, trehalose, sucrose, or a mixture of two or more thereof.
16. The stable pharmaceutical formulation of claim 15, wherein the sugar or the derivative thereof (C) comprises trehalose.
17. The stable pharmaceutical formulation of claim 1, wherein the sugar or the derivative thereof (C) is contained at a concentration of 1 to 20% (w/v).
18. The stable pharmaceutical formulation of claim 1, wherein the buffer (D) comprises an amino acid.
19. The stable pharmaceutical formulation of claim 1, wherein the buffer (D) comprises a free amino acid, an amino acid salt, or a mixture thereof.
20. The stable pharmaceutical formulation of claim 19, wherein the buffer (D) comprises histidine, histidine salt, or a mixture thereof.
21. The stable pharmaceutical formulation of claim 1, wherein the buffer (D) is contained at a concentration of 1 to 20 mM.
22. The stable pharmaceutical formulation of claim 1, wherein the stable pharmaceutical formulation is free of acetic acid, citric acid, phosphoric acid, or a mixture thereof.
23. The stable pharmaceutical formulation of claim 1, further containing (E) an isotonic agent.
24. The stable pharmaceutical formulation of claim 23, wherein the isotonic agent (E) comprises sodium chloride, potassium chloride, calcium chloride, or a mixture of two or more thereof.
25. The stable pharmaceutical formulation of claim 23, wherein the isotonic agent (E) is contained at a concentration of 30 mM or less.
26. The stable pharmaceutical formulation of claim 1, wherein the stable pharmaceutical formulation has a pH of 5.0 to 7.0.
27. The stable pharmaceutical formulation of claim 1, wherein the stable pharmaceutical formulation is free of NaF, KBr, NaBr, Na₂SO₄, NaSCN, K₂SO₄, a mixture thereof.
28. The stable pharmaceutical formulation of claim 1, wherein the stable pharmaceutical formulation is free of a chelating agent.
29. A stable pharmaceutical formulation containing:
 - (A) 5 to 100 mg/ml of a recombinant fusion protein comprising (1) a vascular endothelial growth factor(VEGF) receptor extracellular domain 1 component comprising amino acids 27 to 129 of SEQ ID NO: 2, (2) a VEGF receptor extracellular domain 2 component comprising amino acids 130 to 231 of SEQ ID NO: 2, and (3) an Fc

region component comprising amino acids 232 to 457 of SEQ ID NO: 2;
 (B) 0.01 to 0.1% (w/v) of a surfactant;
 (C) 1 to 20% (w/v) of a sugar or a derivative thereof; and
 (D) 1 to 20 mM of a buffer.

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30. The stable pharmaceutical formulation of claim 29, further containing (E) 30 mM or less of an isotonic agent.

31. A stable pharmaceutical formulation containing:

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(A) a vascular endothelial growth factor (VEGF) antagonist;
 (B) polysorbate;
 (C) a sugar or a derivative thereof; and
 (D) histidine.

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32. The stable pharmaceutical formulation of claim 31, further containing (E) sodium chloride.

33. A stable pharmaceutical formulation containing:

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(A) 5 to 100 mg/ml of a recombinant fusion protein comprising (1) a vascular endothelial growth factor(VEGF) receptor extracellular domain 1 component comprising amino acids 27 to 129 of SEQ ID NO: 2, (2) a VEGF receptor extracellular domain 2 component comprising amino acids 130 to 231 of SEQ ID NO: 2, and (3) an Fc region component comprising amino acids 232 to 457 of SEQ ID NO:2;
 (B) 0.01 to 0.1% (w/v) of polysorbate;
 (C) 1 to 20% (w/v) of a sugar or a derivative thereof; and
 (D) 1 to 20 mM of histidine.

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34. The stable pharmaceutical formulation of claim 33, further containing (E) 30 mM or less of sodium chloride.

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35. The stable pharmaceutical formulation of any one of claims 1 to 34, wherein the number of sub-visible particles having a particle diameter of equal to or more than 10.00 µm to less than 400.00 µm is 50 or less as measured by HiAC after 9 months of storage at 563°C.

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36. The stable pharmaceutical formulation of any one of claims 1 to 34, wherein the stable pharmaceutical formulation shows a main component content of 98% or more after 10 days of storage at 563°C.

37. The stable pharmaceutical formulation of any one of claims 1 to 34, wherein the stable pharmaceutical formulation shows a high-molecular-weight component content of 1% or less after 10 days of storage at 563°C.

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38. The stable pharmaceutical formulation of any one of claims 1 to 34, wherein the stable pharmaceutical formulation shows a low-molecular-weight component content of 0.05% or less after 10 days of storage at 563°C.

39. The stable pharmaceutical formulation of any one of claims 1 to 34, wherein the stable pharmaceutical formulation shows a charge variant content of 87% or more after 9 months of storage at 563°C.

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40. The stable pharmaceutical formulation of any one of claims 1 to 34, wherein the stable pharmaceutical formulation shows a VEGF binding affinity of 90% or more after 9 months of storage at 563°C.

41. The stable pharmaceutical formulation of any one of claims 1 to 34, wherein the stable pharmaceutical formulation is for intracocular administration.

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42. The stable pharmaceutical formulation of any one of claims 1 to 34, wherein the stable pharmaceutical formulation is not subjected to a reconstitution step, a dilution step, or both, before use.

43. A glass vial filled with the stable pharmaceutical formulation set forth in any one of claims 1 to 34.

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44. A pre-filled syringe filled with the stable pharmaceutical formulation set forth in any one of claims 1 to 34.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/KR2021/009870

A. CLASSIFICATION OF SUBJECT MATTER

A61K 9/08(2006.01); A61K 47/26(2006.01); A61K 47/10(2006.01); A61K 47/18(2006.01); A61K 47/22(2006.01);
A61K 38/00(2006.01); A61K 38/17(2006.01); A61K 9/00(2006.01); A61P 27/02(2006.01)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K 9/08(2006.01); A61K 38/18(2006.01); A61K 47/10(2006.01); A61K 47/18(2006.01); A61K 47/26(2006.01);
A61K 9/00(2006.01)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Korean utility models and applications for utility models: IPC as above

Japanese utility models and applications for utility models: IPC as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

eKOMPASS (KIPO internal) & keywords: 재조합용 융단백질 (recombinant fusion protein), 계면활성제 (surfactant), 당 (sugar), 완충제 (buffer), VEGF 길항제 (VEGF antagonist), 면역글로불린 (immunoglobulin), 에플리머셉트 (afibercept), 폴리소르베이트 (polyorbate), 당 (sugar), 완충제 (buffer), 계면활성제 (surfactant), 등장화제 (Tonicity agents)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	KR 10-2020-0084897 A (SAMSUNG BIOEPIS CO., LTD.) 13 July 2020 (2020-07-13) See abstract; paragraphs [0034], [0036], [0039], [0042], [0053] and [0057]; table 2; and claims 1, 2, 16 and 21-22.	1-6,8-21,26-28,31
Y		7,29,33
A		23-25,30,32,34
X	WO 2017-129688 A1 (FORMYCON AG) 03 August 2017 (2017-08-03) See abstract; page 3, fifth paragraph; page 11, third paragraph; page 21, table 1; and claims 1-6 and 9-13.	1-3,8-28,31-32
Y		7,29,30,33,34
Y	US 6833349 B2 (XIA, Y. et al.) 21 December 2004 (2004-12-21) See abstract; SEQ ID NO: 26; and claim 1.	7,29,30,33,34

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"D" document cited by the applicant in the international application

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

22 November 2021

Date of mailing of the international search report

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Government Complex-Daejeon Building 4, 189 Cheongsan-ro, Seo-gu, Daejeon 35208

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Telephone No.

Form PCT/ISA/210 (second sheet) (July 2019)

INTERNATIONAL SEARCH REPORT

International application No.

PCT/KR2021/009870

C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category ^o	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	KR 10-2017-0090356 A (ALTIROGEN, INC) 02 January 2017 (2017-01-02) See abstract; paragraphs [0035]-[0050]; and claims 1-14.	1-6,8-21,26-28,31
Y		7,29,33
X	KR 10-2020-0029374 A (SAMSUNG BIOEPIS CO., LTD.) 18 March 2020 (2020-03-18) See abstract; paragraphs [0024]-[0058]; table 1; and claims 1-43.	1-6,8-21,26-28,31
Y		7,29,33

Form PCT/ISA/210 (second sheet) (July 2019)

INTERNATIONAL SEARCH REPORT

International application No.

PCT/KR2021/009870

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:
 - a. ☒ forming part of the international application as filed:
 - ☒ in the form of an Annex C/ST.25 text file.
 - ☐ on paper or in the form of an image file.
 - b. ☐ furnished together with the international application under PCT Rule 13ter.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.
 - c. ☐ furnished subsequent to the international filing date for the purposes of international search only:
 - ☐ in the form of an Annex C/ST.25 text file (Rule 13ter.1(a)).
 - ☐ on paper or in the form of an image file (Rule 13ter.1(b) and Administrative Instructions, Section 713).
2. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
3. Additional comments:

Form PCT/ISA/210 (continuation of first sheet) (July 2019)

INTERNATIONAL SEARCH REPORT

International application No.

PCT/KR2021/009870

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☒ Claims Nos.: **35-44**
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Form PCT/ISA/210 (continuation of first sheet) (July 2019)

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.

PCT/KR2021/009870

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Form PCT/ISA/210 (patent family annex) (July 2019)

INTERNATIONAL SEARCH REPORT
 Information on patent family members

International application No.

PCT/KR2021/009870

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INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.

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REFERENCES CITED IN THE DESCRIPTION

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A61K 39/00 (2006.01) A61K 47/18 (2017.01)

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(71) Applicant: LEK PHARMACEUTICALS D.D. [SI/SI];
Verovskova 57, 1526 Ljubljana (SI).

(72) Inventors: ŽELA, Aleš; c/o Lek Pharmaceuticals d.d.,
Verovskova 57, 1526 Ljubljana (SI). ZIDAR, Mitja; c/o
Lek Pharmaceuticals d.d., Verovskova 57, 1526 Ljubljana
(SI). BELKO-PARKEL, Kaja; c/o Lek Pharmaceuticals
d.d., Verovskova 57, 1526 Ljubljana (SI). ŠINK, Roman;
c/o Lek Pharmaceuticals d.d., Verovskova 57, 1526 Ljubljana
(SI). LEBAR, Blaž; c/o Lek Pharmaceuticals d.d.,
Verovskova 57, 1526 Ljubljana (SI).

(74) Agent: RÜCKERL, Florian; Delmei & Bettenhausen
Patentanwälte PartmbB, Herzogspitalstr. 11, 80331
München (DE).

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HN, HR, HU, ID, IL, IN, IQ, IR, IS, IT, JM, JO, JP, KE,
KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU,
LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA,
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RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH,
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TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK,
EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV,
MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM,

(84) Title: FORMULATIONS FOR VEGF RECEPTOR FUSION PROTEINS

(57) Abstract: The present invention relates to a liquid formulation comprising a VEGF receptor fusion protein at a concentration of at least 100 mg/ml, and wherein the formulation comprises: i) no buffering agent, ii) a citrate buffer, or iii) a histidine buffer preferably without sucrose and preferably with methionine. In addition, the invention relates to an article of manufacture comprising a container with such liquid formulation as well as the use of the liquid formulation for a method of treatment.

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Formulations for VEGF receptor fusion proteins

The present invention relates to a liquid formulation comprising a VEGF receptor fusion protein at a concentration of at least 100 mg/ml, and wherein the formulation comprises: i) no buffering agent, ii) a citrate buffer, or iii) a histidine buffer preferably without sucrose and preferably with methionine. In addition, the invention relates to an article of manufacture comprising a container with such liquid formulation as well as the use of the liquid formulation for a method of treatment.

Fc-based fusion proteins, i.e. fusion proteins which are composed of an immunoglobulin Fc domain that is linked to another peptide, are among the most relevant protein therapeutics. The fused partners have significant therapeutic potential, and they are attached to an Fc-domain to endow the hybrids with a number of additional beneficial biological and pharmacological properties. Perhaps most important, the presence of the Fc domain markedly increases their plasma half-life. Moreover, from a biophysical perspective, the Fc domain folds independently and can improve the solubility and stability of the fusion partner. Examples for Fc-based fusion proteins are vascular endothelial growth factor (VEGF) receptor Fc fusion proteins like aflibercept.

Advances in biotechnology have made it possible to produce a variety of proteins for pharmaceutical applications. However, as proteins are large and complex (i.e., possessing multiple functional groups in addition to complex three-dimensional structures), the formulation of such proteins poses special problems. Degradation pathways, such as non-native irreversible aggregation and other routes, resulting in undesired post-translational modifications, affect multiple steps in the production of these biotherapeutics, including purification, freezing, transportation and long-term storage. Not only that degraded protein molecules are often unable to perform biological activity, but also protein aggregates in particular can potentially cause serious adverse effects by enhancing pharmaceutical product's immunogenicity and thus reducing its safety and efficacy. This applies in particular for high concentration formulations. While high concentrations formulations (i.e. ≥ 100 mg/ml) allow

for smaller injection volumes of the biotherapeutic protein, they often exhibit a tendency of increased protein aggregation and viscosity, which results in lower overall protein potency, and lower manufacturing and poorer storage stability.

Although there are some formulations for VEGF receptor Fc fusion proteins known to the skilled person, there is still an urgent need to develop new formulations, in particular for formulations with high concentrations of VEGF receptor Fc fusion proteins.

The problem to be solved by the present invention was thus to provide high concentration formulations for VEGF receptor fusion proteins like aflibercept with satisfactory stability, in particular in terms of low aggregation levels.

This problem is solved by the subject-matter as set forth below and in the appended claims.

In a first aspect, the present invention relates to a liquid pharmaceutical formulation comprising a VEGF receptor fusion protein at a concentration of at least 100 mg/ml, and wherein the formulation comprises i) no buffering agent, ii) a citrate buffer, or iii) a histidine buffer preferably without sucrose and preferably with methionine.

The formulation of the present invention is preferably a stable formulation with preferably low aggregation tendency when stored. A "stable" formulation according to the present invention is a formulation in which the VEGF receptor Fc fusion protein retains its physical stability and/or chemical stability and/or biological activity upon storage. Preferably, the VEGF receptor Fc fusion protein essentially retains its physical and chemical stability, as well as its biological activity upon storage. The storage period is generally selected based on the intended shelf-life of the formulation.

Various analytical techniques for measuring protein stability are available in the art. Stability can be evaluated qualitatively and/or quantitatively in a variety of different ways, including evaluation of aggregate formation (for example using size exclusion chromatography, by measuring turbidity, and/or by visual inspection); by assessing charge heterogeneity using cation exchange chromatography, image capillary isoelectric focusing (icIEF) or capillary zone electrophoresis; amino-terminal or carboxy-terminal sequence analysis; mass spectrometric analysis; SDS-PAGE analysis to compare reduced and intact the VEGF receptor Fc fusion

protein; peptide map (for example tryptic or LYS—C) analysis; evaluating biological activity or antigen binding function of the VEGF receptor Fc fusion protein; etc. Instability may involve any one or more of: aggregation, deamidation (e.g. Asn deamidation), oxidation (e.g. Met oxidation), isomerization (e.g. Asp isomerisation), clipping/hydrolysis/fragmentation (e.g. hinge region fragmentation), succinimide formation, unpaired cysteine(s), N-terminal extension, C-terminal processing, glycosylation differences, etc. According to the present invention, a stable formulation is in particular a formulation which shows after storage for 8 weeks at 25°C an increase in aggregates by less than 1.30%, preferably less than 1.20%, most preferably less than 1.10%, as compared to before storage at 25°C for 8 weeks.

The VEGF receptor Fc fusion protein contained in the inventive formulation can be any VEGF receptor Fc fusion protein of interest. For example, the VEGF receptor Fc fusion protein may:

- be encoded by the nucleic acid sequence of SEQ ID NO:1 or nucleotides 79-1374 or 79-1371 of SEQ ID NO: 1;
- comprise amino acids of SEQ ID NO: 2 or amino acids 27-457 or 27-458 of SEQ ID NO: 2;
- comprise:
 - (1) a VEGFR1 component comprising amino acids 27 to 129 of SEQ ID NO:2;
 - (2) a VEGFR2 component comprising amino acids 130 to 231 of SEQ ID NO:2;
 - (3) a multimerization component ("FcΔC1 (a)") comprising amino acids 232 to 457 or 458 of SEQ ID NO:2 (the C-terminal amino acids of SEQ ID NO:2, i.e., K458, may or may not be included in the VEGF receptor fusion proteins). Note that amino acids 1 to 26 of SEQ ID No:2 are the signal sequence;
- comprise an immunoglobulin-like (Ig) domain 2 of a first VEGF receptor (e.g., VEGFR1) and Ig domain 3 of a second VEGF receptor (e.g., VEGFR2), optionally further including an Ig domain 4 of the second VEGF receptor (e.g., VEGFR2) and a multimerizing component (e.g., Fc domain of IgG);
- be conbercept; or
- be aflibercept.

In a preferred embodiment of the invention, the VEGF receptor Fc fusion protein is selected from aflibercept and conbercept. Aflibercept is a 115 kDa recombinant protein that fuses the second extracellular domain of human VEGFR-1 and the third extracellular domain of human VEGFR-2 with the Fc portion of human immunoglobulin IgG1. Conbercept is a 143 kDa recombinant anti-VEGF fusion protein engineered from a full human cDNA sequence in

Chinese hamster ovary cells. The Fab of conbercept comprises the second extracellular domain of VEGFR-1 and the third and fourth extracellular domains of VEGFR-2, which then fuses to the Fc of human IgG1. Most preferably, the VEGF receptor Fc fusion protein in the inventive formulation is aflibercept.

The VEGF receptor Fc fusion protein, in particular aflibercept, is present in the inventive formulation in a concentration of at least 100 mg/ml (high concentration formulation). The VEGF receptor Fc fusion protein, in particular aflibercept, may be present in a concentration of at least about 105 mg/ml, at least about 110 mg/ml, at least about 115 mg/ml, at least about 120 mg/ml, at least about 130 mg/ml, at least about 140 mg/ml, at least about 150 mg/ml, at least about 160 mg/ml, at least about 170 mg/ml, at least about 180 mg/ml, at least about 190 mg/ml, at least about 200 mg/ml, at least about 250 mg/ml, or at least about 300 mg/ml. The VEGF receptor Fc fusion protein, in particular aflibercept, may for example be present in a concentration range from about 100 mg/ml to about 200 mg/ml, from about 105 mg/ml to about 150 mg/ml, from about 100 mg/ml to about 120 mg/ml, or from about 110 mg/ml to about 120 mg/ml. Most preferably, in particular in case where the VEGF receptor Fc fusion protein is aflibercept, the fusion protein is present in a concentration of about 115 mg/ml. The fusion protein, in particular in the case of aflibercept, may for example have a concentration of 114 to 116 mg/ml, in particular 114 to 115 mg/ml. In some embodiments where the fusion protein is aflibercept the concentration thereof may be about 114.3 mg/ml.

The inventive formulation comprises i) no buffering agent, ii) a citrate buffer, or iii) a histidine buffer with optionally methionine and preferably without sucrose. In embodiments where the formulation comprises no buffering agent, substantially all buffering capacity is provided by the VEGF receptor Fc fusion protein itself and other typical buffers such as histidine, acetate, citrate, TRIS, or phosphate buffers are not present, or at least only present in concentrations which are not sufficient to sufficiently buffer the formulations. Such formulation without further buffering agent is typically termed in the art a "self-buffered" formulation (Gokarn, Yatin R., et al. "Self-buffering antibody formulations." *Journal of pharmaceutical sciences* 97.8 (2008): 3051-3066). The inventors have demonstrated that such self-buffered formulations provide for good storage stability for VEGF receptor Fc fusion proteins as regards aggregation formation. Preferably, such self-buffered formulation has a pH between about pH 5.0 to 6.5, about pH 5.5 to 6.2, or about pH 5.8. In the alternative, the inventive formulation may comprise a citrate buffer, which also provides for low aggregation. A "citrate buffer" is a buffer

comprising citrate ions. Examples of citrate buffers include sodium citrate, ammonium citrate, calcium citrate, magnesium citrate and potassium citrate solutions. The citrate buffer has preferably a pH between about pH 5.0 to 6.5, about pH 5.5 to 6.2, or about pH 5.8. Preferably, the concentration of a citrate buffer is in the range from about 5 to about 20 mM, more preferably about 10 to about 20 mM. Finally, the formulation may comprise in a third alternative a histidine buffer, but will in particular in this case preferably not comprise sucrose. A "histidine buffer" is a buffer comprising histidine ions. Examples of histidine buffers include histidine chloride, histidine acetate, histidine phosphate, and histidine sulfate solutions, with histidine chloride (His/HCl) being particularly preferred. The histidine buffer or histidine-HCl buffer has preferably a pH between about pH 5.0 to 6.5, about pH 5.5 to 6.2, or about pH 5.8. Preferably, the concentration of a histidine buffer is in the range from about 5 to about 20 mM, more preferably in the range of about 10 to about 20 mM. It is understood that in the context of the present invention formulations without buffering agent are in particular those, which do not comprise histidine, acetate, citrate, TRIS, and/or phosphate as buffering agent, in particular do not comprise citrate and histidine as buffering agent, or at least none of these buffers in concentrations contributing significantly to the buffer capacity of the formulation.

pH is measured using standard glass bulb pH meter. Unless otherwise indicated, the pH values and ranges defined herein for formulations of the present invention reflect the pH at 25°C. In particular in cases where the VEGF receptor Fc fusion protein is aflibercept, the pH of the formulation is preferably pH 5.8.

Aside of the buffer (or its absence in self-buffered formulations), the inventive formulation may comprise further components. For instance, the formulation may comprise one or more free amino acids (i.e. as individual compounds, not as component of a peptide or protein). However, histidine is, unless a histidine buffer is used, preferably not among these amino acids. The formulation may comprise for example one or more amino acids selected from a first group of amino acids consisting of glycine, alanine, valine, leucine, isoleucine, methionine, proline, phenylalanine and tryptophan. Preferably, the one or more amino acids are selected from proline and methionine. The concentrations of the one or more amino acids may, independently of each other, be in the range of about 5 to about 450 mM. For example, the concentration of one or more of the amino acids may be about 10 mM, about 20 mM, about 25 mM, about 35 mM, about 40 mM, about 50 mM, about 75 mM, about 100 mM, about 125 mM, about 150 mM, about 200 mM, about 250 mM, about 300 mM, about 350 mM, about 400 mM or about

450 mM. Methionine is particularly useful as antioxidant. Preferred concentrations of methionine are in the range of 5 to 25 mM. Most preferably, methionine is used in a concentration of 10 mM. If proline is used, and no sugar (or sugar alcohol) is used, then the concentration of proline may be in the range of 100 to 450 mM, in particular in the range of 250 to 300 mM. In the alternative, or in addition to one or more amino acids selected from the first group of amino acids, the inventive formulation may comprise one or more amino acids selected from a second group of amino acids consisting of arginine and lysine. Preferably, the amino acid from the second group is arginine. Arginine is particularly useful as viscosity reducing agent. Preferred concentrations of arginine are in the range of 25 to 75 mM. Most preferably, arginine is used in a concentration of about 50 mM. Lysine is also suitable as viscosity reducing agent, with preferred concentrations from about 50 to about 150 mM, with 100 mM being most preferred. Preferred combinations of free amino acids are i) methionine plus arginine, ii) proline plus methionine, iii) proline plus arginine, iv) methionine plus arginine plus proline, v) methionine plus lysine, and vi) methionine plus lysine plus proline.

Preferred combinations of buffer and amino acid are a histidine buffer and methionine or a citrate buffer and methionine.

As a further possible but optional component the formulation may comprise a surfactant. The surfactant can be in principle any (non-ionic) surfactant suitable for protein formulation, but it is preferably, selected from the group of polysorbate 20, polysorbate 80, a poloxamer (such as poloxamer 188) and combinations thereof. Most preferably, the surfactant is polysorbate 20 or polysorbate 80. Typically, but not necessarily, the surfactant, and in particular polysorbate 20 or polysorbate 80, will be present in a concentration of about 0.01% to about 0.1% w/v. Formulations of the present invention may for example comprise about 0.1 mg/ml, about 0.2 mg/ml, about 0.3 mg/ml, about 0.4 mg/ml, about 0.5 mg/ml, about 0.6 mg/ml, about 0.7 mg/ml, about 0.8 mg/ml, about 0.9 mg/ml or about 1 mg/ml. In preferred embodiments of the invention, the surfactant is chosen from polysorbate 20 and polysorbate 80, and is present in a concentration of about 0.1 mg/ml to about 0.3 mg/ml. More preferably, the concentration of polysorbate 20 and polysorbate 80 is about 0.2 mg/ml.

A further but optional component of the inventive formulation is a stabilizer selected from the group of sugars and sugar alcohols. Examples of sugars are lactose, fructose, maltose, trehalose and sucrose. The sugar may be sucrose (except in cases where the formulation is a histidine

buffer: there the stabilizer is preferably not sucrose). Preferred examples of sugar alcohols are arabitol, mannitol and sorbitol. Sorbitol can help to suppress aggregation. In some embodiments, sorbitol is present in a concentration no greater than approximately 300 mM. The concentration of sorbitol can for example be in the range of 100 to 350 mM, more preferably in the range of 100 to 300 mM. If the inventive formulation contains sucrose, it is preferably used in the range of 100 to 300 mM sucrose, preferably in the range of 140 to 210 mM sucrose, preferably 146 mM sucrose. However, the present invention also specifically contemplates to use formulations according to the present invention without sucrose. Typical embodiments for such scenario are formulations which do neither comprise a buffering agent nor sucrose.

A further, optional, component of the inventive formulation is a chelator and/or oxygen-scavenger or combinations of both. Typical chelators are citrate, diethylenetriaminepentaacetic acid (DTPA), and ethylenediaminetetraacetic acid (EDTA). Examples for oxygen scavengers are methionine, sodium thiosulfate, catalase, or platinum, wherein methionine is the preferred oxygen scavenger for the present invention. In case the inventive formulation comprises a chelator, such as DTPA or EDTA, the such chelator may be present in a concentration in the range of 5 to 150 μ M, preferably in the range of 20 to 100 μ M. Particularly preferred concentrations are 20 μ M, 50 μ M, and 100 μ M. Most preferred is a chelator concentration of 20 μ M. In case the inventive formulation comprises an oxygen scavenger such as methionine, then such scavenger is preferably present in a concentration of about 100 μ M to 15 mM. A particularly preferred concentration of methionine is 10 mM. Instead of using a chelator/and or oxygen scavenger, one may also consider to flush the headspace of the container containing the inventive formulation with an inert gas, e.g. with nitrogen, in order to displace oxygen and to minimize oxidation.

Finally, the inventive formulation may optionally also comprise an inorganic salt such as sodium sulphate or sodium chloride or combinations thereof. Sodium chloride can reduce the viscosity of a formulation. The inventive formulation may — without being limited thereto — comprise 10 to 100 mM salt, for example 10 to 20 mM sodium sulphate, in particular 16 mM sodium sulphate, or may comprise 25 to 75 mM sodium chloride, in particular 40 to 60 mM sodium chloride, in particular 50 mM sodium chloride. However, using a salt is optional and the present invention contemplates formulations without salt, e.g. without sodium chloride.

Formulations of the present invention may for example be selected from the following formulations comprising:

- i) 100 to 120 mg aflibercept, in particular 114 to 115 mg aflibercept, no buffering agent, pH 5.8, proline and, optionally, methionine and/or a surfactant; or
- ii) 100 to 120 mg aflibercept, in particular 114 to 115 mg aflibercept, a citrate buffer, pH 5.8, sucrose, arginine and, optionally, methionine and/or a surfactant.

Further specific examples for formulations of the present invention may for instance be selected from the following group:

- i) 100 to 120 mg aflibercept, preferably 114 mg aflibercept, a citrate buffer, pH 5.8, sucrose or trehalose, polysorbate 20 (e.g. 0.3 mg/ml), and arginine and preferably no histidine;
- ii) 100 to 120 mg aflibercept, preferably 114 mg aflibercept, no buffering agent, pH 5.8, proline, arginine, polysorbate 20 (e.g. 0.3 mg/ml), said formulation preferably not comprising any sugar or sugar alcohol, and
- iii) 100 to 120 mg aflibercept, preferably 114 mg aflibercept, no buffering agent, pH 5.8, proline, methionine, polysorbate 20 (e.g. 0.3 mg/ml), said formulation preferably not comprising any sugar or sugar alcohol.

In a further aspect, the present invention relates to articles of manufacture comprising containers and injection devices (which may be sterile) containing a liquid formulation according to the present invention and optionally instructions for its use. The article of manufacture may in particular be a container like a glass vial or test tube; an injection device such as a pre-filled syringe (e.g., a filled glass syringe or filled plastic syringe), or an intravitreal implant, e.g., a refillable implant.

A "pre-filled" syringe is a syringe which is filled with a formulation of the present invention prior to sale or use by the physician or patient. It could contain one or more dose line graduations and/or is a dose metering system.

"Sterile" herein refers to aseptic or free from substantially all, or all, living microorganisms and their spores.

Containers and injection devices may be coated with silicone (e.g., silicone oil or baked-silicone (e.g., <40 pg or <100 pg), are substantially metal-free or substantially tungsten-free or low-tungsten.

Finally, the present invention relates to a formulation according to the present invention for use in a method of treating a disease of the human or animal body, in particular wherein the disease is a VEGF related disease such as angiogenic eye disorders or cancer.

Angiogenic eye disorders herein refer to any disease of the eye which is caused by or associated with the growth or proliferation of blood vessels and/or by blood vessel leakage. Non-limiting examples of angiogenic eye disorders that are treatable or preventable using the formulations and methods herein, include but not limited to: neovascular (wet) age-related macular degeneration (AMD), macular edema, macular edema following retinal vein occlusion, retinal vein occlusion (RVO), diabetic macular edema (DME) choroidal neovascularization (CNV), iris neovascularization, neovascular glaucoma, post-surgical fibrosis in glaucoma, proliferative vitreoretinopathy (PVR), optic disc neovascularization, corneal neovascularization, retinal neovascularization, vitreal neovascularization, vascular retinopathy, diabetic retinopathies (e.g. non-proliferative diabetic retinopathy or proliferative diabetic retinopathy, e.g., in a subject that does not suffer from DME) and or diabetic retinopathy in a patient who has diabetic macular edema (DME).

The cancer may be any type of cancer for which VEGF receptor Fc fusion proteins are therapeutically effective. Cancers include those whose growth, proliferation, survival and/or metastasis is dependent, to a degree, on angiogenesis. In an embodiment of the invention, the cancer is colorectal cancer, lung cancer, skin cancer, breast cancer, brain cancer, stomach cancer, renal cancer, prostate cancer, liver cancer or pancreatic cancer.

The liquid composition may be administered through an oral or parenteral route. In case of parenteral administration (for example, injection), it may be administered by intravenous administration, subcutaneous administration, intramuscular administration, intraperitoneal administration, endothelial administration, local administration, intranasal administration, intrapulmonary administration, intrarectal administration, intratumoral administration, intravitreal administration, etc.

In a specific embodiment, the liquid composition may be an ophthalmic solution comprising a VEGF antagonist as described above, and in this case, may be parenteral formulation to be administered into a vitreous humor of an eye.

The term "comprising", as used herein, shall not be construed as being limited to the meaning "consisting of" (i.e. excluding the presence of additional other matter). Rather, "comprising" implies that optionally additional matter, features or steps may be present. The term "comprising" encompasses as particularly envisioned embodiments falling within its scope "consisting of" (i.e. excluding the presence of additional other matter) and "comprising but not consisting of" (i.e. requiring the presence of additional other matter, features or steps), with the former being more preferred.

The use of the word "a" or "an", when used herein, may mean "one," but it is also consistent with the meaning of "one or more," "at least one," and "one or more than one."

Figures

In the following a brief description of the appended figures will be given. The figures are intended to illustrate the present invention in more detail. However, it is not intended to limit the scope of the invention to only these specifically illustrated embodiments.

Fig. 1: provides a table illustrating various formulations of aflibercept (each with 115 mg/ml) and their impact on aggregate formation after storage for eight weeks at 25°C.

Fig. 2: illustrates score contributions of different buffers/excipients for aflibercept. Score of each buffer/excipient represents its effect on reducing aggregation (in % of aggregates). The lower the score contribution, the better the effect on protein stability.

Examples

In the following, a specific example illustrating various embodiments and aspects of the invention is presented. However, the present invention shall not to be limited in scope by the specific embodiment described herein. Indeed, various modifications of the invention in addition to those described herein will become readily apparent to those skilled in the art from

the foregoing description, accompanying figures and the example below. All such modifications fall within the scope of the appended claims.

Example 1: Aggregate formation in various aflibercept formulations

The objective of this study was to evaluate the effects of different buffers and excipients (sugars, antioxidants, viscosity reducing agents (VRAs) on aflibercept stability. Briefly, preparation of samples included pH adjustment, concentration of protein material above target concentration (using 50K Amicon® Ultra centrifugal filter tubes (Merck Millipore) and centrifuging until concentrations of 150 mg/mL are reached), and dilution with excipient stocks to target concentration (115 mg/ml), see Fig. 1. Furthermore, samples were exposed to temperature stress conditions for eight weeks at 25 °C. Samples taken before (t_0) and after eight weeks at 25°C were used for size exclusion chromatography (SEC) analysis and assessment of aggregation and degradation products.

For SEC analysis, samples were analysed at 40 °C on a Waters™ ACQUITY UPLC System with a SEC column (200 Å pore size, 1.7 mm bead size and 4.6 mm x 150 mm column dimensions). Sample load was 0.75 µl. The mobile phase (50 mM sodium dihydrogen phosphate and 400 mM sodium perchlorate, pH 6.0) flow rate was 0.4 mL/min with a total run time of 5 min. Samples were diluted to 1 mg/ml in 150 mM sodium phosphate, pH 7, and held at 2–8 °C in the autosampler prior to injection. The data was analysed with Empower 3 software. The variability of the relative aggregate content measurement (aggregates/monomer) at described column loading was estimated to be 0.1% (absolute value).

The results, provided as increase of aggregate products (in %) of temperature stressed samples after 8 weeks (pull point; PP) at 25°C as compared to aggregates present at t_0 (before temperature stress exposure), are given in the table in Fig 1.

In addition, the score contribution of the individual formulation components (buffers/excipients, see table in Fig 1) on reducing aggregation has been evaluated. Briefly, the results were evaluated with linear regression, elucidating excipient contributions. It must be noted that this approach assumes that contributions are linearly additive. Formulation components were used as features for the fit ("one-hot encoding"). Deviation from the average aggregate increase (SEC AP column in table in Fig. 1) was used as response to which the linear

function was fitted. Fit coefficients of individual formulation components are defined as their scores - the lower the value, the better the excipient. Bufferless formulation was treated as having no buffer component ("zero contribution"). A positive score indicates an increase in aggregate formation as compared to bufferless formulation while a negative score implies less aggregate formation than in bufferless formulations.

The individual contribution of the various formulation components to aggregation are depicted in Fig. 2. As can be taken from said figure, histidine buffer, bufferless and, to a lower extent, citric acid buffers are preferred buffer choices for high concentration aflibercept formulations. Moreover, addition of free amino acids such as lysine, arginine, methionine or proline is also advantageous in general.

CLAIMS

1. A liquid pharmaceutical formulation comprising a VEGF receptor fusion protein at a concentration of at least 100 mg/ml, and wherein the formulation comprises:
 - i) no buffering agent,
 - ii) a citrate buffer, or
 - iii) a histidine buffer with methionine.
2. The liquid formulation of claim 1, wherein the formulation does not comprise a buffering agent.
3. The liquid formulation of claim 1, wherein the formulation comprises no buffering agent or comprises a citrate buffer, and wherein in addition the formulation does not comprise histidine.
4. The liquid formulation of any of claims 1 to 3, wherein the formulation comprises one or more free amino acids.
5. The liquid formulation of any of claims 1 to claim 4, wherein the VEGF receptor fusion protein is aflibercept.
6. The liquid formulation of any of claims 1 to 4, wherein the concentration of the VEGF receptor protein is about 115 mg/ml.
7. The liquid formulation of claim 5, wherein the concentration of aflibercept is about 115 mg/ml.
8. The liquid formulation of claim 5, wherein the concentration of aflibercept is 114 to 115 mg/ml.
9. The liquid formulation of claim 5, wherein the concentration of aflibercept is 114.3 mg/ml.

10. The liquid formulation of any of claims 1 to 9, wherein the formulation comprises one or more amino acids selected from the group consisting of glycine, alanine, valine, leucine, isoleucine, methionine, proline, phenylamine and tryptophan, preferably selected from the group consisting of proline and methionine.
11. The liquid formulation of any of claims 1 to 10, wherein the formulation comprises methionine, in particular wherein the formulation comprises a histidine buffer and methionine or a citrate buffer and methionine.
12. The liquid formulation of any of claims 1 to 11, wherein the formulation does not comprise sucrose, in particular wherein the formulation does neither comprise a buffering agent nor sucrose.
13. The liquid formulation of any of claims 1 to 12, wherein the formulation comprises proline, in particular wherein the formulation comprises proline but no sucrose, in particular wherein the formulation comprises proline and no stabilizer selected from the group consisting of sugars and sugar alcohols.
14. The liquid formulation of any of claims 1 to 13, wherein the formulation comprises one or more amino acids selected from the group consisting of lysine and arginine, preferably arginine.
15. The liquid formulation of any of claims 1 to 14, wherein the formulation comprises a surfactant such as polysorbate 20 or polysorbate 80.
16. The liquid formulation of any of claims 1 to 15, wherein the formulation comprises polysorbate 80.
17. The liquid formulation of any of claims 1 to 15, wherein the formulation comprises polysorbate 20.
18. The liquid formulation of any of claims 1 to 17, wherein the formulation shows after storage for 8 weeks at 25°C an increase in aggregates by less than 1.30% .

19. The liquid formulation of any of claims 1 to 18, wherein the pH of the formulation is 5.8.
20. The liquid formulation of any of claims 1 to 19, wherein the histidine buffer or citrate buffer has a concentration of 5 to 20 mM, in particular wherein the buffer is a histidine buffer having a concentration of 20 mM or is a citrate buffer having a concentration of 10 mM.
21. The liquid formulation of any of claims 1 to 15, wherein the formulation comprises aflibercept, a citrate buffer, pH 5.8, sucrose or trehalose, polysorbate 20, arginine and no histidine.
22. The liquid formulation of any of claims 1 to 15, wherein the formulation comprises aflibercept, no buffering agent, pH 5.8, proline, arginine, and polysorbate 20.
23. The liquid formulation of any of claims 1 to 15, wherein the formulation comprises aflibercept, no buffering agent, pH 5.8, proline, methionine, and polysorbate 20.
24. An article of manufacture comprising a container with a liquid pharmaceutical formulation of any one of claims 1 to 23, and instructions for its use.
25. The article of claim 24, wherein the article is a pre-filled syringe or glass vial.
26. The liquid pharmaceutical formulation of any one of claims 1 to 23, wherein the VEGF receptor fusion protein for use in a method of treating a disease of the human or animal body.

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Buffer	Buffer conc. [mM]	pH	Sugar	Sugar conc. [mM]	Free amino acid 1	Free amino acid 1 conc. [mM]	Free amino acid 2	Free amino acid 2 conc. [mM]	SEC AP (PP-t0)
His/HCl	20	5.8	Sucrose	146	Arg	50	Met	10	0.65
His/HCl	20	5.8	Sucrose	146	Arg	50			0.82
Citric/NaOH	10	5.8	Sucrose	146	Arg	50			1.07
Bufferless	-	5.8			Pro	300			1.08
Phosphoric/NaOH	10	5.8	Sucrose	146	Arg	50			1.14
Bufferless	-	5.8	Sucrose	292					1.16
Acetic/NaOH	10	5.8	Sucrose	146	Arg	50			1.24
Succinic/NaOH	10	5.8	Sorbitol	137	Lys	100			1.25
Bufferless	-	5.8	Sorbitol	274					1.27
Glutamic/NaOH	20	5.8	Sorbitol	137	Lys	100			1.28
Succinic/NaOH	10	5.8			Pro	200	Arg	50	1.3
Succinic/Arg	20	5.8	Sorbitol	137	Arg	34.5	Met	10	1.31
Glutamic/NaOH	20	5.8	Sorbitol	137	Arg	50			1.32
Succinic/NaOH	20	5.8			Pro	250			1.39
Succinic/Arg	20	5.8	Sorbitol	137	Arg	34.5			1.4

Fig. 1

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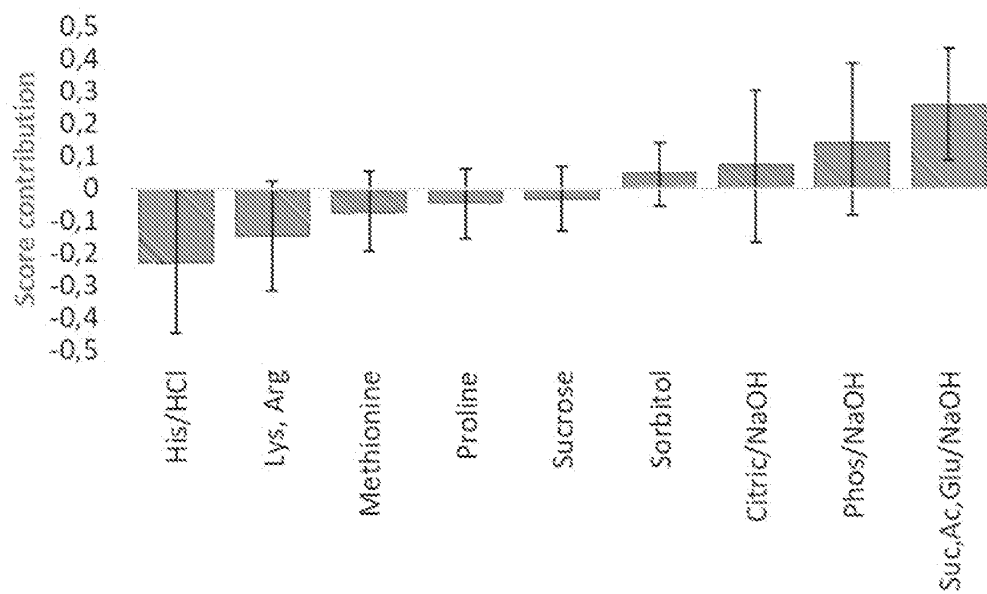


Fig. 2

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2022/074711

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K9/08 A61K39/00 A61K47/12 A61K47/18
 ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CN 104 906 576 B (SICHUAN KELUN PHARMACEUTICAL) 19 June 2018 (2018-06-19) formulations A-X	1-26
X	WO 2017/117202 A1 (ONCOBIOLOGICS INC [US]) 6 July 2017 (2017-07-06) examples 1-4	1-26
X	US 2020/246423 A1 (LIU JUN [US] ET AL) 6 August 2020 (2020-08-06) table 86, G-6; examples 9-14	1-26
X	US 11 103 552 B2 (REGENERON PHARMA [US]) 31 August 2021 (2021-08-31) table 7-1, F2, F8; tables 3-1; 9-2; 9-3; column 2, lines 5-55	1-26
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☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

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Date of the actual completion of the international search

29 November 2022

Date of mailing of the international search report

06/12/2022

Name and mailing address of the ISA:

European Patent Office, P.O. Box 5616 Patentlaan 2
 NL - 2260 HV Rijswijk
 Tel. (+31-70) 340-2040
 Fax: (+31-70) 340-3016

Authorized officer

Kontner, Jörg

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page 1 of 2

PGR2026-00039
 Biocon Ex.1002
 Page 835 of 4945

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2022/074711

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2019/203694 A1 (LLC INTERNATIONAL BIOTECHNOLOGY CENTER GENERIUM LLC IBC GENERIUM [RU]) 24 October 2019 (2019-10-24) examples 1-3; claims 1-19 -----	1-26
X	WO 2021/125852 A1 (PROGEN CO LTD [KR]) 24 June 2021 (2021-06-24) examples 1-6 -----	1-26

INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP2022/074711

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:
 - a. ☒ forming part of the international application as filed.
 - b. ☐ furnished subsequent to the international filing date for the purposes of international search (Rule 13ter.1(a)).

☐ accompanied by a statement to the effect that the sequence listing does not go beyond the disclosure in the international application as filed.
2. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, this report has been established to the extent that a meaningful search could be carried out without a WIPO Standard ST.26 compliant sequence listing.
3. Additional comments:

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2022/074711

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		WO 2021125852 A1	24-06-2021

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(71) Applicant: **REGENERON PHARMACEUTICALS, INC.** [US/US]; 777 Old Saw Mill River Road, Tarrytown, New York 10591-6707 (US).

(72) Inventors: **GRAHAM, Kenneth S.**; 218 Robbott Road, Pleasant Valley, NY 12569 (US). **WADHWA, Saurabh**; 19 Rime Road, Nanuet, NY 10954 (US).

(74) Agent: **TERMES, Lance A.**; Schwabe, Williamson & Wyatt, 1211 SW 5th Avenue, Suite 1900, Portland, OR 97204 (US).

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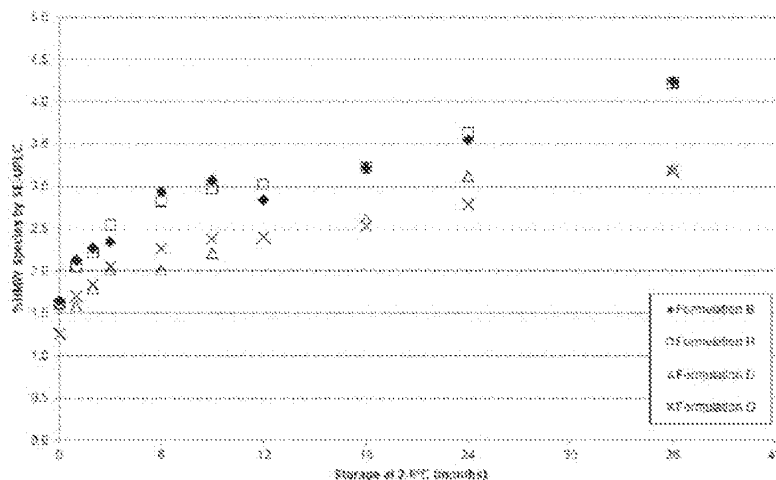


FIG. 1A

(57) Abstract: The present invention provides ophthalmic formulations having high concentrations of vascular endothelial growth factor (VEGF) receptor fusion protein and high stability during storage. Methods for treating angiogenic eye disorders using the high concentration formulations are also provided.

[Continued on next page]

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HIGH CONCENTRATION VEGF RECEPTOR FUSION PROTEIN CONTAINING FORMULATIONS

[001] This application claims the benefit of U.S. Provisional Patent Application No. 62/813,882, filed March 5, 2019; U.S. Provisional Patent Application No. 62/769,876, filed November 20, 2018; U.S. Provisional Patent Application No. 62/752,127, filed October 29, 2018; and U.S. Provisional Patent Application No. 62/669,506, filed May 10, 2018; each of which is herein incorporated by reference in its entirety.

TECHNICAL FIELD

[002] Embodiments herein relate generally to high concentration VEGF receptor fusion protein containing formulations suitable for ocular administration. More particularly, embodiments herein provide liquid pharmaceutical formulations for intravitreal administration, where the formulations include more than 40 mg/ml VEGF receptor fusion protein, and show pharmaceutically acceptable potency, stability, viscosity and pH.

SEQUENCE LISTING

[003] An official copy of the sequence listing is submitted concurrently with the specification electronically via EFS-Web as an ASCII formatted sequence listing with a file name of "10430P1-US_SEQ_LIST_ST25.txt", a creation date of May 9, 2018, and a size of about 7 KB. The sequence listing contained in this ASCII formatted document is part of the specification and is herein incorporated by reference in its entirety.

BACKGROUND OF THE INVENTION

[004] The development of a therapeutically useful liquid formulation requires a combination of ingredients, at differing amounts, to provide a functional and stable delivery vehicle for a drug of interest. This is particularly true where the drug is a protein, and furthermore, an antibody. Antibody formulations have long presented challenges to drug developers and manufacturers, as antibody activity and administration typically require a pharmaceutically acceptable potency, osmolality, protein stability, viscosity, and proper pH. These challenges are exacerbated when the antibody is at higher concentrations in the formulation, for example, beyond 20 to 40 mg/ml, the concentration of most pharmaceutically sold antibodies.

[005] Higher concentration antibody formulations allow for shorter injection times, smaller injection volumes, lower frequency of antibody administration, and more efficient manufacturing and storage utility. However, as noted above, the higher the antibody or protein concentration, the more difficult it is to maintain the proper activity and delivery parameters for the formulation. In particular, high concentration antibody and protein

formulations often contend with increased protein aggregation and viscosity, which results in lower overall antibody or protein potency, and lower manufacturing and poorer storage stability. Because of the issues related to high concentration protein or antibody formulations, few such pharmaceutically acceptable formulations have been developed. There is a need in the art for preparing high concentration, high stability, antibody and protein formulations that include the proper potency, stability, viscosity, osmolality and pH.

[006] One such protein in need of high concentration formulations is the vascular endothelial growth factor (VEGF) receptor fusion protein. VEGF receptor fusion proteins are used to block VEGF function in a number of ophthalmic formulations, for example, EYLEA® (Regeneron Pharmaceuticals, Inc.). High concentration VEGF receptor fusion protein containing formulations could allow for shorter ocular injection times, smaller injection volumes, fewer possible injections per administration cycle, and more efficient manufacturing and storage.

[007] The present invention is directed toward overcoming one or more of the problems discussed above.

SUMMARY OF THE INVENTION

[008] Various embodiments described herein encompass high concentration protein containing formulations (e.g., which are suitable for intravitreal administration), and in particular, high concentration vascular endothelial growth factor (VEGF) receptor fusion protein containing formulations. High concentration VEGF receptor fusion protein containing formulations provide a number of therapeutic and economic benefits, including, pharmaceutically acceptable potency, long term manufacturing and storage stability, and a viscosity and pH compatible with ocular injection. High concentration VEGF receptor fusion protein containing formulations also allow for reduced ocular administration volumes, a benefit for avoiding undesired effects on the limited volume of the eye.

[009] Embodiments herein provide formulations having a VEGF receptor fusion protein, a buffer, a thermal stabilizer, a viscosity reducing agent, and a surfactant. In other embodiments, the formulations do not include a viscosity reducing agent. Formulations of the present invention have a pH and viscosity suitable for injection, and in particular, for therapeutic ocular injection.

[0010] In an embodiment of the invention, a pharmaceutical formulation of the present invention is provided having a VEGF receptor fusion protein at a concentration of at least 41 mg/ml or a concentration that contains a single dose of VEGF receptor fusion protein (which is discussed herein) in less than about 100 µl, less than about 50 µl, about 50 µl, about 57 µl, about 60 µl, about 70 µl, or about 75 µl, a buffer, optionally a thermal stabilizer and/or a

viscosity reducing agent, and a surfactant, where the formulation has a pH of from about 5.0 to about 6.8 (*e.g.*, 5.8).

[0011] In an embodiment of the invention, the VEGF receptor fusion protein concentration is about 30 mg/ml, 60 mg/ml, 114 mg/ml, 120 mg/ml or 140 mg/ml.

[0012] In an embodiment of the invention, the surfactant can be a non-ionic surfactant (*e.g.*, about 0.02% to about 0.1%; or about 0.03% (w/v)). In an embodiment of the invention, the surfactant is a non-ionic surfactant having a polyoxyethylene moiety, for example, polysorbate 20 (PS20), polysorbate 80 (PS80), poloxamer 188, polyethylene glycol 3350 or mixtures thereof.

[0013] In an embodiment of the invention, the buffer is a histidine-based buffer (*e.g.*, 10 mM or 20 mM), such as histidine, histidine HCl or histidine acetate; a phosphate-based buffer, such as sodium phosphate (*e.g.*, 10 mM); an acetate-based buffer, such as sodium acetate and acetic acid, or a citrate-based buffer, such as sodium citrate or citric acid. In an embodiment of the invention, if the buffer is phosphate buffer, the pH is from about 5.7 to about 8.0, about 5.8 to about 8.0, about 5.7 to about 7.0, about 5.8 to about 7.0, about 5.9 to about 7.0 or about 6.0 to about 7.0; if the buffer is histidine buffer, the pH is from about 5.5 to about 6.5; if the buffer is citrate buffer, the pH is from about 3.0 to about 6.2 or about 5.0 to about 6.0; and if the buffer is acetate buffer, the pH is from about 3.7 to about 5.6 or about 5.0 to about 6.0.

[0014] In an embodiment of the invention, the thermal stabilizer is a sugar, such as sucrose (*e.g.*, about 2.5%, 5% or 8%, 10% or 20% (w/v), *e.g.*, about 2-20%), mannitol, sorbitol, or trehalose; L-proline (*e.g.*, about 2%, 3% or 4% (w/v)); glycine (*e.g.*, about 50 mM), glycerol, taurine (*e.g.*, about 50 mM) or propane sulfonic acid (*e.g.*, about 50 mM) or any combination of the above.

[0015] In some embodiments of the invention, the pharmaceutical formulations of the present invention include a viscosity reducing agent, for example, arginine hydrochloride (*e.g.*, L-arginine monohydrochloride) (*e.g.*, 50 mM), lysine, sodium chloride (*e.g.*, 40 mM or 50 mM), or magnesium chloride. Alternatively, in other embodiments, the formulations of the present invention specifically exclude substantially all, if not all, viscosity reducing agents.

[0016] In an embodiment of the invention, the pharmaceutical formulations of the present invention comprise, consists of or consists essentially of the constituents in any one of formulations A-KKKK as set forth herein.

[0017] In aspects herein, the pharmaceutical formulations of the present invention may include a VEGF receptor fusion protein (*e.g.*, aflibercept or conbercept) at a concentration of from about 41 mg/ml to about 275 mg/ml, from about 80 mg/ml to about 275 mg/ml, about 140 mg/ml to about 150 mg/ml, about 140 mg/ml to about 159 or 160 mg/ml; including about 60 mg/ml, about 80 mg/ml, about 100 mg/ml, about 113.3 mg/ml, about 114.3 mg/ml, about

120 mg/ml, about 133.3 mg/ml, about 140 mg/ml, about 150 mg/ml, about 200 mg/ml or about 250 mg/ml. In an embodiment of the invention, the formulation comprises about 40 mg/ml of the VEGF receptor fusion protein.

[0018] Some aspects of the pharmaceutical formulations of the present invention include a thermal stabilizer at a concentration of from about 2% (w/v) to about 9% (w/v) or from about 4% (w/v) to about 9% (w/v), with the proviso, that when the thermal stabilizer is taurine or propane sulfonic acid, the stabilizer is at a concentration of from about 25 mM to about 100 mM, surfactant is at a concentration of from about 0.02% (w/v) to about 0.1% (w/v) (e.g., about 0.03%), and buffer is of from about 5 mM to about 15 mM.

[0019] The VEGF receptor fusion protein can, for example:

- be encoded by the nucleic acid sequence of SEQ ID NO:1 or nucleotides 79-1374 or 79-1371 of SEQ ID NO: 1;
- comprise amino acids of SEQ ID NO: 2 or amino acids 27-457 or 27-458 of SEQ ID NO: 2;
- comprise:
 - (1) a VEGFR1 component comprising amino acids 27 to 129 of SEQ ID NO:2;
 - (2) a VEGFR2 component comprising amino acids 130 to 231 of SEQ ID NO:2;
 - (3) a multimerization component ("FcΔC1(a)") comprising amino acids 232 to 457 or 458 of SEQ ID NO:2 (the C-terminal amino acids of SEQ ID NO:2, i.e., K458, may or may not be included in the VEGF receptor fusion proteins). Note that amino acids 1 to 26 of SEQ ID NO:2 are the signal sequence;
- comprise an immunoglobulin-like (Ig) domain 2 of a first VEGF receptor (e.g., VEGFR1) and Ig domain 3 of a second VEGF receptor (e.g., VEGFR2), optionally further including an Ig domain 4 of the second VEGF receptor (e.g., VEGFR2) and a multimerizing component (e.g., Fc domain of IgG);
- be conbercept; or
- be allibercept.

VEGF Trap

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 (SEQ ID NO: 1)

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 VFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTY
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 QVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGN
 VFSCSVMHEALHNHYTOKSLSLSPGK

(SEQ ID NO: 2)

AAs 1-26 = Signal Sequence

AAs 27-129 = Flt1-D2 (VEGFR1-D2)

AAs 130-231 = Flk1-D3 (VEGFR2-D3)

AAs 232-458 = FcΔC1

[0020] In another embodiment of the present invention, a container containing an aqueous solution of from about 5 mM to about 25 mM pharmaceutically acceptable buffer, from about 4% (w/v) to about 9% (w/v) of a pharmaceutically acceptable thermal stabilizer, from about 0.02% (w/v) to about 0.1% (w/v) of a pharmaceutically acceptable surfactant, and from about 41 mg/ml to about 275 mg/ml VEGF receptor fusion protein, is provided. When the thermal stabilizer includes either taurine or propane sulfonic acid, the taurine or propane sulfonic

acid is at a concentration of from about 25 mM to about 100 mM. The aqueous solution has a pH of from about 5.0 to about 6.8, and can be from about 5.5 to about 6.2 (*e.g.*, 5.8). In some aspects, the container is a vial or syringe. In other aspects, the aqueous solution does not include an inorganic salt. When the thermal stabilizer is a sugar it can be sucrose, mannitol, sorbitol or trehalose, and can be present at between about 4% (w/v) and 9% (w/v); the surfactant can be a non-ionic surfactant, and can include a polyoxyethylene moiety, such as polysorbate 20, polysorbate 80, poloxamer 188, or polyethylene glycol 3350, at a concentration of from about 0.02% to about 0.1% weight per volume (w/v), and more typically, 0.02% to about 0.04% (w/v). In an embodiment of the invention, the VEGF receptor fusion protein is encoded by the nucleic acid sequence of SEQ ID NO:1 or nucleotides 79-1374 or 79-1371 of SEQ ID NO: 1; comprises amino acids of SEQ ID NO: 2 or amino acids 27-457 or 27-458 of SEQ ID NO: 2; comprises (1) a VEGFR1 component comprising amino acids 27 to 129 of SEQ ID NO:2; (2) a VEGFR2 component comprising amino acids 130 to 231 of SEQ ID NO:2; and (3) a multimerization component ("FcΔC1(a)") comprising amino acids 232 to 457 of SEQ ID NO:2 (the C-terminal amino acids of SEQ ID NO:2, *i.e.*, K458, may or may not be included in the VEGF receptor fusion proteins); comprises an immunoglobulin-like (Ig) domain 2 of a first VEGF receptor (*e.g.*, VEGFR1) and Ig domain 3 of a second VEGF receptor (*e.g.*, VEGFR2), optionally further including an Ig domain 4 of the second VEGF receptor (*e.g.*, VEGFR2) and a multimerizing component (*e.g.*, Fc domain of IgG); is conbercept or is aflibercept.

[0021] In still other embodiments, pharmaceutical formulations of the present invention are provided having a VEGF receptor fusion protein in an aqueous vehicle, where the aqueous vehicle has a viscosity of from about 10 cP to about 15 cP at 20°C, more typically about 10 cP to about 13 cP at 20°C, and most typically from about 11 cP to about 12 cP at 20°C (*e.g.*, about 6.0, 7.3, 11.5 or 12.0 cP at 20°C). In an embodiment of the invention, the viscosity is about 12 cP to about 15 cP at 20°C. The pH of the formulation can be from about 5.8 to about 6.5 (*e.g.*, about 5.8). In some cases, the formulations do not include a viscosity reducing agent, for example, do not include arginine hydrochloride, lysine, sodium chloride, or magnesium chloride. In other cases, the formulations include 10 mM histidine hydrochloride or 10 mM histidine-acetate. The sugar can be sucrose, mannitol, sorbitol or trehalose, and can be present at between about 4% (w/v) and 9% (w/v) (*e.g.*, about 5%); the surfactant can be a non-ionic surfactant, and can include a polyoxyethylene moiety, such as polysorbate 20, polysorbate 80, poloxamer 188, or polyethylene glycol 3350, at a concentration of from about 0.02% to about 0.1% weight per volume (w/v), and more typically, 0.02% to about 0.04% (w/v) (*e.g.*, 0.03%). In addition, the formulation can additionally include a thermal stabilizer selected from either taurine or propane sulfonic acid at a concentration of between about 25 mM to about 100 mM, and more typically about, 50

mM to about 70 mM. In an embodiment of the invention, a formulation comprises VEGF receptor fusion protein, such as aflibercept, (e.g., at a concentration of about 41-275 mg/ml, about 50 mg/ml, about 100 mg/ml, about 115 mg/ml, about 125 mg/ml, about 150 mg/ml, about 200 mg/ml or any of the "high" concentrations discussed herein), about 10 mM histidine-based buffer, about 5% (w/v) sucrose, about 0.03% (w/v) non-ionic surfactant such as polysorbate e.g., polysorbate 20, and about 50 mM arginine, L-arginine or L-arginine monohydrochloride, with a pH of about 5.8. In an embodiment of the invention, the VEGF receptor fusion protein is encoded by the nucleic acid sequence of SEQ ID NO:1 or nucleotides 79-1374 or 79-1371 of SEQ ID NO: 1; comprises amino acids of SEQ ID NO: 2 or amino acids 27-457 or 27-458 of SEQ ID NO: 2; comprises (1) a VEGFR1 component comprising amino acids 27 to 129 of SEQ ID NO:2; (2) a VEGFR2 component comprising amino acids 130 to 231 of SEQ ID NO:2; and (3) a multimerization component ("FcΔC1(a)") comprising amino acids 232 to 457 of SEQ ID NO:2 (the C-terminal amino acids of SEQ ID NO:2, i.e., K458, may or may not be included in the VEGF receptor fusion proteins); comprises an immunoglobulin-like (Ig) domain 2 of a first VEGF receptor (e.g., VEGFR1) and Ig domain 3 of a second VEGF receptor (e.g., VEGFR2), optionally further including an Ig domain 4 of the second VEGF receptor (e.g., VEGFR2) and a multimerizing component (e.g., Fc domain of IgG); is conbercept or is aflibercept.

[0022] In yet another embodiment, a pharmaceutical formulation of the present invention is provided that includes a VEGF receptor fusion protein at a concentration of from about 80 mg/ml to about 275 mg/ml in a pharmaceutically acceptable buffer. In some cases, the stable pharmaceutical formulations can also include taurine or propane sulfonic acid. The formulations can be stable at a temperature of about 2°C to about 8°C for about 24-36 months. In some cases, the VEGF receptor fusion protein shows less than about a 5% increase in high molecular weight species, and more typically, less than about 4.5% increase in high molecular weight species, less than about 4.0% increase in high molecular weight species, less than about 3.5% increase in high molecular weight species, less than about 3.0% increase in high molecular weight species, less than about 2.5% increase in high molecular weight species, less than about 2.0 increase in high molecular weight species and/or less than about 1.5% increase in high molecular weight species, when stored at these temperatures and for this amount of time. In other cases, the VEGF receptor fusion protein shows less than a 2.0% to 3.0% increase in high molecular weight species when the formulations are stored at these temperatures and for this amount of time.

[0023] Embodiments herein can also include pharmaceutical formulations of the present invention that include aflibercept, a pH buffered solution, a sugar and a surfactant, where the aflibercept is at a concentration of 41 mg/ml to about 275 mg/ml. Alternatively, embodiments can be stable liquid pharmaceutical formulations that include conbercept, a pH buffered

solution, a sugar and a surfactant, where the conbercept is at a concentration of 41 mg/ml to about 275 mg/ml. Stable liquid pharmaceutical formulations can also include taurine or propane sulfonic acid. In some aspects, the aflibercept or conbercept is at a concentration of either 80 mg/ml or 150 mg/ml. In other aspects, the formulations do not include an inorganic salt, sodium chloride for example.

[0024] Some embodiments are directed to sterile syringes such that the syringes are pre-filled with an aqueous solution having 80 mg/ml aflibercept, conbercept, 10 mM histidine hydrochloride, histidine acetate or sodium phosphate, 5% (w/v) sucrose, mannitol, sorbitol or trehalose, 0.03% (w/v) polysorbate 20, polysorbate 80, poloxamer 188, or polyethylene glycol 3350, and 40 mM sodium chloride. Aspects herein include the further addition of about 25 mM to about 100 mM, and more typically about 50 mM to about 70 mM, of either taurine or propane sulfonic acid. In some aspects, the syringes are pre-filled with an aqueous solution having 80 mg/ml aflibercept, conbercept, 10 mM histidine HCl, histidine acetate or sodium phosphate, 8% (w/v) sucrose, mannitol, sorbitol or trehalose, and 0.03% (w/v) polysorbate 20, polysorbate 80, poloxamer 188, or polyethylene glycol 3350. Aspects herein include the further addition of about 25 mM to about 100 mM, and more typically about 50 mM to about 70 mM, of either taurine or propane sulfonic acid. In still other aspects, the syringes are pre-filled with an aqueous solution having 150 mg/ml aflibercept, conbercept, 10 mM histidine hydrochloride, histidine acetate, or sodium phosphate, 5% (w/v) sucrose, mannitol, sorbitol or trehalose, 0.03% (w/v) polysorbate 20, polysorbate 80, poloxamer 188, or polyethylene glycol 3350 and 40 mM sodium chloride, with a pH of about 6.2. Aspects herein can include the further addition of either taurine or propane sulfonic acid. In yet still other aspects, the syringes are pre-filled with an aqueous solution having 150 mg/ml aflibercept, conbercept, 10 mM histidine hydrochloride, histidine acetate, or sodium phosphate, 8% (w/v) sucrose, mannitol, sorbitol or trehalose, and 0.03% (w/v) polysorbate 20, polysorbate 80, poloxamer 188, or polyethylene glycol 3350, with a pH of about 6.2 and the aqueous solution does not include an inorganic salt. Aspects can further include about 25 mM to about 100 mM, and more typically, about 50 mM to about 70 mM, of either taurine or propane sulfonic acid. In yet still other aspects, the syringes are pre-filled with an aqueous solution having 150 mg/ml aflibercept or conbercept, 10 mM sodium acetate or acetic acid, 5% (w/v) glycerol and 0.03% (w/v) polysorbate 20, polysorbate 80, poloxamer 188, or polyethylene glycol 3350 and 40 mM sodium chloride, with a pH of about 6.2. In yet still other aspects, the syringes are pre-filled with an aqueous solution having 150 mg/ml aflibercept or conbercept, 10 mM sodium acetate or acetic acid, 8% (w/v) glycerol, and 0.03% (w/v) polysorbate 20, polysorbate 80, poloxamer 188, or polyethylene glycol 3350 and 40 mM sodium chloride, with a pH of about 6.2.

[0025] The present invention also provides a method for making any formulation set forth herein comprising the step of combining each component of the formulation into a single composition. Such a method may include the step of adding the resulting formulation into a vial or injection device. Any composition that is the product of such a method also forms part of the present invention. For example, embodiments herein also include methods for preparing a formulation by combining a histidine-based, citrate-based, acetate-based or phosphate-based buffer, with sucrose, polysorbate 20 and a VEGF receptor fusion protein; and, optionally, one or more additional components, *e.g.*, as discussed herein. In some cases, the formulation is prepared to also include taurine or propane sulfonic acid, but where it does not include taurine or propane sulfonic acid, it may also not include an inorganic salt. In aspects herein, the sucrose is at a weight per volume of from about 4% to about 10%, the polysorbate 20 has a weight per volume of about 0.02% to about 0.1%, and the receptor fusion protein is at a concentration of from about 41 mg/ml to about 275 mg/ml. Where the formulation includes taurine or propane sulfonic acid, it is present at, for example, about 25 mM to about 100 mM, but may also be included at 50 mM to 70 mM. The method can include loading a predetermined volume of prepared formulation into a sterile syringe, such that the volume has a 0.1 mg to 10 mg dose of the VEGF receptor fusion protein.

[0026] The present invention also provides a method for administering a formulation of the present invention to a subject (*e.g.*, a human) comprising intraocularly injecting (*e.g.*, intravitreal injection) the formulation into the eye of the subject. The present invention also provides a method for administering a formulation of the present invention to a subject (*e.g.*, a human) comprising implanting an intravitreal implant that contains a formulation of the present invention into the vitreous of the subject.

[0027] Embodiments herein also include methods for treating an angiogenic eye disorder, *e.g.*, age-related macular degeneration (wet), macular edema following retinal vein occlusion, retinal vein occlusion (RVO), central retinal vein occlusion (CRVO) branch retinal vein occlusion (BRVO), diabetic macular edema (DME), choroidal neovascularization (CNV), iris neovascularization, neovascular glaucoma, post-surgical fibrosis in glaucoma, proliferative vitreoretinopathy (PVR), optic disc neovascularization, corneal neovascularization, retinal neovascularization, vitreal neovascularization, pannus, pterygium, vascular retinopathy or diabetic retinopathy (*e.g.*, non-proliferative diabetic retinopathy and/or proliferative diabetic retinopathy) in a subject in need thereof by intraocularly injecting at least about 2 mg (*e.g.*, 4 mg, 6 mg or 8 mg) of VEGF receptor fusion protein (*e.g.*, aflibercept or conbercept) into the eye of a subject in need thereof, for example, any formulation set forth herein. In an embodiment of the invention, the injection volume is 100 microliters or less (*e.g.*, 100 microliters, 50 microliters or 57 microliters). The method comprises an intravitreal injection of a pre-mixed aqueous solution having a VEGF receptor

fusion protein at a concentration of from 41 mg/ml to about 275 mg/ml, a pharmaceutically acceptable sugar, a pharmaceutically acceptable buffer, and a pharmaceutically acceptable surfactant. Treatment methods using the pre-mixed aqueous solution do not require dilution. In aspects herein, the pre-mixed aqueous solution has a pH from about 6.0 and about 6.5, and has a viscosity of between about 10 cP and 13 cP.

[0028] In aspects of the treatment method, the VEGF receptor fusion protein comprises VEGFR1R2-FcΔC1(a) encoded by the nucleic acid sequence of SEQ ID NO:1, amino acids 27 to 129 of SEQ ID NO:2, a VEGFR2 component comprising amino acids 130 to 231 of SEQ ID NO:2, or a multimerization component comprising amino acids 232 to 457 of SEQ ID NO:2, or any combination thereof. In an embodiment of the invention, the VEGF receptor fusion protein is aflibercept or conbercept.

[0029] Other embodiments in accordance with the disclosure herein will become apparent from a review of the ensuing detailed description.

BRIEF DESCRIPTION OF THE DRAWINGS

[0030] The above and other aspects, features and advantages of embodiments disclosed herein will become more apparent to those of ordinary skill in the art with reference to the accompanying drawings.

[0031] **Figure 1A** is a graph determining VEGF receptor fusion protein (aflibercept) stability in four different formulations (B, H, D and G) over the course of 36 months at 2°C to 8°C. VEGF receptor fusion protein stability was tested using size-exclusion ultra-performance liquid chromatography (SE-UPLC) to identify formation of high molecular weight (HMW) species (a sign of protein degradation).

[0032] **Figure 1B** is also a graph determining VEGF receptor fusion protein (aflibercept) stability in four formulations (B, H, D and G) over the course of 36 months at 2°C to 8°C. VEGF receptor fusion protein stability was tested using SE-UPLC to identify the percent of the main species in each formulation.

[0033] **Figure 1C** is a bar graph showing formation of VEGF receptor fusion protein charge variants in four formulations (B, H, D and G) over the course of 36 months at 2°C to 8°C. The level of acidic species was tested at manufacture (0.0), 12 months, 24 months and 36 months using imaged capillary isoelectric focusing (iCIEF).

[0034] **Figure 1D** is a bar graph showing formation of VEGF receptor fusion protein charge variants in four formulations (B, H, D and G) over the course of 36 months at 2°C to 8°C. Identification of the main species was tested at manufacture (0.0), 12 months, 24 months and 36 months using iCIEF.

[0035] **Figure 2A** is a graph showing 150 mg/ml VEGF receptor fusion protein (aflibercept) stability in a 10 mM sodium phosphate, 8% (w/v) sucrose and 0.03% polysorbate 20 (w/v)

formulation pH6.2 with and without L-arginine monohydrochloride over the course of 28 days at 37°C. VEGF receptor fusion protein stability was tested using SE-UPLC to identify formation of HMW species.

[0036] **Figure 2B** is a graph showing 150 mg/ml VEGF receptor fusion protein stability in a 10 mM sodium phosphate, 8% sucrose (w/v) and 0.03% polysorbate 20 (w/v) formulation pH6.2 with and without L-arginine monohydrochloride over the course of 28 days at 37°C. VEGF receptor fusion protein stability was tested using SE-UPLC to identify the percent of the main species in each formulation.

[0037] **Figure 3A** is a bar graph showing viscosity of 10 mM sodium phosphate buffered formulations having 155 mg/ml VEGF receptor fusion protein and no salt, 100 mM arginine, 200 mM arginine, 50 mM lysine, 200 mM lysine, 50 mM sodium chloride or 100 mM sodium chloride. Viscosity was measured in cP at 20°C.

[0038] **Figure 3B** is a bar graph showing viscosity of 10 mM histidine buffered formulations having 155 mg/ml VEGF receptor fusion protein and no salt, 100 mM arginine, 200 mM arginine, 50 mM lysine, 200 mM lysine, 50 mM sodium chloride or 100 mM sodium chloride. Viscosity was measured in cP at 20°C.

[0039] **Figure 3C** is a graph showing viscosity of various concentrations of VEGF receptor fusion protein under different formulation conditions (with or without 50 mM arginine hydrochloride). Viscosity was measured in cP at 20°C.

[0040] **Figure 4A** is a graph showing 150 mg/ml VEGF receptor fusion protein stability in 10 mM sodium phosphate, 8% (w/v) sucrose, and 0.03% (w/v) polysorbate 20, pH6.2 with and without 50 mM L-arginine monohydrochloride over 12 months at 5°C. The VEGF receptor fusion protein was at 150 mg/ml. VEGF receptor fusion protein stability was tested using SE-UPLC to identify formation of HMW species.

[0041] **Figure 4B** is a graph showing 150 mg/ml VEGF receptor fusion protein stability in 10 mM sodium phosphate, 8% (w/v) sucrose, and 0.03% (w/v) polysorbate 20, pH6.2 with and without 50 mM L-arginine monohydrochloride over 12 months at 5°C. The VEGF receptor fusion protein was at 150 mg/ml. VEGF receptor fusion protein stability was tested using SE-UPLC to identify the percent of the main species in each formulation.

[0042] **Figure 5** is a graph that shows viscosity of formulations under two buffer conditions at 20°C, 10 mM phosphate buffer or 10 mM histidine buffer. The VEGF receptor fusion protein concentration is varied from 10 mg/ml to 170 mg/ml. Viscosity was measured in mPa-S.

[0043] **Figure 6** shows a dynamic light scattering screen for a number of different formulation conditions, each having from 2 to 10 mg/ml protein. The diffusion interaction parameter indicated that taurine and PSA (propane sulfonic acid) improved Kd.

[0044] **Figure 7** is a graph monitoring the percentage of high molecular weight (HMW) species in formulations F1-F9 (formulations WW-EEE) over time as measured by size-exclusion ultra-performance liquid chromatography (SE-UPLC) after storage at 5°C for 6 months. Formulations F1-F9 are set forth in Table 7-1 herein.

[0045] **Figure 8 (A-B)** measures the percentage of high molecular weight species, by SE-UPLC, after storage at 5°C for 3 months (A) or incubation at 37°C for 28 days (B). Formulations F1-F4 (EEE, SSS, CCC (140 mg/ml) and TTT) are set forth in Table 8-1 below.

[0046] **Figure 9** shows the viscosity (cp) for Formulations F1-F12, at 20°C, at the initial time point. Formulations F1-F12 are set forth in Table A below.

Table A. Formulations F1-F12.

Formulation #	VEGF Trap (mg/mL)	Buffer	Other Excipients	Screening Excipients (mM)
F1 (GGG)	140	20 mM Histidine, pH 5.8	5% Sucrose, 0.03% Polysorbate 20	50mM Sodium sulfate
F2 (HHH)	140	20 mM Histidine, pH 5.8	5% Sucrose, 0.03% Polysorbate 20	50mM Sodium thiocyanate
F3 (III)	140	20 mM Histidine, pH 5.8	5% Sucrose, 0.03% Polysorbate 20	40mM Sodium citrate
F4 (JJJ)	140	20 mM Histidine, pH 5.8	5% Sucrose, 0.03% Polysorbate 20	50mM Glycine
F5 (KKK)	140	20 mM Histidine, pH 5.8	5% Sucrose, 0.03% Polysorbate 20	50mM Sodium chloride
F6 (LLL)	140	20 mM Histidine, pH 5.8	5% Sucrose, 0.03% Polysorbate 20	50mM Lysine
F7 (MMM)	140	20 mM Histidine, pH 5.8	5% Sucrose, 0.03% Polysorbate 20	50mM Sodium aspartate
F8 (NNN)	140	20 mM Histidine, pH 5.8	5% Sucrose, 0.03% Polysorbate 20	50mM Sodium glutamate
F9 (OOO)	140	20 mM Histidine, pH 5.8	5% Sucrose, 0.03% Polysorbate 20	50mM Sodium Citrate + 50mM Arginine hydrochloride
F10 (PPP)	140	20 mM Histidine, pH 5.8	5% Sucrose, 0.03% Polysorbate 20	50mM Glycine + 50mM Arginine hydrochloride
F11 (QQQ)	140	20 mM Histidine, pH 5.8	5% Sucrose, 0.03% Polysorbate 20	50mM Sodium aspartate +

		pH 5.8	Polysorbate 20	50mM Arginine hydrochloride
F12 (RRR)	140	20 mM Histidine, pH 5.8	5% Sucrose, 0.03% Polysorbate 20	50mM Sodium glutamate + 50mM Arginine hydrochloride

[0047] **Figure 10** shows the osmolality (mmol/Kg) of Formulations F1-F12 (set forth in Table A herein).

[0048] **Figure 11 (A-B)** measures the percentage of high molecular weight species in formulations F1-F6 (Formulations GGG, HHH, III, JJJ, LLL and KKK) over time, by SE-UPLC, after storage at 37°C for up to 28 days (A) or 5°C for up to 3 months (B) over time.

[0049] **Figure 12** shows the dynamic light scattering (diffusion coefficient ($\text{cm}^2/\text{second}$), radius (nm) and %Pd) at the initial time point of the formulations shown in Table 9-3 (GGG-RRR).

[0050] **Figure 13** shows the baseline FA images and OCT (30 degree lens) for two different rabbits (326-OS and 329-OD) before administration of aflibercept (OD=*oculus dexter* (right eye); OS=*oculus sinister* (left eye)). (A) FA image for rabbit 326, left eye; (B) OCT image for rabbit 326, left eye; (c) FA image for rabbit 329, right eye; (D) OCT image for rabbit 329, right eye.

[0051] **Figure 14 (A-F)** shows a time course of rabbit FA images at days 1 (A), 7 (B) and 14 (C) and the OCT at days 1 (D), 7 (E) and 14 (F) for one rabbit (326-OS) administered the histidine buffer formulation (30 degree lens) (7 mg/eye).

[0052] **Figure 15 (A-H)** shows a time course of rabbit FA images at 3 weeks (A), 4 weeks (B), 7 weeks (C) and 8 weeks (D); and the OCT at 3 weeks (E), 4 weeks (F), 7 weeks (G) and 8 weeks (H) for one rabbit (326-OS) administered the histidine buffer formulation (55 degree lens) (7 mg/eye).

[0053] **Figure 16 (A-F)** shows a time course of rabbit FA images at day 1 (A), week 1 (B) and week 2 (C) and the OCT at day 1 (D), week 1 (E) and week 2 (F) for one rabbit (329-OS) administered the phosphate buffer formulation (30 degree lens) (7 mg/eye).

[0054] **Figure 17 (A-H)** shows a time course of rabbit FA images at week 3 (A), week 4 (B), week 7 (C) and week 8 (D) and the OCT at week 3 (E), week 4 (F), week 7 (G) and week 8 (H) for one rabbit (329-OS) administered the phosphate buffer formulation (55 degree lens) (7 mg/eye).

[0055] **Figure 18 (A-B)** shows the purity (percentage of native species) (A) and percentage of high molecular weight (HMW) species (B) in formulations UUU-BBBB over time at 37°C (up to one month) (see Table 11-1) as analyzed by SE-UPLC.

[0056] **Figure 19 (A-E)** shows stability and purity analysis of a formulation having 114.3 mg/mL VEGF Trap (aflibercept) formulated in 10 mM Histidine, pH 5.8, 5% Sucrose, 0.03% Polysorbate 20, 50 mM Arginine Monohydrochloride by size exclusion chromatographic determination of the percentage of (i) high molecular weight species (HMW) after incubation at 5°C or 37°C for up to 2 months (A) and (ii) main species (Main peak) after incubation at 5°C or 37°C for up to 2 months (B); as well as by microflow imaging to determine the presence of subvisible particulate matter after incubation at 37°C for up to 28 days (C), by particle light obscuration analysis to determine the presence of subvisible particulate matter after incubation at 37°C for up to 28 days (D), and by microscopic determination of subvisible particulate matter after incubation at 37°C for up to 28 days (E).

[0057] **Figure 20** shows stability and purity analysis of formulation CCC, having 80, 100, 120 or 140 mg/ml aflibercept, by SE-UPLC determination of the percentage of high molecular weight species (HMW) after incubation at 2-8°C for up to 6 months (A) or 37°C for up to 28 days (B).

[0058] **Figure 21** shows the percentage of eyes in rabbits tested with complete leak suppression over time, when administered 500 micrograms or 2 mg aflibercept, over time (Gehan-Breslow-Wilcoxon test (P 0.0453)).

DETAILED DESCRIPTION

[0059] The present invention provides formulations having high concentrations of VEGF receptor fusion proteins (e.g., aflibercept), showing excellent functional and storage properties which were developed in spite of significant technical hurdles. For example, a common method for identifying suitable excipients for a formulation that includes a polypeptide drug (such as a VEGF receptor fusion protein) is by assessment of polypeptide stability under accelerated stress conditions, such as high temperature (e.g., 37°C). Excipients, which are not suitable under non-stress conditions (e.g., a low temperature such as 5°C), will typically cause an undesired effect, within a short period of time, while under stress, e.g., protein aggregation. This approach is common in the biotechnology and pharmaceutical industry insofar as it expedites the elimination of excipients unlikely to stabilize the drug product. See e.g., Magari, *Assessing Shelf Life Using Real-Time and Accelerated Stability Tests*, Biopharm Intl. 16(11): 36-48 (2003). In some cases, a product may be released based on accelerated stability data, but this must be done in parallel with real-time shelf-life analysis (non-accelerated). Magari (2003) and FDA, *Guidelines for Submitting Documentation for the Stability of Human Drugs and Biologics*, Rockville, MD (1987). Here, however, at 5°C, the presence of arginine in histidine formulations was stabilizing, though arginine, it appeared, tended to decrease stability when under temperature stress (37°C). See Figure 8 (A-B). This property of the formulations set forth

herein would have presented a technical difficulty guiding a practitioner away from choosing arginine; thus, making it unlikely that a practitioner would have chosen arginine as an excipient. Nevertheless, the formulations set forth herein resulted from the overcoming of technical hurdles such as this to achieve a formulation with high stability. Formulation of VEGF trap in histidine buffer also led to a beneficial decrease in viscosity relative to that observed with a phosphate buffer formulation. Since small needle bores are preferred for performing intravitreal injections (due to decreased patient discomfort and eye trauma), a relative low viscosity is desirable. A lower viscosity formulation requires less force to push the formulation through the needle, thus making injection of the formulation through the needle easier for the treating physician. In addition, histidine and arginine containing formulation were well tolerated in rabbit eyes.

[0060] Reference will now be made in detail to representative embodiments. It should be understood that the following descriptions are not intended to limit the embodiments to one preferred embodiment. To the contrary, they are intended to cover alternatives, modifications, and equivalents as can be included within the spirit and scope of the described embodiments as defined in the appended claims.

[0061] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which the disclosure pertains. As used herein, the term "about," when used in reference to a particular recited numerical value, means that the value may vary from the recited value by no more than 1%. So for example, as used herein, the expression "about 100" includes 99 and 101 and all values in between (e.g., 99.1%, 99.2%, 99.3%, 99.4%, etc.).

[0062] In an embodiment of the invention, a pharmaceutical formulation of the present invention is compliant with USP<789> for small volume injection (SVP) of ophthalmic solutions, e.g., contains less than about 50 particles $\geq 10 \mu\text{m}$ in diameter per ml; contains less than about 5 particles $\geq 25 \mu\text{m}$ in diameter per ml; or contains less than about 2 particles $\geq 50 \mu\text{m}$ in diameter per ml.

[0063] Note that for purposes herein, "intravitreal injection" refers to injection into the vitreous of the eye (near the retina at the back of the eye). The expressions "suitable for intravitreal administration," "suitable for intravitreal injection," and the like mean that the formulation in question can be safely injected into the vitreous of a subject's eye without causing any adverse reactions beyond those known to be associated with intravitreal injection of EYLEA.

[0064] The term "pharmaceutical formulation" herein refers to formulations including pharmaceutically acceptable carriers, e.g., used to administer VEGF receptor fusion proteins (e.g., aflibercept or conbercept) to a subject for a therapeutic/medicinal use.

[0065] The term "pharmaceutically acceptable" refers to a formulation that within the scope of sound medical judgement is suitable for administration with the eye.

[0066] The term "subject" herein refers to any mammalian (e.g., rabbit, mouse, rat or monkey) subject, particularly a human, e.g., for whom diagnosis, prognosis or therapy is desired with the formulations as described herein.

[0067] The term "aqueous" formulation refers to a formulation which includes water.

[0068] The term "treat" or "treatment" refers to a therapeutic measure that reverses, stabilizes or eliminates an undesired disease or disorder (e.g., an angiogenic eye disorder or cancer), for example, by causing the regression, stabilization or elimination of one or more symptoms or indicia of such disease or disorder by any clinically measurable degree, e.g., with regard to an angiogenic eye disorder, by causing a reduction in or maintenance of diabetic retinopathy severity score (DRSS), by improving or maintaining vision (e.g., in best corrected visual acuity e.g., as measured by an increase in ETDRS letters), increasing or maintaining visual field and/or reducing or maintaining central retinal thickness and, with respect to cancer, stopping or reversing the growth, survival and/or metastasis of cancer cells in the subject. Typically, the therapeutic measure is administration of one or more doses of a therapeutically effective amount of VEGF receptor fusion protein to the subject with the disease or disorder.

[0069] "Prevent" or "prevention" refer to a prophylactic measure to cease the development of an undesired disease or disorder (e.g., an angiogenic eye disorder).

[0070] SE-UPLC can be used in the present invention to quantitate the presence of high molecular weight species in a formulation. SE refers to size exclusion chromatography. UPLC refers to ultra-performance liquid chromatography. Suitable SE columns, which may be used in a UPLC system, to characterize such HMW species of VEGF receptor fusion proteins (e.g., aflibercept or conbercept) in a formulation, are capable of resolving molecules in the molecular weight range of about 10,000–450,000 Daltons. See for example, the ACQUITY UPLC Protein BEH SEC 200Å Column. In an embodiment of the invention, two of such columns are connected in tandem when quantitating HMW species in a formulation. UPLC brings improvements over HPLC (high performance liquid chromatography) in sensitivity and resolution. UPLC uses instrumentation that operates at high pressures and uses finer particles (typically less than about 2.5µm) than that used in HPLC. Moreover, the UPLC mobile phases operate at high linear velocities than HPLC.

[0071] Embodiments herein include formulations that comprise a high concentration (e.g., about 60 mg/ml, about 80 mg/ml, about 90 mg/ml, about 100 mg/ml, about 113.3 mg/ml, about 114.3 mg/ml, about 120 mg/ml, about 133.3 mg/ml, about 140 mg/ml, about 150 mg/ml, about 200 mg/ml or about 250 mg/ml) of VEGF receptor fusion protein (e.g., aflibercept or conbercept). Suitable formulations included herein comprise a high

concentration of VEGF receptor fusion protein, a buffer, a thermal stabilizer and a surfactant. In some aspects, a suitable formulation further includes a viscosity reducing agent. In other aspects, the suitable formulation substantially excludes all viscosity reducing agents.

Typical formulations have a pH of from about 5.0 to about 6.8 (*e.g.*, 5.8), but can include any pH useful for administration of the VEGF receptor fusion protein to the eye of a subject.

[0072] The present invention includes formulations that include a VEGF receptor fusion protein (*e.g.*, aflibercept or conbercept) in association with one or more further therapeutic agents (*e.g.*, an Ang-2 inhibitor (*e.g.*, an anti-ANG2 antibody or antigen-binding fragment thereof or nesvacumab), a Tie-2 receptor activator, an anti-PDGF, PDGF receptor or PDGF receptor beta antibody or antigen-binding fragment thereof and/or an additional VEGF antagonist such as bevacizumab, ranibizumab, pegaptanib or a soluble form of human vascular endothelial growth factor receptor-3 (VEGFR-3) comprising extracellular domains 1-3, expressed as an Fc-fusion protein) as well as methods of prevention or treatment comprising administering such formulations as discussed herein. In an embodiment of the invention, a formulation of the present invention includes a VEGF receptor fusion protein, such as aflibercept, but excludes any further therapeutic agent (*e.g.*, which is an antibody or antigen-binding fragment thereof).

[0073] The term "in association with" indicates that a formulation and a further therapeutic agent can be formulated into a single composition, *e.g.*, for simultaneous delivery, or formulated separately into two or more compositions (*e.g.*, a kit). The further therapeutic agent may, itself, be formulated in its own pharmaceutical formulation. Each can be administered to a subject at the same time as the other or at a different time than when the other is administered; for example, each administration may be given non-simultaneously (*e.g.*, separately or sequentially) at intervals over a given period of time. Moreover, the formulation and the further therapeutic agent may be administered to a subject by the same or by a different route.

[0074] In an embodiment of the invention, a formulation of the present invention includes any one or more of sodium sulfate (*e.g.*, 50 mM); sodium thiocyanate (*e.g.*, 50 mM); sodium citrate (*e.g.*, 40 mM); glycine (*e.g.*, 50 mM); sodium chloride (*e.g.*, 50 mM); lysine (*e.g.*, 50 mM); sodium aspartate (*e.g.*, 50 mM); and/or sodium glutamate (*e.g.*, 50 mM). For example, in an embodiment the formulation comprises a combination of sodium citrate (*e.g.*, 50 mM) and arginine hydrochloride (*e.g.*, 50 mM); glycine (*e.g.*, 50 mM) and arginine hydrochloride (*e.g.*, 50 mM); sodium aspartate (*e.g.*, 50 mM) and arginine hydrochloride (*e.g.*, 50 mM); or sodium glutamate (*e.g.*, 50 mM) and arginine hydrochloride (*e.g.*, 50 mM).

VEGF Receptor Fusion Proteins and Other VEGF Inhibitors

[0075] For purposes herein, a "VEGF receptor fusion protein" refers to a molecule that comprises one or more VEGF receptors or domains thereof, fused to another polypeptide, which interferes with the interaction between VEGF and a natural VEGF receptor, e.g., wherein two of such fusion polypeptides are associated thereby forming a homodimer or other multimer. Such VEGF receptor fusion proteins may be referred to as a "VEGF-Trap" or "VEGF Trap". VEGF receptor fusion proteins within the context of the present disclosure that fall within this definition include, chimeric polypeptides which comprise two or more immunoglobulin (Ig)-like domains of a VEGF receptor such as VEGFR1 (also known as Flt1) and/or VEGFR2 (also known as Flk1 or KDR), and may also contain a multimerizing domain (for example, an Fc domain).

[0076] An exemplary VEGF receptor fusion protein is a molecule referred to as VEGF1R2-FcΔC1(a) which is encoded by the nucleic acid sequence of SEQ ID NO:1 or nucleotides 79-1374 or 79-1371 thereof.

[0077] VEGF1R2-FcΔC1(a) comprises three components:

- (1) a VEGFR1 component comprising amino acids 27 to 129 of SEQ ID NO:2;
- (2) a VEGFR2 component comprising amino acids 130 to 231 of SEQ ID NO:2; and
- (3) a multimerization component ("FcΔC1(a)") comprising amino acids 232 to 457 of SEQ ID NO:2 (the C-terminal amino acids of SEQ ID NO:2, i.e., K458, may or may not be included in the VEGF receptor fusion proteins, see U.S. Patent No. 7,396,664 or 7,354,579, incorporated herein for all purposes). Note that amino acids 1 to 26 of SEQ ID NO:2 are the signal sequence.

In an embodiment of the invention, the VEGF receptor fusion protein comprises amino acids 27-458 or 27-457 of SEQ ID NO: 2.

[0078] In an embodiment of the invention, the VEGF receptor fusion protein comprises

- (1) an immunoglobulin-like (Ig) domain 2 of a first VEGF receptor (e.g., VEGFR1), and
- (2) an Ig domain 3 of a second VEGF receptor (e.g., VEGFR2),
- (3) and, optionally, further including an Ig domain 4 of the second VEGF receptor (e.g., VEGFR2) and
- (4) a multimerizing component (e.g., Fc domain of IgG).

For example, in an embodiment of the invention, the VEGF receptor fusion protein has the following arrangement of said domains:

- [VEGFR1 Ig domain 2]-[VEGFR2 Ig domain 3]-[MC] (e.g., a homodimer thereof) or
- [VEGFR1 Ig domain 2]-[VEGFR2 Ig domain 3]-[VEGFR2 Ig domain 4]-[MC] (e.g., a homodimer thereof).

[0079] In an embodiment of the invention, the VEGF receptor fusion protein is a VEGF mini-trap which is a VEGF trap molecule with a truncated multimerizing component (*e.g.*, Fc), *e.g.*, wherein the mini-trap still includes an Fc hinge region. See *e.g.*, WO2005/00895 or U.S. Patent No. 7,396,664.

[0080] Note that the present disclosure also includes, within its scope, high concentration formulations including, instead of a VEGF receptor fusion proteins, VEGF binding molecules and anti-VEGF antibodies and antigen-binding fragments thereof,

- bevacizumab (*e.g.*, at a concentration of about 80-90 or 88 mg/ml),
- ranibizumab (*e.g.*, at a concentration of about 20-40 mg/ml, *e.g.*, 21-35, 21 or 35 mg/ml),
- an anti-VEGF aptamer such as pegaptanib (*e.g.*, pegaptanib sodium),
- a single chain (*e.g.*, V_L-V_H) anti-VEGF antibody such as brotucizumab (*e.g.*, at a concentration of about 200-400 or 200, 210, 400 or 420 mg/ml),
- an anti-VEGF DARPIn such as the Abicipar Pegol DARPIn (*e.g.*, at a concentration of about 70-140, 70 or 140 mg/ml), or
- a bispecific anti-VEGF antibody, *e.g.*, which also binds to ANG2, such as RG7716 (*e.g.*, at a concentration of about 100-400, 100, 105, 400 or 420 mg/ml).

In order to minimize the repetitiveness of the embodiments discussed herein, it is contemplated that the scope of the present invention includes embodiments wherein any of the formulations discussed herein include, in place of a VEGF receptor fusion protein, an anti-VEGF antibody or antibody fragment or other VEGF binding molecule as discussed herein (*e.g.*, substituted with an anti-VEGF DARPIn) at any of the concentrations discussed herein. For example, the present invention includes a formulation having 35 or 80 mg/ml ranibizumab, a buffer, a thermal stabilizer, a viscosity reducing agent and a surfactant.

[0081] DARPins are Designed Ankyrin Repeat Proteins. DARPins generally contain three to four tightly packed repeats of approximately 33 amino acid residues, with each repeat containing a β -turn and two anti-parallel α -helices. This rigid framework provides protein stability whilst enabling the presentation of variable regions, normally comprising six amino acid residues per repeat, for target recognition.

[0082] An "anti-VEGF" antibody or antigen-binding fragment of an antibody refers to an antibody or fragment that specifically binds to VEGF.

[0083] Illustrative VEGF receptor fusion proteins include aflibercept (EYLEA®, Regeneron Pharmaceuticals, Inc.) or conbercept (sold commercially by Chengdu Kanghong Biotechnology Co., Ltd.). See International patent application publication no. WO2005/121176 or WO2007/112675. The terms "aflibercept" and "conbercept" include biosimilar versions thereof. A biosimilar version of a reference product (*e.g.*, aflibercept)

generally refers to a product comprising the identical amino acid sequence, but includes products which are biosimilar under the U.S. Biologics Price Competition and Innovation Act. [0084] Pharmaceutical formulations of the present invention are "high concentration". High concentration pharmaceutical formulations of the present invention include VEGF receptor fusion protein at a concentration of at least 41 mg/ml, of at least 80 mg/ml, of at least 100 mg/ml, of at least 125 mg/ml, of at least 140 mg/ml, of at least 150 mg/ml, of at least 175 mg/ml, of at least 200 mg/ml, of at least 225 mg/ml, of at least 250 mg/ml, or of at least 275 mg/ml. Alternatively, "high concentration" can refer to formulations that include a concentration of VEGF receptor fusion protein of from about 140 mg/ml to about 160 mg/ml, at least about 140 mg/ml but less than 160 mg/ml, from about 41 mg/ml to about 275 mg/ml, from about 70 mg/ml to about 75 mg/ml or from about 80 mg/ml to about 250 mg/ml. In some aspects, the VEGF receptor fusion protein concentration in the formulation is about any of the following concentrations: 41 mg/ml; 42 mg/ml; 43 mg/ml; 44 mg/ml; 45 mg/ml; 46 mg/ml; 47 mg/ml; 48 mg/ml; 49 mg/ml; 50mg/ml; 51 mg/ml; 52 mg/ml; 53 mg/ml; 54 mg/ml; 55 mg/ml; 56 mg/ml; 57 mg/ml; 58 mg/ml; 59 mg/ml; 60 mg/ml; 61 mg/ml; 62 mg/ml; 63 mg/ml; 64 mg/ml; 65 mg/ml; 66 mg/ml; 67 mg/ml; 68 mg/ml; 69 mg/ml; 70 mg/ml; 71 mg/ml; 72 mg/ml; 73 mg/ml; 74 mg/ml; 75 mg/ml; 76 mg/ml; 77 mg/ml; 78 mg/ml; 79 mg/ml; 80 mg/ml; 81 mg/ml; 82mg/ml; 83 mg/ml; 84 mg/ml; 85 mg/ml; 86 mg/ml; 87mg/ml; 88 mg/ml; 89 mg/ml; 90 mg/ml; 91 mg/ml; 92 mg/ml; 93 mg/ml; 94 mg/ml; 95mg/ml; 96 mg/ml; 97 mg/ml; 98 mg/ml; 99 mg/ml; 100 mg/ml; 101 mg/ml; 102 mg/ml; 103 mg/ml; 104 mg/ml; 105 mg/ml; 106mg/ml; 107 mg/ml; 108 mg/ml; 109 mg/ml; 110 mg/ml; 111 mg/ml; 112 mg/ml; 113 mg/ml; 113.3 mg/ml; 114 mg/ml; 114.1 mg/ml; 114.2 mg/ml; 114.3 mg/ml; 114.4 mg/ml; 114.5 mg/ml; 114.6 mg/ml; 114.7 mg/ml; 114.8 mg/ml; 114.9 mg/ml; 115 mg/ml; 116 mg/ml; 117 mg/ml; 118 mg/ml; 119 mg/ml; 120 mg/ml; 121 mg/ml; 122 mg/ml; 123 mg/ml; 124 mg/ml; 125 mg/ml; 126 mg/ml; 127mg/ml; 128 mg/ml; 129 mg/ml; 130 mg/ml; 131 mg/ml; 132 mg/ml; 133 mg/ml; 133.3 mg/ml; 133.4 mg/ml; 134 mg/ml; 135 mg/ml; 136 mg/ml; 137 mg/ml; 138 mg/ml; 139 mg/ml; 140 mg/ml; 141 mg/ml; 142 mg/ml; 143 mg/ml; 144 mg/ml; 145 mg/ml; 146 mg/ml; 147 mg/ml; 148 mg/ml; 149 mg/ml; 150 mg/ml; 151 mg/ml; 152 mg/ml; 153 mg/ml; 154mg/ml; 155 mg/ml; 156 mg/ml; 157mg/ml; 158 mg/ml; 159 mg/ml; 160 mg/ml; 161 mg/ml; 162 mg/ml; 163 mg/ml; 164 mg/ml; 165 mg/ml; 166 mg/ml; 167 mg/ml; 168 mg/ml; 169 mg/ml; 170 mg/ml; 171 mg/ml; 172 mg/ml; 173 mg/ml; 174 mg/ml; 175 mg/ml; 176 mg/ml; 177 mg/ml; 178 mg/ml; 179 mg/ml; 180 mg/ml; 181 mg/ml; 182 mg/ml; 183 mg/ml; 184 mg/ml; 185 mg/ml; 186 mg/ml; 187 mg/ml; 188 mg/ml; 189 mg/ml; 190 mg/ml; 191 mg/ml; 192 mg/ml; 193 mg/ml; 194 mg/ml; 195 mg/ml; 196 mg/ml; 197 mg/ml; 198 mg/ml; 199 mg/ml; 200 mg/ml; 201 mg/ml; 202 mg/ml; 203 mg/ml; 204 mg/ml; 205 mg/ml; 206 mg/ml; 207 mg/ml; 208 mg/ml; 209 mg/ml; 210

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[0085] In an embodiment of the invention, a pharmaceutical formulation of the present invention is of such a concentration as to contain about 4, 6, 8, 10, 12, 14, 16, 18 or 20 mg VEGF receptor fusion protein (e.g., aflibercept), or the amount of such protein in any of the acceptable doses thereof which are discussed herein, in about 100 μ l or less, about 75 μ l or less or about 70 μ l or less, e.g., about 50 μ l; 51 μ l; 52 μ l; 53 μ l; 54 μ l; 55 μ l; 56 μ l; 57 μ l; 58 μ l; 59 μ l; 60 μ l; 61 μ l; 62 μ l; 63 μ l; 64 μ l; 65 μ l; 66 μ l; 67 μ l; 68 μ l; 69 μ l; 70 μ l; 71 μ l; 72 μ l; 73 μ l; 74 μ l; 75 μ l; 76 μ l; 77 μ l; 78 μ l; 79 μ l; 80 μ l; 81 μ l; 82 μ l; 83 μ l; 84 μ l; 85 μ l; 86 μ l; 87 μ l; 88 μ l; 89 μ l; 90 μ l; 91 μ l; 92 μ l; 93 μ l; 94 μ l; 95 μ l; 96 μ l; 97 μ l; 98 μ l; 99 μ l; or 100 μ l.

[0086] The present invention includes any of the formulations set forth under "Illustrative Formulations" herein, but wherein the concentration of the VEGF receptor fusion protein (e.g., aflibercept) is substituted with a concentration which is set forth in this section ("VEGF Receptor Fusion Proteins and Other VEGF inhibitors").

Buffers

[0087] Buffers for use herein refer to solutions that resist pH change by use of acid-base conjugates. Buffers are capable of maintaining pH in the range of from about 5.0 to about 6.8, and more typically, from about 5.8 to about 6.5, and most typically, from about 6.0 to about 6.5. In some cases, the pH of the formulation of the present invention is about 5.0, about 5.1, about 5.2, about 5.3, about 5.4, about 5.5, about 5.6, about 5.7, about 5.8, about 5.9, about 6.0, about 6.1, about 6.2, about 6.3, about 6.4, about 6.5, about 6.6, about 6.7, or about 6.8. Example buffers for inclusion in formulations herein include histidine-based buffers, for example, histidine, histidine hydrochloride, and histidine acetate. Buffers for inclusion in formulations herein can alternatively be phosphate-based buffers, for example, sodium phosphate, acetate-based buffers, for example, sodium acetate or acetic acid, or can

be citrate-based, for example, sodium citrate or citric acid. It is also recognized that buffers can be a mix of the above, as long as the buffer functions to buffer the formulations in the above described pH ranges. In some cases, the buffer is from about 5 mM to about 25 mM, or more typically, about 5 mM to about 15 mM. Buffers can be about 5 mM, about 6 mM, about 7 mM, about 8 mM, about 9 mM, about 10 mM, about 11 mM, about 12 mM, about 13 mM, about 14 mM, about 15 mM, about 16 mM, about 17 mM, about 18 mM, about 19 mM, about 20 mM, about 21 mM, about 22 mM, about 23 mM, about 24 mM, or about 25 mM.

[0088] In an embodiment of the invention, a histidine-based buffer is prepared using histidine and histidine monohydrochloride.

Surfactants

[0089] Surfactant for use herein refers to ingredients that protect the higher concentration of VEGF receptor fusion protein from various surface and interfacial induced stresses. As such, surfactants can be used to limit or minimize VEGF receptor fusion protein aggregation, and promote protein solubility. Suitable surfactants herein have been shown to be non-ionic, and can include surfactants that have a polyoxyethylene moiety. Illustrative surfactants in this category include: polysorbate 20, polysorbate 80, poloxamer 188, polyethylene glycol 3350, and mixtures thereof. Surfactants in the formulations can be present at from about 0.02% to about 0.1% weight per volume (w/v), and more typically, about 0.02% to about 0.04% (w/v). In some cases, the surfactant is about 0.02% (w/v), about 0.03% (w/v), about 0.04% (w/v), about 0.05% (w/v), about 0.06% (w/v), about 0.07% (w/v), about 0.08% (w/v), about 0.09% (w/v), or about 0.1% (w/v).

Thermal Stabilizers

[0090] Thermal stabilizers for use herein refers to ingredients that provide thermal stability against thermal denaturation of the VEGF receptor fusion protein, as well as protect against loss of VEGF receptor fusion protein potency or activity. Suitable thermal stabilizers include sugars, and can be sucrose, trehalose, sorbitol or mannitol, or can be amino acids, for example L-proline, L-arginine (e.g., L-arginine monohydrochloride), or taurine. Additionally, thermal stabilizers may also include substituted acrylamides or propane sulfonic acid, or may be compounds like glycerol.

[0091] In some cases, the formulations herein include both a sugar and taurine, a sugar and an amino acid, a sugar and propane sulfonic acid, a sugar and taurine, glycerol and taurine, glycerol and propane sulfonic acid, an amino acid and taurine, or an amino acid and propane sulfonic acid. In addition, formulations can include a sugar, taurine and propane sulfonic acid, glycerol, taurine and propane sulfonic acid, as well as L-proline, taurine and propane sulfonic acid.

[0092] Embodiments herein typically have thermal stabilizers present alone, each independently present at a concentration of, or present in combination at a total concentration of, from about 2% (w/v) to about 10% (w/v) or 4% (w/v) to about 10% (w/v), or about 4% (w/v) to about 9% (w/v), or about 5% (w/v) to about 8% (w/v). Thermal stabilizers in the formulation can be at a concentration of about 2% (w/v), about 2.5% (w/v), about 3% (w/v), about 4% (w/v), about 5% (w/v), about 6% (w/v), about 7% (w/v), about 8% (w/v), about 9% (w/v), about 10% (w/v) or about 20% (w/v).

[0093] With respect to taurine and propane sulfonic acid, in an embodiment of the invention, these thermal stabilizers can be present in the formulations at about from 25 mM to about 100 mM, and more typically from about 50 mM to about 75 mM (as compared to the other thermal stabilizers).

Viscosity Reducing Agents

[0094] Viscosity reducing agents typically are used to reduce or prevent protein aggregation. Viscosity reducing agents for inclusion herein include: sodium chloride, magnesium chloride, D- or L-arginine (e.g., L-arginine monohydrochloride), lysine, or mixtures thereof. When present herein, viscosity reducing agents can be present at from about 10 mM to about 100 mM, and more typically from about 30 mM to about 75 mM, and even more typically from about 40 mM to about 70 mM. In some cases the viscosity reducing agent is present at about 10 mM, about 15 mM, about 20 mM, about 25 mM, about 30 mM, about 35 mM, about 40 mM, about 45 mM, about 50 mM, about 55 mM, about 60 mM, about 65 mM, about 70 mM, about 75 mM, about 80 mM, about 85 mM, about 90 mM, about 95 mM or about 100 mM.

Formulation Viscosity

[0095] Formulations in accordance with embodiments herein can also have a pharmaceutically acceptable viscosity for ocular administration, for example, intravitreal injection. Viscosity generally refers to the measure of resistance of a fluid which is being deformed by either shear stress or tensile stress (typically measured by techniques known in the art, viscometer or rheometer, for example). Typical viscosities of formulations in accordance with embodiments herein are from about 5.0 cP (centipoise) to about 15 cP, from about 11 cP to about 14 cP, from about 12 cP to about 15 cP or from about 11 cP to about 12 cP. As such, formulation viscosity herein can be about 5.0 cP, about 6.0, about 7.1 cP, about 7.2 cP, about 7.3 cP, about 7.4 cP, about 7.5 cP, about 7.6 cP, about 10 cP, about 10.5 cP, about 11.0 cP, about 11.5 cP, about 12.0 cP, about 12.5 cP, about 13.0 cP, about 13.5 cP, about 14.0 cP, about 14.5 cP, or about 15.0 cP (e.g., when measured at 20°C).

[0096] Various embodiments herein do not require inclusion of an inorganic salt, or other viscosity reducing agent, to maintain these highly useful viscosities. Typically, high concentration protein solutions require viscosity reducing agents to avoid protein aggregation and higher viscosity, making the formulations difficult for intravitreal injection and reducing the potency of the VEGF receptor fusion protein. As such, embodiments herein include formulations that have had substantially no, or no added, sodium chloride (NaCl), magnesium chloride ($MgCl_2$), D- or L-arginine hydrochloride, lysine or other viscosity reducing agent.

Formulation osmolality

[0097] Osmolality is a critical attribute for injectable formulations. It is desirable to have products match physiological osmotic conditions. Furthermore, osmolality provides confirmation of soluble content in solution. In an embodiment of the invention, the osmolality of a formulation of the present invention is less than or equal to about 506 mmol/Kg or from about 250 to about 506 mmol/Kg., e.g., about 250, 260, 270, 280, 290, 299, 300, 310, 314, 315, 316, 324, 343, 346, 349, 369, 384, 403, 426, 430 or 506 mmol/Kg. In an embodiment of the invention, the osmolality is lower than about 250 mmol/Kg.

Purity and Stability of Formulations

[0098] High concentration VEGF receptor fusion protein containing formulations described herein are stable during manufacture and storage. The term "stable" herein refers to formulations that include VEGF receptor proteins that retain both chemical and physical stability over the period of formulation manufacturing and storage, e.g., that maintains integrity and has minimal degradation, denaturation, or unfolding. VEGF receptor protein stability can be determined using analytical techniques available in the art at different temperatures and over different periods of time. In particular, VEGF receptor chemical stability (potency) can be determined using various bioassays (for example, a BAF/3 VEGFR1/EPOR cell line used to determine VEGF₁₆₅ binding by the VEGF receptor fusion proteins herein), and physical stability, by size exclusion (SE) chromatographic analysis, UPLC (ultra-performance liquid chromatography) size exclusion (SE) chromatography, visual appearance, OD, pH, charge variant formation, and rate of high molecular weight (HMW) species formation. A stable VEGF receptor fusion protein is one that shows limited change in its OD, pH, formation of charge variants, and formation of HMW species.

[0099] A "high molecular weight" (HMW) species as used herein, with reference to a formulation containing a given VEGF Trap (e.g., aflibercept), refers to any species of polypeptide or polypeptide complex in the formulation which elutes from a size exclusion column (e.g., SE-UPLC) ahead of (e.g., with a higher molecular weight than) VEGF Trap

polypeptide and/or a homodimer thereof. The percentage of HMW species refers to the percentage of such species relative to the overall quantity of polypeptides in the formulation, e.g., by SE-UPLC analysis.

[00100] In an embodiment of the invention, as discussed more fully in the Examples below, stable formulations show significant VEGF receptor fusion protein potency and physical stability for a period of up to 12 months, up to 24 months, and/or up to 36 months when stored at about 2°C to about 8°C.

[00101] In an embodiment of the invention, formulation of the present invention is one that:

- After about 28 days at about 37°C has about a 3, 5, 10, 11, 12, 13, 14, 15, 16, 17, 18, 20, 30, 35 or 37% (or 10-15% or 15-20% or 10-20%) increase in high molecular weight species (e.g., as measured by SE-UPLC or SEC)
- After about 28 days at about 37°C has about a 5, 6, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21 or 22% (or 5-20% or 5-10% or 10-15% or 15-20%) decrease in main species (e.g., as measured by SE-UPLC or SEC)
- After about 28 days at about 37°C, has about 80, 81, 82, 83, 84, 85, 86 or 87% (or about 80-85%) or more protein as main species (e.g., as measured by SE-UPLC or SEC)
- After about 28 days at about 37°C has about a 1 or 1.5 or 2% (or 1-2%) increase in low molecular weight species (e.g., as measured by SE-UPLC or SEC)
- After about one month at about 37°C has about a 16% increase in high molecular weight species; and/or about a 17% decrease in main species and/or about a 0.5% or <1% increase in low molecular weight species; and/or after about two months at about 5°C, has about a 1% decrease in main species, and/or about a 1% increase in high molecular weight species and/or no significant or detectable amounts low molecular weight (LMW) species; and/or after about 2 months at about 5°C, has about 97% main species (e.g., as measured by SE-UPLC or SEC)
- After about 12 months at about 2-8°C has about a 3-3.5% increase in high molecular weight species (e.g., as measured by SE-UPLC or SEC)
- After about 12 months at about 2-8°C has less than about a 1% or a 1, 2, 3 or 4% (e.g., 1-4% or 3-4%) decrease in main species (e.g., as measured by SE-UPLC or SEC)
- After about 12 months at about 2-8°C, has about 94 or 95% or more protein as main species (e.g., as measured by SE-UPLC or SEC)
- After about 3 months at about 2-8°C has about a 1 or 2% increase in high molecular weight species (e.g., as measured by SE-UPLC or SEC)

- After about 6 months at about 2-8°C has about a <1, 1 or 2% increase in high molecular weight species (*e.g.*, as measured by SE-UPLC or SEC)
- After about 5½ or 6 months at about 5°C has about 2.5, 3.0 or 3.5 (or about 2.5-3.5%) total high molecular weight species (*e.g.*, as measured by SE-UPLC or SEC).
- After about 6 months at about 2-8°C has less than about a 1% or 1 or 2% (or about 0.5-2% or 1-2%) decrease in main species (*e.g.*, as measured by SE-UPLC or SEC)
- After about 6 months at about 2-8°C, has about 96 or 97 or 98% (or 96-98%) or more protein as main species (*e.g.*, as measured by SE-UPLC or SEC)
- After about 24 months or 36 months at about 2-8°C, had less than about 5 or 6 or 7% (*e.g.*, about 1.5, 2, 3, 4 or 5%) (or 1.5-5% or 1.5-2.5%) increase in high molecular weight species; and/or has about 3.0, 3.25, 3.5, 4.0, 4.5 or 5% total high molecular weight species; and/or a decrease of about 2 or 3% (or 2-3%) main species; and/or a total amount of main species of about 95 or 96% or more (or 95-96%) (*e.g.*, as measured by SE-UPLC or SEC)
- After about 1 month at about 37°C, has about 97, 98, 99 or 100% (or 97-100%) of aflibercept in the formulation which is recoverable by RP-HPLC
- Immediately after manufacture and purification, has less than about 1.5, 2, 2.5, 3.0 or 3.5% high molecular weight species (*e.g.*, as measured by SE-UPLC or SEC)
- After about 6 months at about 37°C, has at least about 70% or 75% (*e.g.*, 70-75%) of aflibercept as main species/main peak (*e.g.*, as measured by capillary isoelectric focusing (cIEF) or imaged capillary isoelectric focusing) (non-acidic and non-basic species)
- After about 36 months at about 2-8°C, has about a 1 or 2% (or 1-2%) increase in acidic species (*e.g.*, as measured by capillary isoelectric focusing (cIEF) or imaged capillary isoelectric focusing)
- After about 36 months at about 2-8°C, has about a 1% or less decrease in main species/main peak (*e.g.*, as measured by capillary isoelectric focusing (cIEF) or imaged capillary isoelectric focusing)
- After about 36 months at about 2-8°C, has about 78-79% main species/main peak (*e.g.*, as measured by capillary isoelectric focusing (cIEF) or imaged capillary isoelectric focusing)

and/or

- When administered intravitreally to a mammal, such as a human or rabbit or mouse (*e.g.*, with an angiogenic eye disorder such as wet AMD), does not cause any adverse events that are clinically different from those observed for EYLEA (*e.g.*, when EYLEA is dosed intravitreally at 0.5 or 2.0 mg); or does not cause clinically

significant inflammation in the eye, prolonged intraocular pressure (IOP) increases, prolonged increases in blood pressure or decreases and/or retinal detachment.

[00102] Further, in an embodiment of the invention, high concentration VEGF receptor fusion proteins are stable as they show little or no formation of acidic charge variants over the course of manufacture and storage, for example, little or no formation of charge variants as tested by Imaged Capillary Isoelectric Focusing, for example.

[00103] In an embodiment of the invention, a formulation of the present invention exhibits less than or equal to about 8% low molecular weight (LMW) species.

[00104] In an embodiment of the invention, a formulation of the present invention has less than about 0.2, 0.4 or 0.5 EU (endotoxin units)/ml of endotoxin;

[00105] In an embodiment of the invention, a formulation of the present invention is essentially free of particulate matter or particulate matter of about 1, 2, 5, 10, 25 or 50 micrometers (or more) in size.

[00106] In an embodiment of the invention, when a formulation of the present invention is analyzed by non-reduced CE-SDS (SDS capillary gel electrophoresis), at least 97% of the total peak area is the main peak.

[00107] In an embodiment of the invention, when a formulation of the present invention is analyzed by size-exclusion UPLC (SE-UPLC), at least 93, 94 or 95% of the total peak area is the main peak and less than or equal to 3.5, 4, 5 or 6% is aggregate.

[00108] In an embodiment of the invention, a formulation of the present invention is at about 2°C, 3°C, 4°C, 5°C, 6°C, 7°C or 8°C, 2-8°C (e.g., an average temperature of 5°C), 23°C, 25°C, 30°C or 37°C.

Illustrative Formulations

[00109] Illustrative high concentration VEGF receptor fusion protein containing formulations include the following:

[00110] Formulation A: 80 mg/ml aflibercept, 10 mM histidine-based buffer, 5 % (w/v) sucrose, 0.03% (w/v) polysorbate 20, and 40 mM sodium chloride, with a pH of 5.8 to 6.2.

[00111] Formulation B: 80 mg/ml aflibercept, 10 mM phosphate-based buffer, 5 % (w/v) sucrose, 0.03% (w/v) polysorbate 20, and 40 mM sodium chloride, with a pH of 5.8 to 6.2.

[00112] Formulation C: 80 mg/ml aflibercept, 10 mM citrate-based buffer, 5 % (w/v) sucrose, 0.03% (w/v) polysorbate 20, and 40 mM sodium chloride, with a pH of 5.8 to 6.2.

[00113] Formulation D: 80 mg/ml aflibercept, 10 mM histidine-based buffer, 5 % (w/v) sucrose, 0.03 % (w/v) polysorbate 80, and 40 mM sodium chloride, with a pH of 6.2.

[00114] Formulation E: 80 mg/ml aflibercept, 10 mM phosphate-based buffer, 5 % (w/v) sucrose, 0.03 % (w/v) polysorbate 80, and 40 mM sodium chloride, with a pH of 5.8 to 6.2.

[00115] Formulation F: 80 mg/ml aflibercept, 10 mM citrate-based buffer, 5 % (w/v) sucrose, 0.03 % (w/v) polysorbate 80, and 40 mM sodium chloride, with a pH of 5.8 to 6.2.

[00116] Formulation G: 80 mg/ml aflibercept, 10 mM histidine-based buffer, 8 % (w/v) sucrose, and 0.03 % (w/v) polysorbate 20, with a pH of 5.8 to 6.2, and, optionally, specifically excluding a viscosity reducing agent.

[00117] Formulation H: 80 mg/ml aflibercept, 10 mM phosphate-based buffer, 8 % (w/v) sucrose, and 0.03 % (w/v) polysorbate 20, with a pH of 5.8 to 6.2, and, optionally, specifically excluding a viscosity reducing agent.

[00118] Formulation I: 80 mg/ml aflibercept, 10 mM citrate-based buffer, 8 % (w/v) sucrose, and 0.03 % (w/v) polysorbate 20, with a pH of 5.8 to 6.2, and, optionally, specifically excluding a viscosity reducing agent.

[00119] Formulation J: 80 mg/ml aflibercept, 10 mM histidine-based buffer, 8 % (w/v) sucrose, and 0.03 % (w/v) polysorbate 80, with a pH of 5.8 to 6.2, and, optionally, specifically excluding a viscosity reducing agent.

[00120] Formulation K: 80 mg/ml aflibercept, 10 mM phosphate-based buffer, 8 % (w/v) sucrose, and 0.03 % (w/v) polysorbate 80, with a pH of 5.8 to 6.2, and, optionally, specifically excluding a viscosity reducing agent.

[00121] Formulation L: 80 mg/ml aflibercept, 10 mM citrate-based buffer, 8 % (w/v) sucrose, and 0.03 % (w/v) polysorbate 80, with a pH of 5.8 to 6.2, and, optionally, specifically excluding a viscosity reducing agent.

[00122] Formulation M: 150 mg/ml aflibercept, 10 mM histidine-based buffer, 5 % (w/v) sucrose, 0.03 % (w/v) polysorbate 20, and 40 mM sodium chloride, with a pH of 5.8 to 6.2.

[00123] Formulation N: 150 mg/ml aflibercept, 10 mM phosphate-based buffer, 5 % (w/v) sucrose, 0.03 % (w/v) polysorbate 20, and 40 mM sodium chloride, with a pH of 5.8 to 6.2.

[00124] Formulation O: 150 mg/ml aflibercept, 10 mM citrate-based buffer, 5 % (w/v) sucrose, 0.03 % (w/v) polysorbate 20, and 40 mM sodium chloride, with a pH of 5.8 to 6.2.

[00125] Formulation P: 150 mg/ml aflibercept, 10 mM histidine-based buffer, 5 % (w/v) sucrose, 0.03 % (w/v) polysorbate 80, and 40 mM sodium chloride, with a pH of 6.2.

[00126] Formulation Q: 150 mg/ml aflibercept, 10 mM phosphate-based buffer, 5 % (w/v) sucrose, 0.03 % (w/v) polysorbate 80, and 40 mM sodium chloride, with a pH of 5.8 to 6.2.

- [00127] Formulation R: 150 mg/ml aflibercept, 10 mM citrate-based buffer, 5 % (w/v) sucrose, 0.03 % (w/v) polysorbate 80, and 40 mM sodium chloride, with a pH of 5.8 to 6.2.
- [00128] Formulation S: 150 mg/ml aflibercept, 10 mM histidine-based buffer, 8 % (w/v) sucrose, and 0.03 % (w/v) polysorbate 20, with a pH of 5.8 to 6.2, and, optionally, specifically excluding a viscosity reducing agent.
- [00129] Formulation T: 150 mg/ml aflibercept, 10 mM phosphate-based buffer, 8 % (w/v) sucrose, and 0.03 % (w/v) polysorbate 20, with a pH of 5.8 to 6.2 (*e.g.*, 6.2), and, optionally, specifically excluding a viscosity reducing agent.
- [00130] Formulation U: 150 mg/ml aflibercept, 10 mM citrate-based buffer, 8 % (w/v) sucrose, and 0.03 % (w/v) polysorbate 20, with a pH of 5.8 to 6.2, and, optionally, specifically excluding a viscosity reducing agent.
- [00131] Formulation V: 150 mg/ml aflibercept, 10 mM histidine-based buffer, 8 % (w/v) sucrose, and 0.03 % (w/v) polysorbate 80, with a pH of 5.8 to 6.2, and, optionally, specifically excluding a viscosity reducing agent.
- [00132] Formulation W: 150 mg/ml aflibercept, 10 mM phosphate-based buffer, 8 % (w/v) sucrose, and 0.03 % (w/v) polysorbate 80, with a pH of 5.8 to 6.2, and, optionally, specifically excluding a viscosity reducing agent.
- [00133] Formulation X: 150 mg/ml aflibercept, 10 mM citrate-based buffer, 8 % (w/v) sucrose, and 0.03 % (w/v) polysorbate 80, with a pH of 5.8 to 6.2, and, optionally, specifically excluding a viscosity reducing agent.
- [00134] Formulation Y: 80 mg/ml conbercept, 10 mM histidine-based buffer, 5 % (w/v) sucrose, 0.03 % (w/v) polysorbate 20, and 40 mM sodium chloride, with a pH of 5.8 to 6.2.
- [00135] Formulation Z: 80 mg/ml conbercept, 10 mM phosphate-based buffer, 5 % (w/v) sucrose, 0.03 % (w/v) polysorbate 20, and 40 mM sodium chloride, with a pH of 5.8 to 6.2.
- [00136] Formulation AA: 80 mg/ml conbercept, 10 mM citrate-based buffer, 5 % (w/v) sucrose, 0.03 % (w/v) polysorbate 20, and 40 mM sodium chloride, with a pH of 5.8 to 6.2.
- [00137] Formulation BB: 80 mg/ml conbercept, 10 mM histidine-based buffer, 5 % (w/v) sucrose, 0.03 % (w/v) polysorbate 80, and 40 mM sodium chloride, with a pH of 6.2.
- [00138] Formulation CC: 80 mg/ml conbercept, 10 mM phosphate-based buffer, 5 % (w/v) sucrose, 0.03 % (w/v) polysorbate 80, and 40 mM sodium chloride, with a pH of 5.8 to 6.2.
- [00139] Formulation DD: 80 mg/ml conbercept, 10 mM citrate-based buffer, 5 % (w/v) sucrose, 0.03 % (w/v) polysorbate 80, and 40 mM sodium chloride, with a pH of 5.8 to 6.2.

- [00140] Formulation EE: 80 mg/ml conbercept, 10 mM histidine-based buffer, 8 % (w/v) sucrose, and 0.03 % (w/v) polysorbate 20, with a pH of 5.8 to 6.2, and, optionally, specifically excluding a viscosity reducing agent.
- [00141] Formulation FF: 80 mg/ml conbercept, 10 mM phosphate-based buffer, 8 % (w/v) sucrose, and 0.03 % (w/v) polysorbate 20, with a pH of 5.8 to 6.2, and, optionally, specifically excluding a viscosity reducing agent.
- [00142] Formulation GG: 80 mg/ml conbercept, 10 mM citrate-based buffer, 8 % (w/v) sucrose, and 0.03 % (w/v) polysorbate 20, with a pH of 5.8 to 6.2, and, optionally, specifically excluding a viscosity reducing agent.
- [00143] Formulation HH: 80 mg/ml conbercept, 10 mM histidine-based buffer, 8 % (w/v) sucrose, and 0.03 % (w/v) polysorbate 80, with a pH of 5.8 to 6.2, and, optionally, specifically excluding a viscosity reducing agent.
- [00144] Formulation II: 80 mg/ml conbercept, 10 mM phosphate-based buffer, 8 % (w/v) sucrose, and 0.03 % (w/v) polysorbate 80, with a pH of 5.8 to 6.2, and, optionally, specifically excluding a viscosity reducing agent.
- [00145] Formulation JJ: 80 mg/ml conbercept, 10 mM citrate-based buffer, 8 % (w/v) sucrose, and 0.03 % (w/v) polysorbate 80, with a pH of 5.8 to 6.2, and, optionally, specifically excluding a viscosity reducing agent.
- [00146] Formulation KK: 150 mg/ml conbercept, 10 mM histidine-based buffer, 5 % (w/v) sucrose, 0.03 % (w/v) polysorbate 20, and 40 mM sodium chloride, with a pH of 5.8 to 6.2.
- [00147] Formulation LL: 150 mg/ml conbercept, 10 mM phosphate-based buffer, 5 % (w/v) sucrose, 0.03 % (w/v) polysorbate 20, and 40 mM sodium chloride, with a pH of 5.8 to 6.2.
- [00148] Formulation MM: 150 mg/ml conbercept, 10 mM citrate-based buffer, 5 % (w/v) sucrose, 0.03 % (w/v) polysorbate 20, and 40 mM sodium chloride, with a pH of 5.8 to 6.2.
- [00149] Formulation NN: 150 mg/ml conbercept, 10 mM histidine-based buffer, 5 % (w/v) sucrose, 0.03 % (w/v) polysorbate 80, and 40 mM sodium chloride, with a pH of 6.2.
- [00150] Formulation OO: 150 mg/ml conbercept, 10 mM phosphate-based buffer, 5 % (w/v) sucrose, 0.03 % (w/v) polysorbate 80, and 40 mM sodium chloride, with a pH of 5.8 to 6.2.
- [00151] Formulation PP: 150 mg/ml conbercept, 10 mM citrate-based buffer, 5 % (w/v) sucrose, 0.03 % (w/v) polysorbate 80, and 40 mM sodium chloride, with a pH of 5.8 to 6.2.

[00152] Formulation QQ: 150 mg/ml conbercept, 10 mM histidine-based buffer, 8 % (w/v) sucrose, and 0.03 % (w/v) polysorbate 20, with a pH of 5.8 to 6.2, and, optionally, specifically excluding a viscosity reducing agent.

[00153] Formulation RR: 150 mg/ml conbercept, 10 mM phosphate-based buffer, 8 % (w/v) sucrose, and 0.03 % (w/v) polysorbate 20, with a pH of 5.8 to 6.2, and, optionally, specifically excluding a viscosity reducing agent.

[00154] Formulation SS: 150 mg/ml conbercept, 10 mM citrate-based buffer, 8 % (w/v) sucrose, and 0.03 % (w/v) polysorbate 20, with a pH of 5.8 to 6.2, and, optionally, specifically excluding a viscosity reducing agent.

[00155] Formulation TT: 150 mg/ml conbercept, 10 mM histidine-based buffer, 8 % (w/v) sucrose, and 0.03 % (w/v) polysorbate 80, with a pH of 5.8 to 6.2, and, optionally, specifically excluding a viscosity reducing agent.

[00156] Formulation UU: 150 mg/ml conbercept, 10 mM phosphate-based buffer, 8 % (w/v) sucrose, and 0.03 % (w/v) polysorbate 80, with a pH of 5.8 to 6.2, and, optionally, specifically excluding a viscosity reducing agent.

[00157] Formulation VV: 150 mg/ml conbercept, 10 mM citrate-based buffer, 8 % (w/v) sucrose, and 0.03 % (w/v) polysorbate 80, with a pH of 5.8 to 6.2, and, optionally, specifically excluding a viscosity reducing agent.

[00158] Formulation WW: 140 mg/ml VEGF receptor fusion protein (e.g., aflibercept), 10 mM histidine-based buffer, 5 % (w/v) sucrose, 0.03 % (w/v) polysorbate 20, and 50 mM taurine, with a pH of 5.8.

[00159] Formulation XX: 140 mg/ml VEGF receptor fusion protein (e.g., aflibercept), 20 mM histidine-based buffer, 4 % (w/v) proline, 0.03 % (w/v) polysorbate 20, and 50 mM arginine hydrochloride, with a pH of 5.8.

[00160] Formulation YY: 140 mg/ml VEGF receptor fusion protein (e.g., aflibercept), 20 mM histidine-based buffer, 2.5 % (w/v) sucrose, 2.0 % (w/v) proline, 0.03 % (w/v) polysorbate 20, and 50 mM taurine, with a pH of 5.8.

[00161] Formulation ZZ: 140 mg/ml VEGF receptor fusion protein (e.g., aflibercept), 10 mM histidine-based buffer, 2.5 % (w/v) sucrose, 2.0 % (w/v) proline, 0.03 % (w/v) polysorbate 20, and 50 mM arginine hydrochloride, with a pH of 5.8.

[00162] Formulation AAA: 140 mg/ml VEGF receptor fusion protein (e.g., aflibercept), 20 mM histidine-based buffer, 5 % (w/v) sucrose, 0.03% (w/v) polysorbate 20, and 50 mM PSA, with a pH of 5.8.

[00163] Formulation BBB: 140 mg/ml VEGF receptor fusion protein (e.g., aflibercept), 20 mM histidine-based buffer, 2.5 % (w/v) sucrose, 2.0 % (w/v) proline, 0.03 % (w/v) polysorbate 20, and 50 mM PSA, with a pH of 5.8.

- [00164] Formulation CCC: 80, 100, 120 or 140 mg/ml VEGF receptor fusion protein (e.g., aflibercept), 20 mM histidine-based buffer, 5 % (w/v) sucrose, 0.03 % (w/v) polysorbate 20, and 50 mM arginine hydrochloride, with a pH of 5.8.
- [00165] Formulation DDD: 140 mg/ml VEGF receptor fusion protein (e.g., aflibercept), 10 mM histidine-based buffer, 4 % (w/v) proline, 0.03 % (w/v) polysorbate 20, and 50 mM PSA, with a pH of 5.8.
- [00166] Formulation EEE: 140 mg/ml VEGF receptor fusion protein (e.g., aflibercept), 20 mM histidine-based buffer, 5 % (w/v) sucrose, and 0.03 % (w/v) polysorbate 20 and, optionally, no thermal stabilizer, with a pH of 5.8.
- [00167] Formulation FFF: 140 mg/ml VEGF receptor fusion protein (e.g., aflibercept), 10mM sodium phosphate, 5 % (w/v) sucrose and 0.03 % polysorbate 20 with a pH of 6.2.
- [00168] Formulation GGG: 140 mg/ml VEGF receptor fusion protein (e.g., aflibercept); 20 mM histidine, pH 5.8; 5% sucrose; 0.03 % polysorbate 20; 50 mM sodium sulfate
- [00169] Formulation HHH: 140 mg/ml VEGF receptor fusion protein (e.g., aflibercept); 20 mM histidine, pH 5.8; 5% sucrose; 0.03 % polysorbate 20; 50 mM sodium thiocyanate
- [00170] Formulation III: 140 mg/ml VEGF receptor fusion protein (e.g., aflibercept); 20 mM histidine, pH 5.8; 5 % sucrose, 0.03 % polysorbate 20; 40 mM sodium citrate
- [00171] Formulation JJJ: 140 mg/ml VEGF receptor fusion protein (e.g., aflibercept); 20 mM histidine, pH 5.8; 5% Sucrose, 0.03 % polysorbate 20; 50 mM glycine
- [00172] Formulation KKK: 140 mg/ml VEGF receptor fusion protein (e.g., aflibercept); 20 mM histidine, pH 5.8; 5 % sucrose, 0.03 % polysorbate 20; 50 mM sodium chloride
- [00173] Formulation LLL: 140 mg/ml VEGF receptor fusion protein (e.g., aflibercept); 20 mM histidine, pH 5.8; 5 % sucrose; 0.03 % polysorbate 20; 50 mM lysine
- [00174] Formulation MMM: 140 mg/ml VEGF receptor fusion protein (e.g., aflibercept); 20 mM histidine, pH 5.8; 5 % sucrose; 0.03% polysorbate 20; 50 mM sodium aspartate
- [00175] Formulation NNN: 140 mg/ml VEGF receptor fusion protein (e.g., aflibercept); 20 mM histidine, pH 5.8; 5 % sucrose; 0.03 % polysorbate 20; 50 mM sodium glutamate
- [00176] Formulation OOO: 140 mg/ml VEGF receptor fusion protein (e.g., aflibercept); 20 mM histidine, pH 5.8; 5 % sucrose; 0.03% polysorbate 20; 50 mM sodium citrate; 50 mM arginine hydrochloride
- [00177] Formulation PPP: 140 mg/ml VEGF receptor fusion protein (e.g., aflibercept); 20 mM histidine, pH 5.8; 5 % sucrose; 0.03% polysorbate 20; 50 mM glycine; 50 mM arginine hydrochloride
- [00178] Formulation QQQ: 140 mg/ml VEGF receptor fusion protein (e.g., aflibercept); 20 mM histidine, pH 5.8; 5 % sucrose; 0.03% polysorbate 20; 50 mM sodium aspartate; 50 mM arginine hydrochloride

- [00179] Formulation RRR: 140 mg/ml VEGF receptor fusion protein (*e.g.*, aflibercept); 20 mM histidine, pH 5.8; 5 % sucrose; 0.03% polysorbate 20; 50 mM sodium glutamate; 50 mM arginine hydrochloride
- [00180] Formulation SSS: 140 mg/ml VEGF receptor fusion protein (*e.g.*, aflibercept); 20 mM His, pH 5.8; 5 % sucrose; 0.03 % polysorbate 20; 10 mM L-arginine hydrochloride
- [00181] Formulation TTT: 140 mg/ml VEGF receptor fusion protein (*e.g.*, aflibercept); 20 mM His, pH 5.8; 5 % sucrose; 0.03 % polysorbate 20; 100 mM L-arginine hydrochloride
- [00182] Formulation UUU: 30 mg/ml VEGF receptor fusion protein (*e.g.*, aflibercept), 10 % sucrose, 10 mM phosphate, 0.03 % polysorbate 20, pH 6.2
- [00183] Formulation VVV: 30 mg/ml VEGF receptor fusion protein (*e.g.*, aflibercept), 20 % sucrose, 10 mM phosphate, 0.03 % polysorbate 20, pH 6.2
- [00184] Formulation WWW: 60 mg/ml VEGF receptor fusion protein (*e.g.*, aflibercept), 10 % sucrose, 10 mM phosphate, 0.03 % polysorbate 20, pH 6.2
- [00185] Formulation XXX: 60 mg/ml VEGF receptor fusion protein (*e.g.*, aflibercept), 20 % sucrose, 10 mM phosphate, 0.03 % polysorbate 20, pH 6.2
- [00186] Formulation YYY: 120 mg/ml VEGF receptor fusion protein (*e.g.*, aflibercept), 10 % sucrose, 10 mM phosphate, 0.03 % polysorbate 20, pH 6.2
- [00187] Formulation ZZZ: 120 mg/ml VEGF receptor fusion protein (*e.g.*, aflibercept), 20 % sucrose, 10 mM phosphate, 0.03 % polysorbate 20, pH 6.2
- [00188] Formulation AAAA: 120 mg/ml VEGF receptor fusion protein (*e.g.*, aflibercept), 10 % sucrose, 10 mM phosphate, 0.03 % polysorbate 20, 50 mM NaCl, pH 6.2
- [00189] Formulation BBBB: 120 mg/ml VEGF receptor fusion protein (*e.g.*, aflibercept), 20 % sucrose, 10 mM phosphate, 0.03 % polysorbate 20, 50 mM NaCl, pH 6.2
- [00190] Formulation CCCC: 140 mg/ml VEGF receptor fusion protein (*e.g.*, aflibercept), 10 mM sodium phosphate, 5 % sucrose, 40 mM sodium chloride, 0.03 % PS20, pH 6.2
- [00191] Formulation DDDD: 80 mg/ml VEGF receptor fusion protein (*e.g.*, aflibercept), 20 mM histidine-based buffer, 5 % (w/v) sucrose, 0.03 % (w/v) polysorbate 20, and 50 mM L-arginine monohydrochloride, with a pH of 5.8.
- [00192] Formulation EEEE: 120.0 mg/ml VEGF receptor fusion protein (*e.g.*, aflibercept) (*e.g.*, ± 12 mg/ml), 20 mM histidine-based buffer (*e.g.*, ± 2 mM), 5 % (w/v) sucrose (*e.g.*, $\pm 0.5\%$), 0.03 % (w/v) polysorbate 20 (*e.g.*, 0.02-0.04%), and 50 mM L-arginine monohydrochloride (*e.g.*, ± 5 mM), with a pH of 5.8 (*e.g.*, 5.6-6.0 or 5.5-6.1).
- [00193] Formulation FFFF: 113.3 mg/ml VEGF receptor fusion protein (*e.g.*, aflibercept) (*e.g.*, 102-125 mg/ml), 20 mM histidine-based buffer (*e.g.*, ± 2 mM), 5 % (w/v) sucrose (*e.g.*, $\pm 0.5\%$), 0.03 % (w/v) polysorbate 20 (*e.g.*, 0.02-0.04%), and 50 mM L-arginine monohydrochloride (*e.g.*, ± 5 mM), with a pH of 5.8 (*e.g.*, 5.6-6.0 or 5.5-6.1).

[00194] Formulation GGGG: 114.3 mg/ml VEGF receptor fusion protein (*e.g.*, aflibercept) (*e.g.*, 103-126 mg/ml), 10 mM histidine-based buffer (*e.g.*, ± 1 mM), 5 % (w/v) sucrose (*e.g.*, $\pm 0.5\%$), 0.03 % (w/v) polysorbate 20 (*e.g.*, 0.02-0.04%), and 50 mM L-arginine monohydrochloride (*e.g.*, ± 5 mM), with a pH of 5.8 (*e.g.*, 5.6-6.0 or 5.5-6.1).

[00195] Formulation HHHH: 100.0 mg/ml VEGF receptor fusion protein (*e.g.*, aflibercept) (*e.g.*, ± 10 mg/ml), 20 mM histidine-based buffer (*e.g.*, ± 2 mM), 5 % (w/v) sucrose (*e.g.*, $\pm 0.5\%$), 0.03 % (w/v) polysorbate 20 (*e.g.*, 0.02-0.04%), and 50 mM L-arginine monohydrochloride (*e.g.*, ± 5 mM), with a pH of 5.8 (*e.g.*, 5.6-6.0 or 5.5-6.1).

[00196] Formulation IIII: 133.3 mg/ml VEGF receptor fusion protein (*e.g.*, aflibercept) (*e.g.*, ± 13 mg/ml), 20 mM histidine-based buffer (*e.g.*, ± 2 mM), 5 % (w/v) sucrose (*e.g.*, $\pm 0.5\%$), 0.03 % (w/v) polysorbate 20 (*e.g.*, 0.02-0.04%), and 50 mM L-arginine monohydrochloride (*e.g.*, ± 5 mM), with a pH of 5.8 (*e.g.*, 5.6-6.0 or 5.5-6.1).

[00197] Formulation JJJJ: 150 mg/ml aflibercept (*e.g.*, aflibercept) (*e.g.*, ± 15 mg/ml), 10 mM sodium phosphate, 8% (w/v) sucrose (*e.g.*, $\pm 0.8\%$), 0.03% (w/v) polysorbate 20 (*e.g.*, 0.02-0.04%) and 50 mM L-arginine hydrochloride, pH 6.2 (*e.g.*, 6.0-6.4 or 5.9-6.5).

[00198] Formulation KKKK: 114.3 mg/ml VEGF receptor fusion protein (*e.g.*, aflibercept) (*e.g.*, ± 14 mg/ml), 20 mM histidine-based buffer (*e.g.*, ± 2 mM), 5% (w/v) sucrose (*e.g.*, $\pm 0.5\%$), 0.03% (w/v) polysorbate 20 (*e.g.*, 0.02-0.04%), and 50 mM L-arginine monohydrochloride (*e.g.*, ± 5 mM), with a pH of 5.8 (*e.g.*, 5.6-6.0 or 5.5-6.1);

[00199] or any formulation which is set forth herein.

[00200] In an embodiment of the invention, the concentration of any formulation constituent (*e.g.*, all constituents) listed above (*e.g.*, any one of formulations A-KKKK) or which is discussed herein is $\pm$ about 3%, 5% or about 10% of the concentration specifically mentioned.

Methods of Manufacture

[00201] Embodiments herein include methods of manufacturing a pharmaceutical formulation of the present invention including a VEGF receptor fusion protein (*e.g.*, any of formulations A-KKKK as set forth herein) comprising combining the components of the formulation into a single composition, and, optionally, introducing the formulation into a vessel or device *e.g.*, a vial, or delivery device, *e.g.*, a pre-filled syringe. The formulations, vials or devices that are the product of such methods are part of the present invention.

[00202] In an embodiment of the invention, the method of manufacturing a VEGF receptor fusion protein containing pharmaceutical formulation of the present invention (*e.g.*, any of formulations A-KKKK as set forth herein) comprises the steps of culturing a host cell (*e.g.*, Chinese hamster ovary cell) comprising one or more polynucleotides encoding a VEGF receptor fusion protein (*e.g.*, aflibercept) in a culture medium and under conditions

whereby the protein is expressed; and, purifying the protein from the host cell and/or culture medium and combining a portion of the protein with excipients of a pharmaceutical formulation as set forth herein. Again, the formulations, vials or devices that are the product of such methods are part of the present invention.

[00203] In an embodiment of the invention, a determination is made as to the amount and type of VEGF receptor fusion protein needed in the formulation to make it a high concentration and for its end-use. The same determination is made regarding the amount and type of buffer, the amount and type of surfactant, the amount and type of thermal stabilizer, and the inclusion, or specific exclusion, of a viscosity reducing agent. These components are combined and mixed, making sure that the formulation pH is at the desired value, *e.g.*, between about 5.0 and about 6.8 (*e.g.*, 5.8), and/or that the viscosity is at a desired value, *e.g.*, about 6.0, 7.3, 11.5 or 12.0 cP at 20°C. In an embodiment of the invention, high concentration VEGF receptor fusion protein containing formulations can be sterilized and stored in a stable condition, *e.g.*, for up to 24 or 36 months at 2°C to 8°C (*e.g.*, 5°C).

[00204] See, *e.g.*, Hardman, *et al.* (2001) Goodman and Gilman's The Pharmacological Basis of Therapeutics, McGraw-Hill, New York, N.Y.; Gennaro (2000) Remington: The Science and Practice of Pharmacy, Lippincott, Williams, and Wilkins, New York, N.Y.; Avis, *et al.* (eds.) (1993) Pharmaceutical Dosage Forms: Parenteral Medications, Marcel Dekker, NY; Lieberman, *et al.* (eds.) (1990) Pharmaceutical Dosage Forms: Tablets, Marcel Dekker, NY; Lieberman, *et al.* (eds.) (1990) Pharmaceutical Dosage Forms: Disperse Systems, Marcel Dekker, NY; Weiner and Kotkoskie (2000) Excipient Toxicity and Safety, Marcel Dekker, Inc., New York, N.Y.

Angiogenic Eye Disorders and Cancer

[00205] The pharmaceutical formulations of the present invention comprising VEGF receptor fusion proteins (*e.g.*, any of pharmaceutical formulations A-KKKK) can be used in the treatment or prevention of any angiogenic eye disorder by administration of a therapeutically effective amount of VEGF receptor fusion protein in a formulation of the present invention to a subject in need thereof, *e.g.*, by intravitreal injection. Angiogenic eye disorders herein refer to any disease of the eye which is caused by or associated with the growth or proliferation of blood vessels and/or by blood vessel leakage. Non-limiting examples of angiogenic eye disorders that are treatable or preventable using the formulations and methods herein, include:

- age-related macular degeneration (wet),
- macular edema,
- macular edema following retinal vein occlusion,

- retinal vein occlusion (RVO),
- central retinal vein occlusion (CRVO),
- branch retinal vein occlusion (BRVO),
- diabetic macular edema (DME),
- choroidal neovascularization (CNV),
- iris neovascularization,
- neovascular glaucoma,
- post-surgical fibrosis in glaucoma,
- proliferative vitreoretinopathy (PVR),
- optic disc neovascularization,
- corneal neovascularization,
- retinal neovascularization,
- vitreal neovascularization,
- pannus,
- pterygium,
- vascular retinopathy,
- diabetic retinopathies (*e.g.*, non-proliferative diabetic retinopathy (*e.g.*, characterized by a Diabetic Retinopathy Severity Scale (DRSS) level of about 47 or 53) or proliferative diabetic retinopathy; *e.g.*, in an subject that does not suffer from DME) and
- Diabetic retinopathy in a patient who has diabetic macular edema (DME).

[00206] The pharmaceutical formulations of the present invention comprising VEGF receptor fusion proteins (*e.g.*, any of pharmaceutical formulations A-KKKK) can be used in the treatment or prevention of any cancer by administration of a therapeutically effective amount of VEGF receptor fusion protein in a formulation of the present invention to a subject in need thereof, *e.g.*, by intramuscular, intratumoral, subcutaneous or intravenous injection. Cancers include those whose growth, proliferation, survival and/or metastasis is dependent, to a degree, on angiogenesis. In an embodiment of the invention, the cancer is colorectal cancer, lung cancer, skin cancer, breast cancer, brain cancer, stomach cancer, renal cancer, prostate cancer, liver cancer or pancreatic cancer.

[00207] Thus, the present invention provides methods for treating or preventing an angiogenic eye disorder in a subject in need thereof comprising administering a therapeutically effective amount of VEGF receptor fusion protein (*e.g.*, aflibercept) (*e.g.*, about 4, 6, or 8.0, 8.1, 8.4 or 8.5 mg), *e.g.*, in a pharmaceutical formulation according to the present invention, intraocularly, *e.g.*, into the vitreous, of an eye of the subject. In an embodiment of the invention, both eyes are administered the VEGF receptor fusion protein.

In an embodiment of the invention, therapeutically effective doses of the VEGF receptor fusion protein are administered about every 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 11 weeks, 12 weeks, 13 weeks, 14 weeks, 15 weeks, 16 weeks, 17 weeks, 18 weeks, 19 weeks, 20 weeks, 21 weeks, 22 weeks, 23 weeks or 24 weeks. In an embodiment of the invention, such methods of treatment or prevention are done in the absence of significant increases in blood pressure (systolic and/or diastolic) and/or the development of hypertension (e.g., Grade 1, Grade 2 or Grade 3) and/or abnormally high intraocular pressure in the subject. In an embodiment of the invention, the method includes the step of, following said administration, monitoring the subject for significant increases in blood pressure (systolic and/or diastolic) and/or the development of hypertension (e.g., Grade 1, Grade 2 or Grade 3) and/or abnormally high intraocular pressure.

Modes of Administration

[00208] The pharmaceutical formulations of the present invention which include a VEGF receptor fusion protein may be administered in accordance with known medically approved delivery systems. In embodiments herein, these delivery systems may include administering the formulations to the patient by ocular, intraocular, intrachoroidal, intravitreal or subconjunctival injection. Alternatively, pharmaceutical formulations of the present invention can also be administered to the patient by topical routes, e.g., eye drops, eye gels, eye ointments, and the like. Other possible routes of delivery for the formulations herein include intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, epidural and oral.

[00209] In an embodiment of the invention, intravitreal injection of a pharmaceutical formulation of the present invention includes the step of piercing the eye with a syringe and needle (e.g., 30-gauge injection needle) containing the formulation and injecting the formulation (e.g., less than or equal to about 100 microliters; about 40, 50, 55, 56, 57, 57.1, 58, 60, 70 or 75 microliters) into the vitreous of the eye (e.g., with a sufficient volume as to deliver a therapeutically effective amount of VEGF receptor fusion protein, e.g., of about 4, 5, 6, 7, 8.0, 8.1, 8.2, 8.3, 8.4, 8.5, 8.6, 8.7, 8.8 or 8.9, 9, 10, 12, 14, 16, 18 or 20 mg VEGF receptor fusion protein). Optionally, the method includes the steps of administering a local anesthetic (e.g., proparacaine, lidocaine or tetracaine), an antibiotic (e.g., a fluoroquinolone), antiseptic (e.g., povidone-iodine) and/or a pupil dilating agent to the eye being injected. In an embodiment of the invention, a sterile field around the eye to be injected is established before the injection. In an embodiment of the invention, following intravitreal injection, the subject is monitored for elevations in intraocular pressure and/or blood pressure. In an embodiment of the invention, the other eye is also injected by the same procedure.

Amounts of VEGF Receptor Fusion Protein to be Administered

[00210] Each dose of high concentration VEGF receptor fusion protein to a subject over the course of a treatment may contain the same or substantially the same amount of fusion protein. Alternatively, the quantity of any one dose may be different or variable over a treatment course.

[00211] An effective or therapeutically effective amount of VEGF receptor fusion protein for treating or preventing cancer (*e.g.*, which is mediated, at least in part, by angiogenesis) or an angiogenic eye disorder refers to the amount of the VEGF receptor fusion protein sufficient to cause the regression, stabilization or elimination of the cancer or angiogenic eye disorder, *e.g.*, by regressing, stabilizing or eliminating one or more symptoms or indicia of the cancer or angiogenic eye disorder by any clinically measurable degree, *e.g.*, with regard to an angiogenic eye disorder, by causing a reduction in or maintenance of diabetic retinopathy severity score (DRSS), by improving or maintaining vision (*e.g.*, in best corrected visual acuity *e.g.*, as measured by an increase in ETDRS letters), increasing or maintaining visual field and/or reducing or maintaining central retinal thickness and, with respect to cancer, stopping or reversing the growth, survival and/or metastasis of cancer cells in the subject. In an embodiment of the invention, an effective or therapeutically effective amount of VEGF receptor fusion protein for treating or preventing an angiogenic eye disorder is about 0.5 mg to about 10 mg or 0.5 mg to about 20 mg per dose, including: about 0.5 mg or more; or about 2 mg or more, *e.g.*, about 2.1 mg; 2.2 mg; 2.3 mg; 2.4 mg; 2.5 mg; 2.6 mg; 2.7 mg; 2.8 mg; 2.9 mg; 3.0 mg; 3.1 mg; 3.2 mg; 3.3 mg; 3.4 mg; 3.5 mg; 3.6 mg; 3.7 mg; 3.8 mg; 3.9 mg; 4.0 mg; 4.1 mg; 4.2 mg; 4.3 mg; 4.4 mg; 4.5 mg; 4.6 mg; 4.7 mg; 4.8 mg; 4.9 mg; 5.0 mg; 5.1 mg; 5.2 mg; 5.3 mg; 5.4 mg; 5.5 mg; 5.6 mg; 5.7 mg; 5.8 mg; 5.9 mg; 6.0 mg; 6.1 mg; 6.2 mg; 6.3 mg; 6.4 mg; 6.5 mg; 6.6 mg; 6.7 mg; 6.8 mg; 6.9 mg; 7.0 mg; 7.1 mg; 7.2 mg; 7.3 mg; 7.4 mg; 7.5 mg; 7.6 mg; 7.7 mg; 7.8 mg; 7.9 mg; 8.0 mg; 8.1 mg; 8.2 mg; 8.3 mg; 8.4 mg; 8.5 mg; 8.6 mg; 8.7 mg; 8.8 mg; 8.9 mg; 9 mg; 9.1 mg; 9.2 mg; 9.3 mg; 9.4 mg; 9.5 mg; 9.6 mg; 9.7 mg; 9.8 mg; 9.9 mg; 10.0 mg; 10.1 mg; 10.2 mg; 10.3 mg; 10.4 mg; 10.5 mg; 10.6 mg; 10.7 mg; 10.8 mg; 10.9 mg; 11 mg; 11.1 mg; 11.2 mg; 11.3 mg; 11.4 mg; 11.5 mg; 11.6 mg; 11.7 mg; 11.8 mg; 11.9 mg; 12 mg; 12.1 mg; 12.2 mg; 12.3 mg; 12.4 mg; 12.5 mg; 12.6 mg; 12.7 mg; 12.8 mg; 12.9 mg; 13 mg; 13.1 mg; 13.2 mg; 13.3 mg; 13.4 mg; 13.5 mg; 13.6 mg; 13.7 mg; 13.8 mg; 13.9 mg; 14 mg; 14.1 mg; 14.2 mg; 14.3 mg; 14.4 mg; 14.5 mg; 14.6 mg; 14.7 mg; 14.8 mg; 14.9 mg; 15 mg; 15.1 mg; 15.2 mg; 15.3 mg; 15.4 mg; 15.5 mg; 15.6 mg; 15.7 mg; 15.8 mg; 15.9 mg; 16 mg; 16.1 mg; 16.2 mg; 16.3 mg; 16.4 mg; 16.5 mg; 16.6 mg; 16.7 mg; 16.8 mg; 16.9 mg; 17 mg; 17.1 mg; 17.2 mg; 17.3 mg; 17.4 mg; 17.5 mg; 17.6 mg; 17.7 mg; 17.8 mg; 17.9 mg; 18 mg; 18.1 mg; 18.2 mg; 18.3 mg; 18.4 mg; 18.5 mg; 18.6 mg; 18.7 mg; 18.8 mg; 18.9 mg; 19 mg; 19.1

mg; 19.2 mg; 19.3 mg; 19.4 mg; 19.5 mg; 19.6 mg; 19.7 mg; 19.8 mg; 19.9 mg; or 20 mg. In an embodiment of the invention, an effective or therapeutically effective amount of VEGF receptor fusion protein for treating or preventing cancer is about 4 mg/kg (e.g., intravenously). This dose may be administered, for example, every 2 weeks.

[00212] In an embodiment of the invention, a VEGF receptor fusion protein is administered in a volume sufficient to deliver the desired dose of fusion protein, e.g., as discussed above. In an embodiment of the invention, the volume delivered (e.g., for treating or preventing an angiogenic eye disorder, e.g., by intravitreal injection) is less than or equal to about 100 microliters (e.g., about any of the following volumes: 25 microliters; 26 microliters; 27 microliters; 28 microliters; 29 microliters; 30 microliters; 31 microliters; 32 microliters; 33 microliters; 34 microliters; 35 microliters; 36 microliters; 37 microliters; 38 microliters; 39 microliters; 40 microliters; 41 microliters; 42 microliters; 43 microliters; 44 microliters; 45 microliters; 46 microliters; 47 microliters; 48 microliters; 49 microliters; 50 microliters; 51 microliters; 52 microliters; 53 microliters; 54 microliters; 55 microliters; 56 microliters; 57 microliters; 58 microliters; 59 microliters; 60 microliters; 61 microliters; 62 microliters; 63 microliters; 64 microliters; 65 microliters; 66 microliters; 67 microliters; 68 microliters; 69 microliters; 70 microliters; 71 microliters; 72 microliters; 73 microliters; 74 microliters; 75 microliters; 76 microliters; 77 microliters; 78 microliters; 79 microliters; 80 microliters; 81 microliters; 82 microliters; 83 microliters; 84 microliters; 85 microliters; 86 microliters; 87 microliters; 88 microliters; 89 microliters; 90 microliters; 91 microliters; 92 microliters; 93 microliters; 94 microliters; 95 microliters; 96 microliters; 97 microliters; 98 microliters or 99 microliters).

[00213] In an embodiment of the invention, the formulation is administered (e.g., for treating or preventing an angiogenic eye disorder, e.g., by intravitreal injection) in a volume which is about 60 microliters or less, about 70 microliters or less or about 75 microliters or less or about 100 microliters or less. For example, in an embodiment of the invention, about 2, 4, 6, 8.0, 8.1, 8.0-8.1, 8.2, 8.3, 8.4, 8.5, 8.6, 8.7, 8.8 or 8.9, 9.0 or 10 mg of VEGF receptor fusion protein is administered in about 50, 60, 70 or 75 microliters.

[00214] The scope of the present invention also encompasses methods for delivering 0.5 or 2 mg of VEGF receptor fusion protein (e.g., for treating or preventing an angiogenic eye disorder, e.g., by intravitreal injection) in pharmaceutical formulation of the present invention in a low volume such as less than 50 μ l (e.g., about 1, 5, 10, 17, 17.5, 18, 18.5, 20, 30, 40 or 45 μ l).

[00215] The present invention also includes a composition including or consisting or consisting essentially of a "single dosage volume" of pharmaceutical formulation of the present invention, i.e., a volume containing a single dose of VEGF receptor fusion protein (e.g., aflibercept) in a pharmaceutical formulation of the present invention (e.g., about 50 μ l

or 60 µl, 70 µl or 75 µl or whatever volume contains about 4, 6, 8 or 10 mg of VEGF receptor fusion protein). As discussed below, a container (e.g., vial or injection device) comprising a single dosage volume, optionally including a small overfill volume of formulation, is also part of the present invention.

Containers and Injection Devices

[00216] High concentration VEGF receptor fusion protein formulations in accordance with embodiments herein (e.g., any of formulations A-KKKK) can be pre-packaged or pre-loaded in various useful containers and injection devices. Thus, the present invention includes containers and injection devices containing such formulations. In one embodiment herein, the container is a vial which may be sterile. In another embodiment herein, the container is a test tube which may be sterile. In an embodiment of the invention, an injection device (which may be sterile) is a syringe (e.g., a pre-filled syringe or autoinjector). In an embodiment of the invention, the injection device is an intravitreal implant, e.g., a refillable intravitreal implant.

[00217] A "pre-filled" syringe is a syringe which is filled with a formulation of the present invention prior to sale or use by the physician or patient.

[00218] "Sterile" herein refers to aseptic or free from substantially all, or all, living microorganisms and their spores.

[00219] Syringes as used herein include barrels made, for example, of glass or polymer, for example, cycloolefin as described in U.S. Patent Publication No. 2017/0232199, incorporated herein for all purposes, a plunger and a needle.

[00220] Containers and injection devices may be coated with silicone (e.g., silicone oil or baked-silicone (e.g., ≤ 40 µg or ≤ 100 µg)).

[00221] In an embodiment of the invention, a container or injection device is substantially metal-free or substantially tungsten-free or low-tungsten.

[00222] In an embodiment of the invention, the syringe contains one or more dose line graduations and/or is a dose metering system.

[00223] Containers in accordance with embodiments herein can hold the high concentration VEGF receptor fusion protein formulations. In some aspects, the container or injection device can include a label stating indications of use. In some instances, the container or injection device herein can include package inserts with instructions for use as described throughout this specification.

[00224] In other embodiments, a volume containing a single dose or multiple doses (e.g., 2 or more than 2) of a high concentration VEGF receptor fusion protein (e.g., wherein the dose is 2 mg, 4 mg, 6 mg, 8 mg or 10 mg of VEGF receptor fusion protein), as described above, can be pre-packaged into a container or injection device, e.g., a sterile syringe, for

example, for storage until use. In one example, the volume in the container includes a single dose of VEGF receptor fusion protein optionally further including a small amount of overfill volume. Sterile, pre-loaded syringes can be maintained under storage conditions (e.g., 2°C-8°C), for example, for up to 12 months, 24 months or 36 months. Overfill is an excess volume that is meant to be sufficient to permit withdrawal and/or administration of the proper volume. In an embodiment of the invention, the container has a single dosage volume or multiple dosage volumes and about 5%-10% overfill volume.

[00225] Syringe sizes can be, for example, 0.3 cc, 0.5 cc or 1 cc, for example. Sterile syringes typically include a needle useful for ocular injection, typically about ½ inch, or 12.5 mm to 16 mm in length, and can be 29 gauge, 30 gauge, 31 gauge, 32 gauge or 33 gauge based on the patient and health care specialist preference. Other needle lengths and gauges can be used, as long as the needle is effective at accomplishing intravitreal injection.

[00226] While the invention has been particularly shown and described with reference to a number of embodiments, it would be understood by those skilled in the art that changes in the form and details may be made to the various embodiments disclosed herein without departing from the spirit and scope of the invention and that the various embodiments disclosed herein are not intended to act as limitations on the scope of the claims.

Additional formulations

[00227] The present invention includes the following formulations comprising greater than 40 mg/ml VEGF receptor fusion protein (e.g., aflibercept or conbercept) and:

[00228] (a) a buffer including a histidine salt (e.g., histidine-HCl or histidine-acetate, for example, 10 mM to 50 mM) and having pH ranging from 5.7 to 6.2; a sugar (e.g., more than 6%, but not more than 10%) such as sucrose, trehalose, mannitol or glucose; a surfactant selected from the group consisting of polysorbate 20 and polysorbate 80 (e.g., 0% to 0.1%);

[00229] (b) a histidine containing buffer such as L-histidine/histidine hydrochloride (e.g., 10 mM); a non-ionic surfactant such as polysorbate 20 (e.g., 0.03%), an inorganic salt such as NaCl (e.g., 40 mM), and a carbohydrate such as sucrose (e.g., 5%), e.g. pH 6.0-6.5 (e.g., 6.2 or 6.5);

[00230] (c) citric acid (e.g., 5 mM, 10 mM, 15 mM, 20 mM, 25 mM or 30 mM), sucrose (e.g., 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9% or 10%), arginine (e.g., 5 mM, 10 mM, 15 mM, 20 mM, 25 mM, 30 mM, 35 mM, 40 mM, 45 mM or 50 mM or 100 mM), and polysorbate 20 (e.g., 0.01%, 0.02%, 0.03%, 0.04%, 0.05%, 0.06%, 0.07%, 0.08%, 0.09% or 0.10%);

[00231] (d) a buffer such as phosphate, histidine, acetate, succinate, citrate, glutamate, and/or lactate (e.g., at 5-20 or 5-50 mM); a non-ionic surfactant such as a

polysorbate (e.g., PS20 or PS80), a polyethylene glycol dodecyl ether, a poloxamer, 4-(1,1,3,3-Tetramethylbutyl)phenyl-polyethylene glycol, an alkylsaccharide or an alkylglycoside, a tonicifying agent such as a polyol or an amino acid, for example, sucrose, trehalose, sorbitol, mannitol, glycerol, proline, arginine, methionine, glycine, or lysine, wherein the formulation has a final osmolality of about 300 mOsm/kg, and wherein the concentration of chloride anion is less than about 10 mM; pH 5.0-6.5; or

[00232] (e) 10 mM sodium phosphate, 40 mM sodium chloride, 0.03% polysorbate 20, and 5% sucrose, pH 6.2.

EXAMPLES

[00233] The following examples are provided for illustrative purposes only and are not intended to limit the scope of the invention. Efforts have been made to ensure accuracy with respect to numbers used, but some experimental errors and deviations should be accounted for. Any formulations set forth in these examples are part of the present invention.

[00234] In these examples, when an experiment is conducted at 2-8°C, the temperature is targeted to 5°C with a tolerance of $\pm 3^\circ\text{C}$ variation.

Example 1: 80 mg/ml VEGF Receptor Fusion Protein Formulations Maintain Potency, Physical Stability and Charge Over A 36 Month Period.

[00235] A series of four different formulations having 80 mg/ml VEGF receptor fusion protein (aflibercept) were tested for long term potency, physical stability and development of charge variants. The ingredient listing of each of the four formulations is shown in Table 1-1. Each formulation was evaluated for VEGF receptor fusion protein HMW species formation over the course of storage at 2°C to 8°C for 36 months, as well as for the percent main species by SE-UPLC. Each VEGF receptor fusion protein containing formulation was also evaluated using Imaged Capillary Isoelectric Focusing over the same course of time and temperature. Finally, each formulation's potency was tested by bioassay over the same course of time and temperature.

Table 1-1. VEGF Receptor Fusion Protein Containing Formulations

Formulation	VEGFT (mg/mL)	Sodium phosphate (mM)	Histidine (mM)	Sucrose (w/v)	Polysorbate 20 (w/v)	Sodium Chloride (mM)	pH
F1 (B)	80	10	NA	5	0.03	40	6.2
F2 (H)	80	10	NA	8	0.03	0	6.2
F3 (D)	80	NA	10	5	0.03	40	6.2
F4 (G)	80	NA	10	8	0.03	0	6.2

Table 1-2. %HMW Species

	Formulation B	Formulation H	Formulation D	Formulation G
	Formulation 1	Formulation 2	Formulation 3	Formulation 4
Months at 2- 8C				
0.0	1.7	1.6	1.6	1.3
1	2.1	2.1	1.6	1.7
2.0	2.3	2.2	1.8	1.8
3.0	2.4	2.5	2.0	2.1
6.0	2.9	2.8	2.0	2.3
9.0	3.1	3.0	2.2	2.4
12.0	2.8	3.0		2.4
18.0	3.2	3.2	2.6	2.5
24.0	3.6	3.6	3.1	2.8
36.0	4.2	4.2	3.2	3.2

Table 1-3. %Main Peak

	Formulation B	Formulation H	Formulation D	Formulation G
	Formulation 1	Formulation 2	Formulation 3	Formulation 4
Months at 2- 8C				
0.0	98.4	98.4	98.4	98.8
1	97.9	98.0	98.4	98.3
2.0	97.7	97.8	98.2	98.2
3.0	97.7	97.5	98.0	98.0
6.0	97.1	97.2	97.9	97.7
9.0	96.9	97.0	97.8	97.6
12.0	97.2	97.0		97.4
18.0	96.8	96.8	97.4	97.5
24.0	96.5	96.4	96.8	97.2
36.0	95.7	95.7	96.8	96.8

Table 1-4. %Acidic Species

	Formulation B	Formulation H	Formulation D	Formulation G
	Formulation 1	Formulation 2	Formulation 3	Formulation 4
Months at 2-8°C				
0.0	15.8	15.1	16.0	15.2
12	15.6	15.9	NP	16.0
24.0	16.0	17.1	16.2	16.9
36.0	16.9	17.4	17.2	17.6

Table 1-5. %Main Species

	Formulation B	Formulation H	Formulation D	Formulation G
	Formulation 1	Formulation 2	Formulation 3	Formulation 4
Months at 2-8°C				
0.0	78.9	79.1	79.2	79.9
12	79.3	79.3	NP	79.7
24.0	79.3	78.5	79.5	79.3
36.0	78.6	78.1	78.7	78.6

[00236] Data is shown in Figures 1A, 1B, 1C and 1D. Figure 1A shows the percent of VEGF receptor fusion protein HMW species formed for each of the four formulations. VEGF TRAP shows a slightly slower rate of HMW species formation when the formulation is histidine-based, as compared to sodium phosphate. As shown in Figure 1A, the %HMW species after storage at 2° to 8°C for 36 months increased by 2.6% in sodium phosphate formulations (Formulations 1 and 2), as compared to the 1.6 to 1.9% increase in histidine buffers (Formulations 3 and 4). The data was confirmed, as shown in Figure 1B, where SE-UPLC was used to identify the percent of the VEGF receptor fusion protein main species present over the same time frame and temperature range. As a comparison point, assays were run on the current EYLEA® formulation (40 mg/ml) having 10 mM sodium phosphate, which showed a 1.2% increase in the %HMW species after storage at 2° to 8°C for 36 months (not shown). In addition, each of the four 80 mg/ml VEGF TRAP formulations was tested for potency and compared to EYLEA® activity (not shown). Potency was maintained by bioassay for all four formulations as well as EYLEA®. These data show that formulations herein are able to maintain VEGF receptor fusion protein stability comparable to EYLEA®.

[00237] Referring to Figures 1C and 1D, the percent of VEGF TRAP charge variants formed after storage at 2° to 8°C for 36 months was also tested. Figure 1C shows that the

VEGF TRAP in Formulations 1 - 4 showed no meaningful change in percent acidic species over the course of 36 months, and Figure 1D shows the same finding for percent main species over the course of 36 months. The finding that the VEGF TRAP maintained charge variant species during storage shows that the quality of the VEGF TRAP was maintained, and processes like deamination, N-terminal pyroglutamate formation, isomerization, aggregation, etc. did not occur over the course of the storage parameters.

[00238] The data in Example 1 shows that formulations having double the VEGF TRAP concentration found in EYLEA®, can maintain physical stability, quality and potency over the course of 36 months at 2° to 8°C. Further, although all four formulations showed similar potency over the period, histidine containing formulations resulted in a slightly smaller increase in HMW species formation (sign of protein degradation), showing that under some circumstances, histidine may be a buffer of choice. However, the findings for both histidine and phosphate based buffers showed excellent stability over the course of the study.

Example 2: 150 mg/ml VEGF TRAP Stability in Sodium Phosphate Buffer/Sucrose Formulations.

[00239] Two sodium phosphate formulations were tested for physical stability of 150 mg/ml VEGF Trap (aflibercept) at 37°C for 28 days. The ingredient listing of each of the two formulations is shown in Table 2-1. Each formulation was evaluated for HMW species formation over the course of storage at 37°C for the 28 days as well as for the percent main species by SE-UPLC.

Table 2-1. VEGF Receptor Fusion Protein (aflibercept) Containing Formulations for Example 2

Formulation	VEGFT (mg/mL)	Sodium phosphate (mM)	Sucrose (w/v)	Polysorbate 20 (w/v)	Arginine-HCl (mM)	pH
F1 (T)	150	10	8%	0.03	N/A	6.2
F2 (JJJJ)	150	10	8%	0.03	50	6.2

Table 2-2. %HMW Species

	10 mM Sodium Phosphate, 8% Sucrose, 0.03% Polysorbate 20, pH 6.2	10 mM Sodium Phosphate, 8% Sucrose, 0.03% Polysorbate 20, 50 mM L-Arginine Monohydrochloride, pH 6.2
	Phosphate	Phosphate-Arginine
Days at 37C		
0.0	2.4	1.9
7	6.4	6.1
14.0	8.4	8.3
21.0	10.4	10.5
28.0	12.2	12.5

Table 2-3. %Main Peak

	10 mM Sodium Phosphate, 8% Sucrose, 0.03% Polysorbate 20, pH 6.2	10 mM Sodium Phosphate, 8% Sucrose, 0.03% Polysorbate 20, 50 mM L-Arginine Monohydrochloride, pH 6.2
	Phosphate	Phosphate-Arginine
Days at 37C		
0.0	97.6	98.1
7	93.6	93.9
14.0	91.0	91.1
21.0	88.9	89.0
28.0	87.1	86.9

[00240] Figure 2A shows that there was no meaningful difference of %HMW species formed between the two formulations during storage at 37°C for 28 days, which as confirmed by the percent of main species by SE-UPLC (Figure 2B). There was no change in the appearance, turbidity or pH of the two formulations over the course of the 28 days (not shown).

[00241] The results were then compared to formulations that included 40 mg/ml EYLEA®, and Formulation 1 from Example 1 (80 mg/ml VEGF TRAP in sodium phosphate buffer). As expected, the 150 mg/ml VEGF TRAP formulations showed a higher percent of HMW species formation as compared to the EYLEA® formulation, and a somewhat higher percent of HMW species formation as compared to Formulation 1 of Example 1.

[00242] Further testing was performed on high concentration VEGF TRAP containing formulations, and histidine containing formulations showed better protection of these molecules than did formulations based in sodium phosphate. Further, inclusion of sodium chloride into each of the tested formulations actually caused destabilization of the VEGF

TRAP at 37°C. The data in Example 2 shows that even at high concentrations of 150 mg/ml VEGF receptor fusion protein, and fairly extreme temperature storage, the formulations herein provide excellent protection for physical stability.

Example 3: Pharmaceutically Acceptable Formulation Viscosity Can be Attained for 150 mg/ml VEGF TRAP.

[00243] A number of VEGF Trap (aflibercept) containing formulations were tested for their viscosity behavior. Formulations having from between 10 mg/ml to 160 mg/ml VEGF Trap were tested in the presence and absence of various viscosity reducing agents.

[00244] Figure 3A shows formulations having 155 mg/ml VEGF Trap in 10 mM sodium phosphate buffer, 5% sucrose and a pH of 6.2 in combination with no inorganic salt, arginine, lysine, sodium chloride and magnesium chloride showed little difference in viscosity. In each case viscosity was measured in cP at 20°C. A range of viscosity between about 17 cP (no inorganic salt) and 15 cP (100 mM magnesium chloride) was observed, with little variation between which viscosity reducing agent was used, or with the presence of a viscosity reducing agent at all. Figure 3B shows a similar series of formulations, except that the base buffer is 10 mM histidine and pH 5.8. Here, the lack of any inorganic salt provided a formulation with a viscosity of 11.5 cP, and 50 mM lysine a viscosity of 14 cP. The histidine containing buffer provided excellent viscosity, one in line with other low-concentration biologic injectables.

[00245] Figure 3C shows viscosity of VEGF Trap between the concentrations of 10 mg/ml and 160 mg/ml, with 10 mM sodium phosphate, 5% sucrose at a pH of 6.2 in the absence of arginine, and in 50 mM of arginine hydrochloride. Inclusion of the viscosity reducing agent resulted in similar viscosities for all VEGF Trap concentrations tested. As shown in Figures 3A and 3B, the viscosity reducing agent had little positive effect on the formulation viscosity, even at higher protein concentrations. This is a surprising result, as arginine and other viscosity reducing agents have previously been shown to have beneficial properties on high concentration protein viscosity.

Table 3-1. Viscosity-Phosphate formulations (cP at 20°C)

Buffer Composition	10 mM Sodium Phosphate, 5% Sucrose, pH 6.2
No Viscosity Reducer	17.3
100 mM Arginine	16.2
200 mM Arginine	15.8
50 mM Lysine	16.2
100 mM Sodium Chloride	16.5
50 mM Magnesium Chloride	16.3
100 mM Magnesium Chloride	15.3

Table 3-2. Viscosity-Histidine formulations (cP at 20°C)

Buffer Composition	10 mM Histidine, pH 5.8
No Viscosity Reducer	11.5
100 mM Arginine	12.0
200 mM Arginine	12.7
50 mM Lysine	14.0
200 mM Lysine	14.1
50 mM Sodium Chloride	13.1
100 mM Sodium Chloride	12.1
50 mM Magnesium Chloride	12.6
100 mM Magnesium Chloride	11.4

Example 4: Arginine Hydrochloride Improves Stability of 150 mg/ml VEGF**TRAP In Sodium Phosphate Buffer/Sucrose Formulations.**

[00246] Two sodium phosphate formulations were tested for physical stability of 150 mg/ml VEGF Trap (afibercept) at 2-8°C for 12 months. The ingredient listing of each of the two formulations is shown in Table 4-1. Formulation 2 further includes 50 mM arginine hydrochloride. Each formulation was evaluated for HMW species formation over the course of storage at 37°C for the 12 months as well as for the percent main species by SE-UPLC.

Table 4-1. VEGF Receptor Fusion Protein (afibercept) Containing Formulations for Example 3

Formulation	VEGFT (mg/mL)	Sodium phosphate (mM)	Sucrose (w/v)	Polysorbate 20 (w/v)	pH	Arginine Hydrochloride (mM)
F1 (T)	150	10	8%	0.03	6.2	0
F2 (JJJJ)	150	10	8%	0.03	6.2	50

[00247] Figure 4A shows that inclusion of 50 mM arginine hydrochloride to the formulation improved the VEGF TRAP physical stability. This stabilizing attribute on the VEGF TRAP was confirmed in Figure 4B, where the percent main species remains higher for the VEGF TRAP in the presence of 50 mM arginine hydrochloride. This data shows that there are situations under which addition of arginine hydrochloride provides a stabilizing effect to the stored VEGF TRAP. Tabulated size-exclusion chromatography data are set forth in Table 4-2 and 4-3.

Table 4-2. %HMW Species

	10 mM Sodium Phosphate, 8% Sucrose, 0.03% Polysorbate 20, pH 6.2	10 mM Sodium Phosphate, 8% Sucrose, 0.03% Polysorbate 20, 50 mM L-Arginine Monohydrochloride, pH 6.2
Months at 2-8C		
0.0	2.4	1.9
1	3.3	2.8
2.0	3.8	3.2
3.0	4.1	3.5
6.0	4.9	4.1
9.0	5.5	4.7
12.0	5.9	5.0

Table 4-3. %Main Peak

	10 mM Sodium Phosphate, 8% Sucrose, 0.03% Polysorbate 20, pH 6.2	10 mM Sodium Phosphate, 8% Sucrose, 0.03% Polysorbate 20, 50 mM L-Arginine Monohydrochloride, pH 6.2
Months at 2-8C		
0.0	97.6	98.1
1	96.8	97.2
2.0	96.2	96.8
3.0	95.9	96.5
6.0	95.1	95.8
9.0	94.5	95.3
12.0	94.1	94.5

Example 5: Viscosity of 10 mg/ml to 170 mg/ml VEGF TRAP in Histidine and Phosphate Buffers

[00248] Figure 5 showed that 10 mM phosphate buffer and 10 mM histidine buffer both had highly useful viscosities for a range of VEGF Trap (afibercept) concentrations. At higher VEGF Trap concentrations, the histidine buffer showed an improvement in viscosity (relative to phosphate). Viscosity was measured at 20°C.

Example 6: Taurine and Propane Sulfonic Acid Provide Improved Stability to High Concentration VEGF Trap (afibercept) Formulations.

[00249] An experiment was conducted to determine the effect on protein stability with a number of formulation combinations. Figure 6 shows a dynamic light scattering plot for formulations having anywhere from 2 mg/ml protein to 10 mg/ml protein (afibercept). Formulations that included 70 mM taurine or 70 mM PSA showed reduced self-interaction at higher concentrations. These data indicate that taurine and PSA can be useful inclusions in high concentration protein formulations, like the ones at issue in this case.

Example 7: Long Term Study of Stability of Various Histidine Containing Formulations.

[00250] A total of 9 different afibercept formulations were tested with varying buffer concentration, thermal stabilizers and hydrophobic salts. The 9 formulations, F1-F9, are summarized below in Table 7-1.

Table 7-1. Formulations F1-F9.

Formulation	VEGFT (mg/mL)	Buffer Type	Buffer Concentration (mM)	Sucrose (%w/v)	Proline (%w/v)	Polysorbate 20 (w/v)	Stabilizer (mM)	Stabilizer Concentration (mM)	pH
F1 (WW)	140	His	10	5	0	0.03	Taurine	50	5.8
F2 (XX)	140	His	20	0	4	0.03	Arginine HCl	50	5.8
F3 (YY)	140	His	20	2.5	2	0.03	Taurine	50	5.8
F4 (ZZ)	140	His	10	2.5	2	0.03	Arginine HCl	50	5.8
F5 (AAA)	140	His	20	5	0	0.03	PSA	50	5.8
F6 (BBB)	140	His	20	2.5	2	0.03	PSA	50	5.8

F7 (CCC)	140	His	20	5	0	0.03	Arginine HCl	50	5.8
F8 (DDD)	140	His	10	0	4	0.03	PSA	50	5.8
F9 (EEE)	140	His	20	5	0	0.03	NA	NA	5.8

VEGFT=VEGF Trap (afibercept)

[00251] Fourteen (14) mL of each formulation was compounded in 15 mL Falcon tubes. The formulation was then sterile filtered using a 0.22 μ m syringe filter and filled in sterile 2 mL Type 1 glass vials. Eight (8) vials were filled for each formulation with 0.4 mL volume in a laminar flow hood.

[00252] SE-UPLC (molecular weight species) was performed on all samples to determine the chemical stability of each formulation.

[00253] The percentage of HMW species over time for each of formulations F1-F9 are shown in Figure 7 (see also Table 7-2). Formulations F4 and F7 exhibited the lowest percentage of HMW species after 4 months at 5°C. The results showed that addition of excipients like arginine and proline significantly reduced the rate of %HMW species formation in VEGF Trap formulations.

Table 7-2. SE-UPLC Analysis (2-8°C)

	F1 (WW)		F2 (XX)		F3 (YY)	
Months at 2-8C	%HMW	%Main Peak	%HMW	%Main Peak	%HMW	%Main Peak
0.0	1.53	98.46	1.48	98.52	1.39	98.61
0.5	1.87	98.13	1.87	98.13	1.92	98.08
1.0	2.19	97.81	2.16	97.84	2.19	96.15
2.0	2.64	97.36	2.63	97.37	2.71	97.29
3.0	2.83	97.17	2.76	97.24	2.87	97.13
4.0	3.07	96.93	3.00	97.00	3.11	96.89
5.0	3.24	96.76	3.11	96.89	3.28	96.72
6.0	3.35	96.65	3.24	96.76	3.38	96.62

F4 (ZZ)		F5 (AAA)		F6 (BBB)	
%HMW	%Main Peak	%HMW	%Main Peak	%HMW	%Main Peak
1.31	98.69	1.55	98.45	1.45	98.55
1.69	98.31	1.79	98.21	1.96	98.04
1.95	98.05	2.31	97.69	2.26	97.74
2.37	97.63	2.80	97.20	2.72	97.28
2.61	97.39	2.99	97.01	2.91	97.09
2.84	97.16	3.26	96.74	3.17	96.83
3.03	96.97	3.44	96.56	3.35	96.65
3.13	96.87	3.52	96.48	3.41	96.59

F7 (CCC)		F8 (DDD)		F9 (EEE)	
%HMW	%Main Peak	%HMW	%Main Peak	%HMW	%Main Peak
1.20	98.80	1.56	98.44	1.53	98.47
1.74	98.26	1.87	98.13	2.05	97.95
2.08	97.92	2.16	97.84	2.39	97.61
2.52	97.48	2.59	97.41	2.89	97.11
2.76	97.24	2.80	97.20	3.07	96.93
2.97	97.03	3.06	96.94	3.34	96.66
3.14	96.86	3.21	96.79	3.51	96.49
3.26	96.74	3.28	96.72	3.69	96.31

Example 8: Stability Study of 140 mg/mL VEGF Trap with Varying Arginine**Concentrations.**

[00254] The impact of varying the concentration of arginine-HCl on the stability of four 140 mg/mL VEGF Trap (afibercept) eye drug product formulations was studied. The evaluation of stability was performed at the storage condition of 2-8°C. The drug product (DP) was also incubated under stress (37°C) conditions. The four formulations being evaluated in this stability study (F1-F4) are described in Table 8-1 set forth below.

Table 8-1. Formulations F1-F4

Formulation Number	Composition					pH
	VEGFT (mg/mL)	Histidine (mM)	Sucrose (w/v)	Polysorbate 20	L-Arginine	
F1	140	20	5	0.03	0	5.8
F2					10	
F3					50	
F4					100	

[00255] Approximately 145 mL of 187 mg/mL VEGF Trap histidine formulations were thawed. Thirty six (36) mL of each formulation, with the exception of F3, was compounded. 39 mL of bulk F3 was compounded. Each formulation was filter sterilized within a LFH (laminar flow hood) using a 0.22 µm Durapore PVDF sterilizing filter prior to filling. Clean depyrogenated 2 mL type I Schott glass vials stoppered with 13 mm serum stoppers (S2-F451 4432/50B2-40) were used to perform stability studies.

[00256] SE-UPLC analysis of the formulations was performed as set forth above. The %HMW measurements, using SE-UPLC, in each formulation over time are set forth in Figure 8 (A-B). See also Tables 8-2 and 8-3.

[00257] When stored at 5°C, these formulations exhibited a reduction in the rate of formation of %HMW species that was proportional to the concentration of arginine-HCl. Under stress, however, this effect was reversed. The formulations, at 37°C, exhibited an apparent increase in %HMW species proportional to the concentration of arginine-HCl. This property made the discovery of arginine's beneficial effects on aflibercept in the presence of histidine buffer highly unlikely. Typically, for formulation development in the biotechnology industry, the effect of various excipients on a drug is initially screened under stress (e.g., at elevated temperature such as 37°C) for a short period of time. The purpose of this approach is to rapidly eliminate excipients which will not likely perform well in the absence of stress (e.g., at lower temperature such as 5°C) over a longer period of time. Here, arginine was identified as a helpful excipient in spite of its effect on stability at 37°C. Since formulated drug product is typically stored for months at 4-5°C after manufacture, aflibercept in arginine

and histidine buffer would be a highly valuable formulation for long term, stable drug product storage.

Table 8-2. SE-UPLC Analysis (2-8°C)

Months at 2-8°C	F1 (EEE)		F2 (SSS)	
	%Main Peak	%HMW	%Main Peak	%HMW
0.0	97.79	2.21	97.78	2.22
0.5	97.56	2.43	97.59	2.41
1.0	97.30	2.70	97.34	2.66
1.5	97.21	2.79	97.26	2.74
2.0	97.05	2.95	97.08	2.92
2.5	96.96	3.04	97.02	2.98
3.0	96.82	3.18	96.88	3.12
6.0	96.35	3.65	96.40	3.60

F3 (CCC)		F4 (TTT)	
%Main Peak	%HMW	%Main Peak	%HMW
97.85	2.15	97.81	2.19
97.67	2.33	97.73	2.27
97.47	2.53	97.59	2.41
97.37	2.63	97.50	2.50
97.22	2.78	97.36	2.64
97.14	2.86	97.31	2.69
97.04	2.96	97.16	2.84
96.60	3.40	96.77	3.23

Table 8-3. SE-UPLC Analysis (37°C)

Days at 37°C	F1 (EEE)		F2 (SSS)	
	%Main Peak	%HMW	%Main Peak	%HMW
0.0	97.79	2.21	97.78	2.22
7	93.66	6.34	93.32	6.68
14.0	89.48	10.35	88.79	10.98
21.0	86.64	13.08	85.69	13.82
28.0	83.90	15.85	82.66	16.90

F3 (CCC)		F4 (TTT)	
%Main Peak	%HMW	%Main Peak	%HMW
97.85	2.15	97.81	2.19
92.38	7.61	91.32	8.68
86.90	12.91	84.61	15.21
83.11	16.65	80.11	19.47
79.44	20.29	75.80	23.91

Example 9: VEGF Trap Stability in the presence of counterions from the Hofmeister Series and other Excipients.

[00258] The effect of various counterions and other excipients on stability of several formulations was determined.

A. Counterion Screening

[00259] Counter ions (e.g., sulfate, thiocyanate and citrate) were tested in the form of sodium salts with high concentration VEGF Trap (afibercept) formulations (140 mg/ml). Additionally, other amino acid excipients (e.g., glycine and lysine) were also tested.

[00260] Approximately 42 ml of 187 mg/ml VEGF Trap eye drug substance were thawed. 50 ml of intermediate formulated drug substance (155.56 mg/ml), having a 110% concentration of the 140 mg/ml formulated drug substance and target excipient concentration (excluding the counterions, glycine and lysine), were prepared.

[00261] The intermediate formulated drug substance was further diluted with the 0.5 M stock excipient solutions (counterions, glycine or lysine) to produce the 140 mg/ml formulated drug substance formulations listed in Table 9-1 below. Each final formulation was filter sterilized with a 0.22 µm PVDF syringe filter within a laminar flow hood prior to filling into clean depyrogenated 2mL type I Schott glass vials stoppered with 13 mm serum stoppers S2-F451 4432/50 82-40 (ELN item# 19700004 Wash# 0 000078949). Sixty (60) vials were filled with 0.5 ml of each formulation. Six (6) vials were filled with 1.5 ml.

Table 9-1. Formulations for Counterion Screening

Excipient (mg)	Excipient (mg)	Excipient (mg)
Sodium Sulfate 50mg	20mg Histidine 0.23M 0.205% Sucrose 50mg	140
Sodium thiosulfate 50mg	20mg Histidine 0.23M 0.205% Sucrose 50mg	140
Sodium Citrate 50mg	20mg Histidine 0.23M 0.205% Sucrose 50mg	140
Glycine 50mg	20mg Histidine 0.23M 0.205% Sucrose 50mg	140
Sodium chloride 50mg	20mg Histidine 0.23M 0.205% Sucrose 50mg	140
Lysine 50mg	20mg Histidine 0.23M 0.205% Sucrose 50mg	140

B. Glutamate And Aspartate Screening

[00262] The stability of VEGF Trap (afibercept) high concentration formulations (140 mg/ml) in the presence of organic counter ions in combination with arginine hydrochloride was tested. In addition, two new counter ions (glutamate and aspartate) were tested for compatibility with high concentration VEGF Trap (in combination and without arginine hydrochloride). The formulations tested are summarized below in Table 9-2.

[00263] Approximately 50 ml of 187 mg/ml VEGF Trap drug substance were thawed. 60 ml of intermediate formulated drug substance (155.56 mg/ml) with a 110% of the 140 mg/ml formulated drug substance and target excipient concentration (excluding the counterions, citrate, glycine, glutamate and aspartate) was prepared. The intermediate formulated drug substance was further diluted with the 1M stock excipient solutions (arginine hydrochloride, sodium citrate, glycine, sodium glutamate and sodium aspartate) to produce the 140 mg/ml formulated drug substance formulations listed in the table below. Each final formulation was filter sterilized with a 0.22 µm PVDF syringe filter within a laminar flow hood prior to filling into clean depyrogenated 2 ml type I Schott glass vials stoppered with 13 mm serum stoppers S2-F451 4432/50 B2-40 (ELN item# 19700004 Wash# 0000078949). Sixty (60) vials were filled with 0.5 ml of each formulation. Six (6) vials were filled with 1.5 ml.

Table 9-2. Formulations for Glutamate And Aspartate Screening

Excipient (mg)	Excipient (mg)	Excipient (mg)
Sodium Citrate 50mg + Arginine Hydrochloride 50mg	20mg Histidine 0.23M 0.205% Sucrose 50mg	140
Glycine 50mg + Arginine hydrochloride 50mg	20mg Histidine 0.23M 0.205% Sucrose 50mg	140
Sodium aspartate 50mg + Arginine hydrochloride 50mg	20mg Histidine 0.23M 0.205% Sucrose 50mg	140
Sodium glutamate 50mg + Arginine hydrochloride 50mg	20mg Histidine 0.23M 0.205% Sucrose 50mg	140
Sodium aspartate 50mg	20mg Histidine 0.23M 0.205% Sucrose 50mg	140
Sodium glutamate 50mg	20mg Histidine 0.23M 0.205% Sucrose 50mg	140

[00264] Viscosity testing was performed using a RHEOSENSE m-VROC® viscometer. Approximately, 0.5 mL of undiluted sample was loaded onto a glass syringe. The sample was equilibrated to the desired temperature and injected into a chip or measuring cell. Viscosity was calculated by measuring the pressure drop from inlet to the outlet which is correlated to the shear-stress at the wall of the chip. Results are expressed as mPas-1 or cp. See Figure 9 and Table 9-3.

[00265] Osmolality testing was performed using a VAPRO vapor pressure osmometer. Approximately, 10 µL of undiluted sample was inoculated into a paper disc. The dew point temperature depression, a function of the solution vapor pressure, was measured through a sensitive thermocouple and reported as osmolality of the solution. Results are expressed as mmol/kg or mOsm. See Figure 10 and Table 9-3.

[00266] High molecular weight species in certain formulations over time, after storage at 37°C or 5°C, was also evaluated by SE-UPLC. See Figure 11 (A-B) and Tables 9-4 and 9-5.

[00267] Dynamic light scattering experiments were performed using a DynaPro® Plate Reader II. Approximately, 100 µL of undiluted sample was loaded onto a 96-well plate. Thirty five acquisitions were obtained for each well at 25°C. Analysis of autocorrelation function using regularization was performed on the DYNAMICS v7.1 software. Radius (nm) vs %intensity plots and % mass vs radius (nm) plots were generated to derive the average molecular radius and % polydispersity values (%Pd) for each sample. See Figure 12.

Table 9-3. Viscosity and Osmolality of Various Formulations

Parameter tested	50mM Sodium Sulfate (GGG)	50mM Sodium thiocyanate (HHH)	40mM Sodium citrate (III)	50mM Glycine (JJJ)	50mM Sodium Chloride (KKK)	50mM Lysine (LLL)
viscosity (cp)	11.9	12.4	14.8	12.2	11.6	11.8
Osmolality(mOsmol/Kg)	384	324	403	299	349	249

50mM Sodium Aspartate (MMM)	50mM Sodium Glutamate (NNN)	50mM Sodium citrate+50mM Arginine HCl (OOO)	50mM Glycine+ 50mM Arginine HCl (PPP)	50mM Sodium Aspartate+ 50mM Arginine HCl (QQQ)	50mM Sodium Glutamate + 50mM Arginine HCl (RRR)
13.0	13.1	14.8	12.5	13.1	13.3
343	346	506	369	426	430

Table 9-4. SE-UPLC Analysis; %HMW (37°C)

%HMW (Days at 37°C)	50mM Sodium Sulfate (GGG)	50mM Sodium thiocyanate (HHH)	40mM Sodium citrate (III)	50mM Glycine (JJJ)	50mM Sodium Chloride (KKK)	50mM Lysine (LLL)
0	2.3	2.3	2.3	2.3	2.3	2.2
7	8.6	15.5	6.2	6.3	8.1	7.7
14	13.5	24.8	12.1	9.5	12.4	11.7
26	22.0	39.2	19.1	15.3	20.4	19.3

Table 9-5. SE-UPLC Analysis; %HMW (5°C)

%HMW (Months at 5°C)	50mM Sodium Sulfate (GGG)	50mM Sodium thiocyanate (HHH)	40mM Sodium citrate (III)	50mM Glycine (JJJ)	50mM Sodium Chloride (KKK)	50mM Lysine (LLL)
0	2.3	2.3	2.3	2.3	2.3	2.2
0.25	2.3	2.4	2.4	2.3	2.3	2.3
0.5	2.4	2.5	2.5	2.4	2.4	2.3
1	2.5	2.8	2.7	2.6	2.6	2.5
2	2.8	2.9	2.9	2.8	2.8	2.8
3	3.1	3.3	3.2	3.1	3.2	3.0

Example 10: Tolerability of IVT delivery of High Dose VEGF Trap (140mg/ml) in**Normal Rabbits.**

[00268] Anti-VEGF therapeutics, administered via intravitreal injection, are currently the standard of care for treatment of neovascular age-related macular degeneration, diabetic macular edema, and retinal vascular occlusive disease. However, the monthly or bi-monthly intravitreal injections represent a significant treatment burden on patients, caregivers, and physicians. There is a pressing need for more effective and durable therapies in clinical practice. This study is to investigate the tolerability of stably formulated high dose VEGF Trap (140 mg/ml, equivalently 14 folds of the clinical dose) in normal New Zealand white rabbit eyes.

[00269] Two formulations of high dose VEGF-Trap (aflibercept) in histidine buffer or in phosphate buffer were tested. Three rabbits per cohort received 7mg of VEGF Trap in 50 μ L by single bilateral intravitreal injection of each formulation. Ocular inflammation signs were monitored by slit lamp, optical coherence tomography (OCT) and fundus angiograph at day 1, day 4, week 1 then weekly until 12 weeks post-intravitreal administration. Intraocular pressure was measured with Tonopen before and 10 minutes and 30 minutes post intravitreal injection, then at every follow up time point. Animals were euthanized at week 12.

[00270] The rabbit eyes were dosed with either:

(1) 140 mg/ml aflibercept, 20 mM Histidine, 5% Sucrose, 50 mM Arginine HCl, 0.03% PS20, pH 5.8;

or

(2) 140 mg/ml aflibercept, 10 mM Sodium phosphate, 5% Sucrose, 40 mM Sodium Chloride, 0.03% PS20, pH 6.2.

[00271] Two of six eyes from the histidine buffer group showed dark shadows in the vitreous until 8 weeks post IVT, which were confirmed by slit-lamp examination as local cataract due to posterior lens injury, procedure related. One of 5 eyes the from phosphate buffer group showed dark shadows in the vitreous until 8 weeks post IVT, which were confirmed by slit-lamp examination as local cataract due to posterior lens injury (procedure related).

[00272] The high dose VEGF Trap (140 mg/ml) formulations tested were well tolerated in normal New Zealand White rabbit eyes within 12 weeks post-single intravitreal administration. After a single intravitreal injection of 7 mg of VEGF Trap, no signs of abnormalities or inflammation were seen in the fundus. The vitreous was clear and the retinal vascular pattern appeared normal. No retinal detachment, hemorrhage or optic nerve head changes were seen. There was no intraocular pressure change compared to baseline. The baseline fluorescein angiography (FA) and OCT images of rabbit eyes are represented in Figure 13(A-D). The time course FA and OCT images of rabbit eyes in each treatment group over 8 weeks is represented in figures 14, 15, 16 and 17. Data from the left eye (OS) or right eye (OD) of rabbits 326 and 329 are shown.

Example 11: Evaluation of Stability of Formulations UUU-BBBB

[00273] This study examined the stability of 60 mg/ml and 120 mg/ml VEGF Trap (aflibercept) in 10 mM phosphate, 10% or 20% sucrose (Suc.), 0 or 50 mM NaCl, 0.03% polysorbate 20, pH 6.2 when incubated at 37°C for up to 6 months. The formulations for this stability study are set forth below in Table 11-1.

Table 11-1. Formulations UUU-BBBB

Formulation Designation	[VEGF Trap] mg/mL	% Sucrose	mM NaCl
F1 (UUU)	30	10	-
F2 (VVV)	30	20	-
F3 (WWW)	60	10	-
F4 (XXX)	60	20	-
F5 (YYY)	120	10	-
F6 (ZZZ)	120	20	-
F7 (AAAA)	120	10	50
F8 (BBBB)	120	20	50

Base formulation: 10 mM phosphate, 0.03% polysorbate 20, pH 6.2

VEGF Trap=afibercept

[00274] The formulation was filter sterilized with a PVDF 0.2 μ m filter in a laminar flow hood prior to dispensing.

[00275] Vials containing each formulation were stored at 37°C for 1 month.

Table 11-2. Reverse-phase High Performance Liquid Chromatography (RP-HPLC)

Results

Formulation	Storage Condition	Actual Incubation (months)	% VEGFT Recovered	[VGFT] mg/ml
30 mg/mL 10% sucrose (UUU)	37°C	0.0	100.0	29.99
		1.0	97.9	29.37
30 mg/mL 20% sucrose (VVV)	37°C	0.0	100.0	29.97
		1.0	98.2	29.44
60 mg/mL 10% sucrose (WWW)	37°C	0.0	100.0	58.90
		1.0	98.3	57.89
60 mg/mL 20% sucrose (XXX)	37°C	0.0	100.0	58.80
		1.0	98.9	58.18
120 mg/mL 10% sucrose (YYY)	37°C	0.0	100.0	120.80
		1.0	97.4	117.63
120 mg/mL 20% sucrose (ZZZ)	37°C	0.0	100.0	117.85
		1.0	98.9	116.51
120 mg/mL 10% sucrose 50 mM NaCl (AAAA)	37°C	0.0	100.0	120.14
		1.0	97.9	117.64
120 mg/mL 20% sucrose 50 mM NaCl (BBBB)	37°C	0.0	100.0	120.55
		1.0	97.0	116.94

VGFT=VEGF Trap, aflibercept

Table 11-3. Size-exclusion Ultra Performance Liquid Chromatography (SE-UPLC) Results

Formulation	Storage Condition	Actual Incubation (months)	Total % HMW	%Native	Total % LMW
30 mg/mL VGFT 10% sucrose (UUU)	37°C	0	0.8	99.0	0.1
		1.0	4.1	94.0	1.9
30 mg/mL VGFT 20% sucrose (VVV)	37°C	0	0.8	99.0	0.2
		1.0	2.4	95.6	2.0
60 mg/mL VGFT 10% sucrose (WWW)	37°C	0	1.0	98.8	0.2
		1.0	7.8	89.5	2.7
60 mg/mL VGFT 20% sucrose (XXX)	37°C	0	1.0	98.8	0.2
		1.0	4.4	92.8	2.7
120 mg/mL VGFT 10% sucrose (YYY)	37°C	0	1.3	98.5	0.2
		1.0	18.3	79.5	2.2
120 mg/mL VGFT 20% sucrose (ZZZ)	37°C	0	1.2	98.5	0.2
		1.0	10.7	87.1	2.2
120 mg/mL VGFT 10% sucrose 50 mM NaCl (AAAA)	37°C	0	1.3	98.5	0.2
		1.0	20.8	77.1	2.2
120 mg/mL VGFT 20% sucrose 50 mM NaCl (BBBB)	37°C	0	1.2	98.5	0.3
		1.0	13.0	84.8	2.2

VGFT=VEGF Trap, aflibercept

[00276] All of the formulations were essentially particle-free by visual inspection and optical density measurement. There was no significant protein loss in recovery by RP-HPLC after 1 month at 37°C (Table 11-2) and this trend continued out to 6 months.

[00277] The main degradation pathway for VEGF Trap was aggregation under these conditions (Figure 18 (A-B); Table 11-3). The stability of VEGF Trap was dependent on the protein and sucrose concentrations. Formulations with lower VEGF Trap concentrations and higher sucrose were more stable. Maintaining the same protein:sucrose ratio did not result in the same degradation rate. For example, F1 and F4 have the same protein:sucrose ratio of 3:1 but F4 was less stable than F1 due to its higher protein concentration. Similar trends were observed out to 6 months.

Example 12: Repeat-Dose Intravitreal Toxicology Study in Monkeys with Different Aflibercept Formulations.

[00278] The safety of various formulations in cynomolgus monkeys is assessed in this example. A total of 7 intravitreal doses are administered to both eyes approximately Q4W to Groups 1-3; a total of 3 intravitreal doses are administered to both eyes approximately Q4W to groups 4-9. A terminal necropsy is performed approximately one week after last dose (N=3/sex/group) with recovery necropsy (2/sex/group) approximately 12-week after last dose

[00279] The following assessments are performed:

- Safety assessment based on clinical signs, body weights, vital signs, electrocardiographic data (pre-dose end of treatment and end of recovery), blood pressure measurements (via tail cuff), clinical and anatomic pathology
- Comprehensive ocular exams at regular intervals during the dosing and recovery intervals including slit lamp microscopy, indirect ophthalmoscopy and intraocular pressure measurements
- Fundus photography, fluorescein angiography and electroretinography at pre-treatment, during study week 9 (all groups), week 26 (Groups 1-3 only) and end of recovery period
- Blood and vitreous samples (at termination) for bioanalytical, ADA analysis and toxicokinetic evaluation

Table 13. Study group summary*

Group	Test Material	IVT Dose Volume (μ L/dose/eye)	mg aflibercept/eye	N/sex	N/sex for terminal necropsy	N/sex for Recovery
1	20 mM Histidine, 50 mM Arginine, 5% Sucrose, 0.03% PS20	50	0 (control)	5	3	2
2	80 mg/mL Aflibercept in 20 mM Histidine, 50mM Arginine, 5% Sucrose, 0.03% PS20	50	4	5	3	2
3	~140 mg/mL Aflibercept in 20 mM Histidine, 50mM Arginine, 5% Sucrose, 0.03% PS20	50	~7	5	3	2
4	20 mM Histidine, 5% Sucrose, 0.03% PS20	50	0 (control)	5	3	2
5	80 mg/mL Aflibercept in 20 mM Histidine, 5% Sucrose, 0.03% PS20	50	4	5	3	2
6	~140 mg/mL Aflibercept in 20 mM Histidine, 5% Sucrose, 0.03% PS20	50	~7	5	3	2
7	20 mM Histidine, 50 mM Glycine, 5% Sucrose, 0.03% PS20	50	0 (control)	5	3	2
8	80 mg/mL Aflibercept in 20 mM Histidine, 50 mM Glycine, 5% Sucrose, 0.03% PS20	50	4	5	3	2
9	~140 mg/mL Aflibercept in 20 mM Histidine, 50 mM Glycine, 5% Sucrose, 0.03% PS20	50	~7	5	3	2

*each of said formulations are part of the present invention

[00280] It is expected that the formulations tested in any one or more of Groups 1, 2, 3, 4, 5, 6, 7, 8 and/or 9 will be determined to have a safety profile comparable to EYLEA in cynomolgous monkeys as measured in the assessments discussed above.

Example 13: Stability Study with VEGF Trap Product.

[00282] A formulation including 114.3 mg/mL VEGF Trap (aflibercept) and 10 mM Histidine, pH 5.8, 5% Sucrose, 0.03% Polysorbate 20, 50 mM Arginine Monohydrochloride was prepared within a LFH (laminar flow hood) using a 0.22 μ m Durapore PVDF sterilizing filter prior to filling. Clean depyrogenated 3 mL type I Schott glass vials were filled with 0.3 mL of Drug Product and stoppered with 13 mm serum stoppers (S2-F451 4432/5082-40). Samples were analyzed at various timepoints after storage at 37°C or 5°C for purity by size-exclusion chromatography (SEC) to determine the presence (%) of high molecular weight species (HMW), low molecular weight species (LMW) and the main peak (main); as well as microflow imaging, HIAC liquid particle counting (by light obscuration) and microscopically to determine the presence of particles of various sizes.

[00283] Stability and purity data after storage at 37°C, 25°C and 2-8°C are shown in Figure 19 (A-E). See also Tables 13-1 – 13-4.

Table 13-1. Size-Exclusion Chromatography (SEC) Purity Analysis

37°C			
Months	%Main	%HMW	%LMW
0	98.23	1.77	0
0.229	92.88	7.07	0.05
0.459	88.59	11.18	0.23
0.688	84.67	15.03	0.3
0.918	81.84	17.59	0.57
5°C			
Months	%Main	%HMW	%LMW
0	98.23	1.77	0
1	97.73	2.27	0
2	97.4	2.59	0

Table 13-2. Microflow Imaging/Subvisible Particles

37°C					
Months	$\geq 1\mu$ m	$\geq 2\mu$ m	$\geq 5\mu$ m	$\geq 10\mu$ m	$\geq 25\mu$ m
T=0	1125	234	42	9	0
28 days	1128	184	17	0	0

Table 13-3. Subvisible Particulate Matter as Measured by Light Obscuration (HIAC)/Subvisible Particles

37°C			
Months	≥10µm	≥25µm	≥50µm
T=0	15	0	0
28 days	23	1	1

Table 13-4. Microscopic Analysis of Subvisible Particles

37°C			
Months	≥10µm	≥25µm	≥50µm
T=0	8	1	1
28 days	6	2	1

Example 14: Stability Study with Varying VEGF Trap Concentrations.

[00284] The impact of varying the concentration of VEGF Trap on the stability of four VEGF Trap (afibercept) eye drug product formulations was studied. The concentrations ranged between 80 and 140 mg/mL. The evaluation of stability was performed at the storage condition of 2-8°C. The drug product (DP) was also incubated under stress (37°C) conditions. The four formulations (each of which is named "CCC" herein) being evaluated in this stability study are described in Table 14-1 set forth below.

[00285] Approximately 27 mL of each formulation was prepared within a LFH (laminar flow hood) using a 0.22 µm Durapore PVDF sterilizing filter prior to filling. Clean depyrogenated 2 mL type I Schott glass vials were filled and stoppered with 13 mm serum stoppers (S2-F451 4432/50B2-40). Samples were analyzed at various timepoints after storage at 37°C or 2-8°C for purity by size-exclusion-ultraperformance liquid chromatography (SE-UPLC) to determine the presence (%) of high molecular weight species (HMW) and the main peak (main).

[00286] Data showing the percentage HMW after incubation at 2-8°C or 37°C for up to 6 months are set forth in Figure 20 (A-B). See also Tables 14-2 and 14-3. When stored at 37°C and 5°C, these formulations exhibited a positive correlation of the rate of HMW

formation to the concentration of VEGF Trap. The 140 mg/mL formulation exhibited highest rate of %HMW species formation.

Table 14-1. Formulations tested.

Formulation Number	composition					
	L-Arginine mM	Histidine (mM)	Sucrose (w/v)	Polysorbate 20 (w/v)	VEGFT (mg/mL)	pH
F1 (CCC)	50	20	5	0.03	80	5.8
F2 (CCC)					100	
F3 (CCC)					120	
F4 (CCC)					140	

Table 14-2. SE-UPLC Analysis (2-8°C)

Months at 2-8°C	F1 (CCC): 80 mg/mL		F2 (CCC): 100 mg/mL		F4 (CCC): 120 mg/mL		F3 (CCC): 140 mg/mL	
	%Main Peak	%HMW	%Main Peak	%HMW	%Main Peak	%HMW	%Main Peak	%HMW
0.0	97.90	2.10	97.86	2.14	97.83	2.17	97.85	2.15
1	97.91	2.09	97.79	2.21	97.65	2.35	97.47	2.53
2.0	97.78	2.22	97.56	2.44	97.38	2.62	97.22	2.78
3.0	97.61	2.39	97.38	2.62	97.17	2.83	97.04	2.96
5.5	97.39	2.61	97.10	2.90	96.79	3.21		
6.0	97.36	2.64	97.04	2.96	96.74	3.26	96.60	3.40

Table 14-3. SE-UPLC Analysis (37°C)

Days at 37°C	F1 (CCC): 80 mg/mL		F2 (CCC): 100 mg/mL		F4 (CCC): 120 mg/mL		F3 (CCC): 140 mg/mL	
	%Main Peak	%HMW	%Main Peak	%HMW	%Main Peak	%HMW	%Main Peak	%HMW
0.0	97.90	2.10	97.86	2.14	97.83	2.17	97.85	2.15
7	94.83	5.15	93.82	6.17	92.81	7.18	92.38	7.61
14.0	92.00	7.77	90.31	9.39	88.67	11.13	86.90	12.91
21.0	89.47	10.31	87.00	12.58	85.04	14.85	83.11	16.65
28.0	86.76	12.71	83.98	15.55	81.19	18.46	79.44	20.29

Example 15: High dose Eylea has Prolonged Duration of Action in the D,L-AAA Model of Sustained Neovascular Leak.

[00287] The effect of a four-fold increase in dose on duration of action of aflibercept to inhibit chronic retinal vascular leak in the D,L-AAA model was determined in this Example.

[00288] Animals used were New Zealand White rabbits 3 months post-DL-AAA (DL- α -aminoadipic acid) disease induction. The treatment groups were:

- Placebo (formulation buffer) 50 μ l/eye; n= 6 eyes
- Aflibercept 500 μ g/eye in 50 μ l; n= 7 eyes
- Aflibercept 2 mg/eye in 50 μ l; n= 8 eyes

[00289] The formulation used in each treatment group was: 10 mM Histidine, 8% sucrose, 0.03% PS20, pH 5.8. Ophthalmic exams, which were performed at baseline and at weeks 1, 2, 4, 6, 7, 9, 10, 11, 13 and 18, were intra-ocular pressure (IOP), red-free (RF) imaging (to determine blood vessel morphology), fluorescein angiography (FA; to determine vascular leak), optical coherence tomography (OCT; to identify vitreal inflammation). Serum (ADA) and plasma (drug levels) were collected at baseline and at weeks 1, 2, 4, 6 and 9.

[00290] Data from FA exams of each group are set forth in Figure 21. These data demonstrated that vascular leak inhibition in the retinas of animals receiving higher doses of aflibercept lasted longer than that of animals receiving lower doses. The number of treated eyes in which vascular permeability was completely inhibited was significantly greater in the 2 mg dose group at all sampling times up to 18 weeks post dosing.

What is claimed is:

1. An aqueous pharmaceutical formulation comprising:
 - a VEGF receptor fusion protein, anti-VEGF antibody or antigen-binding fragment or VEGF binding molecule at a concentration of at least about 100 mg/ml;
 - about 5% sucrose
 - a histidine buffer; and
 - about 0.03% surfactant;
 - optionally, in association with a further therapeutic agent;
 - wherein the formulation has a pH of about 5.0 to about 6.8.
2. The formulation of claim 1 which is suitable for intravitreal administration.
3. The formulation of any one of claims 1-2 further comprising sodium sulfate, sodium thiocyanate, glycine, NaCl, sodium aspartate, L-arginine and/or sodium glutamate.
4. The formulation of any one of claims 1-3, wherein the VEGF receptor fusion protein or anti-VEGF antibody or antibody fragment or VEGF binding molecule is:
 - (i) a VEGF receptor fusion protein comprising two polypeptides that comprise (1) a VEGFR1 component comprising amino acids 27 to 129 of SEQ ID NO:2; (2) a VEGFR2 component comprising amino acids 130-231 of SEQ ID NO:2; and (3) a multimerization component comprising amino acids 232-457 of SEQ ID NO:2;
 - (ii) a VEGF receptor fusion protein comprising two polypeptides that comprise immunoglobulin-like (Ig) domain 2 of a first VEGF receptor and Ig domain 3 of a second VEGF receptor, and a multimerizing component;
 - (iii) a VEGF receptor fusion protein comprising two polypeptides that comprise an immunoglobulin-like (Ig) domain 2 of a first VEGF receptor, an Ig domain 3 of a second VEGF receptor, an Ig domain 4 of said second VEGF receptor and a multimerizing component;
 - (iv) a VEGF receptor fusion protein comprising two polypeptides that comprise an immunoglobulin-like (Ig) domain 2 of VEGFR1, an Ig domain 3 of a VEGFR2, and a multimerizing component;

- (v) a VEGF receptor fusion protein comprising two polypeptides that comprise an immunoglobulin-like (Ig) domain 2 of VEGFR1, an Ig domain 3 of VEGFR2, an Ig domain 4 of VEGFR2 and a multimerizing component;
- (vi) a VEGF receptor fusion protein comprising two VEGFR1R2-Fc Δ C1(a) polypeptides encoded by the nucleic acid sequence of SEQ ID NO:1; or
- (vii) selected from the group consisting of: bevacizumab, ranibizumab, pegaptanib, brolucizumab, an anti-VEGF DARPin and a bispecific anti-VEGF/ANG2 antibody.

5. The formulation of any one of claims 1-4, wherein the VEGF receptor fusion protein or anti-VEGF antibody or antibody fragment or VEGF binding molecule is a VEGF receptor fusion protein selected from the group consisting of: aflibercept and conbercept.

6. The formulation of any one of claims 1-5 wherein the VEGF receptor fusion protein or anti-VEGF antibody or antibody fragment or VEGF binding molecule is a VEGF receptor fusion protein is a VEGF receptor fusion protein at a concentration of from about 41 to about 275 mg/ml.

7. The formulation of any one of claims 1-6, wherein the VEGF receptor fusion protein or anti-VEGF antibody or antibody fragment or VEGF binding molecule is a VEGF receptor fusion protein is a VEGF receptor fusion protein at a concentration of:

- about 100 mg/ml;
- about 111.5 mg/ml;
- about 112.0 mg/ml;
- about 113.3 mg/ml;
- about 114.3 mg/ml;
- about 115.6 mg/ml;
- about 116.3 mg/ml;
- about 120 mg/ml;
- about 133 mg/ml;
- about 140 mg/ml;
- about 150 mg/ml;
- about 200 mg/ml;
- about 250 mg/ml;
- that which contains about 4 mg VEGF receptor fusion protein in about 100 μ l or less, about 70 μ l or less, about 75 μ l or less, about 50 μ l or less or about 60 μ l or less;
- that which contains about 6 mg VEGF receptor fusion protein in about 100 μ l or less, about 70 μ l or less, about 75 μ l or less, about 50 μ l or less or about 60 μ l or less;

- that which contains about 8 mg VEGF receptor fusion protein in about 100 μ l or less, about 70 μ l or less, about 75 μ l or less, about 50 μ l or less or about 60 μ l or less; or
 - that which contains about 10 mg VEGF receptor fusion protein in about 100 μ l or less, about 70 μ l or less, about 75 μ l or less, about 50 μ l or less or about 60 μ l or less.
8. The formulation of any one of claims 1-7 wherein:
- (i) the osmolality is about 299 to about 506 mmol/Kg; and/or
- (ii) the viscosity is from about 6-15 cP at 20°C.
9. The formulation of any one of claims 1-8 wherein the pH is 5.8 to 6.5.
10. The formulation of claim 9 wherein the pH is about 5.8.
11. The formulation of any one of claims 1-10, wherein the surfactant is a non-ionic surfactant.
12. The formulation of claim 11, wherein the non-ionic surfactant is selected from the group consisting of polysorbate 20, polysorbate 80, poloxamer 188, polyethylene glycol 3350 and mixtures thereof.
13. The formulation of any one of claims 1-12, wherein the histidine is histidine hydrochloride.
14. The formulation of claim 13 comprising about 10 mM to 20 mM histidine hydrochloride.
15. The formulation of any one of claims 1-14, comprising a thermal stabilizer which is a sugar.
16. The formulation of claim 15, wherein the sugar is sucrose, mannitol, sorbitol or trehalose.
17. The formulation of any one of claims 15-16 comprising about 2.5% (w/v), about 5% (w/v), about 8% (w/v), about 10% (w/v) or about 20% (w/v) sucrose.

18. The formulation of any one of claims 1-17 comprising surfactant at a concentration of about 0.03% (w/v).
19. The formulation of any one of claims 1-18, comprising L-arginine monohydrochloride.
20. The formulation of any one of claims 1-19 wherein the VEGF receptor fusion protein or anti-VEGF antibody or antibody fragment or VEGF binding molecule is a VEGF receptor fusion protein which has less than about 3.5% high molecular weight species immediately after manufacture and purification and/or less than or equal to about 6% high molecular weight species after storage for about 24 months at about 2-8°C.
21. A formulation comprising the components in a formulation selected from the group consisting of:
- Formulation A: 80 mg/ml aflibercept, 10 mM histidine-based buffer, 5% (w/v) sucrose, 0.03% (w/v) polysorbate 20, and 40 mM sodium chloride, with a pH of 5.8 to 6.2;
- Formulation B: 80 mg/ml aflibercept, 10 mM phosphate-based buffer, 5% (w/v) sucrose, 0.03% (w/v) polysorbate 20, and 40 mM sodium chloride, with a pH of 5.8 to 6.2;
- Formulation C: 80 mg/ml aflibercept, 10 mM citrate-based buffer, 5% (w/v) sucrose, 0.03% (w/v) polysorbate 20, and 40 mM sodium chloride, with a pH of 5.8 to 6.2;
- Formulation D: 80 mg/ml aflibercept, 10 mM histidine-based buffer, 5% (w/v) sucrose, 0.03% (w/v) polysorbate 80, and 40 mM sodium chloride, with a pH of 6.2;
- Formulation E: 80 mg/ml aflibercept, 10 mM phosphate-based buffer, 5% (w/v) sucrose, 0.03% (w/v) polysorbate 80, and 40 mM sodium chloride, with a pH of 5.8 to 6.2;
- Formulation F: 80 mg/ml aflibercept, 10 mM citrate-based buffer, 5% (w/v) sucrose, 0.03% (w/v) polysorbate 80, and 40 mM sodium chloride, with a pH of 5.8 to 6.2;
- Formulation G: 80 mg/ml aflibercept, 10 mM histidine-based buffer, 8% (w/v) sucrose, and 0.03% (w/v) polysorbate 20, with a pH of 5.8 to 6.2;
- Formulation H: 80 mg/ml aflibercept, 10 mM phosphate-based buffer, 8% (w/v) sucrose, and 0.03% (w/v) polysorbate 20, with a pH of 5.8 to 6.2;
- Formulation I: 80 mg/ml aflibercept, 10 mM citrate-based buffer, 8% (w/v) sucrose, and 0.03% (w/v) polysorbate 20, with a pH of 5.8 to 6.2;
- Formulation J: 80 mg/ml aflibercept, 10 mM histidine-based buffer, 8% (w/v) sucrose, and 0.03% (w/v) polysorbate 80, with a pH of 5.8 to 6.2;
- Formulation K: 80 mg/ml aflibercept, 10 mM phosphate-based buffer, 8% (w/v) sucrose, and 0.03% (w/v) polysorbate 80, with a pH of 5.8 to 6.2;
- Formulation L: 80 mg/ml aflibercept, 10 mM citrate-based buffer, 8% (w/v) sucrose, and 0.03% (w/v) polysorbate 80, with a pH of 5.8 to 6.2;

Formulation M: 150 mg/ml aflibercept, 10 mM histidine-based buffer, 5% (w/v) sucrose, 0.03% (w/v) polysorbate 20, and 40 mM sodium chloride, with a pH of 5.8 to 6.2;

Formulation N: 150 mg/ml aflibercept, 10 mM phosphate-based buffer, 5% (w/v) sucrose, 0.03% (w/v) polysorbate 20, and 40 mM sodium chloride, with a pH of 5.8 to 6.2;

Formulation O: 150 mg/ml aflibercept, 10 mM citrate-based buffer, 5% (w/v) sucrose, 0.03% (w/v) polysorbate 20, and 40 mM sodium chloride, with a pH of 5.8 to 6.2;

Formulation P: 150 mg/ml aflibercept, 10 mM histidine-based buffer, 5% (w/v) sucrose, 0.03% (w/v) polysorbate 80, and 40 mM sodium chloride, with a pH of 6.2;

Formulation Q: 150 mg/ml aflibercept, 10 mM phosphate-based buffer, 5% (w/v) sucrose, 0.03% (w/v) polysorbate 80, and 40 mM sodium chloride, with a pH of 5.8 to 6.2;

Formulation R: 150 mg/ml aflibercept, 10 mM citrate-based buffer, 5% (w/v) sucrose, 0.03% (w/v) polysorbate 80, and 40 mM sodium chloride, with a pH of 5.8 to 6.2;

Formulation S: 150 mg/ml aflibercept, 10 mM histidine-based buffer, 8% (w/v) sucrose, and 0.03% (w/v) polysorbate 20, with a pH of 5.8 to 6.2;

Formulation T: 150 mg/ml aflibercept, 10 mM phosphate-based buffer, 8% (w/v) sucrose, and 0.03% (w/v) polysorbate 20, with a pH of 5.8 to 6.2;

Formulation U: 150 mg/ml aflibercept, 10 mM citrate-based buffer, 8% (w/v) sucrose, and 0.03% (w/v) polysorbate 20, with a pH of 5.8 to 6.2;

Formulation V: 150 mg/ml aflibercept, 10 mM histidine-based buffer, 8% (w/v) sucrose, and 0.03% (w/v) polysorbate 80, with a pH of 5.8 to 6.2;

Formulation W: 150 mg/ml aflibercept, 10 mM phosphate-based buffer, 8% (w/v) sucrose, and 0.03% (w/v) polysorbate 80, with a pH of 5.8 to 6.2;

Formulation X: 150 mg/ml aflibercept, 10 mM citrate-based buffer, 8% (w/v) sucrose, and 0.03% (w/v) polysorbate 80, with a pH of 5.8 to 6.2;

Formulation Y: 80 mg/ml conbercept, 10 mM histidine-based buffer, 5% (w/v) sucrose, 0.03% (w/v) polysorbate 20, and 40 mM sodium chloride, with a pH of 5.8 to 6.2;

Formulation Z: 80 mg/ml conbercept, 10 mM phosphate-based buffer, 5% (w/v) sucrose, 0.03% (w/v) polysorbate 20, and 40 mM sodium chloride, with a pH of 5.8 to 6.2;

Formulation AA: 80 mg/ml conbercept, 10 mM citrate-based buffer, 5% (w/v) sucrose, 0.03% (w/v) polysorbate 20, and 40 mM sodium chloride, with a pH of 5.8 to 6.2;

Formulation BB: 80 mg/ml conbercept, 10 mM histidine-based buffer, 5% (w/v) sucrose, 0.03% (w/v) polysorbate 80, and 40 mM sodium chloride, with a pH of 6.2;

Formulation CC: 80 mg/ml conbercept, 10 mM phosphate-based buffer, 5% (w/v) sucrose, 0.03% (w/v) polysorbate 80, and 40 mM sodium chloride, with a pH of 5.8 to 6.2;

Formulation DD: 80 mg/ml conbercept, 10 mM citrate-based buffer, 5% (w/v) sucrose, 0.03% (w/v) polysorbate 80, and 40 mM sodium chloride, with a pH of 5.8 to 6.2;

Formulation EE: 80 mg/ml conbercept, 10 mM histidine-based buffer, 8% (w/v) sucrose, and 0.03% (w/v) polysorbate 20, with a pH of 5.8 to 6.2;

Formulation FF: 80 mg/ml conbercept, 10 mM phosphate-based buffer, 8% (w/v) sucrose, and 0.03% (w/v) polysorbate 20, with a pH of 5.8 to 6.2;

Formulation GG: 80 mg/ml conbercept, 10 mM citrate-based buffer, 8% (w/v) sucrose, and 0.03% (w/v) polysorbate 20, with a pH of 5.8 to 6.2;

Formulation HH: 80 mg/ml conbercept, 10 mM histidine-based buffer, 8% (w/v) sucrose, and 0.03% (w/v) polysorbate 80, with a pH of 5.8 to 6.2;

Formulation II: 80 mg/ml conbercept, 10 mM phosphate-based buffer, 8% (w/v) sucrose, and 0.03% (w/v) polysorbate 80, with a pH of 5.8 to 6.2;

Formulation JJ: 80 mg/ml conbercept, 10 mM citrate-based buffer, 8% (w/v) sucrose, and 0.03% (w/v) polysorbate 80, with a pH of 5.8 to 6.2;

Formulation KK: 150 mg/ml conbercept, 10 mM histidine-based buffer, 5% (w/v) sucrose, 0.03% (w/v) polysorbate 20, and 40 mM sodium chloride, with a pH of 5.8 to 6.2;

Formulation LL: 150 mg/ml conbercept, 10 mM phosphate-based buffer, 5% (w/v) sucrose, 0.03% (w/v) polysorbate 20, and 40 mM sodium chloride, with a pH of 5.8 to 6.2;

Formulation MM: 150 mg/ml conbercept, 10 mM citrate-based buffer, 5% (w/v) sucrose, 0.03% (w/v) polysorbate 20, and 40 mM sodium chloride, with a pH of 5.8 to 6.2;

Formulation NN: 150 mg/ml conbercept, 10 mM histidine-based buffer, 5% (w/v) sucrose, 0.03% (w/v) polysorbate 80, and 40 mM sodium chloride, with a pH of 6.2;

Formulation OO: 150 mg/ml conbercept, 10 mM phosphate-based buffer, 5% (w/v) sucrose, 0.03% (w/v) polysorbate 80, and 40 mM sodium chloride, with a pH of 5.8 to 6.2;

Formulation PP: 150 mg/ml conbercept, 10 mM citrate-based buffer, 5% (w/v) sucrose, 0.03% (w/v) polysorbate 80, and 40 mM sodium chloride, with a pH of 5.8 to 6.2;

Formulation QQ: 150 mg/ml conbercept, 10 mM histidine-based buffer, 8% (w/v) sucrose, and 0.03% (w/v) polysorbate 20, with a pH of 5.8 to 6.2;

Formulation RR: 150 mg/ml conbercept, 10 mM phosphate-based buffer, 8% (w/v) sucrose, and 0.03% (w/v) polysorbate 20, with a pH of 5.8 to 6.2;

Formulation SS: 150 mg/ml conbercept, 10 mM citrate-based buffer, 8% (w/v) sucrose, and 0.03% (w/v) polysorbate 20, with a pH of 5.8 to 6.2;

Formulation TT: 150 mg/ml conbercept, 10 mM histidine-based buffer, 8% (w/v) sucrose, and 0.03% (w/v) polysorbate 80, with a pH of 5.8 to 6.2;

Formulation UU: 150 mg/ml conbercept, 10 mM phosphate-based buffer, 8% (w/v) sucrose, and 0.03% (w/v) polysorbate 80, with a pH of 5.8 to 6.2;

Formulation VV: 150 mg/ml conbercept, 10 mM citrate-based buffer, 8% (w/v) sucrose, and 0.03% (w/v) polysorbate 80, with a pH of 5.8 to 6.2;

Formulation WW: 140 mg/ml VEGF receptor fusion protein, 10 mM histidine-based buffer, 5% (w/v) sucrose, 0.03% (w/v) polysorbate 20, and 50 mM taurine, with a pH of 5.8;

Formulation XX: 140 mg/ml VEGF receptor fusion protein, 20 mM histidine-based buffer, 4% (w/v) proline, 0.03% (w/v) polysorbate 20, and 50 mM arginine hydrochloride, with a pH of 5.8;

Formulation YY: 140 mg/ml VEGF receptor fusion protein, 20 mM histidine-based buffer, 2.5% (w/v) sucrose, 2.0 % (w/v) proline, 0.03% (w/v) polysorbate 20, and 50 mM taurine, with a pH of 5.8;

Formulation ZZ: 140 mg/ml VEGF receptor fusion protein, 10 mM histidine-based buffer, 2.5% (w/v) sucrose, 2.0% (w/v) proline, 0.03% (w/v) polysorbate 20, and 50 mM arginine hydrochloride, with a pH of 5.8;

Formulation AAA: 140 mg/ml VEGF receptor fusion protein, 20 mM histidine-based buffer, 5% (w/v) sucrose, 0.03% (w/v) polysorbate 20, and 50 mM PSA, with a pH of 5.8;

Formulation BBB: 140 mg/ml VEGF receptor fusion protein, 20 mM histidine-based buffer, 2.5% (w/v) sucrose, 2.0% (w/v) proline, 0.03% (w/v) polysorbate 20, and 50 mM PSA, with a pH of 5.8;

Formulation CCC: 80, 100, 120 or 140 mg/ml VEGF receptor fusion protein, 20 mM histidine-based buffer, 5% (w/v) sucrose, 0.03% (w/v) polysorbate 20, and 50 mM arginine hydrochloride, with a pH of 5.8;

Formulation DDD: 140 mg/ml VEGF receptor fusion protein, 10 mM histidine-based buffer, 4% (w/v) proline, 0.03% (w/v) polysorbate 20, and 50 mM PSA, with a pH of 5.8;

Formulation EEE: 140 mg/ml VEGF receptor fusion protein, 20 mM histidine-based buffer, 5% (w/v) sucrose, and 0.03% (w/v) polysorbate 20 and no thermal stabilizer, with a pH of 5.8;

Formulation FFF: 140 mg/ml VEGF receptor fusion protein, 10 mM sodium phosphate, 5 % (w/v) sucrose and 0.03 % polysorbate 20 with a pH of 6.2;

Formulation GGG: 140 mg/ml VEGF receptor fusion protein; 20 mM histidine, pH 5.8; 5% Sucrose; 0.03% polysorbate 20; 50 mM sodium sulfate;

Formulation HHH: 140 mg/ml VEGF receptor fusion protein; 20 mM histidine, pH 5.8; 5% sucrose; 0.03% polysorbate 20; 50 mM sodium thiocyanate;

Formulation III: 140 mg/ml VEGF receptor fusion protein; 20 mM histidine, pH 5.8; 5% sucrose, 0.03% polysorbate 20; 40 mM sodium citrate;

Formulation JJJ: 140 mg/ml VEGF receptor fusion protein; 20 mM histidine, pH 5.8; 5% Sucrose, 0.03% polysorbate 20; 50 mM glycine;

Formulation KKK: 140 mg/ml VEGF receptor fusion protein; 20 mM histidine, pH 5.8; 5% sucrose, 0.03% polysorbate 20; 50 mM sodium chloride;

Formulation LLL: 140 mg/ml VEGF receptor fusion protein; 20 mM Histidine, pH 5.8; 5% sucrose; 0.03% polysorbate 20; 50 mM lysine;

Formulation MMM: 140 mg/ml VEGF receptor fusion protein; 20 mM histidine, pH 5.8; 5% sucrose; 0.03% polysorbate 20; 50 mM sodium aspartate;

Formulation NNN: 140 mg/ml VEGF receptor fusion protein; 20 mM histidine, pH 5.8; 5% sucrose; 0.03% polysorbate 20; 50 mM sodium glutamate;

Formulation OOO: 140 mg/ml VEGF receptor fusion protein; 20 mM histidine, pH 5.8; 5% sucrose; 0.03% polysorbate 20; 50 mM sodium Citrate; 50 mM arginine hydrochloride;

Formulation PPP: 140 mg/ml VEGF receptor fusion protein; 20 mM histidine, pH 5.8; 5% sucrose; 0.03% polysorbate 20; 50mM glycine; 50 mM arginine hydrochloride;

Formulation QQQ: 140 mg/ml VEGF receptor fusion protein; 20 mM histidine, pH 5.8; 5% sucrose; 0.03% polysorbate 20; 50 mM sodium aspartate; 50 mM arginine hydrochloride;

Formulation RRR: 140 mg/ml VEGF receptor fusion protein; 20 mM histidine, pH 5.8; 5% sucrose; 0.03% polysorbate 20; 50 mM sodium glutamate; 50 mM arginine hydrochloride;

Formulation SSS: 140 mg/ml VEGF receptor fusion protein; 20 mM His, pH 5.8; 5% sucrose; 0.03% polysorbate 20; 10 mM L-arginine hydrochloride;

Formulation TTT: 140 mg/ml VEGF receptor fusion protein; 20 mM His, pH 5.8; 5% sucrose; 0.03% polysorbate 20; 100 mM L-arginine hydrochloride;

Formulation UUU: 30 mg/ml VEGF receptor fusion protein, 10% sucrose, 10 mM phosphate, 0.03% polysorbate 20, pH 6.2;

Formulation VVV: 30 mg/ml VEGF receptor fusion protein, 20% sucrose, 10 mM phosphate, 0.03% polysorbate 20, pH 6.2;

Formulation WWW: 60 mg/ml VEGF receptor fusion protein, 10% sucrose, 10 mM phosphate, 0.03% polysorbate 20, pH 6.2;

Formulation XXX: 60 mg/ml VEGF receptor fusion protein, 20% sucrose, 10 mM phosphate, 0.03% polysorbate 20, pH 6.2;

Formulation YYY: 120 mg/ml VEGF receptor fusion protein, 10% sucrose, 10 mM phosphate, 0.03% polysorbate 20, pH 6.2;

Formulation ZZZ: 120 mg/ml VEGF receptor fusion protein, 20% sucrose, 10 mM phosphate, 0.03% polysorbate 20, pH 6.2;

Formulation AAAA: 120 mg/ml VEGF receptor fusion protein, 10% sucrose, 10 mM phosphate, 0.03% polysorbate 20, 50 mM NaCl, pH 6.2;

Formulation BBBB: 120 mg/ml VEGF receptor fusion protein, 20% sucrose, 10 mM phosphate, 0.03% polysorbate 20, 50 mM NaCl, pH 6.2;

Formulation CCCC: 140 mg/ml VEGF receptor fusion protein, 10 mM sodium phosphate, 5% sucrose, 40 mM sodium chloride, 0.03% PS20, pH 6.2;

Formulation DDDD: 80.0 mg/ml VEGF receptor fusion protein, 20 mM histidine-based buffer, 5% (w/v) sucrose, 0.03% (w/v) polysorbate 20, and 50 mM L-arginine monohydrochloride, with a pH of 5.8;

Formulation EEEE: 120.0 mg/ml VEGF receptor fusion protein, 20 mM histidine-based buffer, 5% (w/v) sucrose, 0.03% (w/v) polysorbate 20, and 50 mM L-arginine monohydrochloride, with a pH of 5.8;

Formulation FFFF: 113.3 mg/ml VEGF receptor fusion protein, 20 mM histidine-based buffer, 5% (w/v) sucrose, 0.03% (w/v) polysorbate 20, and 50 mM L-arginine monohydrochloride, with a pH of 5.8;

Formulation GGGG: 114.3 mg/ml VEGF receptor fusion protein, 10 mM histidine-based buffer, 5% (w/v) sucrose, 0.03% (w/v) polysorbate 20, and 50 mM L-arginine monohydrochloride, with a pH of 5.8;

Formulation HHHH: 100.0 mg/ml VEGF receptor fusion protein, 20 mM histidine-based buffer, 5% (w/v) sucrose, 0.03% (w/v) polysorbate 20, and 50 mM L-arginine monohydrochloride, with a pH of 5.8; and

Formulation IIII: 133.3 mg/ml VEGF receptor fusion protein, 20 mM histidine-based buffer, 5% (w/v) sucrose, 0.03% (w/v) polysorbate 20, and 50 mM L-arginine monohydrochloride, with a pH of 5.8;

Formulation JJJJ: 150 mg/ml aflibercept, 10 mM sodium phosphate, 8% (w/v) sucrose, 0.03% (w/v) polysorbate 20 and 50 mM arginine hydrochloride, pH 6.2;

Formulation KKKK: 114.3 mg/ml VEGF receptor fusion protein, 20 mM histidine-based buffer, 5% (w/v) sucrose, 0.03% (w/v) polysorbate 20, and 50 mM L-arginine monohydrochloride, with a pH of 5.8;

Formulation LLLL: 90 mg/ml VEGF receptor fusion protein, 10 mM histidine, 5% (w/v) sucrose, 0.03% (w/v) polysorbate 20, pH 5.75; and

Formulation MMMM: 90 mg/ml VEGF receptor fusion protein, 10 mM histidine, 7% (w/v) sucrose, 0.03% (w/v) polysorbate 20, pH 5.75.

22. The formulation of claim 21 wherein the VEGF receptor fusion protein is aflibercept or conbercept.

23. The formulation of any one of claims 21-22 wherein the VEGF receptor fusion protein has less than about 3.5% high molecular weight species immediately after manufacture and purification and/or less than or equal to about 6% high molecular weight species after storage for about 24 months at about 2-8°C.

24. A container or injection device comprising the formulation of any one of claims 1-23.

25. The container or injection device of claim 24, which is a vial, syringe, autoinjector or pre-filled syringe.
26. A method for preparing the formulation of any one of claims 1-23, comprising combining the components of said formulation into a single composition.
27. The method of claim 26, further comprising loading a volume of the formulation into a syringe.
28. A formulation which is the product of the method of any one of claims 26-27.
29. A method for administering a formulation of any one of claims 1-22 and 27 to a subject comprising intraocularly injecting the formulation into the eye of the subject.
30. A method for treating an angiogenic eye disorder in a subject in need thereof comprising administering an intraocular injection of more than about 2 mg of a VEGF receptor fusion protein to the eye of the subject.
31. The method of claim 30 comprising administering about 4 mg, about 6 mg, about 8 mg or about 10 mg of the VEGF receptor fusion protein to the eye of the subject.
32. A method for treating an angiogenic eye disorder in a subject in need thereof, the method comprising intraocularly injecting more than about 2 mg of VEGF receptor fusion protein in a formulation of any one of claims 1-23 and 28 into an eye of the subject.
33. The method of claim 32, comprising injecting about 4 mg, about 6 mg, about 8 mg or about 10 mg of the VEGF receptor fusion protein into the eye of the subject.
34. The method of any one of claims 30-33, wherein the intraocular injection is an intravitreal injection.
35. The method of any one of claims 30-34, wherein the angiogenic eye disorder is age-related macular degeneration (wet), macular edema, macular edema following retinal vein occlusion, retinal vein occlusion (RVO), central retinal vein occlusion (CRVO) branch retinal vein occlusion (BRVO), diabetic macular edema (DME), choroidal neovascularization (CNV), iris neovascularization, neovascular glaucoma, post-surgical fibrosis in glaucoma.

proliferative vitreoretinopathy (PVR), optic disc neovascularization, corneal neovascularization, retinal neovascularization, vitreal neovascularization, pannus, pterygium, vascular retinopathy, diabetic retinopathy, non-proliferative diabetic retinopathy and/or proliferative diabetic retinopathy.

36. The method of any one of claims 30-35 wherein the VEGF receptor fusion protein is administered in about 100 microliters or less, about 90 microliters, about 80 microliters, about 75 microliters, about 70 microliters, about 60 microliters or about 50 microliters.

37. The method of any one of claims 30-36, wherein the VEGF receptor fusion protein is contained within a formulation comprising: about 5% sucrose; a histidine buffer; and about 0.03% surfactant.

38. The method of any one of claims 30-37 wherein more than about 2.0 mg of the VEGF receptor fusion protein is injected once every 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23 or 24 weeks.

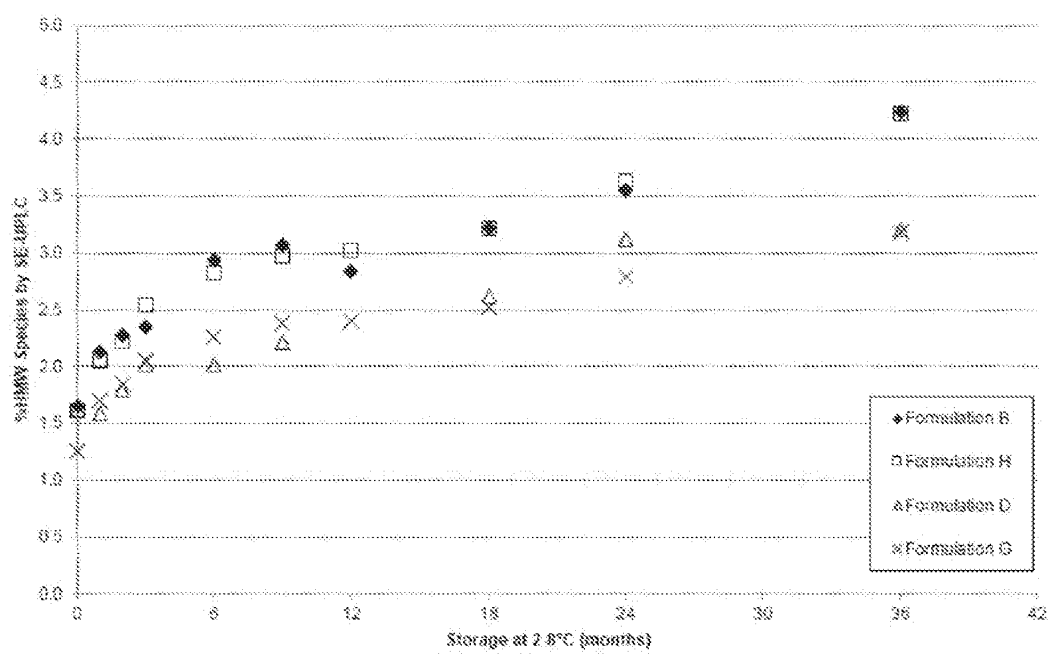


FIG. 1A

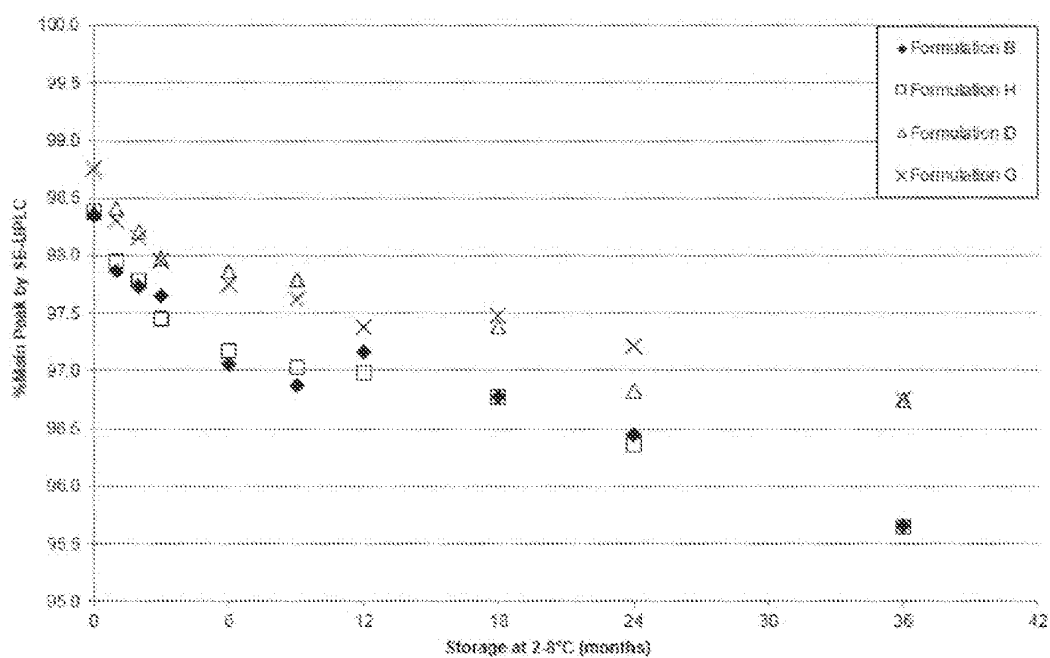


FIG. 1B

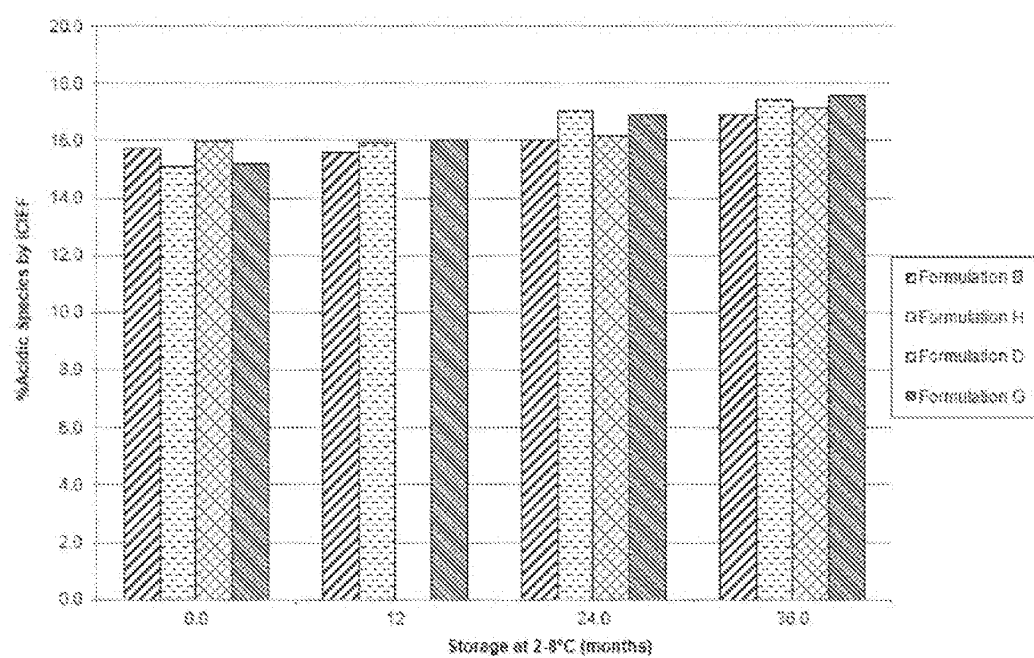


FIG. 1C

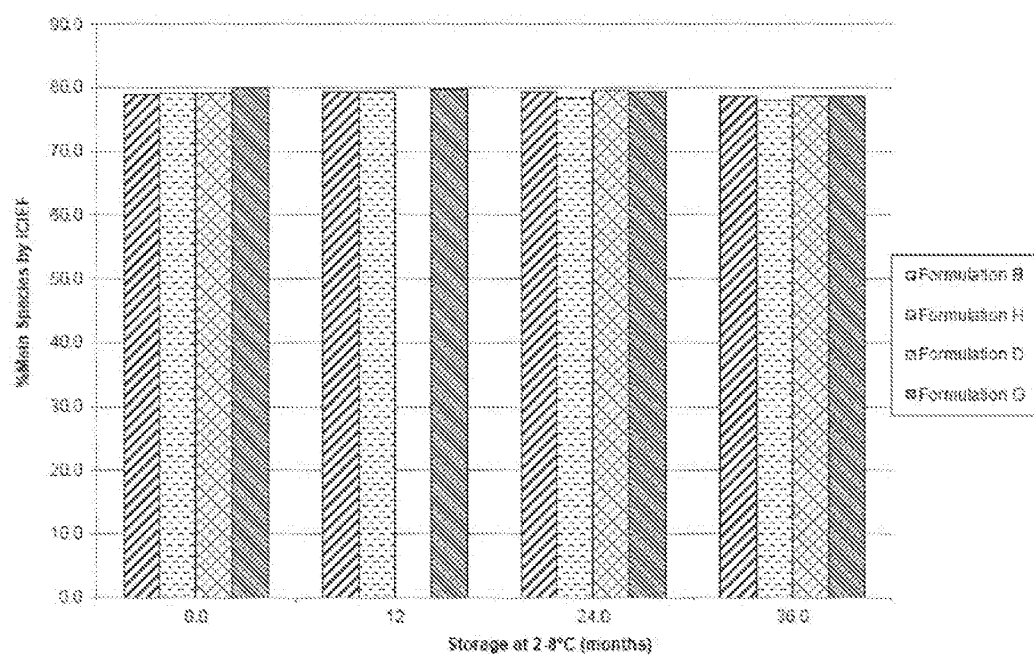


FIG. 1D

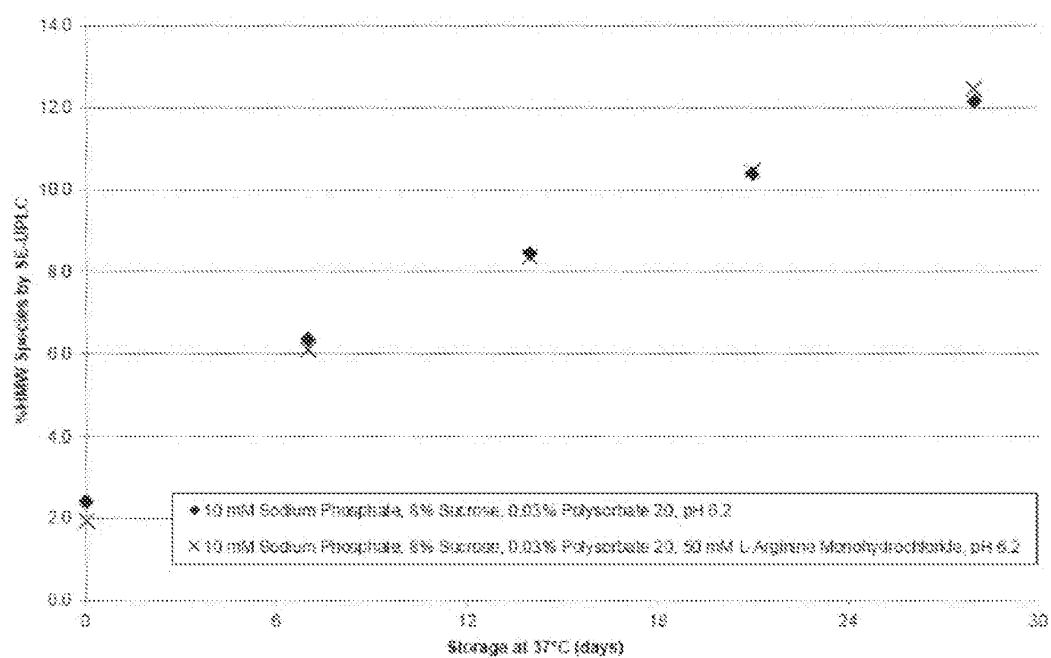


FIG. 2A

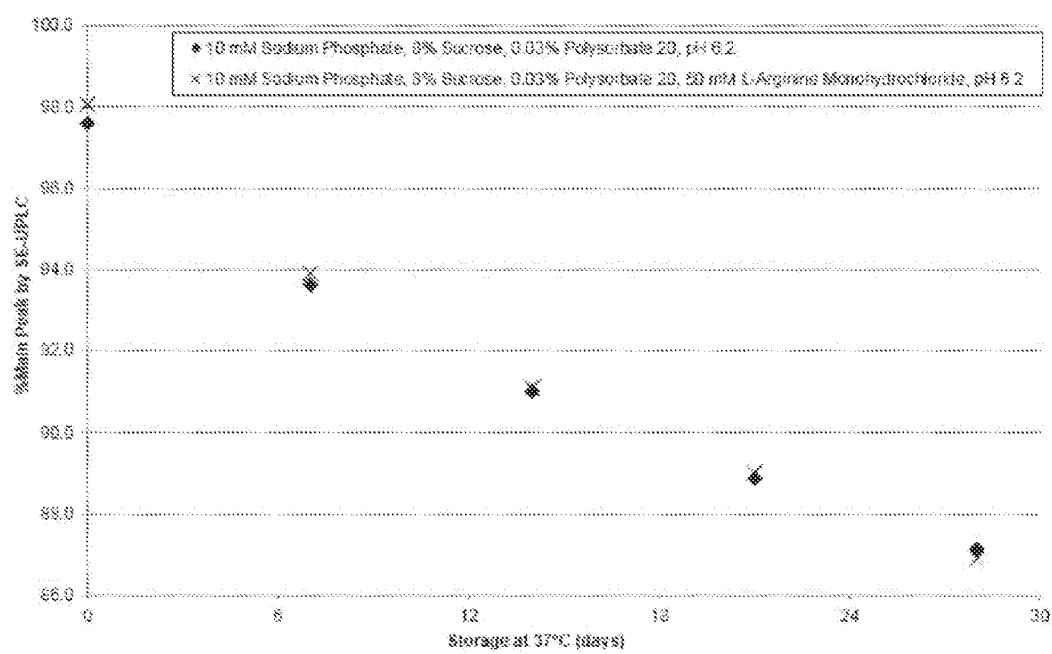


FIG. 2B

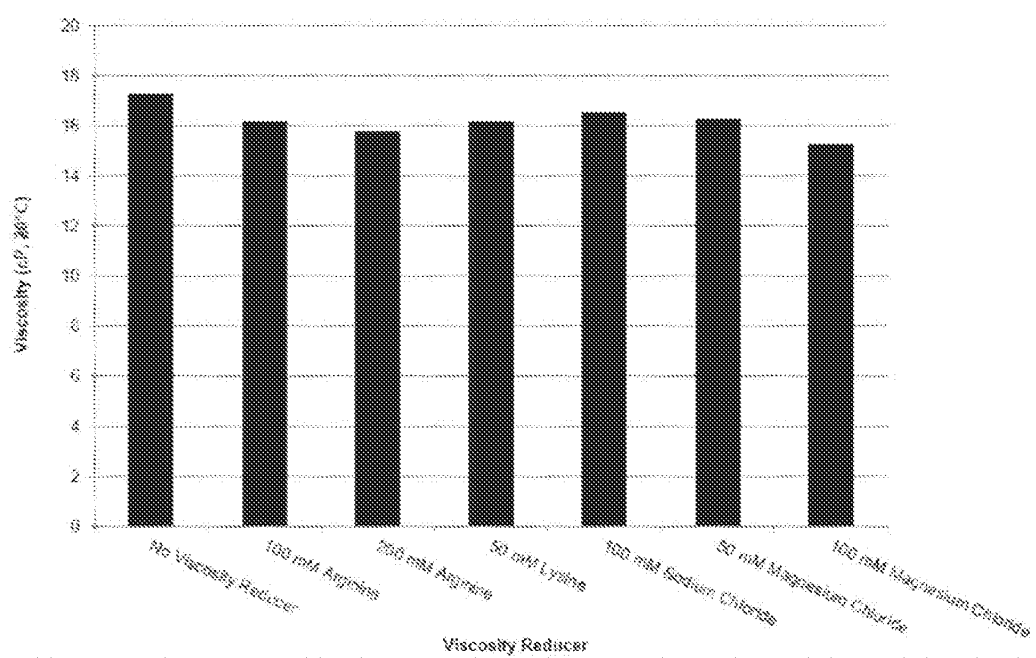


FIG. 3A

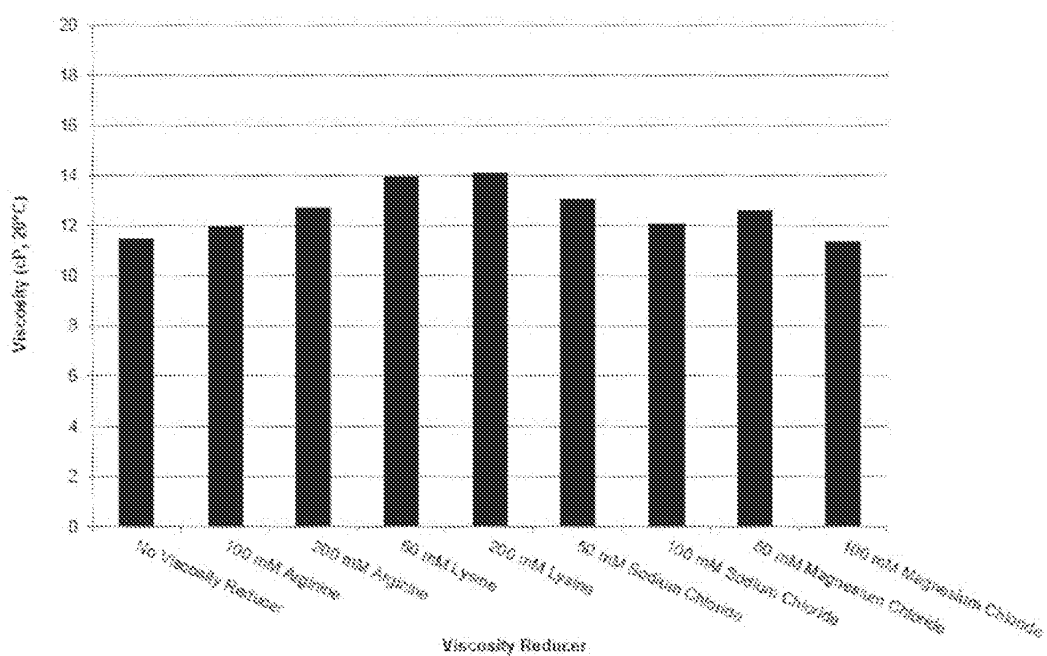


FIG. 3B

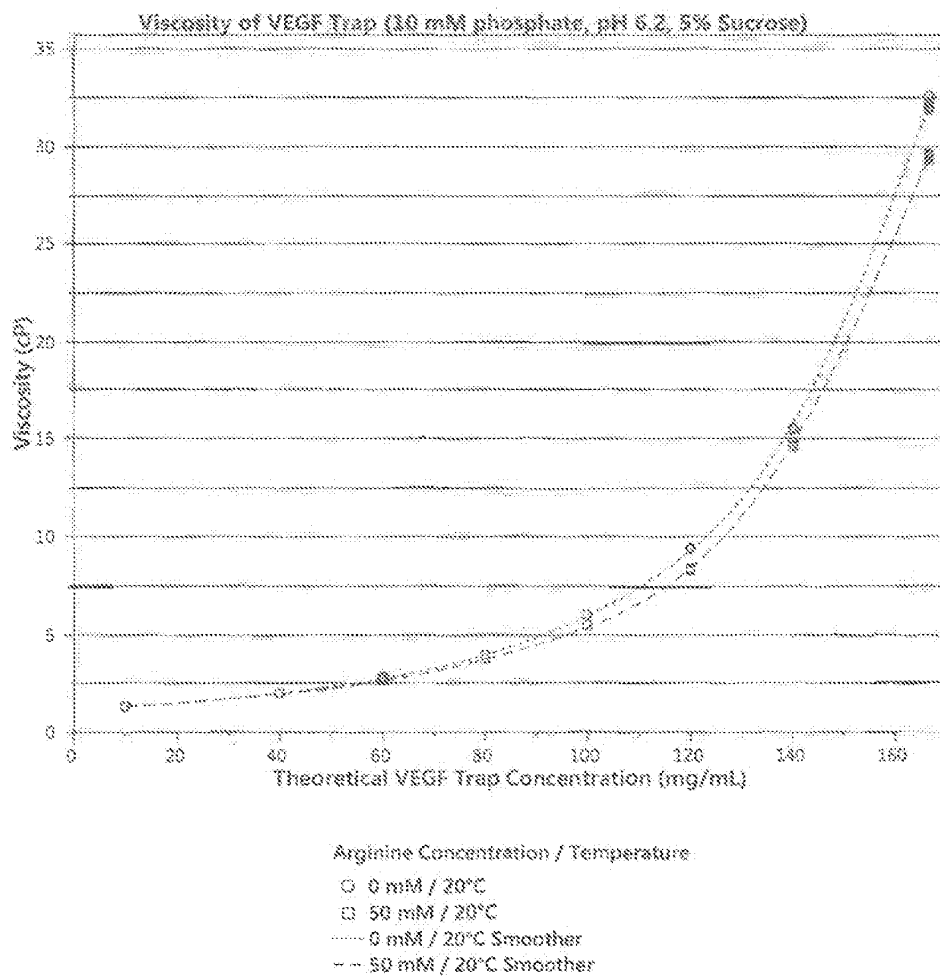


FIG. 3C

INCORPORATED BY REFERENCE (RULE 20.6)

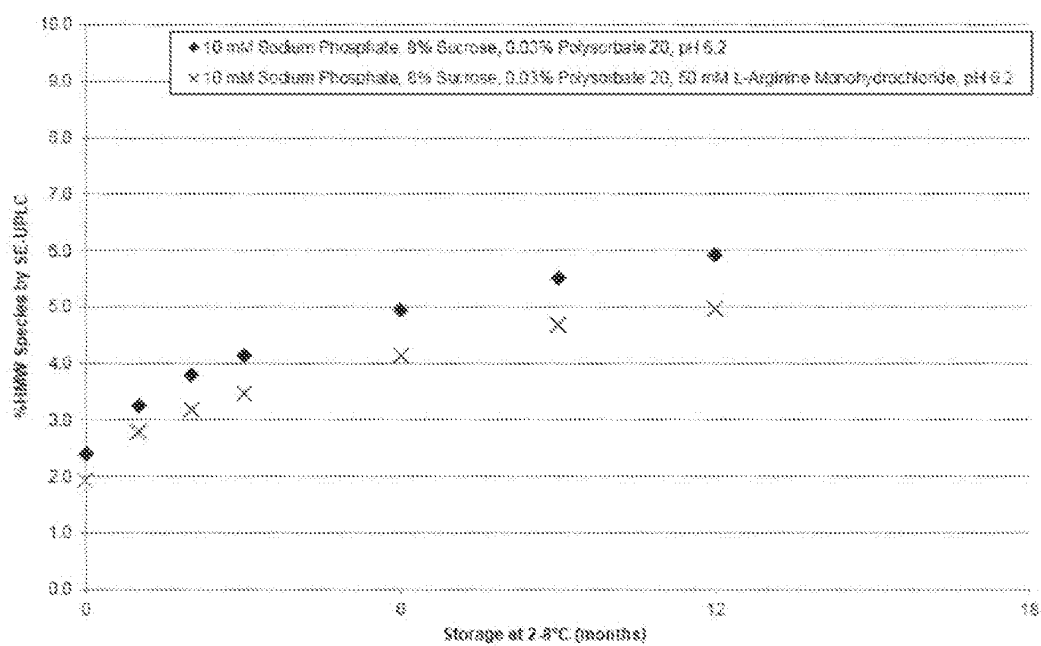


FIG. 4A

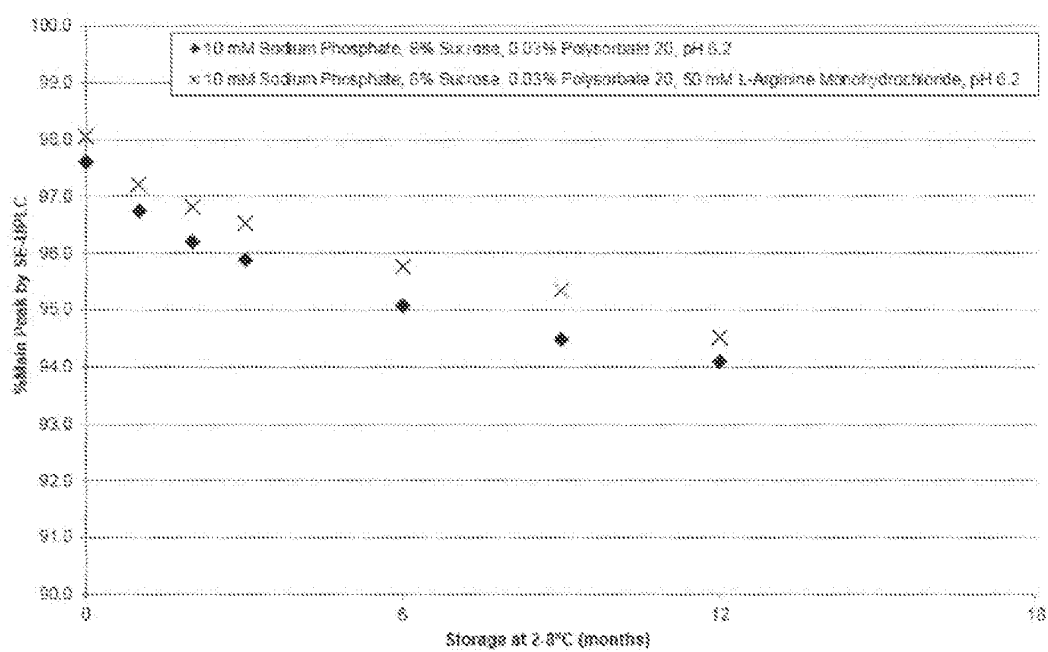


FIG. 4B

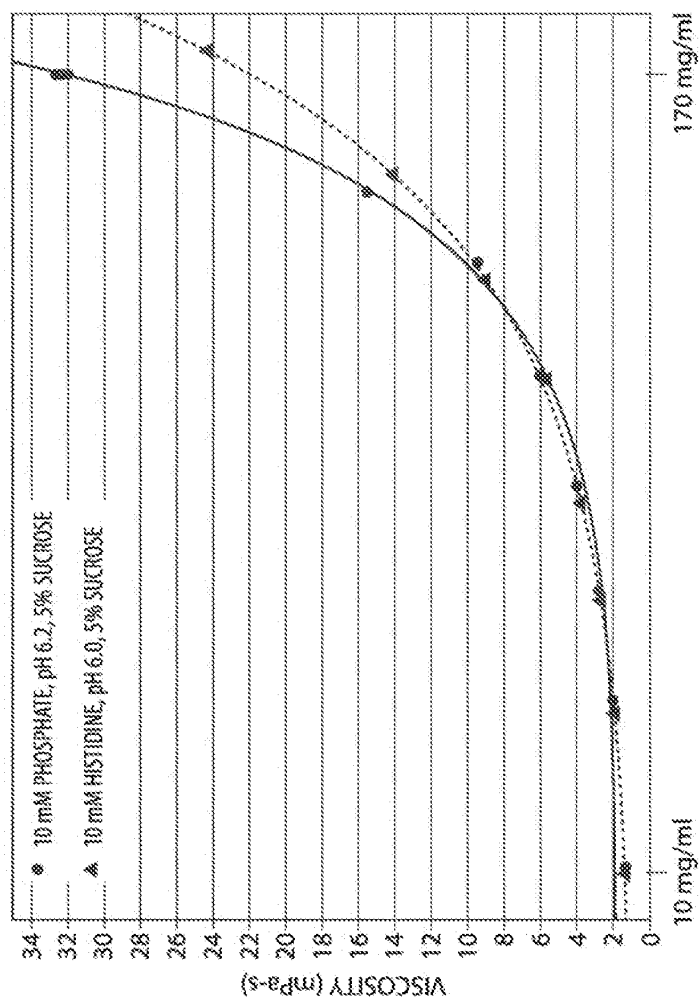


FIG. 5

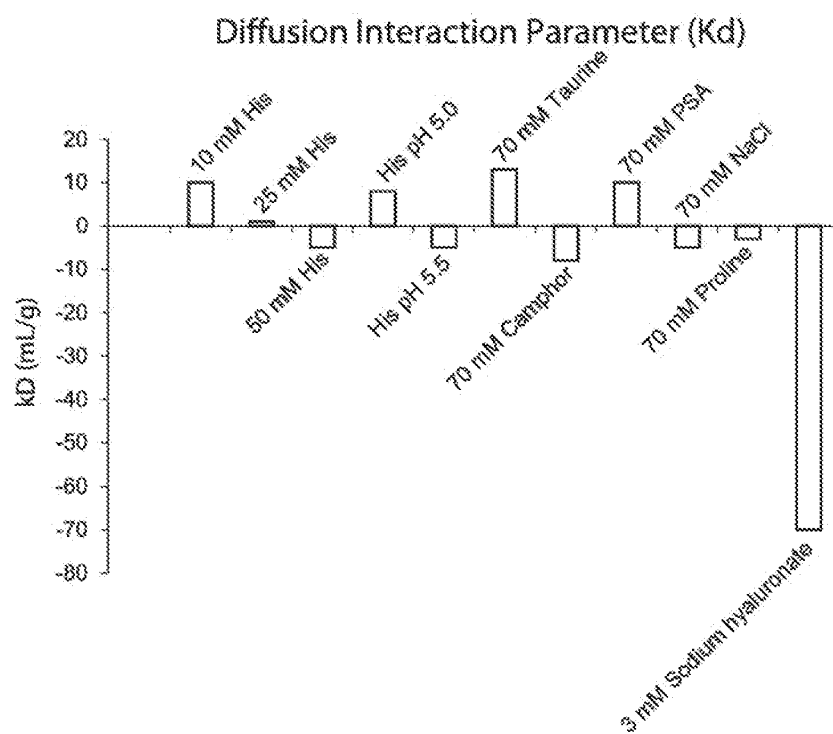


FIG. 6

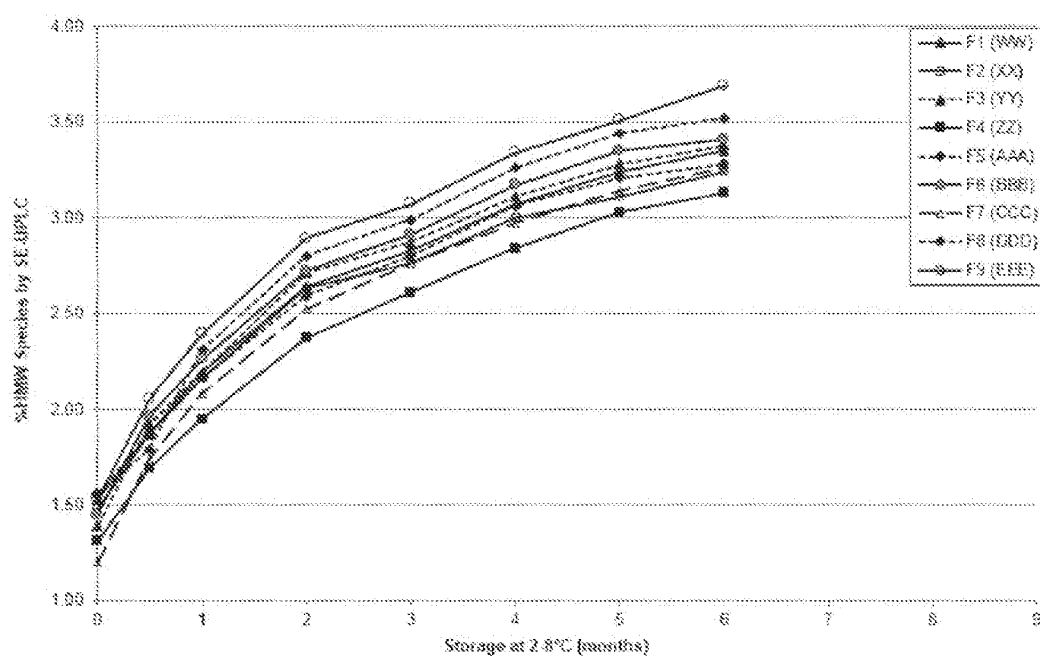


FIG. 7

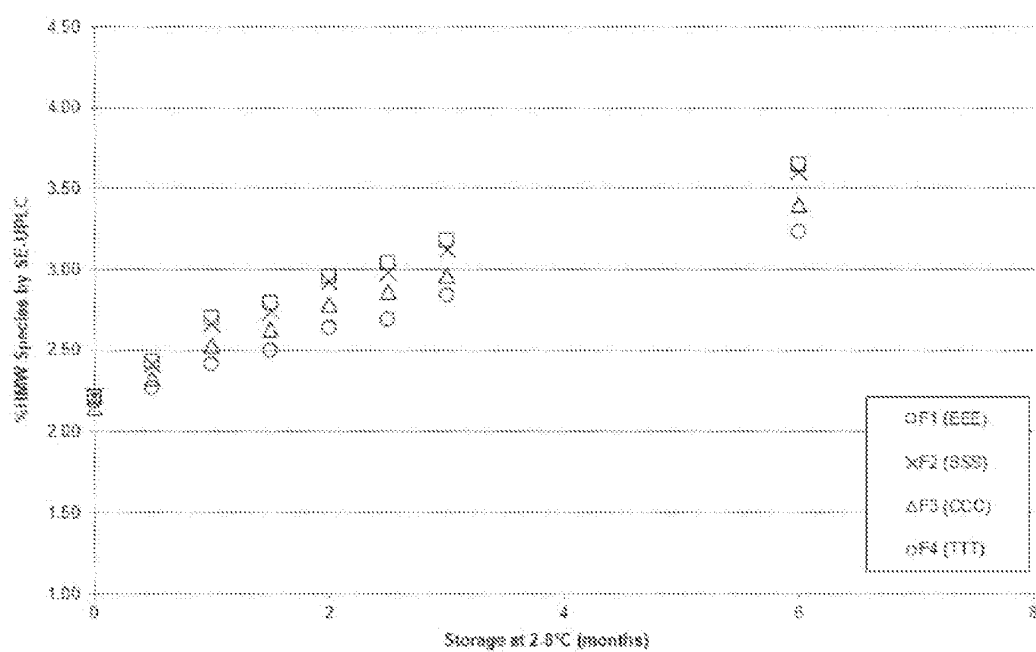


FIG. 8A

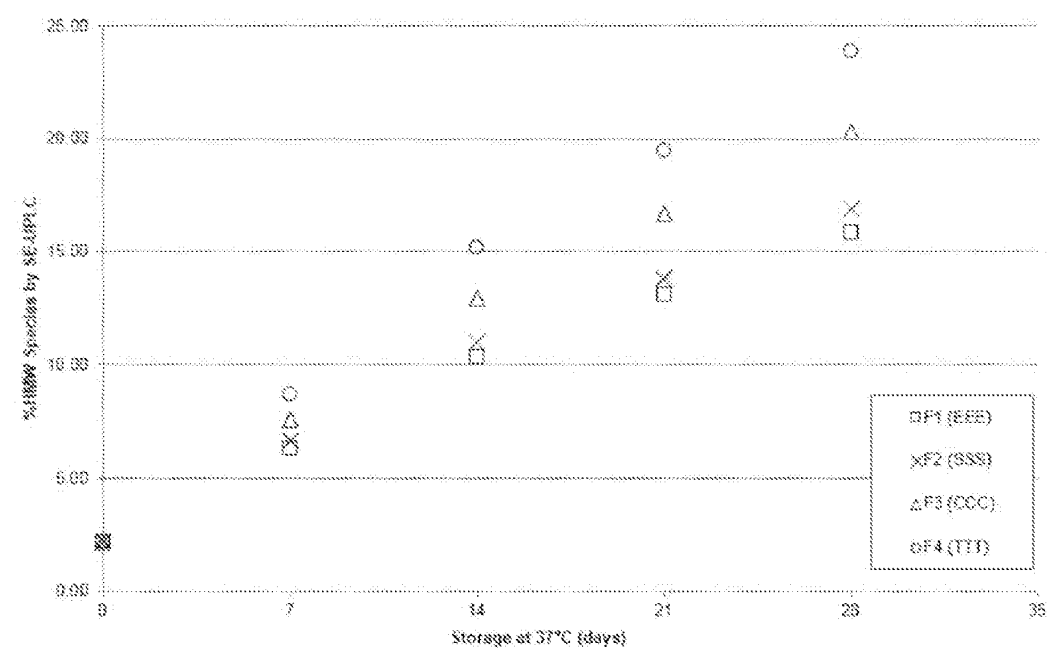


FIG. 8B

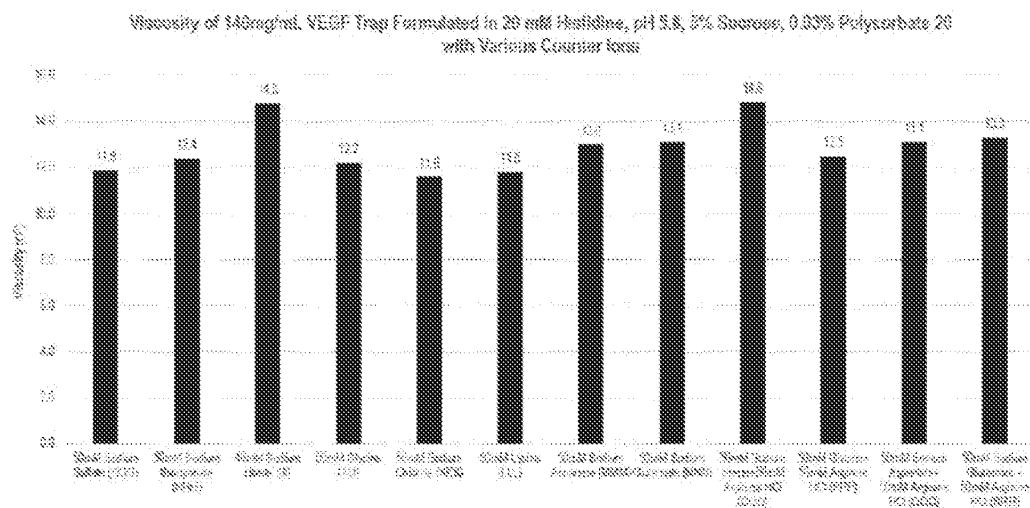


FIG. 9

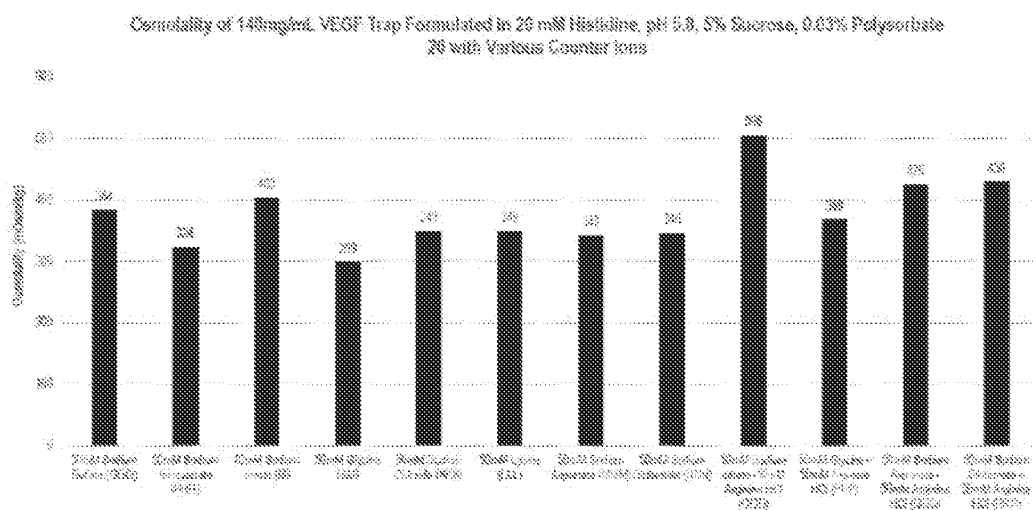


FIG. 10