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THE UNITED STATES OF AMERICA

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UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

November 29, 2022

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APPLICATION NUMBER: *15/471,506*
FILING DATE: *March 28, 2017*
PATENT NUMBER: *10130681*
ISSUE DATE: *November 20, 2018*

Certified by

Performing the Functions and Duties of the
Under Secretary of Commerce
for Intellectual Property
and Director of the United States
Patent and Trademark Office

DocCode – SEQ.TXT

SCORE Placeholder Sheet for IFW Content

Application Number: 15471506 Document Date: 03/28/2017

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- Sequence Listing

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Form Revision Date: August 26, 2013

Electronically Filed

PRELIMINARY AMENDMENT Under CFR 1.115 Address to: Mail Stop Patent Application Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450		
	Attorney Docket No.	REGN-008CIPCON2
	Confirmation No.	To Be Assigned
	First Named Inventor	YANCOPOULOS, GEORGE D.
	Application Number	To Be Assigned
	Filing Date	March 28, 2017
	Group Art Unit	To Be Assigned
	Examiner Name	To Be Assigned
	Title: *"Use of a VEGF Antagonist to Treat Angiogenic Eye Disorders"*	

Sir:

Prior to the examination of the above-referenced application on the merits, please enter the amendments below.

AMENDMENTS TO THE SPECIFICATION

Please amend paragraph [0001] on page1 of the specification to read as follows:

[0001] This application **is a continuation of U.S. Patent Application Serial No. 14/972,560, filed December 17, 2015 (now allowed) which is a continuation of U.S. Patent Application Serial No. 13/940,370 filed July 12, 2013, now U.S. Patent No. 9,254,338 issued February 9, 2016 which** is a continuation-in-part of International Patent Application No. PCT/US2012/020855, filed on January 11, 2012, which claims the benefit of US Provisional Application Nos. 61/432,245, filed on January 13, 2011, 61/434,836, filed on January 21, 2011, and 61/561,957, filed on November 21, 2011, the contents of which are hereby incorporated by reference in their entireties.

AMENDMENTS TO THE CLAIMS

1. - 20. (**Canceled**)

21. (**New**) A method for treating an angiogenic eye disorder in a patient, said method comprising sequentially administering to the patient a single initial dose of a VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonist;

wherein each secondary dose is administered 2 to 4 weeks after the immediately preceding dose; and

wherein each tertiary dose is administered at least 8 weeks after the immediately preceding dose;

wherein the VEGF antagonist is a VEGF receptor-based chimeric molecule comprising (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;

wherein exclusion criteria for the patient include all of:

(1) active intraocular inflammation;

(2) active ocular or periocular infection;

(3) any ocular or periocular infection within the last 2 weeks prior to treatment.

22. (**New**) The method of claim 21, wherein only a single secondary dose is administered to the patient, and wherein the single secondary dose is administered 4 weeks after the initial dose of the VEGF antagonist.

23. (**New**) The method of claim 21, wherein only two secondary doses are administered to the patient, and wherein each secondary dose is administered 4 weeks after the immediately preceding dose.

24. (**New**) The method of claim 23, wherein each tertiary dose is administered 8 weeks after the immediately preceding dose.

25. (**New**) The method of claim 21, wherein at least 5 tertiary doses of the VEGF antagonist are administered to the patient, and wherein the first four tertiary doses are administered 8 weeks after

the immediately preceding dose, and wherein each subsequent tertiary dose is administered 8 or 12 weeks after the immediately preceding dose.

26. (**New**) The method of claim 21, wherein the angiogenic eye disorder is selected from the group consisting of: age related macular degeneration, diabetic retinopathy, diabetic macular edema, central retinal vein occlusion, branch retinal vein occlusion, and corneal neovascularization.

27. (**New**) The method of claim 26, wherein the angiogenic eye disorder is age related macular degeneration.

28. (**New**) The method of claim 21, wherein all doses of the VEGF antagonist are administered to the patient by topical administration or by intraocular administration.

29. (**New**) The method of claim 28, wherein all doses of the VEGF antagonist are administered to the patient by intraocular administration.

30. (**New**) The method of claim 29, wherein the intraocular administration is intravitreal administration.

31. (**New**) The method of claim 30, wherein all doses of the VEGF antagonist comprise from about 0.5 mg to about 2 mg of the VEGF antagonist.

32. (**New**) The method of claim 31, wherein all doses of the VEGF antagonist comprise 0.5 mg of the VEGF antagonist.

33. (**New**) The method of claim 31, wherein all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist.

34. (**New**) A method for treating an angiogenic eye disorder in a patient, said method comprising sequentially administering to the patient a single initial dose of a VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonist;

wherein each secondary dose is administered 2 to 4 weeks after the immediately preceding dose; and

wherein each tertiary dose is administered at least 8 weeks after the immediately preceding dose;

wherein the VEGF antagonist is a VEGF receptor-based chimeric molecule comprising VEGFR1R2-FcΔC1(a) encoded by the nucleic acid sequence of SEQ ID NO:1;

wherein exclusion criteria for the patient include all of:

(1) active intraocular inflammation;

(2) active ocular or periocular infection;

(3) any ocular or periocular infection within the last 2 weeks prior to treatment.

35. (**New**) The method of claim 34, wherein only a single secondary dose is administered to the patient, and wherein the single secondary dose is administered 4 weeks after the initial dose of the VEGF antagonist.

36. (**New**) The method of claim 34, wherein only two secondary doses are administered to the patient, and wherein each secondary dose is administered 4 weeks after the immediately preceding dose.

37. (**New**) The method of claim 36, wherein each tertiary dose is administered 8 weeks after the immediately preceding dose.

38. (**New**) The method of claim 37, wherein the angiogenic eye disorder is age related macular degeneration.

39. (**New**) The method of claim 34, wherein at least 5 tertiary doses of the VEGF antagonist are administered to the patient, and wherein the first four tertiary doses are administered 8 weeks after the immediately preceding dose, and wherein each subsequent tertiary dose is administered 8 or 12 weeks after the immediately preceding dose.

40. (**New**) The method of claim 34, wherein the angiogenic eye disorder is selected from the group consisting of: age related macular degeneration, diabetic retinopathy, diabetic macular edema, central retinal vein occlusion, branch retinal vein occlusion, and corneal neovascularization.

41. (**New**) The method of claim 34, wherein all doses of the VEGF antagonist are administered to the patient by topical administration or by intraocular administration.

42. (**New**) The method of claim 41, wherein all doses of the VEGF antagonist are administered to the patient by intraocular administration.

43. (**New**) The method of claim 41, wherein the intraocular administration is intravitreal administration.

44. (**New**) The method of claim 43, wherein all doses of the VEGF antagonist comprise from about 0.5 mg to about 2 mg of the VEGF antagonist.

45. (**New**) The method of claim 44, wherein all doses of the VEGF antagonist comprise 0.5 mg of the VEGF antagonist.

46. (**New**) The method of claim 44, wherein all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist.

REMARKS UNDER 37 CFR § 1.115

Formal Matters

Claims 21-46 are pending after entry of the amendments set forth herein.

Claims 1-20 are canceled without prejudice.

Claims 21-46 are added.

Claims 21-46 are identical to claims 1-26 of issued U.S. Patent 9,254,338 with two exceptions. Specifically, the independent claims 21 and 34 include limitations with respect to exclusion criteria for patients. These exclusion criteria are disclosed within the original application in paragraph [0050]. Specifically, they are the exclusion criteria 18, 19 and 20 of paragraph [0050].

The specification has been amended to update the cross-reference to related application section.

No new matter has been added.

PARENT APPLICATION

The parent application has been allowed. Further, as indicated above, correspondence and support for the current claims relative to those of the parent application can be reviewed and confirmed. In the event the Examiner has any questions with respect to claim support or other issues in connection with the application, the Examiner is respectfully requested to contact the undersigned attorney at the indicated telephone number to arrange for an interview to expedite this position of this application.

STATEMENT UNDER 37 C.F.R. §§1.56 AND 1.2

Applicants hereby advise the Examiner of the status of a co-pending application in compliance with the Applicant's duty to disclose under 37 C.F.R. §§1.56 and 1.2 (see also MPEP §2001.06(b)) as discussed in *McKesson Info. Soln. Inc., v. Bridge Medical Inc.*, 487 F.3d 897; 82 USPQ2d 1865 (Fed. Cir. 2007).

The Applicants wish to bring to the Examiner's attention U.S. Patent Application No. 13/940,370, filed July 12, 2013 which issued on February 9, 2016 as U.S. Patent 9,254,338.

The Applicants wish to bring to the Examiner's attention that a Notice of Allowance was mailed on March 6, 2017 and the issue fee was paid on March 28, 2017 in co-pending U.S. Patent Application No. 14/972,560, filed December 17, 2015.

These documents are available on PAIR, and thus are not provided with this communication. Please inform the undersigned if there is any difficulty in obtaining the documents from PAIR.

CONCLUSION

Applicant submits that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees up to a strict limit of $3,000.00 beyond that authorized on the credit card, but not more than $3,000.00 in additional fees due with any communication for the above referenced patent application, including but not limited to any necessary fees for extensions of time, or credit any overpayment of any amount to Deposit Account No. 50-0815, order number REGN-008CIPCON2.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: 28 March 2017

By: /Karl Bozicevic, Reg. No. 28,807/
Karl Bozicevic
Registration No. 28,807

Bozicevic, Field & Francis LLP
201 Redwood Shores Parkway, Suite 200
Redwood City, California 94065
Telephone: (650) 327-3400
Direct: (650) 833-7735
Facsimile: (650) 327-3231

Electronically Filed

NOTIFICATION OF PRIOR SEQUENCE LISTING		
	Attorney Docket	REGN-008CIPCON2
	First Named Inventor	YANCOPOULOS, GEORGE D.
	Application Number	To Be Assigned
	Filing Date	28 March 2017
Address to: Mail Stop Patent Application Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Confirmation Number	To Be Assigned
	Group Art Unit	To Be Assigned
	Examiner Name	To Be Assigned
	Title: "USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS"	

Sir:

The above-identified patent application contains sequences of nucleic acid and polypeptides. A sequence listing was prepared for parent application, **14/927,560,** filed **December 17, 2015**, in paper and computer-readable format. The sequence information in the paper or compact disk copy of the sequence listing (required by 1.821(c)) of this application is identical to the sequence information in the computer-readable format (CRF) of the above-identified other application. No new matter has been added. Therefore, please transfer to this application, in accordance with 37 CFR § 1.821(e), the fully compliant computer readable copy from applicants' other application. A paper (.txt) copy of this sequence listing is enclosed.

Applicants respectfully submit that the present patent application is now in compliance with 37 CFR §§ 1.821 - 1.825. The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number REGN-008CIPCON2.

Respectfully submitted,

BOZICEVIC, FIELD & FRANCIS LLP

Dated: 28 March 2017

By: /Karl Bozicevic, Reg. No. 28,807/
Karl Bozicevic
Registration No. 28,807

BOZICEVIC, FIELD & FRANCIS LLP
201 Redwood Shores Parkway, Suite 201
Redwood City, California 94065
Telephone: (650) 327-3400
Facsimile: (650) 327-3231

Electronic Patent Application Fee Transmittal	
Application Number:	
Filing Date:	
Title of Invention:	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS
First Named Inventor/Applicant Name:	GEORGE D. YANCOPOULOS
Filer:	Karl Bozicevic/Kimberly Zuehlke
Attorney Docket Number:	REGN-008CIPCON2
Filed as Large Entity	
Filing Fees for Utility under 35 USC 111(a)	

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
UTILITY APPLICATION FILING	1011	1	280	280
UTILITY SEARCH FEE	1111	1	600	600
UTILITY EXAMINATION FEE	1311	1	720	720
Pages:				
Claims:				
CLAIMS IN EXCESS OF 20	1202	6	80	480
Miscellaneous-Filing:				
Petition:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	2080

Electronic Acknowledgement Receipt	
EFS ID:	28758182
Application Number:	15471506
International Application Number:	
Confirmation Number:	8014
Title of Invention:	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS
First Named Inventor/Applicant Name:	GEORGE D. YANCOPOULOS
Customer Number:	96387
Filer:	Karl Bozicevic
Filer Authorized By:	
Attorney Docket Number:	REGN-008CIPCON2
Receipt Date:	28-MAR-2017
Filing Date:	
Time Stamp:	15:02:24
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$2080
RAM confirmation Number	032917INTEFSW15025400
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	Application Data Sheet	REGN-008CIPCON2_2017-03-28_ADS.pdf	1823602 2834e41e9193695ad5d6080d920b4006ce1dce46c	no	9
Warnings:					
Information:					
2		REGN-008CIPCON2_Specification.pdf	529155 66488c53637f4b7715ffe32f0b6596663f6e02cd	yes	24
	Multipart Description/PDF files in .zip description				
	Document Description		**Start**	**End**	
	Specification		1	21	
	Claims		22	23	
	Abstract		24	24	
Warnings:					
Information:					
3	Drawings-only black and white line drawings	REGN-008CIPCON2_Figure.pdf	105393 2d582f645d0c5d17d717e589b029a39331991bdb	no	1
Warnings:					
The page size in the PDF is too large. The pages should be 8.5 x 11 or A4. If this PDF is submitted, the pages will be resized upon entry into the Image File Wrapper and may affect subsequent processing					
Information:					
4	Oath or Declaration filed	REGN-008CIPCON2_declaration.pdf	173097 6bda7272374e6af80c8c3d8cf30d012e4657b588	no	2
Warnings:					
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Information:					

5		REGN-008CIPCON2_2017-03-28_pre_amend_asfld.pdf	65192 da1c454ceb9521e936f1b0bea05fe67122482d93	yes	8
	Multipart Description/PDF files in .zip description				
	Document Description		**Start**	**End**	
	Preliminary Amendment		1	1	
	Specification		2	2	
	Claims		3	6	
	Applicant Arguments/Remarks Made in an Amendment		7	8	
Warnings:					
Information:					
6	Sequence Listing	REGN-0008CIPCON2_seq_list_trans.pdf	27159 15712f98903ec6052e7e5f716b4a6b7016901474	no	1
Warnings:					
Information:					
7	Sequence Listing (Text File)	REGN-008CIPCON2_SeqList.txt	6076	no	-
Warnings:					
Information:					
8	Fee Worksheet (SB06)	fee-info.pdf	37141 66a646fa2e7f56edc76cb7306d608b0aede4f7b0	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	2766815		

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.

PTO/AIA/14 (11-15)
Approved for use through 04/30/2017. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	REGN-008CIPCON2
	Application Number	
Title of Invention	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS	

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

Secrecy Order 37 CFR 5.2:

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

Inventor Information:

Inventor 1 — Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Geroge	D.	YANCOPOULOS	

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

City	State/Province	Country of Residence
Yorktown Heights	NY	US

Mailing Address of Inventor:

Address 1	c/o Regeneron Pharmaceuticals, Inc.
Address 2	777 Old Saw Mill River Road

City	State/Province	Postal Code	Country
Tarrytown	NY	10591	US

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

Correspondence Information:

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

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

Customer Number	96387		
Email Address	docket@bozpat.com	Add Email	Remove Email

Application Information:

Title of the Invention	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS		
Attorney Docket Number	REGN-008CIPCON2	**Small Entity Status Claimed**	☐
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	1	**Suggested Figure for Publication (if any)**	1

PTO/AIA/14 (11-15)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	REGN-008CIPCON2
	Application Number	
Title of Invention	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS	

Filing By Reference:

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

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

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

Publication Information:

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

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

Representative Information:

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

Please Select One:	● Customer Number	US Patent Practitioner	○ Limited Recognition (37 CFR 11.9)
Customer Number	96387		

Domestic Benefit/National Stage Information:

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

Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
	Continuation of	14972560	2015-12-17

PTO/AIA/14 (11-15)
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	REGN-008CIPCON2
	Application Number	
Title of Invention	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS	

Prior Application Status	Patented			Remove	
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
14972560	Continuation of	13940370	2013-07-12	9254338	2016-02-09
Prior Application Status	Expired			Remove	
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)		
13940370	Continuation in part of	PCT/US2012/020855	2012-01-11		
Prior Application Status	Expired			Remove	
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)		
PCT/US2012/020855	Claims benefit of provisional	61432245	2011-01-13		
Prior Application Status	Expired			Remove	
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)		
PCT/US2012/020855	Claims benefit of provisional	61434836	2011-01-21		
Prior Application Status	Expired			Remove	
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)		
PCT/US2012/020855	Claims benefit of provisional	61561957	2011-11-21		
Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add** button.				Add	

Foreign Priority Information:

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

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

PTO/AIA/14 (11-15)
Approved for use through 04/30/2017. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	REGN-008CIPCON2
	Application Number	
Title of Invention	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS	

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

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

PTO/AIA/14 (11-15)
Approved for use through 04/30/2017. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	REGN-008CIPCON2
	Application Number	
Title of Invention	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS	

Authorization or Opt-Out of Authorization to Permit Access:

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

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

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

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

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

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	REGN-008CIPCON2
	Application Number	
Title of Invention	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS	

Applicant Information:

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

Applicant 1 Remove

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

Clear

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

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

Name of the Deceased or Legally Incapacitated Inventor:

If the Applicant is an Organization check here. ☒

Organization Name	REGENERON PHARMACEUTICALS, INC.		
Mailing Address Information For Applicant:			
Address 1	777 Old Saw Mill River Road		
Address 2			
City	Tarrytown	**State/Province**	NY
Country	US	Postal Code	10591
Phone Number		Fax Number	
Email Address			

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

Assignee Information including Non-Applicant Assignee Information:

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Assignee 1

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

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Organization Name	REGENERON PHARMACEUTICALS, INC.

Mailing Address Information For Assignee including Non-Applicant Assignee:

Address 1	777 Old Saw Mill River Road		
Address 2			
City	Tarrytown	**State/Province**	NY
Country i	US	Postal Code	10591
Phone Number		Fax Number	
Email Address			

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Signature	/Karl Bozicevic, Reg. No. 28,807/			Date (YYYY-MM-DD)	2017-03-28
First Name	Karl	Last Name	Bozicevic	Registration Number	28,807

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	REGN-008CIPCON2
	Application Number	
Title of Invention	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS	

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

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

USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application is a continuation-in-part of International Patent Application No. PCT/US2012/020855, filed on January 11, 2012, which claims the benefit of US Provisional Application Nos. 61/432,245, filed on January 13, 2011, 61/434,836, filed on January 21, 2011, and 61/561,957, filed on November 21, 2011, the contents of which are hereby incorporated by reference in their entireties.

FIELD OF THE INVENTION

[0002] The present invention relates to the field of therapeutic treatments of eye disorders. More specifically, the invention relates to the administration of VEGF antagonists to treat eye disorders caused by or associated with angiogenesis.

BACKGROUND

[0003] Several eye disorders are associated with pathological angiogenesis. For example, the development of age-related macular degeneration (AMD) is associated with a process called choroidal neovascularization (CNV). Leakage from the CNV causes macular edema and collection of fluid beneath the macula resulting in vision loss. Diabetic macular edema (DME) is another eye disorder with an angiogenic component. DME is the most prevalent cause of moderate vision loss in patients with diabetes and is a common complication of diabetic retinopathy, a disease affecting the blood vessels of the retina. Clinically significant DME occurs when fluid leaks into the center of the macula, the light-sensitive part of the retina responsible for sharp, direct vision. Fluid in the macula can cause severe vision loss or blindness. Yet another eye disorder associated with abnormal angiogenesis is central retinal vein occlusion (CRVO). CRVO is caused by obstruction of the central retinal vein that leads to a back-up of blood and fluid in the retina. The retina can also become ischemic, resulting in the growth of new, inappropriate blood vessels that can cause further vision loss and more serious complications. Release of vascular endothelial growth factor (VEGF) contributes to increased vascular permeability in the eye and inappropriate new vessel growth. Thus, inhibiting the angiogenic-promoting properties of VEGF appears to be an effective strategy for treating angiogenic eye disorders.

[0004] FDA-approved treatments of angiogenic eye disorders such as AMD and CRVO include the administration of an anti-VEGF antibody called ranibizumab (Lucentis®, Genentech, Inc.) on a monthly basis by intravitreal injection.

[0005] Methods for treating eye disorders using VEGF antagonists are mentioned in, *e.g.*, US 7,303,746; US 7,306,799; US 7,300,563; US 7,303,748; and US 2007/0190058. Nonetheless,

there remains a need in the art for new administration regimens for angiogenic eye disorders, especially those which allow for less frequent dosing while maintaining a high level of efficacy.

BRIEF SUMMARY OF THE INVENTION

[0006] The present invention provides methods for treating angiogenic eye disorders. The methods of the invention comprise sequentially administering multiple doses of a VEGF antagonist to a patient over time. In particular, the methods of the invention comprise sequentially administering to the patient a single initial dose of a VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonists. The present inventors have surprisingly discovered that beneficial therapeutic effects can be achieved in patients suffering from angiogenic eye disorders by administering a VEGF antagonist to a patient at a frequency of once every 8 or more weeks, especially when such doses are preceded by about three doses administered to the patient at a frequency of about 2 to 4 weeks. Thus, according to the methods of the present invention, each secondary dose of VEGF antagonist is administered 2 to 4 weeks after the immediately preceding dose, and each tertiary dose is administered at least 8 weeks after the immediately preceding dose. An example of a dosing regimen of the present invention is shown in Figure 1. One advantage of such a dosing regimen is that, for most of the course of treatment (*i.e.*, the tertiary doses), it allows for less frequent dosing (*e.g.*, once every 8 weeks) compared to prior administration regimens for angiogenic eye disorders which require monthly administrations throughout the entire course of treatment. (*See*, *e.g.*, prescribing information for Lucentis® [ranibizumab], Genentech, Inc.).

[0007] The methods of the present invention can be used to treat any angiogenic eye disorder, including, *e.g.*, age related macular degeneration, diabetic retinopathy, diabetic macular edema, central retinal vein occlusion, corneal neovascularization, etc.

[0008] The methods of the present invention comprise administering any VEGF antagonist to the patient. In one embodiment, the VEGF antagonist comprises one or more VEGF receptor-based chimeric molecule(s), (also referred to herein as a "VEGF-Trap" or "VEGFT"). An exemplary VEGF antagonist that can be used in the context of the present invention is a multimeric VEGF-binding protein comprising two or more VEGF receptor-based chimeric molecules referred to herein as "VEGFR1R2-FcΔC1(a)" or "aflibercept."

[0009] Various administration routes are contemplated for use in the methods of the present invention, including, *e.g.*, topical administration or intraocular administration (*e.g.*, intravitreal administration).

[0010] Aflibercept (EYLEA™, Regeneron Pharmaceuticals, Inc) was approved by the FDA in November 2011, for the treatment of patients with neovascular (wet) age-related macular degeneration, with a recommended dose of 2 mg administered by intravitreal injection every 4

weeks for the first three months, followed by 2 mg administered by intravitreal injection once every 8 weeks.

[0011] Other embodiments of the present invention will become apparent from a review of the ensuing detailed description.

BRIEF DESCRIPTION OF THE FIGURE

[0012] Figure 1 shows an exemplary dosing regimen of the present invention. In this regimen, a single "initial dose" of VEGF antagonist ("VEGFT") is administered at the beginning of the treatment regimen (*i.e.* at "week 0"), two "secondary doses" are administered at weeks 4 and 8, respectively, and at least six "tertiary doses" are administered once every 8 weeks thereafter, *i.e.*, at weeks 16, 24, 32, 40, 48, 56, etc.).

DETAILED DESCRIPTION

[0013] Before the present invention is described, it is to be understood that this invention is not limited to particular methods and experimental conditions described, as such methods and conditions may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting, since the scope of the present invention will be limited only by the appended claims.

[0014] 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 this invention belongs. 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%. 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.).

[0015] Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods and materials are now described.

DOSING REGIMENS

[0016] The present invention provides methods for treating angiogenic eye disorders. The methods of the invention comprise sequentially administering to a patient multiple doses of a VEGF antagonist. As used herein, "sequentially administering" means that each dose of VEGF antagonist is administered to the patient at a different point in time, *e.g.*, on different days separated by a predetermined interval (*e.g.*, hours, days, weeks or months). The present invention includes methods which comprise sequentially administering to the patient a single initial dose of a VEGF

antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonist.

[0017] The terms "initial dose," "secondary doses," and "tertiary doses," refer to the temporal sequence of administration of the VEGF antagonist. Thus, the "initial dose" is the dose which is administered at the beginning of the treatment regimen (also referred to as the "baseline dose"); the "secondary doses" are the doses which are administered after the initial dose; and the "tertiary doses" are the doses which are administered after the secondary doses. The initial, secondary, and tertiary doses may all contain the same amount of VEGF antagonist, but will generally differ from one another in terms of frequency of administration. In certain embodiments, however, the amount of VEGF antagonist contained in the initial, secondary and/or tertiary doses will vary from one another (*e.g.*, adjusted up or down as appropriate) during the course of treatment.

[0018] In one exemplary embodiment of the present invention, each secondary dose is administered 2 to 4 (*e.g.*, 2, 2½, 3, 3½, or 4) weeks after the immediately preceding dose, and each tertiary dose is administered at least 8 (*e.g.*, 8, 8½, 9, 9½, 10, 10½, 11, 11½, 12, 12½, 13, 13½, 14, 14½, or more) weeks after the immediately preceding dose. The phrase "the immediately preceding dose," as used herein, means, in a sequence of multiple administrations, the dose of VEGF antagonist which is administered to a patient prior to the administration of the very next dose in the sequence with no intervening doses.

[0019] In one exemplary embodiment of the present invention, a single initial dose of a VEGF antagonist is administered to a patient on the first day of the treatment regimen (*i.e.*, at week 0), followed by two secondary doses, each administered four weeks after the immediately preceding dose (*i.e.*, at week 4 and at week 8), followed by at least 5 tertiary doses, each administered eight weeks after the immediately preceding dose (*i.e.*, at weeks 16, 24, 32, 40 and 48). The tertiary doses may continue (at intervals of 8 or more weeks) indefinitely during the course of the treatment regimen. This exemplary administration regimen is depicted graphically in Figure 1.

[0020] The methods of the invention may comprise administering to a patient any number of secondary and/or tertiary doses of a VEGF antagonist. For example, in certain embodiments, only a single secondary dose is administered to the patient. In other embodiments, two or more (*e.g.*, 2, 3, 4, 5, 6, 7, 8, or more) secondary doses are administered to the patient. Likewise, in certain embodiments, only a single tertiary dose is administered to the patient. In other embodiments, two or more (*e.g.*, 2, 3, 4, 5, 6, 7, 8, or more) tertiary doses are administered to the patient.

[0021] In embodiments involving multiple secondary doses, each secondary dose may be administered at the same frequency as the other secondary doses. For example, each secondary dose may be administered to the patient 4 weeks after the immediately preceding dose. Similarly, in embodiments involving multiple tertiary doses, each tertiary dose may be administered at the same frequency as the other tertiary doses. For example, each tertiary dose may be administered

to the patient 8 weeks after the immediately preceding dose. Alternatively, the frequency at which the secondary and/or tertiary doses are administered to a patient can vary over the course of the treatment regimen. For example, the present invention includes methods which comprise administering to the patient a single initial dose of a VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by at least 5 tertiary doses of the VEGF antagonist, wherein the first four tertiary doses are administered 8 weeks after the immediately preceding dose, and wherein each subsequent tertiary dose is administered from 8 to 12 (*e.g.*, 8, 8½, 9, 9½, 10, 10½, 11, 11½, 12) weeks after the immediately preceding dose. The frequency of administration may also be adjusted during the course of treatment by a physician depending on the needs of the individual patient following clinical examination.

VEGF ANTAGONISTS

[0022] The methods of the present invention comprise administering to a patient a VEGF antagonist according to specified dosing regimens. As used herein, the expression "VEGF antagonist" means any molecule that blocks, reduces or interferes with the normal biological activity of VEGF.

[0023] VEGF antagonists include molecules which interfere with the interaction between VEGF and a natural VEGF receptor, *e.g.*, molecules which bind to VEGF or a VEGF receptor and prevent or otherwise hinder the interaction between VEGF and a VEGF receptor. Specific exemplary VEGF antagonists include anti-VEGF antibodies, anti-VEGF receptor antibodies, and VEGF receptor-based chimeric molecules (also referred to herein as "VEGF-Traps").

[0024] VEGF receptor-based chimeric molecules include chimeric polypeptides which comprise two or more immunoglobulin (Ig)-like domains of a VEGF receptor such as VEGFR1 (also referred to as Flt1) and/or VEGFR2 (also referred to as Flk1 or KDR), and may also contain a multimerizing domain (*e.g.*, an Fc domain which facilitates the multimerization [*e.g.*, dimerization] of two or more chimeric polypeptides). An exemplary VEGF receptor-based chimeric molecule is a molecule referred to as VEGFR1R2-FcΔC1(a) which is encoded by the nucleic acid sequence of SEQ ID NO:1. VEGFR1R2-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 acid of SEQ ID NO:2 [*i.e.*, K458] may or may not be included in the VEGF antagonist used in the methods of the invention; *see e.g.*, US Patent 7,396,664). Amino acids 1-26 of SEQ ID NO:2 are the signal sequence.

[0025] The VEGF antagonist used in the Examples set forth herein below is a dimeric molecule comprising two VEGFR1R2-FcΔC1(a) molecules and is referred to herein as "VEGFT." Additional

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VEGF receptor-based chimeric molecules which can be used in the context of the present invention are disclosed in US 7,396,664, 7,303,746 and WO 00/75319.

ANGIOGENIC EYE DISORDERS

[0026] The methods of the present invention can be used to treat any angiogenic eye disorder. The expression "angiogenic eye disorder," as used herein, means any disease of the eye which is caused by or associated with the growth or proliferation of blood vessels or by blood vessel leakage. Non-limiting examples of angiogenic eye disorders that are treatable using the methods of the present invention include age-related macular degeneration (*e.g.*, wet AMD, exudative AMD, etc.), retinal vein occlusion (RVO), central retinal vein occlusion (CRVO; *e.g.*, macular edema following CRVO), branch retinal vein occlusion (BRVO), diabetic macular edema (DME), choroidal neovascularization (CNV; *e.g.*, myopic 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, and diabetic retinopathies.

PHARMACEUTICAL FORMULATIONS

[0027] The present invention includes methods in which the VEGF antagonist that is administered to the patient is contained within a pharmaceutical formulation. The pharmaceutical formulation may comprise the VEGF antagonist along with at least one inactive ingredient such as, *e.g.*, a pharmaceutically acceptable carrier. Other agents may be incorporated into the pharmaceutical composition to provide improved transfer, delivery, tolerance, and the like. The term “pharmaceutically acceptable” means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly, in humans. The term “carrier” refers to a diluent, adjuvant, excipient, or vehicle with which the antibody is administered. A multitude of appropriate formulations can be found in the formulary known to all pharmaceutical chemists: Remington's Pharmaceutical Sciences (15th ed, Mack Publishing Company, Easton, Pa., 1975), particularly Chapter 87 by Blaug, Seymour, therein. These formulations include, for example, powders, pastes, ointments, jellies, waxes, oils, lipids, lipid (cationic or anionic) containing vesicles (such as LIPOFECTIN™), DNA conjugates, anhydrous absorption pastes, oil-in-water and water-in-oil emulsions, emulsions carbowax (polyethylene glycols of various molecular weights), semi-solid gels, and semi-solid mixtures containing carbowax. Any of the foregoing mixtures may be appropriate in the context of the methods of the present invention, provided that the VEGF antagonist is not inactivated by the formulation and the formulation is physiologically compatible and tolerable with the route of administration. See also Powell et al. PDA (1998) J Pharm Sci

Technol. 52:238-311 and the citations therein for additional information related to excipients and carriers well known to pharmaceutical chemists.

[0028] Pharmaceutical formulations useful for administration by injection in the context of the present invention may be prepared by dissolving, suspending or emulsifying a VEGF antagonist in a sterile aqueous medium or an oily medium conventionally used for injections. As the aqueous medium for injections, there are, for example, physiological saline, an isotonic solution containing glucose and other auxiliary agents, etc., which may be used in combination with an appropriate solubilizing agent such as an alcohol (e.g., ethanol), a polyalcohol (e.g., propylene glycol, polyethylene glycol), a nonionic surfactant [e.g., polysorbate 80, HCO-50 (polyoxyethylene (50 mol) adduct of hydrogenated castor oil)], etc. As the oily medium, there may be employed, e.g., sesame oil, soybean oil, etc., which may be used in combination with a solubilizing agent such as benzyl benzoate, benzyl alcohol, etc. The injection thus prepared can be filled in an appropriate ampoule if desired.

MODES OF ADMINISTRATION

[0029] The VEGF antagonist (or pharmaceutical formulation comprising the VEGF antagonist) may be administered to the patient by any known delivery system and/or administration method. In certain embodiments, the VEGF antagonist is administered to the patient by ocular, intraocular, intravitreal or subconjunctival injection. In other embodiments, the VEGF antagonist can be administered to the patient by topical administration, *e.g.*, via eye drops or other liquid, gel, ointment or fluid which contains the VEGF antagonist and can be applied directly to the eye. Other possible routes of administration include, *e.g.*, intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, epidural, and oral.

AMOUNT OF VEGF ANTAGONIST ADMINISTERED

[0030] Each dose of VEGF antagonist administered to the patient over the course of the treatment regimen may contain the same, or substantially the same, amount of VEGF antagonist. Alternatively, the quantity of VEGF antagonist contained within the individual doses may vary over the course of the treatment regimen. For example, in certain embodiments, a first quantity of VEGF antagonist is administered in the initial dose, a second quantity of VEGF antagonist is administered in the secondary doses, and a third quantity of VEGF antagonist is administered in the tertiary doses. The present invention contemplates dosing schemes in which the quantity of VEGF antagonist contained within the individual doses increases over time (*e.g.*, each subsequent dose contains more VEGF antagonist than the last), decreases over time (*e.g.*, each subsequent dose contains less VEGF antagonist than the last), initially increases then decreases, initially decreases then increases, or remains the same throughout the course of the administration regimen.

[0031] The amount of VEGF antagonist administered to the patient in each dose is, in most cases, a therapeutically effective amount. As used herein, the phrase "therapeutically effective amount" means a dose of VEGF antagonist that results in a detectable improvement in one or more symptoms or indicia of an angiogenic eye disorder, or a dose of VEGF antagonist that inhibits, prevents, lessens, or delays the progression of an angiogenic eye disorder. In the case of an anti-VEGF antibody or a VEGF receptor-based chimeric molecule such as VEGFR1R2-FcΔC1(a), a therapeutically effective amount can be from about 0.05 mg to about 5 mg, *e.g.*, about 0.05 mg, about 0.1 mg, about 0.15 mg, about 0.2 mg, about 0.25 mg, about 0.3 mg, about 0.35 mg, about 0.4 mg, about 0.45 mg, about 0.5 mg, about 0.55 mg, about 0.6 mg, about 0.65 mg, about 0.7 mg, about 0.75 mg, about 0.8 mg, about 0.85 mg, about 0.9 mg, about 1.0 mg, about 1.05 mg, about 1.1 mg, about 1.15 mg, about 1.2 mg, about 1.25 mg, about 1.3 mg, about 1.35 mg, about 1.4 mg, about 1.45 mg, about 1.5 mg, about 1.55 mg, about 1.6 mg, about 1.65 mg, about 1.7 mg, about 1.75 mg, about 1.8 mg, about 1.85 mg, about 1.9 mg, about 2.0 mg, about 2.05 mg, about 2.1 mg, about 2.15 mg, about 2.2 mg, about 2.25 mg, about 2.3 mg, about 2.35 mg, about 2.4 mg, about 2.45 mg, about 2.5 mg, about 2.55 mg, about 2.6 mg, about 2.65 mg, about 2.7 mg, about 2.75 mg, about 2.8 mg, about 2.85 mg, about 2.9 mg, about 3.0 mg, about 3.5 mg, about 4.0 mg, about 4.5 mg, or about 5.0 mg of the antibody or receptor-based chimeric molecule.

[0032] The amount of VEGF antagonist contained within the individual doses may be expressed in terms of milligrams of antibody per kilogram of patient body weight (*i.e.*, mg/kg). For example, the VEGF antagonist may be administered to a patient at a dose of about 0.0001 to about 10 mg/kg of patient body weight.

TREATMENT POPULATION AND EFFICACY

[0033] The methods of the present invention are useful for treating angiogenic eye disorders in patients that have been diagnosed with or are at risk of being afflicted with an angiogenic eye disorder. Generally, the methods of the present invention demonstrate efficacy within 104 weeks of the initiation of the treatment regimen (with the initial dose administered at "week 0"), *e.g.*, by the end of week 16, by the end of week 24, by the end of week 32, by the end of week 40, by the end of week 48, by the end of week 56, etc. In the context of methods for treating angiogenic eye disorders such as AMD, CRVO, and DME, "efficacy" means that, from the initiation of treatment, the patient exhibits a loss of 15 or fewer letters on the Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity chart. In certain embodiments, "efficacy" means a gain of one or more (*e.g.*, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or more) letters on the ETDRS chart from the time of initiation of treatment.

EXAMPLES

[0034] The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how to make and use the methods and compositions of the invention, and are not intended to limit the scope of what the inventors regard as their invention. Efforts have been made to ensure accuracy with respect to numbers used (e.g., amounts, temperature, etc.) but some experimental errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, molecular weight is average molecular weight, temperature is in degrees Centigrade, and pressure is at or near atmospheric.

[0035] The exemplary VEGF antagonist used in all Examples set forth below is a dimeric molecule having two functional VEGF binding units. Each functional binding unit is comprised of Ig domain 2 from VEGFR1 fused to Ig domain 3 from VEGFR2, which in turn is fused to the hinge region of a human IgG1 Fc domain (VEGFR1R2-FcΔC1(a); encoded by SEQ ID NO:1). This VEGF antagonist is referred to in the examples below as "VEGFT". For purposes of the following Examples, "monthly" dosing is equivalent to dosing once every four weeks.

Example 1: Phase I Clinical Trial of Intravitreally Administered VEGF Receptor-Based Chimeric Molecule (VEGFT) in Subjects with Neovascular AMD

[0036] In this Phase I study, 21 subjects with neovascular AMD received a single intravitreal (IVT) dose of VEGFT. Five groups of three subjects each received either 0.05, 0.15, 0.5, 2 or 4 mg of VEGFT, and a sixth group of six subjects received 1 mg. No serious adverse events related to the study drug, and no identifiable intraocular inflammation was reported. Preliminary results showed that, following injection of VEGFT, a rapid decrease in foveal thickness and macular volume was observed that was maintained through 6 weeks. At Day 43 across all dose groups, mean excess retinal thickness [excess retinal thickness = (retinal thickness – 179μ)] on optical coherence tomography (OCT) was reduced from 119μ to 27μ as assessed by Fast Macular Scan and from 194μ to 60μ as assessed using a single Posterior Pole scan. The mean increase in best corrected visual acuity (BCVA) was 4.75 letters, and BCVA was stable or improved in 95% of subjects. In the 2 highest dose groups (2 and 4 mg), the mean increase in BCVA was 13.5 letters, with 3 of 6 subjects demonstrating improvement of ≥ 3 lines.

Example 2: Phase II Clinical Trial of Repeated Doses of Intravitreally Administered VEGF Receptor-Based Chimeric Molecule (VEGFT) in Subjects with Neovascular AMD

[0037] This study was a double-masked, randomized study of 3 doses (0.5, 2, and 4 mg) of VEGFT tested at 4-week and/or 12-week dosing intervals. There were 5 treatment arms in this study, as follows: 1) 0.5 mg every 4 weeks, 2) 0.5 mg every 12 weeks, 3) 2 mg every 4 weeks, 4) 2 mg every 12 weeks and 5) 4 mg every 12 weeks. Subjects were dosed at a fixed interval for the

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first 12 weeks, after which they were evaluated every 4 weeks for 9 months, during which additional doses were administered based on pre-specified criteria. All subjects were then followed for one year after their last dose of VEGFT. Preliminary data from a pre-planned interim analysis indicated that VEGFT met its primary endpoint of a statistically significant reduction in retinal thickness after 12 weeks compared with baseline (all groups combined, decrease of 135μ, $p < 0.0001$). Mean change from baseline in visual acuity, a key secondary endpoint of the study, also demonstrated statistically significant improvement (all groups combined, increase of 5.9 letters, $p < 0.0001$). Moreover, patients in the dose groups that received only a single dose, on average, demonstrated a decrease in excess retinal thickness ($p < 0.0001$) and an increase in visual acuity ($p = 0.012$) at 12 weeks. There were no drug-related serious adverse events, and treatment with the VEGF antagonists was generally well-tolerated. The most common adverse events were those typically associated with intravitreal injections.

Example 3: Phase I Clinical Trial of Systemically Administered VEGF Receptor-Based Chimeric Molecule (VEGFT) in Subjects with Neovascular AMD

[0038] This study was a placebo-controlled, sequential-group, dose-escalating safety, tolerability and bioeffect study of VEGFT by IV infusion in subjects with neovascular AMD. Groups of 8 subjects meeting eligibility criteria for subfoveal choroidal neovascularization (CNV) related to AMD were assigned to receive 4 IV injections of VEGFT or placebo at dose levels of 0.3, 1, or 3 mg/kg over an 8-week period.

[0039] Most adverse events that were attributed to VEGFT were mild to moderate in severity, but 2 of 5 subjects treated with 3 mg/kg experienced dose-limiting toxicity (DLT) (one with Grade 4 hypertension and one with Grade 2 proteinuria); therefore, all subjects in the 3 mg/kg dose group did not enter the study. The mean percent changes in excess retinal thickness were: -12%, -10%, -66%, and -60% for the placebo, 0.3, 1, and 3 mg/kg dose groups at day 15 (ANOVA $p< 0.02$), and -5.6%, +47.1%, and -63.3% for the placebo, 0.3, and 1 mg/kg dose groups at day 71 (ANOVA $p< 0.02$). There was a numerical improvement in BCVA in the subjects treated with VEGFT. As would be expected in such a small study, the results were not statistically significant.

Example 4: Phase III Clinical Trials of the Efficacy, Safety, and Tolerability of Repeated Doses of Intravitreal VEGFT in Subjects with Neovascular Age-Related Macular Degeneration

A. Objectives, Hypotheses and Endpoints

[0040] Two parallel Phase III clinical trials were carried out to investigate the use of VEGFT to treat patients with the neovascular form of age-related macular degeneration (Study 1 and Study 2). The primary objective of these studies was to assess the efficacy of IVT administered VEGFT

compared to ranibizumab (Lucentis®, Genentech, Inc.), in a non-inferiority paradigm, in preventing moderate vision loss in subjects with all subtypes of neovascular AMD.

[0041] The secondary objectives were (a) to assess the safety and tolerability of repeated IVT administration of VEGFT in subjects with all sub-types of neovascular AMD for periods up to 2 years; and (b) to assess the effect of repeated IVT administration of VEGFT on Vision-Related Quality of Life (QOL) in subjects with all sub-types of neovascular AMD.

[0042] The primary hypothesis of these studies was that the proportion of subjects treated with VEGFT with stable or improved BCVA (<15 letters lost) is similar to the proportion treated with ranibizumab who have stable or improved BCVA, thereby demonstrating non-inferiority.

[0043] The primary endpoint for these studies was the prevention of vision loss of greater than or equal to 15 letters on the ETDRS chart, compared to baseline, at 52 weeks. Secondary endpoints were as follows: (a) change from baseline to Week 52 in letter score on the ETDRS chart; (b) gain from baseline to Week 52 of 15 letters or more on the ETDRS chart; (c) change from baseline to Week 52 in total NEI VFQ-25 score; and (d) change from baseline to Week 52 in CNV area.

B. Study Design

[0044] For each study, subjects were randomly assigned in a 1:1:1:1 ratio to 1 of 4 dosing regimens: (1) 2 mg VEGFT administered every 4 weeks (2Q4); (2) 0.5 mg VEGFT administered every 4 weeks (0.5Q4); (3) 2 mg VEGFT administered every 4 weeks to week 8 and then every 8 weeks (with sham injection at the interim 4-week visits when study drug was not administered (2Q8); and (4) 0.5 mg ranibizumab administered every 4 weeks (RQ4). Subjects assigned to (2Q8) received the 2 mg injection every 4 weeks to week 8 and then a sham injection at interim 4-week visits (when study drug is not to be administered) during the first 52 weeks of the studies. (No sham injection were given at Week 52).

[0045] The study duration for each subject was scheduled to be 96 weeks plus the recruitment period. For the first 52 weeks (Year 1), subjects received an IVT or sham injection in the study eye every 4 weeks. (No sham injections were given at Week 52). During the second year of the study, subjects will be evaluated every 4 weeks and will receive IVT injection of study drug at intervals determined by specific dosing criteria, but at least every 12 weeks. (During the second year of the study, sham injections will not be given.) During this period, injections may be given as frequently as every 4 weeks, but no less frequently than every 12 weeks, according to the following criteria: (i) increase in central retinal thickness of ≥100 μm compared to the lowest previous value as measured by optical coherence tomography (OCT); or (ii) a loss from the best previous letter score of at least 5 ETDRS letters in conjunction with recurrent fluid as indicated by OCT; or (iii) new or persistent fluid as indicated by OCT; or (iv) new onset classic neovascularization, or new or persistent leak on fluorescein angiography (FA); or (v) new macular hemorrhage; or (vi) 12 weeks

have elapsed since the previous injection. According to the present protocol, subjects must receive an injection at least every 12 weeks.

[0046] Subjects were evaluated at 4 weeks intervals for safety and best corrected visual acuity (BCVA) using the 4 meter ETDRS protocol. Quality of Life (QOL) was evaluated using the NEI VFQ-25 questionnaire. OCT and FA examinations were conducted periodically.

[0047] Approximately 1200 subjects were enrolled, with a target enrollment of 300 subjects per treatment arm.

[0048] To be eligible for this study, subjects were required to have subfoveal choroidal neovascularization (CNV) secondary to AMD. "Subfoveal" CNV was defined as the presence of subfoveal neovascularization, documented by FA, or presence of a lesion that is juxtafoveal in location angiographically but affects the fovea. Subject eligibility was confirmed based on angiographic criteria prior to randomization.

[0049] Only one eye was designated as the study eye. For subjects who met eligibility criteria in both eyes, the eye with the worse VA was selected as the study eye. If both eyes had equal VA, the eye with the clearest lens and ocular media and least amount of subfoveal scar or geographic atrophy was selected. If there was no objective basis for selecting the study eye, factors such as ocular dominance, other ocular pathology and subject preference were considered in making the selection.

[0050] Inclusion criteria for both studies were as follows: (i) signed Informed consent; (ii) at least 50 years of age; (iii) active primary subfoveal CNV lesions secondary to AMD, including juxtafoveal lesions that affect the fovea as evidenced by FA in the study eye; (iv) CNV at least 50% of total lesion size; (v) early treatment diabetic retinopathy study (ETDRS) best-corrected visual acuity of: 20/40 to 20/320 (letter score of 73 to 25) in the study eye; (vi) willing, committed, and able to return for all clinic visits and complete all study-related procedures; and (vii) able to read, understand and willing to sign the informed consent form (or, if unable to read due to visual impairment, be read to verbatim by the person administering the informed consent or a family member).

[0051] Exclusion criteria for both studies were as follows: 1. Any prior ocular (in the study eye) or systemic treatment or surgery for neovascular AMD except dietary supplements or vitamins. 2. Any prior or concomitant therapy with another investigational agent to treat neovascular AMD in the study eye, except dietary supplements or vitamins. 3. Prior treatment with anti-VEGF agents as follows: (a) Prior treatment with anti-VEGF therapy in the study eye was not allowed; (b) Prior treatment with anti-VEGF therapy in the fellow eye with an investigational agent (not FDA approved, e.g. bevacizumab) was allowed up to 3 months prior to first dose in the study, and such treatments were not allowed during the study. Prior treatment with an approved anti-VEGF therapy in the fellow eye was allowed; (c) Prior systemic anti-VEGF therapy, investigational or FDA/Health Canada approved, was only allowed up to 3 months prior to first dose, and was not allowed during

the study. 4. Total lesion size > 12 disc areas (30.5 mm2, including blood, scars and neovascularization) as assessed by FA in the study eye. 5. Subretinal hemorrhage that is either 50% or more of the total lesion area, or if the blood is under the fovea and is 1 or more disc areas in size in the study eye. (If the blood is under the fovea, then the fovea must be surrounded 270 degrees by visible CNV.) 6. Scar or fibrosis, making up > 50% of total lesion in the study eye. 7. Scar, fibrosis, or atrophy involving the center of the fovea. 8. Presence of retinal pigment epithelial tears or rips involving the macula in the study eye. 9. History of any vitreous hemorrhage within 4 weeks prior to Visit 1 in the study eye. 10. Presence of other causes of CNV, including pathologic myopia (spherical equivalent of –8 diopters or more negative, or axial length of 25 mm or more), ocular histoplasmosis syndrome, angioid streaks, choroidal rupture, or multifocal choroiditis in the study eye. 11. History or clinical evidence of diabetic retinopathy, diabetic macular edema or any other vascular disease affecting the retina, other than AMD, in either eye. 12. Prior vitrectomy in the study eye. 13. History of retinal detachment or treatment or surgery for retinal detachment in the study eye. 14. Any history of macular hole of stage 2 and above in the study eye. 15. Any intraocular or periocular surgery within 3 months of Day 1 on the study eye, except lid surgery, which may not have taken place within 1 month of day 1, as long as it was unlikely to interfere with the injection. 16. Prior trabeculectomy or other filtration surgery in the study eye. 17. Uncontrolled glaucoma (defined as intraocular pressure greater than or equal to 25 mm Hg despite treatment with anti-glaucoma medication) in the study eye. 18. Active intraocular inflammation in either eye. 19. Active ocular or periocular infection in either eye. 20. Any ocular or periocular infection within the last 2 weeks prior to Screening in either eye. 21. Any history of uveitis in either eye. 22. Active scleritis or episcleritis in either eye. 23. Presence or history of scleromalacia in either eye. 24. Aphakia or pseudophakia with absence of posterior capsule (unless it occurred as a result of a yttrium aluminum garnet [YAG] posterior capsulotomy) in the study eye. 25. Previous therapeutic radiation in the region of the study eye. 26. History of corneal transplant or corneal dystrophy in the study eye. 27. Significant media opacities, including cataract, in the study eye which might interfere with visual acuity, assessment of safety, or fundus photography. 28. Any concurrent intraocular condition in the study eye (e.g. cataract) that, in the opinion of the investigator, could require either medical or surgical intervention during the 96 week study period. 29. Any concurrent ocular condition in the study eye which, in the opinion of the investigator, could either increase the risk to the subject beyond what is to be expected from standard procedures of intraocular injection, or which otherwise may interfere with the injection procedure or with evaluation of efficacy or safety. 30. History of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that might affect interpretation of the results of the study or render the subject at high risk for treatment complications. 31. Participation as a subject in any clinical study

within the 12 weeks prior to Day 1. 32. Any systemic or ocular treatment with an investigational agent in the past 3 months prior to Day 1. 33. The use of long acting steroids, either systemically or intraocularly, in the 6 months prior to day 1. 34. Any history of allergy to povidone iodine. 35. Known serious allergy to the fluorescein sodium for injection in angiography. 36. Presence of any contraindications indicated in the FDA Approved label for ranibizumab (Lucentis®). 37. Females who were pregnant, breastfeeding, or of childbearing potential, unwilling to practice adequate contraception throughout the study. Adequate contraceptive measures include oral contraceptives (stable use for 2 or more cycles prior to screening); IUD; Depo-Provera®; Norplant® System implants; bilateral tubal ligation; vasectomy; condom or diaphragm plus either contraceptive sponge, foam or jelly.

[0052] Subjects were not allowed to receive any standard or investigational agents for treatment of their AMD in the study eye other than their assigned study treatment with VEGFT or ranibizumab as specified in the protocol until they completed the Completion/Early Termination visit assessments. This includes medications administered locally (e.g., IVT, topical, juxtascleral or periorbital routes), as well as those administered systemically with the intent of treating the study and/or fellow eye.

[0053] The study procedures are summarized as follows:

[0054] Best Corrected Visual Acuity: Visual function of the study eye and the fellow eye were assessed using the ETDRS protocol (The Early Treatment Diabetic Retinopathy Study Group) at 4 meters. Visual Acuity examiners were certified to ensure consistent measurement of BCVA. The VA examiners were required to remain masked to treatment assignment.

[0055] Optical Coherence Tomography: Retinal and lesion characteristics were evaluated using OCT on the study eye. At the Screen Visit (Visit 1) images were captured and transmitted for both eyes. All OCT images were captured using the Zeiss Stratus OCT™ with software Version 3 or greater. OCT images were sent to an independent reading center where images were read by masked readers at visits where OCTs were required. All OCTs were electronically archived at the site as part of the source documentation. A subset of OCT images were read. OCT technicians were required to be certified by the reading center to ensure consistency and quality in image acquisition. Adequate efforts were made to ensure that OCT technicians at the site remained masked to treatment assignment.

[0056] Fundus Photography and Fluorescein Angiography (FA): The anatomical state of the retinal vasculature of the study eye was evaluated by funduscopic examination, fundus photography and FA. At the Screen Visit (Visit 1) funduscopic examination, fundus photography and FA were captured and transmitted for both eyes. Fundus and angiographic images were sent to an independent reading center where images were read by masked readers. The reading center confirmed subject eligibility based on angiographic criteria prior to randomization. All FAs and

fundus photographs were archived at the site as part of the source documentation. Photographers were required to be certified by the reading center to ensure consistency and quality in image acquisition. Adequate efforts were made to ensure that all photographers at the site remain masked to treatment assignment.

[0057] Vision-Related Quality of Life: Vision-related QOL was assessed using the National Eye Institute 25-Item Visual Function Questionnaire (NEI VFQ-25) in the interviewer-administered format. NEI VFQ-25 was administered by certified personnel at a contracted call center. At the screening visit, the sites assisted the subject and initiated the first call to the call center to collect all of the subject's contact information and to complete the first NEI VFQ-25 on the phone prior to randomization and IVT injection. For all subsequent visits, the call center called the subject on the phone, prior to IVT injection, to complete the questionnaire.

[0058] Intraocular Pressure: Intraocular pressure (IOP) of the study eye was measured using applanation tonometry or Tonopen. The same method of IOP measurement was used in each subject throughout the study.

[0059]

C. Results Summary (52 Week Data)

[0060] The primary endpoint (prevention of moderate or severe vision loss as defined above) was met for all three VEGFT groups (2Q4, 0.5Q4 and 2Q8) in this study. The results from both studies are summarized in Table 1.

Table 1

	Ranibizumab 0.5 mg monthly (RQ4)	VEGFT 0.5 mg monthly (0.5Q4)	VEGFT 2 mg monthly (2Q4)	VEGFT 2 mg every 8 weeks[a] (2Q8)
Maintenance of vision* (% patients losing <15 letters) at week 52 versus baseline				
Study 1	94.4%	95.9%**	95.1%**	95.1%**
Study 2	94.4%	96.3%**	95.6%**	95.6%**
Mean improvement in vision* (letters) at 52 weeks versus baseline (p-value vs RQ4)***				
Study 1	8.1	6.9 (NS)	10.9 (p<0.01)	7.9 (NS)
Study 2	9.4	9.7 (NS)	7.6 (NS)	8.9 (NS

[a] Following three initial monthly doses
* Visual acuity was measured as the total number of letters read correctly on the Early Treatment Diabetic Retinopathy Study (ETDRS) eye chart.
** Statistically non-inferior based on a non-inferiority margin of 10%, using confidence interval approach (95.1% and 95% for Study 1 and Study 2, respectively)
*** Test for superiority
NS = non-significant

[0061] In Study 1, patients receiving VEGFT 2mg monthly (2Q4) achieved a statistically significant greater mean improvement in visual acuity at week 52 versus baseline (secondary endpoint), compared to ranibizumab 0.5mg monthly (RQ4); patients receiving VEGFT 2mg monthly on average gained 10.9 letters, compared to a mean 8.1 letter gain with ranibizumab 0.5mg dosed every month ($p<0.01$). All other dose groups of VEGFT in Study 1 and all dose groups in Study 2 were not statistically different from ranibizumab in this secondary endpoint.

[0062] A generally favorable safety profile was observed for both VEGFT and ranibizumab. The incidence of ocular treatment emergent adverse events was balanced across all four treatment groups in both studies, with the most frequent events associated with the injection procedure, the underlying disease, and/or the aging process. The most frequent ocular adverse events were conjunctival hemorrhage, macular degeneration, eye pain, retinal hemorrhage, and vitreous floaters. The most frequent serious non-ocular adverse events were typical of those reported in this elderly population who receive intravitreal treatment for wet AMD; the most frequently reported events were falls, pneumonia, myocardial infarction, atrial fibrillation, breast cancer, and acute coronary syndrome. There were no notable differences among the study arms.

Example 5: Phase II Clinical Trial of VEGFT in Subjects with Diabetic Macular Edema (DME)

[0063] In this study, 221 patients with clinically significant DME with central macular involvement were randomized, and 219 patients were treated with balanced distribution over five groups. The control group received macular laser therapy at baseline, and patients were eligible for repeat laser treatments, but no more frequently than at 16 week intervals. The remaining four groups received VEGFT by intravitreal injection as follows: Two groups received 0.5 or 2 mg of VEGFT once every four weeks throughout the 12-month dosing period (0.5Q4 and 2Q4, respectively). Two groups received three initial doses of 2 mg VEGFT once every four weeks (*i.e.*, at baseline, and weeks 4 and 8), followed through week 52 by either once every 8 weeks dosing (2Q8) or as needed dosing with very strict repeat dosing criteria (PRN). Mean gains in visual acuity versus baseline were as shown in Table 2:

Table 2

	n	Mean change in visual acuity at week 24 versus baseline (letters)	Mean change in visual acuity at week 52 versus baseline (letters)
Laser	44	2.5	-1.3
VEGFT 0.5 mg monthly (0.5Q4)	44	8.6**	11.0**
VEGFT 2 mg monthly (2Q4)	44	11.4**	13.1**
VEGFT 2 mg every 8	42	8.5**	9.7**

weeks[a] (2Q8)			
VEGFT 2 mg as needed[a] (PRN)	45	10.3**	12.0**

[a] Following three initial monthly doses
** p < 0.01 versus laser

[0064] In this study, the visual acuity gains achieved with VEGFT administration at week 24 were maintained or numerically improved up to completion of the study at week 52 in all VEGFT study groups, including 2 mg dosed every other month

[0065] As demonstrated in the foregoing Examples, the administration of VEGFT to patients suffering from angiogenic eye disorders (*e.g.*, AMD and DME) at a frequency of once every 8 weeks, following a single initial dose and two secondary doses administered four weeks apart, resulted in significant prevention of moderate or severe vision loss or improvements in visual acuity.

Example 6: A Randomized, Multicenter, Double-Masked Trial in Treatment Naïve Patients with Macular Edema Secondary to CRVO

[0066] In this randomized, double-masked, Phase 3 study, patients received 6 monthly injections of either 2 mg intravitreal VEGFT (114 patients) or sham injections (73 patients). From Week 24 to Week 52, all patients received 2 mg VEGFT as-needed (PRN) according to retreatment criteria. Thus, "sham-treated patients" means patients who received sham injections once every four weeks from Week 0 through Week 20, followed by intravitreal VEGFT as needed from Week 24 through Week 52. "VEGFT-treated patients" means patients who received VEGFT intravitreal injections once every four weeks from Week 0 through Week 20, followed by intravitreal VEGFT as needed from Week 24 through Week 52. The primary endpoint was the proportion of patients who gained ≥15 ETDRS letters from baseline at Week 24. Secondary visual, anatomic, and Quality of Life NEI VFQ-25 outcomes at Weeks 24 and 52 were also evaluated.

[0067] At Week 24, 56.1% of VEGFT-treated patients gained ≥15 ETDRS letters from baseline vs 12.3% of sham-treated patients (P<0.0001). Similarly, at Week 52, 55.3% of VEGFT-treated patients gained ≥15 letters vs 30.1% of sham-treated patients (P<0.01). At Week 52, VEGFT-treated patients gained a mean of 16.2 letters vs 3.8 letters for sham-treated patients (P<0.001). Mean number of injections was 2.7 for VEGFT-treated patients vs 3.9 for sham-treated patients. Mean change in central retinal thickness was -413.0 µm for VEGFT-treated patients vs -381.8 µm for sham-treated patients. The proportion of patients with ocular neovascularization at Week 24 were 0% for VEGFT-treated patients and 6.8% for sham-treated patients, respectively; at Week 52 after receiving VEGFT PRN, proportions were 0% and 6.8% for VEGFT-treated and sham-treated. At Week 24, the mean change from baseline in the VFQ-25 total score was 7.2 vs 0.7 for the

VEGFT-treated and sham-treated groups; at Week 52, the scores were 7.5 vs 5.1 for the VEGFT-treated and sham-treated groups.

[0068] This Example confirms that dosing monthly with 2 mg intravitreal VEGFT injection resulted in a statistically significant improvement in visual acuity at Week 24 that was maintained through Week 52 with PRN dosing compared with sham PRN treatment. VEGFT was generally well tolerated and had a generally favorable safety profile.

Example 7: Dosing Regimens

[0069] Specific, non-limiting examples of dosing regimens within the scope of the present invention are as follows:

[0070] VEGFT 2 mg (0.05 mL) administered by intravitreal injection once every 4 weeks (monthly).

[0071] VEGFT 2 mg (0.5 mL) administered by intravitreal injection once every 4 weeks for the first 8 weeks, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks.

[0072] VEGFT 2 mg (0.5 mL) administered by intravitreal injection once every 4 weeks for the first 8 weeks, followed by 2 mg (0.05 mL) via intravitreal injection on a less frequent basis based on visual and/or anatomical outcomes (as assessed by a physician or other qualified medical professional).

[0073] VEGFT 2 mg (0.5 mL) administered by intravitreal injection once every 4 weeks for the first 8 weeks, followed by 2 mg (0.05 mL) via intravitreal injection administered *pro re nata* (PRN) based on visual and/or anatomical outcomes (as assessed by a physician or other qualified medical professional).

[0074] VEGFT 2 mg (0.5 mL) administered by intravitreal injection once every 4 weeks for the first 12 weeks, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks.

[0075] VEGFT 2 mg (0.5 mL) administered by intravitreal injection once every 4 weeks for the first 12 weeks, followed by 2 mg (0.05 mL) via intravitreal injection on a less frequent basis based on visual and/or anatomical outcomes (as assessed by a physician or other qualified medical professional).

[0076] VEGFT 2 mg (0.5 mL) administered by intravitreal injection once every 4 weeks for the first 12 weeks, followed by 2 mg (0.05 mL) via intravitreal injection administered *pro re nata* (PRN) based on visual and/or anatomical outcomes (as assessed by a physician or other qualified medical professional).

[0077] VEGFT 2 mg (0.5 mL) administered by intravitreal injection once every 4 weeks for the first 16 weeks, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks.

[0078] VEGFT 2 mg (0.5 mL) administered by intravitreal injection once every 4 weeks for the first 16 weeks, followed by 2 mg (0.05 mL) via intravitreal injection on a less frequent basis based on

visual and/or anatomical outcomes (as assessed by a physician or other qualified medical professional).

[0079] VEGFT 2 mg (0.5 mL) administered by intravitreal injection once every 4 weeks for the first 16 weeks, followed by 2 mg (0.05 mL) via intravitreal injection administered *pro re nata* (PRN) based on visual and/or anatomical outcomes (as assessed by a physician or other qualified medical professional).

[0080] VEGFT 2 mg (0.5 mL) administered by intravitreal injection once every 4 weeks for the first 20 weeks, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks.

[0081] VEGFT 2 mg (0.5 mL) administered by intravitreal injection once every 4 weeks for the first 20 weeks, followed by 2 mg (0.05 mL) via intravitreal injection on a less frequent basis based on visual and/or anatomical outcomes (as assessed by a physician or other qualified medical professional).

[0082] VEGFT 2 mg (0.5 mL) administered by intravitreal injection once every 4 weeks for the first 20 weeks, followed by 2 mg (0.05 mL) via intravitreal injection administered *pro re nata* (PRN) based on visual and/or anatomical outcomes (as assessed by a physician or other qualified medical professional).

[0083] VEGFT 2 mg (0.5 mL) administered by intravitreal injection once every 4 weeks for the first 24 weeks, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks.

[0084] VEGFT 2 mg (0.5 mL) administered by intravitreal injection once every 4 weeks for the first 24 weeks, followed by 2 mg (0.05 mL) via intravitreal injection on a less frequent basis based on visual and/or anatomical outcomes (as assessed by a physician or other qualified medical professional).

[0085] VEGFT 2 mg (0.5 mL) administered by intravitreal injection once every 4 weeks for the first 24 weeks, followed by 2 mg (0.05 mL) via intravitreal injection administered *pro re nata* (PRN) based on visual and/or anatomical outcomes (as assessed by a physician or other qualified medical professional).

[0086] VEGFT 2 mg (0.5 mL) administered by intravitreal injection once every 4 weeks for the first 28 weeks, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks.

[0087] VEGFT 2 mg (0.5 mL) administered by intravitreal injection once every 4 weeks for the first 28 weeks, followed by 2 mg (0.05 mL) via intravitreal injection on a less frequent basis based on visual and/or anatomical outcomes (as assessed by a physician or other qualified medical professional).

[0088] VEGFT 2 mg (0.5 mL) administered by intravitreal injection once every 4 weeks for the first 28 weeks, followed by 2 mg (0.05 mL) via intravitreal injection administered *pro re nata* (PRN) based on visual and/or anatomical outcomes (as assessed by a physician or other qualified medical professional).

[0089] VEGFT 2 mg (0.05 mL) administered by intravitreal injection as a single initial dose, followed by additional doses administered *pro re nata* (PRN) based on visual and/or anatomical outcomes (as assessed by a physician or other qualified medical professional).

[0090] Variations on the above-described dosing regimens would be appreciated by persons of ordinary skill in the art and are also within the scope of the present invention. For example, the amount of VEGFT and/or volume of formulation administered to a patient may be varied based on patient characteristics, severity of disease, and other diagnostic assessments by a physician or other qualified medical professional.

[0091] Any of the foregoing administration regimens may be used for the treatment of, *e.g.*, age-related macular degeneration (*e.g.*, wet AMD, exudative AMD, etc.), retinal vein occlusion (RVO), central retinal vein occlusion (CRVO; *e.g.*, macular edema following CRVO), branch retinal vein occlusion (BRVO), diabetic macular edema (DME), choroidal neovascularization (CNV; *e.g.*, myopic 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, etc.

SEQUENCES

[0092] SEQ ID NO:1 (DNA sequence having 1377 nucleotides):

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[0093] SEQ ID NO:2 (polypeptide sequence having 458 amino acids):

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[0094] The present invention is not to be limited in scope by the specific embodiments described herein. Indeed, various modifications of the invention in addition to those described herein will become apparent to those skilled in the art from the foregoing description and the accompanying figures. Such modifications are intended to fall within the scope of the appended claims.

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What is claimed is:

1. A method for treating an angiogenic eye disorder in a patient, said method comprising sequentially administering to the patient a single initial dose of a VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonist;

wherein each secondary dose is administered 2 to 4 weeks after the immediately preceding dose; and

wherein each tertiary dose is administered at least 8 weeks after the immediately preceding dose.

2. The method of claim 1, wherein only a single secondary dose is administered to the patient, and wherein the single secondary dose is administered 4 weeks after the initial dose of the VEGF antagonist.

3. The method of claim 1, wherein only two secondary doses are administered to the patient, and wherein each secondary dose is administered 4 weeks after the immediately preceding dose.

4. The method of claim 3, wherein each tertiary dose is administered 8 weeks after the immediately preceding dose.

5. The method of claim 1, wherein at least 5 tertiary doses of the VEGF antagonist are administered to the patient, and wherein the first four tertiary doses are administered 8 weeks after the immediately preceding dose, and wherein each subsequent tertiary dose is administered 8 or 12 weeks after the immediately preceding dose.

6. The method of claim 1, wherein the angiogenic eye disorder is selected from the group consisting of: age related macular degeneration, diabetic retinopathy, diabetic macular edema, central retinal vein occlusion, branch retinal vein occlusion, and corneal neovascularization.

7. The method of claim 6, wherein the angiogenic eye disorder is age related macular degeneration.

8. The method of claim 1, wherein the VEGF antagonist is an anti-VEGF antibody or fragment thereof, an anti-VEGF receptor antibody or fragment thereof, or a VEGF receptor-based chimeric molecule.

9. The method of claim 8, wherein the VEGF antagonist is a VEGF receptor-based chimeric molecule.

10. The method of claim 9, wherein the VEGF receptor-based chimeric molecule comprises VEGFR1R2-FcΔC1(a) encoded by the nucleic acid sequence of SEQ ID NO:1.

11. The method of claim 9, wherein the VEGF receptor-based chimeric molecule comprises (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.

12. The method of claim 1, wherein all doses of the VEGF antagonist are administered to the patient by topical administration or by intraocular administration.

13. The method of claim 12, wherein all doses of the VEGF antagonist are administered to the patient by intraocular administration.

14. The method of claim 13, wherein the intraocular administration is intravitreal administration.

15. The method of claim 11, wherein all doses of the VEGF antagonist are administered to the patient by topical administration or by intraocular administration.

16. The method of claim 15, wherein all doses of the VEGF antagonist are administered to the patient by intraocular administration.

17. The method of claim 16, wherein the intraocular administration is intravitreal administration.

18. The method of claim 17, wherein all doses of the VEGF antagonist comprise from about 0.5 mg to about 2 mg of the VEGF antagonist.

19. The method of claim 18, wherein all doses of the VEGF antagonist comprise 0.5 mg of the VEGF antagonist.

20. The method of claim 18, wherein all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist.

ABSTRACT

The present invention provides methods for treating angiogenic eye disorders by sequentially administering multiple doses of a VEGF antagonist to a patient. The methods of the present invention include the administration of multiple doses of a VEGF antagonist to a patient at a frequency of once every 8 or more weeks. The methods of the present invention are useful for the treatment of angiogenic eye disorders such as age related macular degeneration, diabetic retinopathy, diabetic macular edema, central retinal vein occlusion, branch retinal vein occlusion, and corneal neovascularization.

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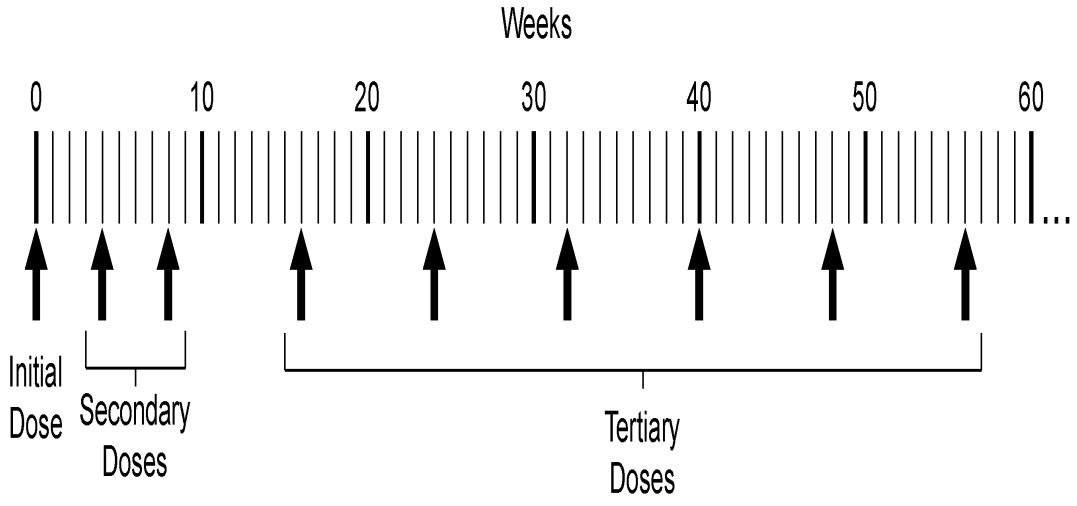
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10
20
30
40
50
60
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Initial Dose
Secondary Doses
Tertiary Doses

Figure 1

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

Title of Invention	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS

As the below named inventor, I hereby declare that:

This declaration is directed to:

☐ The attached application, or

☒ United States application or PCT International application number 13/940,370

filed on July 12, 2013.

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

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

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

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LEGAL NAME OF INVENTOR

Inventor: YANCOPOULOS, GEORGE D. Date (Optional): 10/20/13

Signature: /

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Application Number:	15471506
International Application Number:	
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Title of Invention:	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS
First Named Inventor/Applicant Name:	GEORGE D. YANCOPOULOS
Customer Number:	96387
Filer:	Karl Bozicevic
Filer Authorized By:	
Attorney Docket Number:	REGN-008CIPCON2
Receipt Date:	28-MAR-2017
Filing Date:	
Time Stamp:	15:02:24
Application Type:	Utility under 35 USC 111(a)

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Phe Val Arg Val His Glu Lys Asp Lys Thr His Thr Cys Pro Pro Cys
225                 230                 235                 240
Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
                245                 250                 255
Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
            260                 265                 270
Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
        275                 280                 285
Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
    290                 295                 300
Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
305                 310                 315                 320
His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
                325                 330                 335
Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
            340                 345                 350
```

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Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
        355                 360                 365
Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
    370                 375                 380
Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
385                 390                 395                 400
Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
                405                 410                 415
Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
            420                 425                 430
Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
        435                 440                 445
Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
    450                 455
```

UNITED STATES PATENT AND TRADEMARK OFFICE

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

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
15/471,506	03/28/2017	1629	2220	REGN-008CIPCON2	26	2

CONFIRMATION NO. 8014

96387
Regeneron - Bozicevic, Field & Francis
201 REDWOOD SHORES PARKWAY
SUITE 200
REDWOOD CITY, CA 94065

FILING RECEIPT

OC000000090526339

Date Mailed: 04/11/2017

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

Inventor(s)

Geroge D. YANCOPOULOS, Yorktown Heights, NY;

Applicant(s)

REGENERON PHARMACEUTICALS, INC., Tarrytown, NY

Assignment For Published Patent Application

REGENERON PHARMACEUTICALS, INC., Tarrytown, NY

Power of Attorney: The patent practitioners associated with Customer Number 96387

Domestic Priority data as claimed by applicant

This application is a CON of 14/972,560 12/17/2015
which is a CON of 13/940,370 07/12/2013 PAT 9254338
which is a CIP of PCT/US2012/020855 01/11/2012
which claims benefit of 61/432,245 01/13/2011
and claims benefit of 61/434,836 01/21/2011
and claims benefit of 61/561,957 11/21/2011

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

Permission to Access Application via Priority Document Exchange: Yes

Permission to Access Search Results: Yes

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

If Required, Foreign Filing License Granted: 04/10/2017

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 15/471,506**

Projected Publication Date: 07/20/2017

Non-Publication Request: No

Early Publication Request: No

Title

USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS

Preliminary Class

514

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

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

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

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

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

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Title 37, Code of Federal Regulations, 5.11 & 5.15

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NOT GRANTED

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

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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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Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
15/471,506	03/28/2017	Geroge D. YANCOPOULOS	REGN-008CIPCON2

CONFIRMATION NO. 8014

96387
Regeneron - Bozicevic, Field & Francis
201 REDWOOD SHORES PARKWAY
SUITE 200
REDWOOD CITY, CA 94065

INFORMAL NOTICE

OC000000090526540

Date Mailed: 04/11/2017

INFORMATIONAL NOTICE TO APPLICANT

Applicant is notified that the above-identified application contains the deficiencies noted below. No period for reply is set forth in this notice for correction of these deficiencies. However, if a deficiency relates to the inventor's oath or declaration, the applicant must file an oath or declaration in compliance with 37 CFR 1.63, or a substitute statement in compliance with 37 CFR 1.64, executed by or with respect to each actual inventor no later than the expiration of the time period set in the "Notice of Allowability" to avoid abandonment. See 37 CFR 1.53(f).

The item(s) indicated below are also required and should be submitted with any reply to this notice to avoid further processing delays.

- A properly executed inventor's oath or declaration has not been received for the following inventor(s):
  Geroge D. YANCOPOULOS

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

/tle/

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 15/471,506

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY FEE($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	280
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	600
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	720
TOTAL CLAIMS (37 CFR 1.16(i))	26 minus 20 =	* 6			OR	x 80 =	480
INDEPENDENT CLAIMS (37 CFR 1.16(h))	2 minus 3 =	*				x 420 =	0.00
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						0.00
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							0.00
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	2080

APPLICATION AS AMENDED - PART II

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

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

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.

Document code: WFEE

United States Patent and Trademark Office
Sales Receipt for Accounting Date: 04/10/2017

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To: docket@bozpat.com,,
From: PAIR_eOfficeAction@uspto.gov
Cc: PAIR_eOfficeAction@uspto.gov
Subject: Private PAIR Correspondence Notification for Customer Number 96387

Apr 11, 2017 04:32:30 AM

Dear PAIR Customer:

Regeneron - Bozicevic, Field & Francis
201 REDWOOD SHORES PARKWAY
SUITE 200
REDWOOD CITY, CA 94065
UNITED STATES

The following USPTO patent application(s) associated with your Customer Number, 96387 , have new outgoing correspondence. This correspondence is now available for viewing in Private PAIR.

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

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

Application	Document	Mailroom Date	Attorney Docket No.
15471506	APP.FILE.REC	04/11/2017	REGN-008CIPCON2
	M327	04/11/2017	REGN-008CIPCON2

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

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

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

Thank you for prompt attention to this notice,

UNITED STATES PATENT AND TRADEMARK OFFICE

PATENT APPLICATION INFORMATION RETRIEVAL SYSTEM

Electronically Filed

REQUEST FOR CORRECTED FILING RECEIPT Address to: Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Attorney Docket	REGN-008CIPCON2
	Applicant	YANCOPOULOS, GEORGE D.
	Serial Number	15/471,506
	Filing Date	March 28, 2017
	Group Art Unit	
	Examiner Name	
	Title: *"Use of a VEGF Antagonist to Treat Angiogenic Eye Disorders"*	

Sir:

A filing receipt for the above-identified patent application has been issued by the U.S. Patent and Trademark Office (copy attached) and has been found to contain the following error(s):

(1) Please correct the inventor's name "Geroge" to –George-- as indicated on the attached Official Filing Receipt and supplemental Application Date Sheet.

If for any reason a fee is found to be necessary, the Commissioner is authorized to charge such fee to Deposit Account No. 50-0815.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: April 19, 2017

By: /Karl Bozicevic, Reg. No. 28,807/
Karl Bozicevic, Reg. No. 28,807

BOZICEVIC, FIELD & FRANCIS LLP
201 Redwood Shores Parkway, Suite 200
Redwood City, CA 94065
Telephone: (650) 327-3400
Facsimile: (650) 327-3231

UNITED STATES PATENT AND TRADEMARK OFFICE

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

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
15/471,506	03/28/2017	1629	2220	REGN-008CIPCON2	26	2

CONFIRMATION NO. 8014

96387
Regeneron - Bozicevic, Field & Francis
201 REDWOOD SHORES PARKWAY
SUITE 200
REDWOOD CITY, CA 94065

DOCKETED
By MXM at 2:48 pm, Apr 11, 2017

FILING RECEIPT

OC000000090526339

Date Mailed: 04/11/2017

RECEIVED

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

Inventor(s)
George D. YANCOPOULOS, Yorktown Heights, NY;

Applicant(s)
REGENERON PHARMACEUTICALS, INC., Tarrytown, NY

Assignment For Published Patent Application
REGENERON PHARMACEUTICALS, INC., Tarrytown, NY

Power of Attorney: The patent practitioners associated with Customer Number 96387

Domestic Priority data as claimed by applicant
This application is a CON of 14/972,560 12/17/2015
which is a CON of 13/940,370 07/12/2013 PAT 9254338
which is a CIP of PCT/US2012/020855 01/11/2012
which claims benefit of 61/432,245 01/13/2011
and claims benefit of 61/434,836 01/21/2011
and claims benefit of 61/561,957 11/21/2011

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

Permission to Access Application via Priority Document Exchange: Yes

Permission to Access Search Results: Yes

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

If Required, Foreign Filing License Granted: 04/10/2017

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 15/471,506**

Projected Publication Date: 07/20/2017

Non-Publication Request: No

Early Publication Request: No

Title

USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS

Preliminary Class

514

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

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

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Title 35, United States Code, Section 184

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NOT GRANTED

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

PTO/AIA/14 (11-15)
Approved for use through 04/30/2017. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

SUPPLEMENTAL ADS

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	REGN-008CIPCON2
	Application Number	15/471,506
Title of Invention	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS	

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

Secrecy Order 37 CFR 5.2:

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

Inventor Information:

Inventor 1 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Geroge George	D.	YANCOPOULOS	

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

City	Yorktown Heights	State/Province	NY	Country of Residence	US

Mailing Address of Inventor:

Address 1	c/o Regeneron Pharmaceuticals, Inc.		
Address 2	777 Old Saw Mill River Road		
City	Tarrytown	**State/Province**	NY
Postal Code	10591	**Country**	US

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

Correspondence Information:

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

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

Customer Number	96387		
Email Address	docket@bozpat.com	Add Email	Remove Email

Application Information:

Title of the Invention	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS		
Attorney Docket Number	REGN-008CIPCON2	**Small Entity Status Claimed**	☐
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	1	**Suggested Figure for Publication (if any)**	1

PTO/AIA/14 (11-15)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

SUPPLEMENTAL ADS

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	REGN-008CIPCON2
	Application Number	15/471,506
Title of Invention	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS	

Filing By Reference:

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

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

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

Publication Information:

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

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

Representative Information:

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

Please Select One:	◉ Customer Number	○ US Patent Practitioner	○ Limited Recognition (37 CFR 11.9)
Customer Number	96387		

Domestic Benefit/National Stage Information:

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

Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
15/471,506	Continuation of	14972560	2015-12-17

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	REGN-008CIPCON2
	Application Number	15/471,506
Title of Invention	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS	

Prior Application Status	Patented			Remove	
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
14972560	Continuation of	13940370	2013-07-12	9254338	2016-02-09

Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
13940370	Continuation in part of	PCT/US2012/020855	2012-01-11

Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
PCT/US2012/020855	Claims benefit of provisional	61432245	2011-01-13

Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
PCT/US2012/020855	Claims benefit of provisional	61434836	2011-01-21

Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
PCT/US2012/020855	Claims benefit of provisional	61561957	2011-11-21

Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add** button.

Foreign Priority Information:

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

Remove

Application Number	Country[i]	Filing Date (YYYY-MM-DD)	Access Code[i] (if applicable)

Additional Foreign Priority Data may be generated within this form by selecting the **Add** button.

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

☐ This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.

NOTE: By providing this statement under 37 CFR 1.55 or 1.78, this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA.

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Authorization or Opt-Out of Authorization to Permit Access:

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

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

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

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

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

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

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

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

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

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

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

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Applicant Information:

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

Applicant 1

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

Clear

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

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

Name of the Deceased or Legally Incapacitated Inventor:

If the Applicant is an Organization check here. ☒

Organization Name	REGENERON PHARMACEUTICALS, INC.		
Mailing Address Information For Applicant:			
Address 1	777 Old Saw Mill River Road		
Address 2			
City	Tarrytown	**State/Province**	NY
Country	US	Postal Code	10591
Phone Number		Fax Number	
Email Address			

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

Assignee Information including Non-Applicant Assignee Information:

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

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	Application Number	15/471,506
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Assignee 1

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

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

Organization Name	REGENERON PHARMACEUTICALS, INC.

Mailing Address Information For Assignee including Non-Applicant Assignee:

Address 1	777 Old Saw Mill River Road		
Address 2			
City	Tarrytown	**State/Province**	NY
Country i	US	Postal Code	10591
Phone Number		Fax Number	
Email Address			

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

Signature:

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

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

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

Signature	/Karl Bozicevic, Reg. No. 28,807/			Date (YYYY-MM-DD)	2017-03-28
First Name	Karl	Last Name	Bozicevic	Registration Number	28,807

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

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

Privacy Act Statement

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

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

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

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

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

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

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

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

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

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

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

Electronic Acknowledgement Receipt	
EFS ID:	28966693
Application Number:	15471506
International Application Number:	
Confirmation Number:	8014
Title of Invention:	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS
First Named Inventor/Applicant Name:	Geroge D. YANCOPOULOS
Customer Number:	96387
Filer:	Karl Bozicevic/Savanna Fuentes
Filer Authorized By:	Karl Bozicevic
Attorney Docket Number:	REGN-008CIPCON2
Receipt Date:	19-APR-2017
Filing Date:	28-MAR-2017
Time Stamp:	13:39:26
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Request for Corrected Filing Receipt	REGN-008CIPCON2_2017-04-19_Request_Corr_OFR.pdf	22569 029f5456449b8299944c6b1320e231b226873703	no	1

Warnings:

Information:					
2	Request for Corrected Filing Receipt	REGN-008CIPCON2_0725US03_2017-04-19_OFR_mark-up.pdf	211300 94814da521cd6e4b31408a84b66fa83291c05266	no	4
Warnings:					
Information:					
3	Application Data Sheet	REGN-008CIPCON2_2017-04-19_supp_ADS.pdf	207596 10ba47739d308891bd4ac502c1373c32dd8efab4	no	9
Warnings:					
Information:					
This is not an USPTO supplied ADS fillable form					
			Total Files Size (in bytes):	441465	

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.

Document code: WFEE

United States Patent and Trademark Office
Sales Receipt for Accounting Date: 04/20/2017

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01 FC : 1830 140.00 DA

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

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
15/471,506	03/28/2017	1647	2220	REGN-008CIPCON2	26	2

CONFIRMATION NO. 8014

UPDATED FILING RECEIPT

96387
Regeneron - Bozicevic, Field & Francis
201 REDWOOD SHORES PARKWAY
SUITE 200
REDWOOD CITY, CA 94065

Date Mailed: 04/27/2017

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

Inventor(s)

George D. YANCOPOULOS, Yorktown Heights, NY;

Applicant(s)

REGENERON PHARMACEUTICALS, INC., Tarrytown, NY

Assignment For Published Patent Application

REGENERON PHARMACEUTICALS, INC., Tarrytown, NY

Power of Attorney: The patent practitioners associated with Customer Number 96387

Domestic Priority data as claimed by applicant

This application is a CON of 14/972,560 12/17/2015
which is a CON of 13/940,370 07/12/2013 PAT 9254338
which is a CIP of PCT/US2012/020855 01/11/2012
which claims benefit of 61/432,245 01/13/2011
and claims benefit of 61/434,836 01/21/2011
and claims benefit of 61/561,957 11/21/2011

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

Permission to Access Application via Priority Document Exchange: Yes

Permission to Access Search Results: Yes

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

Projected Publication Date: 07/20/2017

Non-Publication Request: No

Early Publication Request: No

Title

USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS

Preliminary Class

424

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

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

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

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

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

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

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

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

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

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

NOT GRANTED

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
15/471,506	03/28/2017	George D. YANCOPOULOS	REGN-008CIPCON2

CONFIRMATION NO. 8014

96387
Regeneron - Bozicevic, Field & Francis
201 REDWOOD SHORES PARKWAY
SUITE 200
REDWOOD CITY, CA 94065

37 CFR 1.48(f)
ACKNOWLEDGEMENT LETTER

OC000000090816742

Date Mailed: 04/27/2017

NOTICE OF ACCEPTANCE OF REQUEST UNDER 37 CFR 1.48(f)

This is in response to the applicant's request under 37 CFR 1.48(f) submitted on 04/19/2017.

The request under 37 CFR 1.48(f) to correct the inventorship, to correct or update the name of an inventor, or to correct the order of names of joint inventors is accepted.

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

/ylueng/

To: docket@bozpat.com,,
From: PAIR_eOfficeAction@uspto.gov
Cc: PAIR_eOfficeAction@uspto.gov
Subject: Private PAIR Correspondence Notification for Customer Number 96387

Apr 27, 2017 03:36:49 AM

Dear PAIR Customer:

Regeneron - Bozicevic, Field & Francis
201 REDWOOD SHORES PARKWAY
SUITE 200
REDWOOD CITY, CA 94065
UNITED STATES

The following USPTO patent application(s) associated with your Customer Number, 96387 , have new outgoing correspondence. This correspondence is now available for viewing in Private PAIR.

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Application	Document	Mailroom Date	Attorney Docket No.
15471506	APP.FILE.REC	04/27/2017	REGN-008CIPCON2
	R48.REQ.G	04/27/2017	REGN-008CIPCON2

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PATENT APPLICATION INFORMATION RETRIEVAL SYSTEM

Doc Code: PA..
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PTO/AIA/82B (07-13)
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POWER OF ATTORNEY BY APPLICANT

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

Application Number	Filing Date
15/471,506	March 28, 2017

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

☑ I hereby appoint the Patent Practitioner(s) associated with the following Customer Number as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above: 96387

OR

☐ I hereby appoint Practitioner(s) named in the attached list (form PTO/AIA/82C) as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the patent application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above. (Note: Complete form PTO/AIA/82C.)

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OR

Firm or Individual Name					
Address					
City		State		Zip	
Country					
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I am the Applicant (if the Applicant is a juristic entity, list the Applicant name in the box):

Regeneron Pharmaceuticals, Inc.

☐ Inventor or Joint Inventor (title not required below)

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

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

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

SIGNATURE of Applicant for Patent

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

Signature	/Frank R.Cottingham/	Date (Optional)	April 27, 2017
Name	Frank R. Cottingham		
Title	Executive Director, Assistant General Counsel, Patents		

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

☑ Total of 1 forms are submitted.

This collection of information is required by 37 CFR 1.131, 1.32, and 1.33. 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 1.11 and 1.14. This collection is estimated to take 3 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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STATEMENT UNDER 37 CFR 3.73(c)

Applicant/Patent Owner: **REGENERON PHARMACEUTICALS, INC.**

Application No./Patent No.: **15/471,506** Filed/Issue Date: **March 28, 2017**

Titled: **Use of a VEGF Antagonist to Treat Angiogenic Eye Disorders**

REGENERON PHARMACEUTICALS, INC., a **corporation**
(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

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

1. ☒ The assignee of the entire right, title, and interest.

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

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

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

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

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

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

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

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

A. ☒ An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel **042169**, Frame **0019**, or for which a copy thereof is attached.

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

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STATEMENT UNDER 37 CFR 3.73(c)

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

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

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

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

/Karl Bozicevic, Reg. No. 28,807/	**May 19, 2017**
Signature	Date
Karl Bozicevic	**28,807**
Printed or Typed Name	Title or Registration Number

Filed Electronically

PRELIMINARY AMENDMENT UNDER 37 C.F.R. §1.115 Address to: Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Attorney Docket	REGN-008CIPCON2
	Confirmation No.	8014
	First Named Inventor	YANCOPOULOS, GEORGE D.
	Application Number	15/471,506
	Filing Date	March 28, 2017
	Group Art Unit	To Be Assigned
	Examiner Name	To Be Assigned
	Title "Use of a VEGF Antagonist to Treat Angiogenic Eye Disorders"	

Sir:

Prior to the examination of the above-referenced application on the merits, please enter the amendments below.

AMENDMENTS

IN THE SPECIFICATION

Please replace the paragraph [0006] with the following rewritten paragraph:

[0006] The present invention provides methods for treating angiogenic eye disorders. The methods of the invention comprise sequentially administering multiple doses of a VEGF antagonist to a patient over time. In particular, the methods of the invention comprise sequentially administering to the patient a single initial dose of a VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonists. The present inventors have surprisingly discovered that beneficial therapeutic effects can be achieved in patients suffering from angiogenic eye disorders by administering a VEGF antagonist to a patient at a frequency of once every 8 or more weeks, especially when such doses are preceded by about three doses administered to the patient at a frequency of about 2 to 4 weeks. Thus, according to the methods of the present invention, each secondary dose of VEGF antagonist is administered 2 to 4 weeks after the immediately preceding dose, and each tertiary dose is administered at least 8 weeks after the immediately preceding dose. An example of a dosing regimen of the present invention is shown in **the Figure** ~~**Figure 1**~~. One advantage of such a dosing regimen is that, for most of the course of treatment (*i.e.*, the tertiary doses), it allows for less frequent dosing (*e.g.*, once every 8 weeks) compared to prior administration regimens for angiogenic eye disorders which require monthly administrations throughout the entire course of treatment. (*See*, *e.g.*, prescribing information for Lucentis® [ranibizumab], Genentech, Inc.).

Please replace the paragraph [0012] with the following rewritten paragraph:

[0012] ~~**Figure 1**~~ **The Figure** shows an exemplary dosing regimen of the present invention. In this regimen, a single "initial dose" of VEGF antagonist ("VEGFT") is administered at the beginning of the treatment regimen (*i.e.* at "week 0"), two "secondary doses" are administered at weeks 4 and 8, respectively, and at least six "tertiary doses" are administered once every 8 weeks thereafter, *i.e.*, at weeks 16, 24, 32, 40, 48, 56, etc.).

Please replace the paragraph [0019] with the following rewritten paragraph:

[0019] In one exemplary embodiment of the present invention, a single initial dose of a VEGF antagonist is administered to a patient on the first day of the treatment regimen (*i.e.*, at week 0), followed by two secondary doses, each administered four weeks after the immediately preceding dose (*i.e.*, at week 4 and at week 8), followed by at least 5 tertiary doses, each administered eight weeks after the immediately preceding dose (*i.e.*, at weeks 16, 24, 32, 40 and 48). The tertiary doses may continue (at intervals of 8 or more weeks) indefinitely during the course of the treatment regimen. This exemplary administration regimen is depicted graphically in **the Figure** ~~**Figure 1**~~.

LISTING OF THE CLAIMS

1. - 20. (**Canceled**)

21. (Previously Presented) A method for treating an angiogenic eye disorder in a patient, said method comprising sequentially administering to the patient a single initial dose of a VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonist;

wherein each secondary dose is administered 2 to 4 weeks after the immediately preceding dose; and

wherein each tertiary dose is administered at least 8 weeks after the immediately preceding dose;

wherein the VEGF antagonist is a VEGF receptor-based chimeric molecule comprising (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;

wherein exclusion criteria for the patient include all of:

(1) active intraocular inflammation;

(2) active ocular or periocular infection;

(3) any ocular or periocular infection within the last 2 weeks prior to treatment.

22. (Previously Presented) The method of claim 21, wherein only a single secondary dose is administered to the patient, and wherein the single secondary dose is administered 4 weeks after the initial dose of the VEGF antagonist.

23. (Previously Presented) The method of claim 21, wherein only two secondary doses are administered to the patient, and wherein each secondary dose is administered 4 weeks after the immediately preceding dose.

24. (Previously Presented) The method of claim 23, wherein each tertiary dose is administered 8 weeks after the immediately preceding dose.

25. (Previously Presented) The method of claim 21, wherein at least 5 tertiary doses of the VEGF antagonist are administered to the patient, and wherein the first four tertiary doses are

administered 8 weeks after the immediately preceding dose, and wherein each subsequent tertiary dose is administered 8 or 12 weeks after the immediately preceding dose.

26. (Previously Presented) The method of claim 21, wherein the angiogenic eye disorder is selected from the group consisting of: age related macular degeneration, diabetic retinopathy, diabetic macular edema, central retinal vein occlusion, branch retinal vein occlusion, and corneal neovascularization.

27. (Previously Presented) The method of claim 26, wherein the angiogenic eye disorder is age related macular degeneration.

28. (Previously Presented) The method of claim 21, wherein all doses of the VEGF antagonist are administered to the patient by topical administration or by intraocular administration.

29. (Previously Presented) The method of claim 28, wherein all doses of the VEGF antagonist are administered to the patient by intraocular administration.

30. (Previously Presented) The method of claim 29, wherein the intraocular administration is intravitreal administration.

31. (Previously Presented) The method of claim 30, wherein all doses of the VEGF antagonist comprise from about 0.5 mg to about 2 mg of the VEGF antagonist.

32. (Previously Presented) The method of claim 31, wherein all doses of the VEGF antagonist comprise 0.5 mg of the VEGF antagonist.

33. (Previously Presented) The method of claim 31, wherein all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist.

34. (Previously Presented) A method for treating an angiogenic eye disorder in a patient, said method comprising sequentially administering to the patient a single initial dose of a VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonist;

wherein each secondary dose is administered 2 to 4 weeks after the immediately preceding dose; and

wherein each tertiary dose is administered at least 8 weeks after the immediately preceding dose;

wherein the VEGF antagonist is a VEGF receptor-based chimeric molecule comprising VEGFR1R2-FcΔC1(a) encoded by the nucleic acid sequence of SEQ ID NO:1;

wherein exclusion criteria for the patient include all of:

(1) active intraocular inflammation;

(2) active ocular or periocular infection;

(3) any ocular or periocular infection within the last 2 weeks prior to treatment.

35. (Previously Presented) The method of claim 34, wherein only a single secondary dose is administered to the patient, and wherein the single secondary dose is administered 4 weeks after the initial dose of the VEGF antagonist.

36. (Previously Presented) The method of claim 34, wherein only two secondary doses are administered to the patient, and wherein each secondary dose is administered 4 weeks after the immediately preceding dose.

37. (Previously Presented) The method of claim 36, wherein each tertiary dose is administered 8 weeks after the immediately preceding dose.

38. (Previously Presented) The method of claim 37, wherein the angiogenic eye disorder is age related macular degeneration.

39. (Previously Presented) The method of claim 34, wherein at least 5 tertiary doses of the VEGF antagonist are administered to the patient, and wherein the first four tertiary doses are administered 8 weeks after the immediately preceding dose, and wherein each subsequent tertiary dose is administered 8 or 12 weeks after the immediately preceding dose.

40. (Previously Presented) The method of claim 34, wherein the angiogenic eye disorder is selected from the group consisting of: age related macular degeneration, diabetic retinopathy, diabetic macular edema, central retinal vein occlusion, branch retinal vein occlusion, and corneal neovascularization.

41. (Previously Presented) The method of claim 34, wherein all doses of the VEGF antagonist are administered to the patient by topical administration or by intraocular administration.

42. (Previously Presented) The method of claim 41, wherein all doses of the VEGF antagonist are administered to the patient by intraocular administration.

43. (Previously Presented) The method of claim 41, wherein the intraocular administration is intravitreal administration.

44. (Previously Presented) The method of claim 43, wherein all doses of the VEGF antagonist comprise from about 0.5 mg to about 2 mg of the VEGF antagonist.

45. (Previously Presented) The method of claim 44, wherein all doses of the VEGF antagonist comprise 0.5 mg of the VEGF antagonist.

46. (Previously Presented) The method of claim 44, wherein all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist.

REMARKS UNDER 37 CFR § 1.115

Formal Matters

Claims 21-46 remain pending.

No claims are amended.

Amendments have been made to the specification as requested by Examiner Lockard during a telephone interview on April 26, 2017 regarding the parent application Serial No. 14/972,560 to delete the phrase "Figure 1" and replace it with --the Figure--.

No new matter has been added.

CONCLUSION

Applicant submits that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees up to a strict limit of $3,000.00 beyond that authorized on the credit card, but not more than $3,000.00 in additional fees due with any communication for the above referenced patent application, including but not limited to any necessary fees for extensions of time, or credit any overpayment of any amount to Deposit Account No. 50-0815, order number REGN-008CIPCON.

Respectfully submitted,

BOZICEVIC, FIELD & FRANCIS LLP

Date: May 19, 2017

By: /Karl Bozicevic, Reg. No. 28,807/
Karl Bozicevic
Registration No. 28,807

BOZICEVIC, FIELD & FRANCIS LLP
201 Redwood Shores Pkwy, Suite 200
Redwood City, California 94065
Telephone: (650) 327-3400
Direct: (650) 833-7735
Facsimile: (650) 327-3231

Electronic Acknowledgement Receipt	
EFS ID:	29259219
Application Number:	15471506
International Application Number:	
Confirmation Number:	8014
Title of Invention:	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS
First Named Inventor/Applicant Name:	George D. YANCOPOULOS
Customer Number:	96387
Filer:	Karl Bozicevic
Filer Authorized By:	
Attorney Docket Number:	REGN-008CIPCON2
Receipt Date:	19-MAY-2017
Filing Date:	28-MAR-2017
Time Stamp:	13:58:09
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Power of Attorney	REGN-008CIPCON2_0725US03_POA.pdf	209734 3f7da560f91fb532e67de6444379107f352c7d0d	no	1

Warnings:

Information:					
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Warnings:					
Information:					
3		REGN-008CIPCON2_2017-05-19_pre_amend.pdf	61219 0dbe502b0d131584f755e7c3ded399efbe9 ae560	yes	8

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Preliminary Amendment	1	1
	Specification	2	3
	Claims	4	7
	Applicant Arguments/Remarks Made in an Amendment	8	8

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
15/471,506	03/28/2017	George D. YANCOPOULOS	REGN-008CIPCON2

CONFIRMATION NO. 8014

96387
Regeneron - Bozicevic, Field & Francis
201 REDWOOD SHORES PARKWAY
SUITE 200
REDWOOD CITY, CA 94065

POA ACCEPTANCE LETTER

OC000000091530510

Date Mailed: 05/23/2017

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 05/19/2017.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

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/qtran/

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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 15/471,506	Filing Date 03/28/2017	☐ To be Mailed

ENTITY: ☒ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

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

APPLICATION AS AMENDED – PART II

AMENDMENT	05/19/2017	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 26	Minus	** 26	= 0	X $80 =	0
	Independent (37 CFR 1.16(h))	* 2	Minus	***3	= 0	X $420 =	0
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	0

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

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

LDRC
ANDREW JAMES JR

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

To: docket@bozpat.com,,
From: PAIR_eOfficeAction@uspto.gov
Cc: PAIR_eOfficeAction@uspto.gov
Subject: Private PAIR Correspondence Notification for Customer Number 96387

May 23, 2017 03:33:50 AM

Dear PAIR Customer:

Regeneron - Bozicevic, Field & Francis
201 REDWOOD SHORES PARKWAY
SUITE 200
REDWOOD CITY, CA 94065
UNITED STATES

The following USPTO patent application(s) associated with your Customer Number, 96387 , have new outgoing correspondence. This correspondence is now available for viewing in Private PAIR.

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

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

Application	Document	Mailroom Date	Attorney Docket No.
15471506	N570	05/23/2017	REGN-008CIPCON2

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

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

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

Thank you for prompt attention to this notice,

UNITED STATES PATENT AND TRADEMARK OFFICE

PATENT APPLICATION INFORMATION RETRIEVAL SYSTEM

INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	15/471,506
				Filing Date	March 28, 2017
				First Named Inventor	YANCOPOULOS, GEORGE D.
				Art Unit	N/A
				Examiner Name	N/A
Sheet	1	of	3	Attorney Docket Number	REGN-008CIPCON2

U.S. PATENT DOCUMENTS

Examiner Initial*	Cite No.	Patent Number Number-Kind Code (*if known*)	Issue Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1	7396664	2008-07-08	Daly et al.	

U.S. PATENT APPLICATION PUBLICATIONS

Examiner Initial*	Cite No.	Publication Number **Number-Kind Code** (*if known*)	Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1	20050163798	2005-07-28	Papadopoulos et al.	
	2	20050260203	2005-11-24	Wiegand et al.	
	3	20060058234	2006-03-16	Daly et al.	
	4	20060172944	2006-08-03	Wiegand et al.	
	5	20070190058	2007-08-16	Shams	
	6	20030171320	2003-09-11	Guyer	

FOREIGN PATENT DOCUMENTS

Examiner Initial*	Cite No.	Foreign Document Number Country Code-Number-Kind Code (*if known*)	Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T
	1	WO 2000/75319	2000-12-14	Regeneron Pharmaceuitcals, Inc.		
	2	WO 2007/022101 A2	2007-02-22	Regeneron Pharmaceuticals, Inc.		
	3	WO 2008/063932	2008-05-29	Genentech, Inc.		
	4	JP 2010-509369	2010-03-25	Genentech, Inc.	See WO 2008/063932 for English Equivalent	

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T
	1	ANONYMOUS "Lucentis (rangibizymab injection) Intravitreal Injection" pp. 103 (June 2006)	
	2	Information from ClinicalTrials.gov archive View of NCT00637377 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Wet Age-Related Macular Degeneration (AMD) (VIEW 2)" *ClinicalTrials.gov*. Web. 2010-11-30.	
	3	Charles, Steve (Guest Lecturer) "VEGF Trap Has Positive DME Data" Tenth Annual Retina Fellows Forum Jan 29 and 30, Chicago, Article Date 03/01/2010	
	4	Dixon et al., "VEGF Trap-Eye for the treatment of neobascular age-related macular degeneration" Expert Opin. Investig. Drugs (2009) 18 (10): 1-8.	
	5	DO et al., "An exploratory study of the safety, tolerability and bioactivity of a single intravitreal injection of vascular endothelial growth factor Trap-Eye in patients with diabetic macular oedema" Br J Opthamol. 93(2):144-1449 (February 2009)	

Examiner Signature		Date Considered	

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

INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	15/471,506
				Filing Date	March 28, 2017
				First Named Inventor	YANCOPOULOS, GEORGE D.
				Art Unit	N/A
				Examiner Name	N/A
Sheet	2	of	3	Attorney Docket Number	REGN-008CIPCON2

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T
	6	DO et al., "The DA VINCI Study: phase 2 primary results of VEGF Trap-Eye in patients with diabetic macular edema" Opthamology 118(9):1819-1826 (September 2011)	
	7	THE EYETECH STUDY GROUP, "Anti-Vascular Endothelial Growth Factor Therapy for Subfoveal Choroidal Neovascularization Secondary to Age-related Macular Degeneration" American Academy of Ophthamology, 110(5):979-986 (May 2003)	
	8	HEIERet al., " rhuFab V2 (anti-VEGF Antibody) for Treatment of Exudative AMD" Symposium 8:Experimental and Emerging Treatments for Choroidal Neovascularization, 10 pp (2002)	
	9	HEIER et al., "RhuFab V2 in Wet AMD - 6 Month Continued Improvement Following Multiple Intravitreal Injections" Invest Ophthalmol Vis Sci, 44:E-Abstract 972 (2003)	
	10	Information from ClinicalTrials.gov archive on the VIEW 2 study (NCT00637377) "VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD (VIEW 2)" version available and updated on 17 March 2008.	
	11	Information from ClinicalTrials.gov archive on the view of NCT00509795 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Wet Age-Related Macular Degeneration (AMD)" (12-01-2009)	
	12	Information from ClinicalTrials.gov archive on the view of NCT00789477 "DME and VEGF Trap-Eye: Investigation of Clinical Impact" (11-18-2010)	
	13	Information from ClinicalTrials.gov archive on the view of NCT00509795 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Wet Age-Related Macular Degeneration (AMD)" (01-07-2011)	
	14	KRZYSTOLIK et al., "Prevention of Experimental Choroidal NEovascularization With Intravitreal Anti-Vascular Endothelial Growth Factor Antibody Fragment" Arch Ophthamol., 120:338-346 (Mar. 2002)	
	15	Mousa and Mousa, "Current Status of Vascular Endothelial Growth Factor Inhibition in Age-Related Macular Degeneration" Biodrugs 2010; 24(3); 183-194.	
	16	NGUYEN et al., "A Phase I Study of Intravitreal Vascular Endothelial Growth Factor Trap-Eye in Patients with Neovascular Age-Related Macular Degeneration" Opthamology, J.B. Lippincott Co., Philadelphia, PA, US, 116(11):2141-2148 (November 1, 2009)	
	17	NGUYEN et al., "A phase I trial of an IV-administered vascular endothelial growth factor trap for treatment in patients with choroidal neovascularization due to age-related macular degeneration" Ophthalmology (Sept 2006) 113(9):1522e1-1522e14 (epub July 28,2006)	
	18	NICHOLS, EARL R., "AAO: Ranibizumab (rhuRab) May Improve Vision in Age-Related Macular Degeneration" Doctor's Guide Global Edition, www.pslgroup.com/dg/23f2aa.htm, pp. 1-2 (November 24, 20013)	
	19	PAI et al., "Current concepts in intravitreal drug therapy for diabetic retinopathy" Saudi Journal of Opthamology 24(4):143-149 (June 30, 2010)	
	20	Regeneron Pharmaceuticals, Inc. FORM 10-Q, published on 7 November 2007 for the period ending 30 September 2007	

Examiner Signature		Date Considered	

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

INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	15/471,506
				Filing Date	March 28, 2017
				First Named Inventor	YANCOPOULOS, GEORGE D.
				Art Unit	N/A
				Examiner Name	N/A
Sheet	3	of	3	Attorney Docket Number	REGN-008CIPCON2

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T
	21	Regeneron, Press release "Regeneron Reports First Quarter 2008 Financial and Operating Results", May 1, 2008.	
	22	Regeneron Press Release "Bayer and Regeneron Report Positive Top-Line Results of Two Phase 3 Studies with VEGF Trap-Eye in Wet Age-related Macular Degeneration" November 22, 2010	
	23	Regeneron Press Release "Regeneron and Bayer Report Positive Results for VEGF Trap-Eye in Phase 3 Study in Central Retinal Vein Occlusion (CRVO) and in Phase 2 Study in Diabetic Macular Edema (DME)" December 20, 2010	
	24	Simo and Hernandez, "Advances in Medical Treatment of Diabetic Retinopathy" Diabetes Care, Volume 32, Number 8, August 2009	
	25	Slides for the 2008 Retina Society Meeting "VEGF Trap-Eye in Wet AMD CLEAR-IT 2: Summary of One-Year Key Results", September 28, 2008.	
	26	STEWART, "THe expanding role of vascular endothelial growth factor inhibitors in opthamology" Mayo Clin Proc. 87(1):77-88 (January 2012)	
	27	THOMAS REUTERS INTEGRITY "VEGF Trap-Eye final phase II results in age-related macular degeneration presented at 2008 Retina Society Meeting" (September 28, 2008)	
	28	WHO Drug Information, "International Nonproprietary Names for Pharmaceutical Substances (INN)" Vol. 20, No. 2, 2006, pages 115-119.	

Examiner Signature		Date Considered	

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

ClinicalTrials.gov archive
A service of the U.S. National Institutes of Health
Developed by the National Library of Medicine

← History of this study ↑ Current version of this study

View of NCT00637377 on 2010_11_30

ClinicalTrials Identifier: NCT00637377
Updated: 2010_11_30

Descriptive Information

Brief title
Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Wet Age-Related Macular Degeneration (AMD) (VIEW 2)

Official title
A Randomized, Double Masked, Active Controlled, Phase 3 Study of the Efficacy, Safety, and Tolerability of Repeated Doses of Intravitreal VEGF Trap in Subjects With Neovascular Age-related Macular Degeneration (AMD)

Brief summary

This study is a phase III, double-masked, randomized, study of the efficacy and safety of VEGF Trap-Eye in patients with neovascular age-related macular degeneration. Approximately 1200 patients will be randomized in Europe, Asia, Japan, Australia and South America.

Detailed description

Phase	Phase 3
Study type	Interventional
Study design	Treatment
Study design	Randomized
Study design	Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor)
Study design	Active Control
Study design	Parallel Assignment
Study design	Safety/Efficacy Study
Primary outcome	Measure: The proportion of subjects who maintain vision at Week 52, where a subject is classified as maintaining vision if the subject has lost fewer than 15 letters on the ETDRS chart compared to baseline (ie, prevention of moderate vision loss) Time Frame: week 52 Safety Issue? Yes
Secondary outcome	Measure: Mean change from baseline in BCVA as measured by ETDRS letter score at Week 52 Time Frame: week 52 Safety Issue? Yes
Secondary outcome	Measure: The proportion of subjects who gain at least 15 letters of vision at Week 52 Time Frame: week 52 Safety Issue? No
Secondary outcome	Measure: Mean change from baseline in total NEI VFQ-25 score at Week 52

	Safety Issue? No
Secondary outcome	Measure: Mean change from baseline in CNV area at Week 52 Time Frame: week 52 Safety Issue? Yes
Enrollment	1240 (Actual)
Condition	Macular Degeneration
Arm/Group	Arm Label: Arm 3 Experimental
Arm/Group	Arm Label: Arm 1 Experimental
Arm/Group	Arm Label: Arm 2 Experimental
Arm/Group	Arm Label: Arm 4 Active Comparator
Intervention	Drug: VEGF Trap-Eye (BAY86-5321) Arm Label: Arm 1 0.5 mg VEGF Trap-Eye administered every 4 weeks during the first year. Thereafter a dose may be administered as frequently as every 4 weeks, but no less frequently than every 12 weeks.
Intervention	Drug: VEGF Trap-Eye (BAY86-5321) Arm Label: Arm 2 2.0 mg VEGF Trap-Eye administered every 4 weeks during the first year. Thereafter a dose may be administered as frequently as every 4 weeks, but no less frequently than every 12 weeks.
Intervention	Drug: VEGF Trap-Eye (BAY86-5321) Arm Label: Arm 3 2.0 mg VEGF Trap-Eye administered every 8 weeks (including one additional 2,0 mg dose at Week 4) during the first year. Thereafter a dose may be administered as frequently as every 4 weeks, but no less frequently than every 12 weeks.
Intervention	Drug: Ranibizumab Arm Label: Arm 4 0.5 mg administered every 4 weeks during the first year. Thereafter a dose may be administered as frequently as every 4 weeks, but no less frequently than every 12 weeks.
URL	http://www.fda.gov/cder/drug/DrugSafety/DrugIndex.htm
URL	http://www.fda.gov/medwatch/safety.htm
URL	http://www.clinicalstudyresults.org
See also	Click here and search for drug information provided by the FDA.
See also	Click here and search for information on any recalls, market or product safety alerts by the FDA which might have occurred with this product.
See also	Click here to find results for studies related to marketed products.

Recruitment Information

Status	Active, not recruiting
Start date	2008-04
Last follow-up date	2011-08 (Anticipated)
Primary completion date	2010-09 (Actual)

Inclusion Criteria:
-Signed informed consent.
-Men and women >/=50 years of age.
-Active primary or recurrent subfoveal CNV lesions secondary to AMD, including juxtafoveal lesions that affect the fovea as evidenced by FA in the study eye.
-ETDRS best-corrected visual acuity of: 20/40 to 20/320 (letter score of 73 to 25) in the study
eye at 4 meters.
-Willing, committed, and able to return for ALL clinic visits and complete all study-related procedures.
-Able to read, (or, if unable to read due to visual impairment, be read to verbatim by the person administering the informed consent or a family member) understand and willing to sign the informed consent form.
Exclusion Criteria:
-Any prior ocular (in the study eye) or systemic treatment or surgery for neovascular AMD, except dietary supplements or vitamins.
-Any prior or concomitant therapy with another investigational agent to treat neovascular AMD in the study eye.
-Any prior treatment with anti-VEGF agents in the study eye.
-Total lesion size >12 disc areas (30.5 mm, including blood, scars and neovascularization) as assessed by FA in the study eye.
-Subretinal hemorrhages that is either 50% or more of the total lesion area, or if the blood is under the fovea and is 1 or more disc areas in size in the study eye (if the blood is under the fovea, then the fovea must be surrounded by 270 degrees by visible CNV).
-Scar or fibrosis making up >50% of the total lesion in the study eye.
-Scar, fibrosis, or atrophy involving the center of the fovea in the study eye.
- Presence of retinal pigment epithelial tears or rips involving the macula in the study eye.
-History of any vitreous hemorrhage within 4 weeks prior to Visit 1 in the study eye.
-Presence of other causes of CNV in the study eye.
-Prior vitrectomy in the study eye.
-History of retinal detachment or treatment or surgery for retinal detachment in the study eye.
-Any history of macular hole of stage 2 and above in the study eye.
-Any intraocular or periocular surgery within 3 months of Day 1 on the study eye, except lid surgery, which may not have taken place within 1 month of Day 1, as long as it is unlikely to interfere with the injection.
-History or clinical evidence of diabetic retinopathy, diabetic macular edema or any retinal vascular disease other than AMD in either eye.

Gender	Both
Minimum age	50 Years
Healthy volunteers	No

Administrative Data

Organization name	Bayer
Organization study ID	91689
Secondary ID	EurdaCT No.: 2007-000583-25
Sponsor	Bayer
Health Authority	Switzerland: Swiss Medic
Health Authority	Argentina: Ministry of Health
Health Authority	Australia: Department of Health and Ageing Therapeutic Goods

Health Authority	Austria: Federal Office for Safety in Health Care
Health Authority	Belgium: Federal Agency for Medicinal Products and Health Products
Health Authority	Brazil: ANVISA Agencia Nacional de Vigilancia Sanitaria
Health Authority	Colombia: INVIMA Instituto Nacional de Vigilancia de Medicamentos y Alimentos
Health Authority	Czech Republic: State Institute for Drug Control
Health Authority	France: Afssaps - French Health Products Safety Agency
Health Authority	Germany: Federal Institute for Drugs and Medical Devices
Health Authority	Hungary: National Institute of Pharmacy
Health Authority	India: Drugs Controller General of India
Health Authority	Israel: Ministry of Health
Health Authority	Italy: Ethics Committee
Health Authority	Japan: Pharmaceuticals and Medical Devices Agency
Health Authority	South Korea: Korea Food and Drug Administration (KFDA)
Health Authority	Latvia: State Agency of Medicines
Health Authority	Mexico: Federal Commission for Sanitary Risks Protection
Health Authority	Netherlands: The Central Committee on Research Involving Human Subjects (CCMO)
Health Authority	Poland: Office for Registration of Medicinal Products, Medical Devices and Biocidal Products
Health Authority	Portugal: INFARMED National Authority of Medicines and Health Products
Health Authority	Singapore: Health Sciences Authority
Health Authority	Slovakia: State Institute for Drug Control
Health Authority	Spain: Ministry of Health and Consumption
Health Authority	Sweden: Medical Products Agency
Health Authority	United Kingdom: Medicines and Healthcare Products Regulatory Agency

Electronic Acknowledgement Receipt	
EFS ID:	29320097
Application Number:	15471506
International Application Number:	
Confirmation Number:	8014
Title of Invention:	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS
First Named Inventor/Applicant Name:	George D. YANCOPOULOS
Customer Number:	96387
Filer:	Karl Bozicevic
Filer Authorized By:	
Attorney Docket Number:	REGN-008CIPCON2
Receipt Date:	26-MAY-2017
Filing Date:	28-MAR-2017
Time Stamp:	13:07:58
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	REGN-008CIPCON2_2017-05-26_IDS_trans.pdf	54979 818648a553dc3737ac79e3be0269fac71e0f371d	no	2

Warnings:

Information:					
2	Information Disclosure Statement (IDS) Form (SB08)	REGN-008CIPCON2_2017-05-26_IDS_SB08A.pdf	46996 dd8ed385577e233f1a1517616cb9273f018e355a	no	3
Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
3	Non Patent Literature	Clin_trials_View_NCT00637377_2010-11-30.pdf	523422 2a73b8478aec9323861d628e9e186ac35c5c428a	no	4
Warnings:					
Information:					
		Total Files Size (in bytes):	625397		

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.

Electronically Filed

INFORMATION DISCLOSURE STATEMENT Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Attorney Docket	REGN-008CIPCON2
	First Named Inventor	YANCOPOULOS, GEORGE D.
	Application Number	15/471,506
	Confirmation No.	8014
	Filing Date	March 28, 2017
	Group Art Unit	1647
	Examiner Name	LOCKARD, JON MCCLELLAND
	Title: "*Use of a VEGF Antagonist to Treat Angiogenic Eye Disorders*"	

Sir:

Applicants submit herewith documents which may be material to the examination of this application and in respect of which there may be a duty to disclose in accordance with 37 C.F.R. §1.56. This submission is not intended to constitute an admission that any document referred to therein is "prior art" for this invention unless specifically designated as such. A listing of the documents is shown on enclosed Form PTO/SB/.

The Examiner is requested to make the documents listed on the enclosed PTO/SB/08A of record in this application. Applicants would appreciate the Examiner initialing and returning the initialed copy of form PTO/SB/08A, indicating the documents cited therein have been considered and made of record herein.

All of the references identified herein were disclosed in parent application serial number 14/972,560, and as such, only a copy of non-publication number (2) is attached as it is the only reference no cited within the parent application. Copies of the remaining documents are not included pursuant to the provisions of 37 CFR § 1.98(d).

Statements

☒ **No statement**

☐ **PTA Statement under 37 CFR § 1.704(d)(1):** Each item of information contained in the information disclosure statement filed herewith:

(i) Was first cited in any communication from a patent office in a counterpart foreign or international application or from the Office, and this communication was not received by any individual designated in § 1.56(c) more than thirty days prior to the filing of the information disclosure statement; or

(ii) Is a communication that was issued by a patent office in a counterpart foreign or international application or by the Office, and this communication was not

received by any individual designated in § 1.56(c) more than thirty days prior to the filing of the information disclosure statement.

☐ **IDS Statement under 37 CFR § 1.97(e)(1):** 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; or

☐ **IDS Statement under 37 CFR § 1.97(e)(2):** 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 § 1.56(c) more than three months prior to the filing of the information disclosure statement.

Fees

☒ No fee is believed to be due.

☐ The appropriate fee set forth in 37 C.F.R. §1.17(p) accompanies this information disclosure statement.

The Commissioner is hereby authorized to charge any underpayment of fees up to a strict limit of $3,000.00 beyond that authorized on the credit card, but not more than $3,000.00 in additional fees due with any communication for the above referenced patent application, including but not limited to any necessary fees for extensions of time, or credit any overpayment of any amount to Deposit Account No. 50-0815, order number REGN-008CIPCON2.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: May 26, 2017

By: /Karl Bozicevic, Reg. No. 28,807/
Karl Bozicevic, Reg. No. 28,807

BOZICEVIC, FIELD & FRANCIS LLP
201 Redwood Shores Parkway, Suite 200
Redwood City, CA 94065
Telephone: (650) 327-3400
Facsimile: (650) 327-3231

INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	15/471,506
				Filing Date	March 28, 2017
				First Named Inventor	YANCOPOULOS, GEORGE D.
				Art Unit	1647
				Examiner Name	LOCKARD, JON MCCLELLAND
Sheet	1	of	1	Attorney Docket Number	REGN-008CIPCON2

U.S. PATENT DOCUMENTS

Examiner Initial*	Cite No.	Patent Number Number-Kind Code (*if known*)	Issue Date YYYY-MM-DD	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

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	1	HEIER et al., "Intravitreal Aflibercept (VEGF Trap-Eye) in Wet Age-related macular Degeneration," Ophthalmology, 119:2537-2548 (2012	

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Intravitreal Aflibercept (VEGF Trap-Eye) in Wet Age-related Macular Degeneration

*Jeffrey S. Heier, MD,[1] David M. Brown, MD,[2] Victor Chong, MD,[3] Jean-Francois Korobelnik, MD,[4] Peter K. Kaiser, MD,[5] Quan Dong Nguyen, MD,[6] Bernd Kirchhof, MD,[7] Allen Ho, MD,[8] Yuichiro Ogura, MD,[9] George D. Yancopoulos, MD, PhD,[10] Neil Stahl, MD,[10] Robert Vitti, MD,[10] Alyson J. Berliner, MD, PhD,[10] Yuhwen Soo, PhD,[10] Majid Anderesi, MD,[11] Georg Groetzbach, MD,[11] Bernd Sommerauer, PhD,[11] Rupert Sandbrink, MD, PhD,[11,12] Christian Simader, MD,[13] Ursula Schmidt-Erfurth, MD,[13] for the VIEW 1 and VIEW 2 Study Groups**

Objective: Two similarly designed, phase-3 studies (VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD [VIEW 1, VIEW 2]) of neovascular age-related macular degeneration (AMD) compared monthly and every-2-month dosing of intravitreal aflibercept injection (VEGF Trap-Eye; Regeneron, Tarrytown, NY, and Bayer HealthCare, Berlin, Germany) with monthly ranibizumab.

Design: Double-masked, multicenter, parallel-group, active-controlled, randomized trials.

Participants: Patients (n = 2419) with active, subfoveal, choroidal neovascularization (CNV) lesions (or juxtafoveal lesions with leakage affecting the fovea) secondary to AMD.

Intervention: Patients were randomized to intravitreal aflibercept 0.5 mg monthly (0.5q4), 2 mg monthly (2q4), 2 mg every 2 months after 3 initial monthly doses (2q8), or ranibizumab 0.5 mg monthly (Rq4).

Main Outcome Measures: The primary end point was noninferiority (margin of 10%) of the aflibercept regimens to ranibizumab in the proportion of patients maintaining vision at week 52 (losing <15 letters on Early Treatment Diabetic Retinopathy Study [ETDRS] chart). Other key end points included change in best-corrected visual acuity (BCVA) and anatomic measures.

Results: All aflibercept groups were noninferior and clinically equivalent to monthly ranibizumab for the primary end point (the 2q4, 0.5q4, and 2q8 regimens were 95.1%, 95.9%, and 95.1%, respectively, for VIEW 1, and 95.6%, 96.3%, and 95.6%, respectively, for VIEW 2, whereas monthly ranibizumab was 94.4% in both studies). In a prespecified integrated analysis of the 2 studies, all aflibercept regimens were within 0.5 letters of the reference ranibizumab for mean change in BCVA; all aflibercept regimens also produced similar improvements in anatomic measures. Ocular and systemic adverse events were similar across treatment groups.

Conclusions: Intravitreal aflibercept dosed monthly or every 2 months after 3 initial monthly doses produced similar efficacy and safety outcomes as monthly ranibizumab. These studies demonstrate that aflibercept is an effective treatment for AMD, with the every-2-month regimen offering the potential to reduce the risk from monthly intravitreal injections and the burden of monthly monitoring.

Financial Disclosure(s): Proprietary or commercial disclosure may be found after the references.

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**Group members listed online in Appendix 1 (http://aaojournal.org).*

Age-related macular degeneration (AMD) is a leading cause of vision loss and blindness in industrialized countries.[1] The most severe vision loss occurs in the neovascular (or wet) form of AMD, involving choroidal neovascularization (CNV) and associated retinal edema. Early treatments for CNV (laser ablation, photodynamic therapy with verteporfin), although clearly better than no treatment at all, decreased severe vision loss rather than truly stabilizing vision or resulting in clinically significant improvements in visual acuity.[2–4] The suggestion that vascular endothelial growth factor (VEGF) might be driving the CNV and associated edema seen in AMD led to a paradigm shift with the success of the first anti-VEGF therapy, pegaptanib sodium.[5,6] Monthly intravitreal injections of 0.5 mg ranibizumab, a humanized monoclonal antibody fragment that blocks VEGF, not only prevent vision loss in most patients but also lead to significant visual gain in approximately one-third.[7,8] The risk of rare but serious adverse events resulting from the intravitreal procedure, together with the significant burden of making monthly visits to their retinal specialist, have led to extensive efforts to decrease injection and monitoring frequency. However, fixed quarterly[9,10] or "as needed" (pro re nata [PRN]) dosing regimens,[11,12] without requiring monthly monitoring visits, were not effective at maintaining vision.

The Comparison of AMD Treatments Trials (CATT)[13] recently compared monthly ranibizumab with monthly

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bevacizumab, as well as with PRN regimens that required monthly monitoring visits during which treatment decisions primarily were made on the basis of anatomic criteria. Monthly bevacizumab resulted in mean best-corrected visual acuity (BCVA) gains (8.0 letters) similar to those for monthly ranibizumab (8.5 letters), whereas PRN ranibizumab yielded a mean BCVA gain of 1.7 letters less than that of the monthly standard (with a confidence interval [CI] extending to 4.7 letters below) that achieved noninferiority, and PRN bevacizumab yielded a mean BCVA gain 2.6 letters below the monthly standard (with a CI extending to 5.9 letters below) that did not achieve noninferiority. In the CATT, monthly bevacizumab and both PRN regimens were significantly worse than monthly ranibizumab in terms of the proportion of patients who had fluid-free retinas on optical coherence tomography (OCT). Although CIs were not provided for monthly and PRN regimens, switching from monthly to PRN regimens in the second year of the CATT resulted in a significant worsening of BCVA and retinal thickness, as well as a significant decrease in the proportion of patients without retinal fluid.[34] The "alternative treatments to Inhibit VEGF in Age-related choroidal Neovascularization" (IVAN) study also found that the mean foveal retinal thickness and the percentage of patients with fluorescein leakage were significantly higher with the PRN regimen compared with the monthly regimen.[35] In the HARBOR study (Invest Ophthalmol Vis Sci 2012;53:E-Abstract 3677), PRN regimens of both the approved 0.5 mg dose and the higher 2 mg dose of

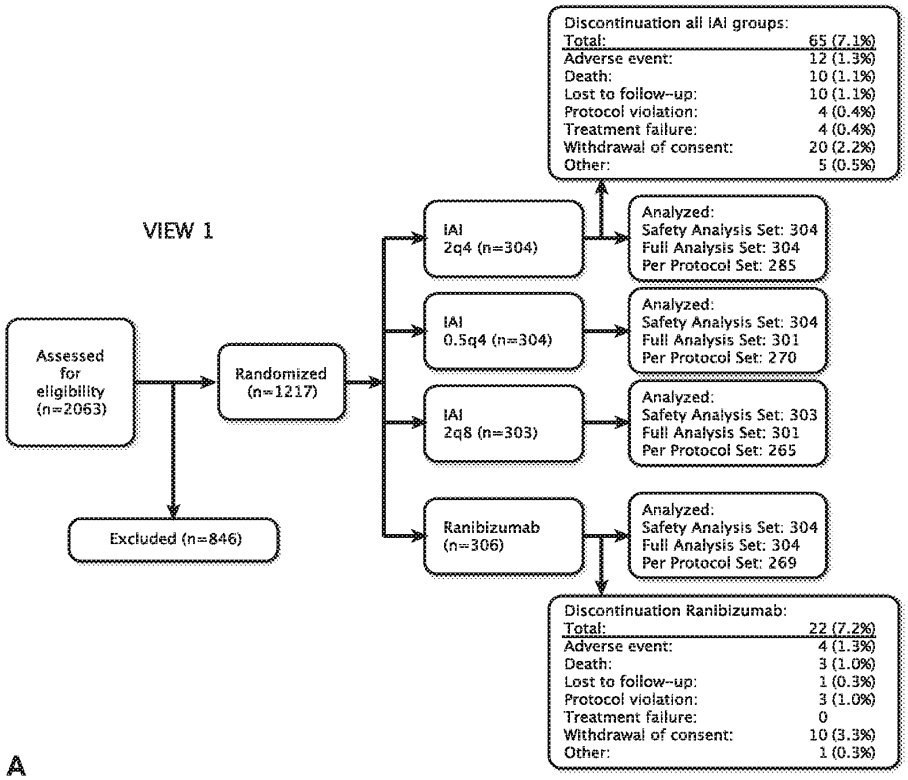

Figure 1. Flowcharts describing treatment allocation and patient disposition in VIEW 1 (**A**) and VIEW 2 (**B**). In both VIEW 1 and VIEW 2 studies, the most common reason for patients to be screened but not randomized was ineligibility based on angiographic characteristics as identified by the reading center. The second most common reason was visual acuity out of range. Discontinuations are those that occurred from the study. Two milligrams intravitreal aflibercept every 2 months (2q8) dosing was performed after 3 initial monthly doses. The numbers of patients who prematurely discontinued study medication in the 2q4, 0.5q4, 2q8, and Rq4 groups were 16 (5.3%), 30 (9.9%), 30 (9.9%), and 27 (8.8%), respectively, in VIEW 1; and 37 (11.8%), 45 (14.5%), 33 (10.5%), and 33 (10.9%), respectively, in VIEW 2. In VIEW 1, 1089 patients were included in the per protocol set (PPS), with 92.6% to 96.1% completing week-52 visual acuity assessment. A total of 128 patients were not included in the PPS for the following reasons (in order of occurrence): missed 2 consecutive injections before ninth injection, major protocol deviation, received <9 injections, had <9 assessments, no baseline assessments, no post-baseline assessments. In VIEW 2, 1081 patients were included in the PPS with 95.9% to 97.8% completing week-52 visual acuity assessment. A total of 159 patients were not included in the PPS for the following main reasons: missed 2 consecutive injections before ninth injection, major protocol deviation, received <9 injections, had <9 assessments, no baseline assessments, no post-baseline assessments, unmasking by investigator or Global Pharmacovigilance. 0.5q4 = 0.5 mg IAI monthly; 2q4 = 2 mg IAI monthly; 2q8 = 2 mg IAI every 2 months after 3 initial monthly doses; IAI = intravitreal aflibercept injection.

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ranibizumab did not achieve noninferiority compared with monthly ranibizumab, with the 0.5 mg PRN regimen yielding a mean BCVA gain 2.0 letters below the monthly standard (with a CI extending to 4.5 letters below). Of note, just like the CATT PRN regimens, the HARBOR PRN regimens still depended on monthly monitoring visits. Thus, there remains a need for new therapies that will provide equivalent efficacy and anatomic disease control to monthly ranibizumab, while reducing the risk of monthly injections and the burden of mandatory monthly monitoring visits.

Intravitreal aflibercept injection (IAI) (previously known in the scientific literature as VEGF Trap-Eye, Regeneron, Tarrytown, NY, and Bayer HealthCare, Berlin, Germany) is a soluble decoy receptor fusion protein[16,17] that is specifically purified and formulated for intraocular injection. Intravitreal aflibercept at doses of 0.5 mg and 2 mg provided the most robust outcomes in the Clinical Evaluation of Antiangiogenesis in the Retina Intravitreal Trial Phase 2 (CLEAR-IT 2) study after 4 monthly administrations followed by PRN dosing to week 52.[18] The binding affinity of intravitreal aflibercept to VEGF is substantially greater than that of bevacizumab or ranibizumab.[17] The greater affinity could translate into a higher efficacy or, as predicted by a mathematic model, into a substantially longer duration of action in the eye,[19] allowing for less frequent dosing, as supported by early clinical trials.[18,20] In this article, we report the first-year results of 2 phase 3 studies comparing intravitreal aflibercept, monthly or every 2 months, with monthly ranibizumab.

Materials and Methods

Study Design

The "VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD" studies (VIEW 1 and VIEW 2) were similarly designed, prospective, double-masked, multinational, parallel-group, active-controlled, randomized clinical trials. The investigators from the VIEW 1 and VIEW 2 studies are listed in Appendix 1, available at http://aaojournal.org. Patients in VIEW 1 (registered at www.clinicaltrials.gov on July 31, 2007; NCT00509795. Accessed August 8, 2012) were randomized at 154 sites in the United States and Canada. Patients in VIEW 2 (registered at www.clinicaltrials.gov on March 12, 2008; NCT00637377. Accessed August 8, 2012) were randomized at 172 sites in Europe, the Middle East, Asia-Pacific, and Latin America; the last patient in both studies completed 52 weeks in September 2010. The study protocols were approved by institutional review boards or ethics committees for each clinical site; all participants provided written informed consent. All the US study sites complied with the Health Insurance

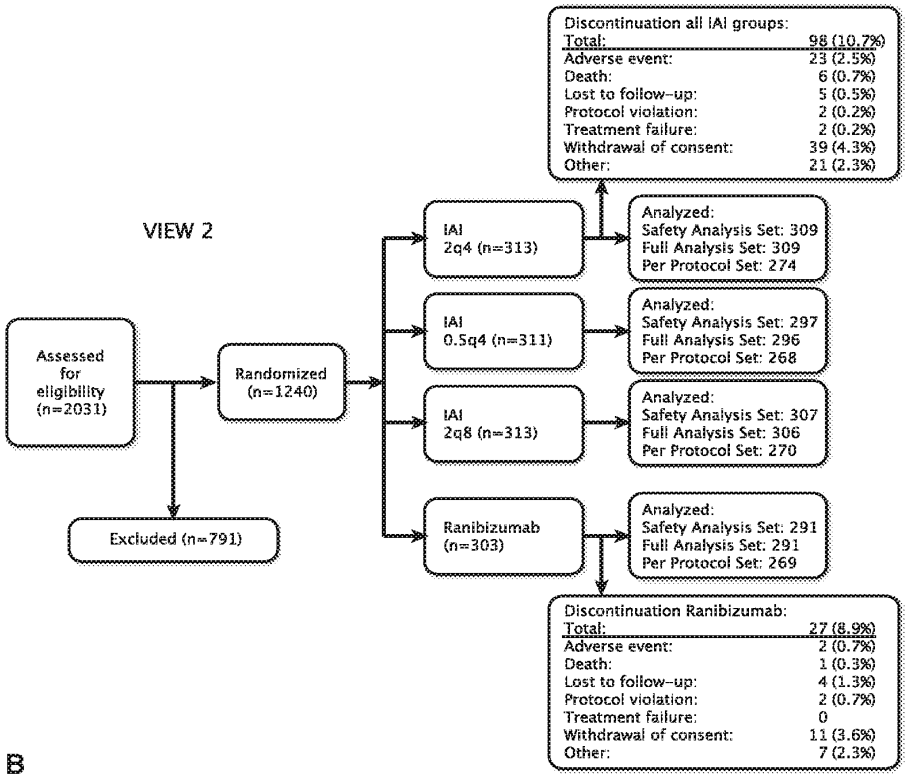

Figure 1. (Continued.)

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Portability and Accountability Act. The 52-week outcomes are reported.

Participants

Inclusion and exclusion criteria were designed to maintain constancy with the pivotal trials for the reference drug ranibizumab, consistent with regulatory guidelines for noninferiority studies, and included (1) age ≥50 years with active subfoveal CNV lesions (any subtype) secondary to AMD; juxtafoveal lesions with leakage affecting the fovea also were allowed; (2) CNV comprising at least 50% of total lesion size; and (3) BCVA between 73 and 25 Early Treatment Diabetic Retinopathy Study chart (ETDRS) letters (20/40–20/320 Snellen equivalent). Patients with prior treatment for AMD (including an investigational agent or anti-VEGF therapy) in the study eye were excluded. Eligibility was determined using fluorescein angiography at the reading center. Complete eligibility criteria are shown in Appendix 2 (available at http://aaojournal.org).

Treatment Groups and Randomization

Patients were randomized in a 1:1:1:1 ratio to the following regimens: 0.5 mg aflibercept every 4 weeks (0.5q4); 2 mg aflibercept every 4 weeks (2q4); 2 mg aflibercept every 8 weeks (2q8) after 3 injections at week 0, 4, and 8 (to maintain masking, sham injections were given at the interim 4-week visits after week 8); or 0.5 mg ranibizumab every 4 weeks (Rq4). Consecutively enrolled patients were assigned to treatment groups on the basis of a predetermined central randomization scheme with balanced allocation, managed by an interactive voice response system.

End Points and Statistical Analyses

The primary end point analysis, noninferiority margins, and definition of "clinical equivalence" were established in discussion with the Food and Drug Administration (FDA) (as part of a Special Protocol Assessment), European Medicines Agency, Pharmaceutical and Medical Device Agency and other regulatory authorities, with the intent of maintaining constancy with the previous ranibizumab pivotal trials[7,8] and preserving the majority of the treatment effect demonstrated in these trials. The primary end point analysis was noninferiority of the intravitreal aflibercept regimens to ranibizumab in the proportion of patients maintaining vision at week 52 (losing <15 ETDRS letters; per protocol data set) in each study. A noninferiority margin of 10% in the individual studies was chosen to preserve approximately two-thirds of the ranibizumab effect for prevention of moderate vision loss (loss of <15 letters) demonstrated in pivotal ranibizumab studies,[7,8] using the 2 CI approach. The FDA suggested that a margin of 5% could determine clinical equivalence. Thus, the margin of 10% was used for assessing noninferiority, and the margin of 5% was used for assessing clinical equivalence. The prespecified analysis plan also included a prospectively planned integrated analysis combining the 2 VIEW studies; in this integrated analysis, the European Medicines Agency/Committee for Medicinal Products for Human Use requested a noninferiority margin of 7%. In the individual studies, the primary end point was assessed by a prespecified hierarchical testing sequence of noninferiority to ranibizumab with the sequence of aflibercept 2q4, 0.5q4, and then 2q8 to control the 5% (4.9% for VIEW 1) overall type I error while maintaining a 5% significance level (4.9% for VIEW 1) for each individual comparison (see Appendices 3 and 4 for details of the statistical analysis, available at http://aaojournal.org). If all aflibercept groups demonstrated noninferiority to ranibizumab for the primary end point, additional comparisons with ranibizumab were prespecified regarding the secondary end points, also using a hierarchical testing sequence in which each secondary end point was tested for superiority of aflibercept over ranibizumab. Prespecified secondary efficacy variables compared baseline and 52-week data regarding mean change in BCVA; gaining ≥15 letters; change in total National Eye Institute 25-Item Visual Function Questionnaire (NEI VFQ-25) score; and change in CNV area on fluorescein angiography. Anatomic measures included retinal thickness and persistent fluid as assessed by OCT. Change in BCVA also was assessed as part of the prospectively planned prespecified integrated analysis combining the 2 studies.

The full analysis set included all randomized patients who received any study medication and had a baseline and at least 1 post-baseline BCVA assessment. The per protocol set (PPS) included all patients in the full analysis set who (1) received at least 9 doses of study drug and attended at least 9 scheduled visits during the first year, (2) had not missed 2 consecutive injections before administration of the ninth injection (per patient), and (3) did not have major protocol violations. Sham injections were counted as doses administered for the purpose of defining the PPS. The PPS included patients who discontinued the study because of treatment failure, without a major protocol deviation, at any time during the first 52 weeks (even if they met points 1 and 2 above). These patients were considered nonresponders for the primary end-point analysis. The last observation carried forward (LOCF) approach was used to impute missing values. When indicated, the robustness of analysis results was assessed by using the observed case or completers' data. A completer was defined as a patient who received treatment for at least 9 months and had efficacy data for at least 9 months during the 52 weeks of study. The missing values for completers also were imputed using the LOCF approach.

Schedule of Visits and Assessments

Patients were examined on the day of treatment initiation and every 4 weeks thereafter through 52 weeks, as well as 1 week after first treatment for safety assessment (subsequent safety assessments occurred by telephone). Each 4-week visit included BCVA assessment and anterior/posterior segment examination (with intraocular pressure determination) before injection (active or sham) and posterior segment examination with intraocular pressure determination 30 to 60 minutes after injection. For the 2q8 treatment group, no treatment decisions were made at the interim monthly visits. The NEI VFQ-25 assessment occurred at screening and weeks 12, 24, 36, and 52. Adverse events were recorded at every visit.

Imaging Assessments

Fundus photography and fluorescein angiography were performed at screening and weeks 24 and 52, and evaluated by an independent center (Digital Angiography Reading Center, New York). Optical coherence tomography was performed using time domain Stratus machines (Carl Zeiss Meditec, Jena, Germany) and evaluated by an independent center (VIEW 1: OCT Reading Center at Duke, Durham, NC; VIEW 2: Vienna Reading Center, Austria). Visual acuity examiners were certified to ensure consistent measurement of BCVA. In VIEW 1, OCT was performed at screening, at the treatment initiation visit, and at weeks 4, 12, 24, 36, and 52

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(and was optional at the investigators' discretion at other study visits). In VIEW 2, OCT was performed at every study visit. Areas of visible CNV (classic or occult) were identified when angiographic analyses showed evidence of late leakage or pooling of dye.

Masking

Patients were masked as to treatments. An unmasked investigator performed the study drug or sham injection. An unmasked investigator also was responsible for the receipt, tracking, preparation, destruction, and administration of study drug, as well as safety assessments both pre- and post-dose. A separate masked physician assessed adverse events and supervised the masked assessment of efficacy. All other study site personnel were masked to treatment assignment by separating study records or masked packaging. Optical coherence tomography technicians and visual acuity examiners remained masked relative to treatment assignment. Intravitreal aflibercept and sham kits were packaged identically. Lucentis (Genentech Inc, South San Francisco, CA) was obtained commercially but only prepared and delivered by unmasked personnel at the sites.

Results

Patient Disposition, Baseline Characteristics, and Exposure

The disposition of patients is shown in Figure 1A-B. In VIEW 1, 1217 patients were randomized, with 91.1% to 96.4% of patients completing 52 weeks. In VIEW 2, 1240 patients were randomized, with 88.1% to 91.1% completing 52 weeks. Baseline demographics and disease characteristics were evenly balanced among all treatment groups (Table 1). The mean number of active injections received by patients in all monthly treatment arms, which were scheduled to receive 13 monthly injections, was 12.1 to 12.5 in VIEW 1 and 12.2 to 12.4 in VIEW 2. The aflibercept every-2-month groups, scheduled to receive 3 initial monthly injections followed by 5 active injections over the next 10 months, received an average of 7.5 active injections in VIEW 1 and in VIEW 2.

Primary End Point Analysis

In both studies, the proportion of patients maintaining vision was similar among all treatment groups in the prespecified per-protocol analysis and the full analysis set (Table 2). All aflibercept groups achieved statistical noninferiority compared with monthly ranibizumab, with the CIs of the difference between ranibizumab and

Table 1. Patient Demographics and Baseline Characteristics

	VIEW 1				VIEW 2			
	Ranibizumab	*Intravitreal Aflibercept*			*Ranibizumab*	*Intravitreal Aflibercept*		
	0.5q4	*2q4*	*0.5q4*	*2q8*	*0.5q4*	*2q4*	*0.5q4*	*2q8*
N (full analysis set)	304	304	301	301	291	309	296	306
Age, yrs (mean ± SD)	78.2±7.6	77.7±7.9	78.4±8.1	77.9±8.4	73.0±9.0	74.1±8.5	74.7±8.6	73.8±8.6
Race								
White	296 (97.4)	295 (97.0)	291 (96.7)	287 (95.3)	213 (73.2)	226 (73.1)	219 (74.0)	217 (70.9)
Black	1 (0.3)	1 (0.3)	0	1 (0.3)	1 (0.3)	0	1 (0.3)	2 (0.7)
Asian	0	3 (1.0)	5 (1.7)	4 (1.3)	60 (20.6)	67 (21.7)	61 (20.6)	69 (22.5)
Other	7 (2.3)	5 (1.6)	5 (1.7)	9 (3.0)	17 (5.8)	16 (5.2)	15 (5.1)	18 (5.9)
Sex								
Men, n (%)	132 (43.4)	110 (36.2)	134 (44.5)	123 (40.9)	122 (41.9)	133 (43.0)	149 (50.3)	131 (42.8)
Women, n (%)	172 (56.6)	194 (63.8)	167 (55.5)	178 (59.1)	169 (58.1)	176 (57.0)	147 (49.7)	175 (57.2)
Baseline ETDRS BCVA (mean ± SD)	54.0±13.4	55.2±13.2	55.6±13.1	55.7±12.8	53.8±13.5	52.8±13.9	51.6±14.2	51.6±13.9
Proportion of patients with ≥20/40 BCVA, % (n)	4.3% (13)	4.9% (15)	6.3% (19)	6.6% (20)	2.7% (8)	2.6% (8)	5.4% (16)	3.3% (10)
CNV area, mm^2 (mean ± SD)	6.53±5.2	6.59±5.1	6.49±4.5	6.57±5.1	7.59±5.3	8.25±5.8	7.70±5.3	7.75±5.5
Lesion type								
Predominantly classic, n (%)	82 (27.0)	87 (28.6)	81 (26.9)	71 (23.6)	70 (24.1)	72 (23.3)	80 (27.0)	88 (28.8)
Minimally classic, n (%)	101 (33.2)	105 (34.5)	97 (32.2)	110 (36.5)	104 (35.7)	112 (36.2)	103 (34.8)	106 (34.6)
Occult, n (%)	115 (37.8)	110 (36.2)	121 (40.2)	118 (39.2)	116 (39.9)	123 (39.8)	113 (38.2)	110 (35.9)
Patients with juxtafoveal lesions, n (%)	15 (4.9)	13 (4.3)	17 (5.6)	17 (5.6)	20 (6.9)	15 (4.9)	11 (3.7)	14 (4.6)
Lesion size, mm^2 (mean ± SD)	6.99±5.5	6.98±5.4	6.95±4.7	6.89±5.2	8.01±5.7	8.72±6.1	8.17±5.5	8.22±5.9
Central retinal thickness, μm (mean ± SD)	315.3±108.3	313.6±103.4	313.2±106.0	324.4±111.2	325.9±110.9	334.6±119.8	326.5±116.5	342.6±124.0
Baseline NEI VFQ-25 scores (mean ± SD)	71.8±17.2	70.4±16.6	71.1±17.8	69.6±16.8	72.9±19.1	70.3±19.4	74.0±18.2	71.3±19.1

0.5q4 = 0.5 mg monthly; 2q4 = 2 mg monthly; 2q8 = 2 mg every 2 months after 3 initial monthly doses; BCVA = best-corrected visual acuity; CNV = choroidal neovascularization; ETDRS = Early Treatment Diabetic Retinopathy Study; NEI VFQ-25 = National Eye Institute 25-Item Visual Functioning Questionnaire; SD = standard deviation.

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Table 2. Prespecified Efficacy

	VIEW 1			
	Ranibizumab	*Intravitreal Aflibercept*		
	0.5q4	*2q4*	*0.5q4*	*2q8*
Primary end point				
N (PPS)	269	285	270	265
Proportion maintaining vision (losing <15 ETDRS letters), % (n)	94.4% (254)	95.1% (271)	95.9% (259)	95.1% (252)
N (full analysis set)	304	304	301	301
Proportion maintaining vision (losing <15 ETDRS letters, LOCF), % (n)	93.8% (285)	95.1% (289)	95.0% (286)	94.4% (284)
Secondary end points				
N (full analysis set)	304	304	301	301
Change in ETDRS BCVA (mean ± SD)	8.1±15.3	10.9±13.8	6.9±13.4	7.9±15.0
LS mean difference between IAI and ranibizumab (95% CI)*		3.15 (0.92 to 5.37)	−0.80 (−3.03 to 1.43)	0.26 (−1.97 to 2.49)
Proportion gaining ≥15 ETDRS letters, % (n)	30.9% (94)	37.5% (114)	24.9% (75)	30.6% (92)
LS mean difference between IAI and ranibizumab (95% CI)*		6.58 (−0.98 to 14.14)	−6.00 (−13.17 to 1.16)	−0.36 (−7.74 to 7.03)
Change in CNV area, mm^2 (mean ± SD)	−4.2±5.6	−4.6±5.5	−3.5±5.3	−3.4±6.0
LS mean difference between IAI and ranibizumab (95% CI)*		−0.33 (−1.04 to 0.38)	0.71 (−0.01 to 1.42)	0.86 (0.15–1.58)
Change in total NEI VFQ-25 score (mean ± SD)	4.9±14.0	6.7±13.5	4.5±11.9	5.1±14.7
LS mean difference between IAI and ranibizumab (95% CI)*		1.28 (−0.73 to 3.28)	−0.67 (−2.69 to 1.35)	−0.60 (−2.61 to 1.42)
Exploratory end point				
Change in central retinal thickness, μm (mean ± SD)	−116.8±109.0	−116.5±98.4	−115.6±104.1	−128.5±108.5
Post hoc end point†				
Proportion with dry retina (absence of cystic intraretinal edema and subretinal fluid on OCT), % (n)	63.6% (171)	64.8% (184)	56.7% (148)	63.4% (168)

0.5q4 = 0.5 mg monthly; 2q4 = 2 mg monthly; 2q8 = 2 mg every 2 months after 3 initial monthly doses; BCVA = best-corrected visual acuity; aflibercept injection; LOCF = last observation carried forward; LS = least-squares; NEI VFQ-25 = National Eye Institute 25-Item Visual
*95.1% CI for VIEW 1.
†Observed case.

each aflibercept group within the prespecified 10% margin (Fig 2), and the point estimates of the differences in means favoring the aflibercept groups in all cases. All the aflibercept regimens also met the prespecified 7% noninferiority margin in the prespecified integrated analysis combining the 2 VIEW studies, as well as the prespecified 5% margin for clinical equivalence compared with ranibizumab in the individual VIEW studies. Moreover, the results of multiple imputation analyses were consistent with those using the LOCF.

Mean Changes in Best-Corrected Visual Acuity and Other Visual Acuity End Points

The mean change in BCVA was a clinically important secondary end point in both studies. On the basis of the hierarchical testing sequence, only the aflibercept 2q4 group was statistically superior to ranibizumab, and only in VIEW 1, with a gain of +10.9 versus +8.1 letters (Table 2). Small numeric differences between treatment groups in one study at any given timepoint were not reproduced in the other study, suggesting that they reflected random variability even in groups of this size (Fig 3A, B); this interpretation was supported by a prespecified integrated analysis that combined the 2 studies (Fig 3C), showing similar visual acuity scores across the entire 52-week study for all treatment groups. All groups behaved similarly in this integrated analysis (Fig 3C), with rapid increases in mean visual acuity after the first injection followed by incremental gains that were durable and maintained through week 52. Regardless of whether the analysis was by LOCF, by multiple imputations, by assessing completers, or by using actual observed data, intravitreal aflibercept dosed every 2 months achieved a mean visual acuity score within 0.3 letters of monthly ranibizumab in the integrated analysis, with a CI of less than 2 letters (Fig 3C, inset).

In both studies, the secondary end point of proportions of patients gaining ≥15 ETDRS letters from baseline to week 52 was similar in all treatment groups (Table 2), as were other exploratory categoric measures of visual outcome (Appendix 5, available at http://aaojournal.org). Likewise, vision-related quality of life, assessed by the change of total score of the NEI VFQ-25, improved in all groups in both studies (Table 2).

Key Anatomic Measures

In both studies, all groups demonstrated a comparable decrease in the secondary end point of change in area of active CNV

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Outcomes at Week 52

	VIEW 2			
	Ranibizumab	*Intravitreal Aflibercept*		
	0.5q4	*2q4*	*0.5q4*	*2q8*
Primary end point				
N (PPS)	269	274	268	270
Proportion maintaining vision (losing <15 ETDRS letters), % (n)	94.4% (254)	95.6% (262)	96.3% (258)	95.6% (258)
N (full analysis set)	291	309	296	306
Proportion maintaining vision (losing <15 ETDRS letters, LOCF), % (n)	94.8% (276)	94.5% (292)	95.3% (282)	95.4% (292)
Secondary end points				
N (full analysis set)	291	309	296	306
Change in ETDRS BCVA (mean ± SD)	9.4±13.5	7.6±12.6	9.7±14.1	8.9±14.4
LS mean difference between IAI and ranibizumab (95% CI)*		−1.95 (−4.10 to 0.20)	−0.06 (−2.24 to 2.12)	−0.90 (−3.06 to 1.26)
Proportion gaining ≥15 ETDRS letters, % (n)	34.0% (99)	29.4% (91)	34.8% (103)	31.4% (96)
LS mean difference between IAI and ranibizumab (95% CI)*		−4.57 (−12.02 to 2.88)	0.78 (−6.91 to 8.46)	−2.65 (−10.18 to 4.88)
Change in CNV area, mm^2 (mean ± SD)	−4.2±5.9	−6.0±6.1	−4.2±6.1	−5.2±5.9
LS mean difference between IAI and ranibizumab (95% CI)*		−1.18 (−1.98 to −0.38)	0.17 (−0.63 to 0.97)	−0.73 (−1.53 to 0.07)
Change in total NEI VFQ-25 score (mean ± SD)	6.3±14.8	4.5±15.0	5.1±13.7	4.9±14.7
LS mean difference between IAI and ranibizumab (95% CI)*		−2.79 (−4.90 to −0.68)	−0.93 (−3.07 to 1.20)	−1.95 (−4.07 to 0.17)
Exploratory end point				
Change in central retinal thickness, μm (mean ± SD)	−138.5±122.2	−156.8±122.8	−129.8±114.8	−149.2±119.7
Post hoc end point†				
Proportion with dry retina (absence of cystic intraretinal edema and subretinal fluid on OCT), % (n)	60.4% (162)	80.3% (220)	63.9% (170)	71.9% (197)

CNV = choroidal neovascularization; CI = confidence interval; ETDRS = Early Treatment Diabetic Retinopathy Study; IAI = intravitreal Functioning Questionnaire; OCT = optical coherence tomography; PPS = per protocol set; SD = standard deviation.

(Table 2). Likewise, all aflibercept groups in both studies had reductions in central retinal thickness similar to those for monthly ranibizumab as assessed by OCT, with a large and rapid reduction evident by week 4 (with retinal thickness approaching normal levels) that was maintained to week 52 (Table 2, Fig 4). Minor fluctuations in central retinal thickness were seen in the 2q8 group after sham injections in the VIEW 2 study; these fluctuations attenuated over time, starting at 17 μm and decreasing to 8 μm over the year, with no apparent negative impact on visual acuity outcomes.

Because of the inability of other regimens in the CATT[13] to match the retinal thickness and retinal fluid improvements seen with monthly ranibizumab, a post hoc analysis was performed to determine the percentage of patients who had fluid-free retinas, which were defined, on OCT, by the absence of both cystic intraretinal edema and subretinal fluid. All intravitreal aflibercept groups were similar to the monthly ranibizumab group in terms of this end point, with numerically higher percentages of dry retinas seen in the 2q4 and 2q8 regimens largely driven by VIEW 2 (Table 2; Appendix 6, available at http://aaojournal.org). Integrated analysis combining both studies for proportions of patients with dry retinas for ranibizumab and the aflibercept regimens of 2q4, 0.5q4, and 2q8 showed percentages of 62.0%, 72.4%, 60.3%, and 67.7%, respectively.

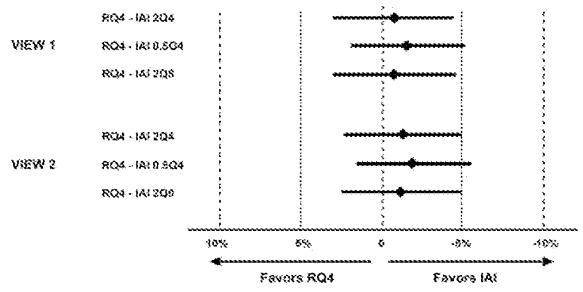

Figure 2. Difference in proportions of patients who maintained vision (losing <15 Early Treatment Diabetic Retinopathy Study [ETDRS] letters) at week 52 in the VIEW studies (per protocol set [PPS]). The *diamond symbol* denotes the difference between the treatment arms, and the *horizontal bars* indicate 95% confidence interval (CI) range. The CI within the left 10% (*dashed vertical lines*) indicates that all intravitreal aflibercept arms were noninferior to ranibizumab. The CI within the left 5% (*dotted vertical line*) indicates clinical equivalence to ranibizumab. The last observation carried forward (LOCF) was used for imputing the missing values. RQ4 = 0.5 mg ranibizumab monthly; 0.5Q4 = 0.5 mg IAI monthly; 2Q4 = 2 mg IAI monthly; 2Q8 = 2 mg IAI every 2 months after 3 initial monthly doses; IAI = intravitreal aflibercept injection.

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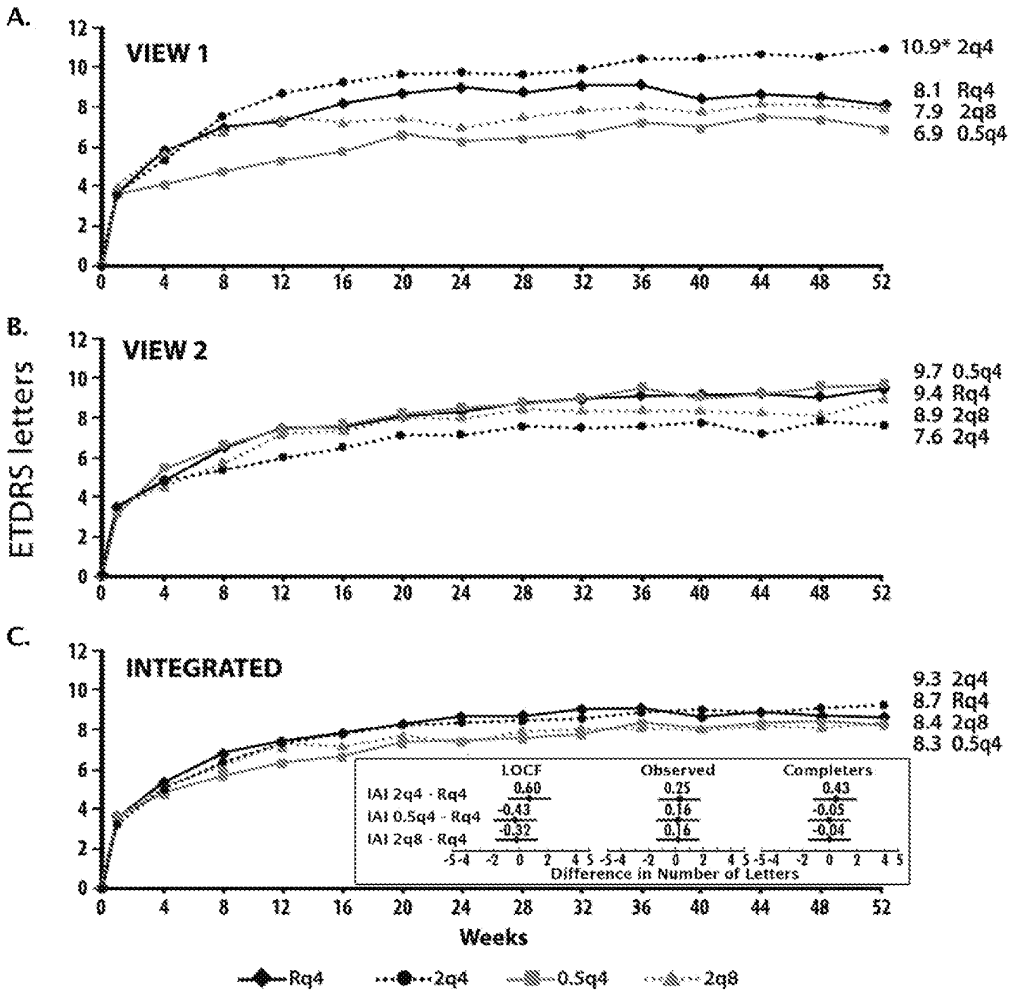

Figure 3. Mean change in best-corrected visual acuity (BCVA) from baseline to week 52 in the individual VIEW studies and in the integrated analysis. Values in the line graphs refer to mean changes in the number of letters from baseline at week 52. Only the intravitreal aflibercept 2q4 arm in VIEW 1 was significantly different from ranibizumab (*P = 0.005 for the difference). The panel inset (integrated analysis) shows the difference in visual acuity between each intravitreal aflibercept arm and ranibizumab (least-square mean with 95% confidence interval [CI]) at week 52, using 3 different analyses: by last observation carried forward (LOCF), using observed case data, and by assessing completers. Rq4 = 0.5 mg ranibizumab monthly; 0.5q4 = 0.5 mg IAI monthly; 2q4 = 2 mg IAI monthly; 2q8 = 2 mg IAI every 2 months after 3 initial monthly doses; ETDRS = Early Treatment Diabetic Retinopathy Study; IAI = intravitreal aflibercept injection.

Safety

Intravitreal aflibercept was generally well tolerated and had a profile of ocular treatment-emergent adverse experiences, including serious ocular adverse events, similar to those for monthly ranibizumab (Table 3; Appendix 7, available at http://aaojournal.org). Differences were noted in the prespecified analyses of intraocular pressure: Fewer patients treated with aflibercept had increases in intraocular pressure over the 52 weeks of the VIEW 1 and VIEW 2 studies (Appendix 7, available at http://aaojournal.org). There were few ocular injection–related treatment-emergent serious adverse events in the study eye. The combined data for both studies showed a rate of events/1000 injections of 1.1, 0.8, 0.1, and 0.2 for the ranibizumab 0.5q4 and intravitreal aflibercept 2q4, 0.5q4, and 2q8 groups, respectively. These events included eye disorders, endophthalmitis, procedural complications, and increased intraocular pressure.

There was a similar overall incidence of systemic (nonocular) adverse events (Appendix 7, available at http://aaojournal.org), serious systemic adverse events, specific arterial thromboembolic end points as set forth by the Anti-Platelet Trialists' Collaboration, and deaths between intravitreal aflibercept and ranibizumab (Table 3). Among the aflibercept treatment groups, there was no evidence of a dose-response for adverse events: The group with the highest exposure, the aflibercept 2q4 group, generally had the lowest rates of adverse events. There was little to no immunogenicity associated with intravitreal aflibercept (Appendix 8, available at http://aaojournal.org).

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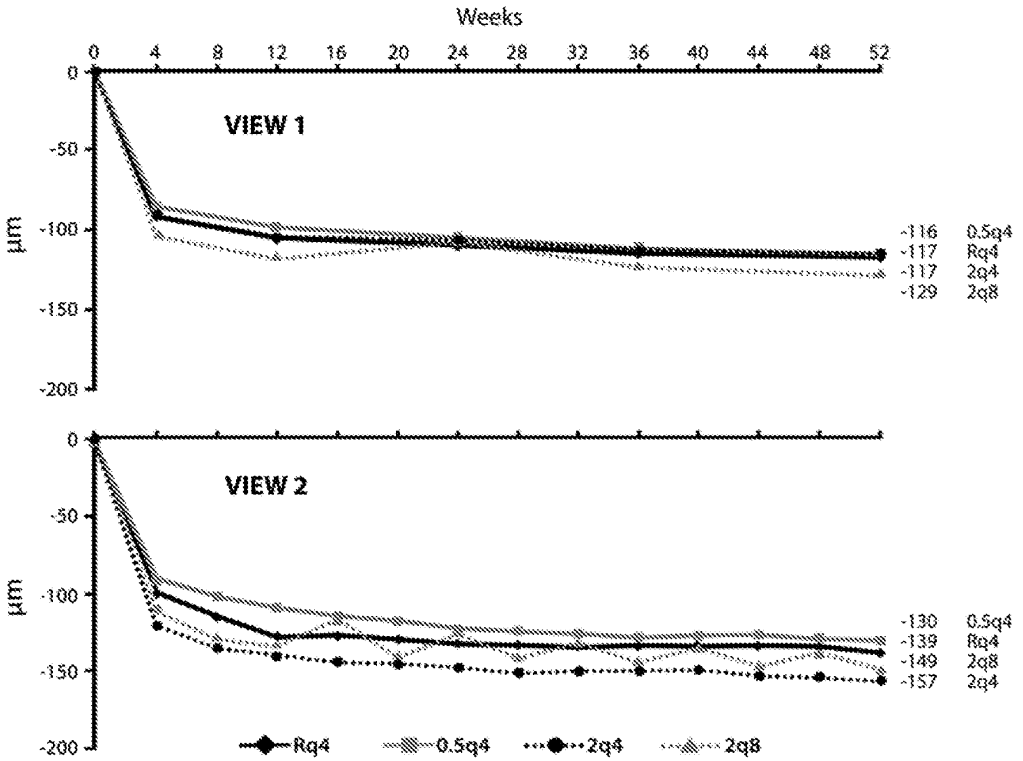

Figure 4. Mean change from baseline in central retinal thickness (full analysis set). As described in the "Materials and Methods" section, in VIEW 1, optical coherence tomography (OCT) was performed at screening, at the treatment initiation visit, and at weeks 4, 12, 24, 36, and 52 (and was optional at the investigators' discretion at other study visits). In VIEW 2, OCT was performed at every study visit. The last observation carried forward (LOCF) was used for imputing the missing values. Rq4 = 0.5 mg ranibizumab monthly; 0.5q4 = 0.5 mg intravitreal aflibercept injection (IAI) monthly; 2q4 = 2 mg IAI monthly; 2q8 = 2 mg IAI every 2 months after 3 initial monthly doses.

Discussion

We have described 2 large and similarly designed clinical trials involving more than 2400 patients with neovascular AMD. In both trials, all 3 aflibercept treatment regimens (including the every-2-month regimen after 3 initial monthly loading doses) were statistically noninferior to monthly ranibizumab in preventing moderate visual acuity loss at 1 year, meeting the primary outcome of the trials; all the aflibercept regimens also met the stricter margin of 5% for clinical equivalence compared with monthly ranibizumab. In terms of mean change in BCVA over time, all aflibercept regimens behaved similarly to monthly ranibizumab, with rapid increases after the first treatment followed by incremental gains that were durable and maintained through week 52. Mean visual acuity scores were within 1 letter of each other at week 52 in the prespecified integrated analysis combining the 2 studies; of note, aflibercept dosed every 2 months achieved a visual acuity score within 0.3 letters of monthly ranibizumab, with a CI of less than 2 letters, regardless of the analysis set used. Because the CATT[13] highlighted the inability of other regimens, including monthly bevacizumab and PRN ranibizumab or bevacizumab, to match the retinal thickness and retinal fluid improvements seen with monthly ranibizumab, it is notable that all 3 aflibercept regimens behaved similarly to monthly ranibizumab in terms of these anatomic measures.

Because of the large treatment burden, extensive efforts have been devoted toward developing an optimized treatment paradigm that avoids the need for monthly injections or monitoring visits. The CATT and HARBOR studies used noninferiority margins of change from baseline BCVA of 5 letters and 4 letters, respectively, to evaluate the efficacy of PRN regimens (Invest Ophthalmol Vis Sci 2012;53:E-Abstract 3677).[13] The CATT[13] generated much interest, in part because it showed that PRN ranibizumab and bevacizumab regimens approached the visual acuity outcomes achieved with monthly ranibizumab; however, these PRN regimens produced numerically smaller gains in BCVA at 52 weeks (by 1.7–2.6 letters) with poorer anatomic outcomes. Switching from a monthly to a PRN regimen during the second year of the CATT significantly worsened visual and anatomic out-

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Table 3. Serious Ocular Adverse Events in the Study Eye and Other Key Nonocular Events Occurring in ≥0.5%* of Patients in Any Study Arm

	VIEW 1				VIEW 2			
	Ranibizumab	*Intravitreal Aflibercept*			*Ranibizumab*	*Intravitreal Aflibercept*		
	0.5q4	*2q4*	*0.5q4*	*2q8*	*0.5q4*	*2q4*	*0.5q4*	*2q8*
N (safety analysis set)	304	304	304	303	291	309	297	307
Patients with at least 1 ocular SAE, n (%)	10 (3.3)	7 (2.3)	6 (2.0)	3 (1.0)	9 (3.1)	6 (1.9)	5 (1.7)	9 (2.9)
Serious ocular adverse event, n (%)								
Endophthalmitis	3 (1.0)	3 (1.0)	0	0	0	0	0	0
Visual acuity reduced	2 (0.7)	1 (0.3)	2 (0.7)	0	1 (0.3)	1 (0.3)	1 (0.3)	5 (1.6)
Retinal hemorrhage	2 (0.7)	0	0	2 (0.7)	1 (0.3)	2 (0.6)	1 (0.3)	1 (0.3)
Posterior capsule opacification	—	—	—	—	2 (0.7)	0	0	0
Serious systemic (or nonocular) adverse event	57 (18.8)	40 (13.2)	50 (16.4)	51 (16.8)	26 (8.9)	36 (11.7)	37 (12.5)	38 (12.4)
APTC ATE events								
Any APTC ATE event	5 (1.6)	2 (0.7)	7 (2.3)	6 (2.0)	5 (1.7)	4 (1.3)	5 (1.7)	8 (2.6)
Vascular death	1 (0.3)	0	1 (0.3)	4 (1.3)	1 (0.3)	1 (0.3)	2 (0.7)	1 (0.3)
Nonfatal myocardial infarction	4 (1.3)	1 (0.3)	4 (1.3)	1 (0.3)	2 (0.7)	2 (0.6)	2 (0.7)	5 (1.6)
Nonfatal stroke	0	1 (0.3)	2 (0.7)	1 (0.3)	2 (0.7)	1 (0.3)	1 (0.3)	2 (0.7)
Any AE of hypertension	29 (9.5)	25 (8.2)	26 (8.6)	31 (10.2)	29 (10.0)	31 (10.0)	22 (7.4)	28 (9.1)
SAEs of interest occurring in any patient								
Venous thromboembolic event	1 (0.3%)	0	1 (0.3%)	0	0	0	0	0
Congestive heart failure event	2 (0.7%)	1 (0.3%)	2 (0.7%)	3 (1.0%)	1 (0.3%)	0	0	1 (0.3%)
GI perforation or fistula event	0	0	0	0	0	0	1 (0.3%)	1 (0.3%)
Nonocular hemorrhagic event	1 (0.3%)	1 (0.3%)	3 (1.0%)	3 (1.0%)	0	2 (0.6%)	0	1 (0.3%)
Delayed wound healing	0	0	0	0	0	0	0	0

0.5q4 = 0.5 mg monthly; 2q4 = 2 mg monthly; 2q8 = 2 mg every 2 months after 3 initial monthly doses; AE = adverse event; APTC ATE = Anti-platelet Trialists' Collaboration Arteriothrombolic Event; GI = gastrointestinal; SAE = serious adverse event.
*For SAEs of interest, occurrence in any patient is reported.

comes and resulted in a decrease in the proportion of patients without retinal fluid.[14] The results from the HARBOR study showed that PRN regimens of ranibizumab (including a higher 2 mg dose) did not achieve noninferiority compared with monthly ranibizumab (Invest Ophthalmol Vis Sci 2012;53:E-Abstract 3677). Moreover, the PRN regimens in both CATT and HARBOR still required mandatory monthly visits, during which treatment decisions had to be made largely on the basis of anatomic measures. The demonstration that monthly aflibercept provides similar efficacy and safety as the current approved standard of monthly ranibizumab is important, but the finding that remarkably similar improvement in vision and anatomic measures can be achieved with less than monthly intravitreal aflibercept injections and without requiring monthly monitoring visits provides an important advance for both patients and their treating physicians. The FDA has approved intravitreal aflibercept injection for AMD and recommended the regimen of 2 mg once every 2 months after 3 initial monthly doses (Eylea [package insert]. Tarrytown, NY: Regeneron Pharmaceuticals, Inc; 2011. Available at: http://www.regeneron.com/Eylea/eylea-fpi.pdf. Accessed August 8, 2012). This approval was based on the evaluation that this regimen provided the best benefit/risk; the approved label notes that aflibercept can be dosed as often as every 4 weeks, although additional efficacy was not reported with such frequent dosing. By halving the need for monthly visits, the every-2-month regimen of aflibercept may markedly decrease the treatment burden experienced by patients and their families. Less frequent injections also should provide an ocular safety benefit. Although the VIEW studies were not powered to see differences in rare but serious intraocular complications (e.g., endophthalmitis and retinal detachment), it is likely that fewer injections may substantially decrease the cumulative population risk of such events, considering that millions of injections are given each year.

After the 1-year primary end point of VIEW 1/VIEW 2 presented in this article, all treatment groups' dosing intervals were changed to a common protocol of modified quarterly dosing with their originally randomized dose and drug (all patients were monitored monthly and received a minimum of dosing every 12 weeks with interim as-needed monthly intravitreal injections). The results of this second year were recently presented (Invest Ophthalmol Vis Sci 2012;53:E-Abstract 6962) and reveal 81.6% to 85.7% patient retention in all groups with comparable visual acuity maintenance (91%–92%) in each group at the 96-week time point. The total number of active injections (baseline to week 96) was 16.0 to 16.2 in the monthly intravitreal aflibercept groups, 16.5 in the monthly ranibizumab group, and 11.2 in the original 2q8 group. The finding that visual acuity maintenance can be achieved for up to 96 weeks in the 2q8 group with similar gains in BCVA compared with ranibizumab despite more than 5 fewer doses is encouraging and implies that the treatment burden of neovascular AMD may be meaningfully reduced with this 2q8 intravitreal aflibercept regimen.

The sustained durability of intravitreal aflibercept as demonstrated by the every-2-month regimen is consistent

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with the rationale that a higher binding affinity could lead to increased durability.[17] It is encouraging that the increased affinity of intravitreal aflibercept did not result in an observed increase in ocular or systemic adverse events. In the VIEW 1 and VIEW 2 trials, no differences in systemic or ocular safety were noted between any of the doses or dosing regimens of intravitreal aflibercept. Systemic exposure of aflibercept injected intravitreally is extremely low (Eylea [package insert]. Tarrytown, NY: Regeneron Pharmaceuticals, Inc; 2011. Available at: http://www.regeneron.com/Eylea/eylea-fpi.pdf. Accessed August 8, 2012). After intravitreal administration of 2 mg per eye of aflibercept to patients with wet AMD, the mean maximum concentration of free aflibercept in the plasma was 0.02 μg/ml (range, 0–0.054 μg/ml) and was attained in 1 to 3 days. The free aflibercept plasma concentrations were undetectable 2 weeks post-dosing in all patients. Aflibercept did not accumulate in plasma when administered as repeated doses intravitreally every 4 weeks. It is estimated that after intravitreal administration of 2 mg to patients, the mean maximum plasma concentration of free aflibercept is more than 100-fold lower than the concentration of aflibercept required to half-maximally bind systemic VEGF.

In conclusion, intravitreal aflibercept dosed monthly or every 2 months after 3 initial monthly doses resulted in similar visual and anatomic outcomes as ranibizumab dosed monthly, as well as similar safety and tolerability. Intravitreal aflibercept dosed every 2 months has the potential to provide patients, their families, and clinicians the opportunity for the optimal vision gains and anatomic disease control they have come to expect from monthly ranibizumab, with a substantially decreased treatment and compliance burden, and a lower cumulative risk of injection-related adverse events.

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References

1. Congdon NG, Friedman DS, Lietman T. Important causes of visual impairment in the world today. JAMA 2003;290: 2057–60.
2. Macular Photocoagulation Study Group. Laser photocoagulation of subfoveal neovascular lesions in age-related macular degeneration. Results of a randomized clinical trial. Arch Ophthalmol 1991;109:1220–31.
3. Treatment of Age-related Macular Degeneration with Photodynamic Therapy (TAP) Study Group. Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin: one-year results of 2 randomized clinical trials–TAP report 1. Arch Ophthalmol 1999; 117:1329–45.
4. Verteporfin in Photodynamic Therapy Study Group. Verteporfin therapy of subfoveal choroidal neovascularization in age-related macular degeneration: two-year results of a randomized clinical trial including lesions with occult with no classic choroidal neovascularization–Verteporfin in Photodynamic Therapy report 2. Am J Ophthalmol 2001;131:541–60.
5. Yancopoulos GD. Clinical application of therapies targeting VEGF. Cell 2010;143:13–6.
6. Ferrara N. VEGF-A: a critical regulator of blood vessel growth. Eur Cytokine Netw 2009;20:158–63.
7. Rosenfeld PJ, Brown DM, Heier JS, et al, MARINA Study Group. Ranibizumab for neovascular age-related macular degeneration. N Engl J Med 2006;355:1419–31.
8. Brown DM, Kaiser PK, Michels M, et al, ANCHOR Study Group. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. N Engl J Med 2006;355: 1432–44.
9. Schmidt-Erfurth U, Eldem B, Guymer R, et al, EXCITE Study Group. Efficacy and safety of monthly versus quarterly ranibizumab treatment in neovascular age-related macular degeneration: the EXCITE study. Ophthalmology 2011;118: 831–9.
10. Regillo CD, Brown DM, Abraham P, et al, PIER Study Group. Randomized, double-masked, sham-controlled trial of ranibizumab for neovascular age-related macular degeneration: PIER Study year 1. Am J Ophthalmol 2008;145:239–48.
11. Boyer DS, Heier JS, Brown DM, et al. A Phase IIIb study to evaluate the safety of ranibizumab in subjects with neovascular age-related macular degeneration. Ophthalmology 2009; 116:1731–9.
12. Singer MA, Awh CC, Sadda S, et al. HORIZON: an open-label extension trial of ranibizumab for choroidal neovascularization secondary to age-related macular degeneration. Ophthalmology 2012;119:1175–83.
13. CATT Research Group, Martin DF, Maguire MG, Ying GS, et al. Ranibizumab and bevacizumab for neovascular age-related macular degeneration. N Engl J Med 2011;364: 1897–908.
14. Comparison of Age-related Macular Degeneration Treatments Trials (CATT) Research Group, Martin DF, Maguire MG, Fine SL, et al. Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: two-year results. Ophthalmology 2012;119:1388–98.
15. IVAN Study Investigators, Chakravarthy U, Harding SP, Rogers CA, et al. Ranibizumab versus bevacizumab to treat neovascular age-related macular degeneration: one-year findings from the IVAN randomized trial. Ophthalmology 2012;119: 1399–411.
16. Economides AN, Carpenter LR, Rudge JS, et al. Cytokine traps: multi-component, high-affinity blockers of cytokine action. Nat Med 2003;9:47–52.
17. Holash J, Davis S, Papadopoulos N, et al. VEGF-Trap: a VEGF blocker with potent antitumor effects. Proc Natl Acad Sci U S A 2002;99:11393–8.
18. Heier JS, Boyer D, Nguyen QD, et al, CLEAR-IT 2 Investigators. The 1-year results of CLEAR-IT 2, a phase 2 study of vascular endothelial growth factor Trap-Eye dosed as-needed after 12-week fixed dosing. Ophthalmology 2011;118:1098–106.
19. Stewart MW, Rosenfeld PJ. Predicted biological activity of intravitreal VEGF Trap. Br J Ophthalmol 2008;92:667–8.
20. Brown DM, Heier JS, Ciulla T, et al, CLEAR-IT 2 Investigators. Primary endpoint results of a phase II study of vascular endothelial growth factor Trap-Eye in wet age-related macular degeneration. Ophthalmology 2011;118: 1089–97.

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Footnotes and Financial Disclosures

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[1] Ophthalmic Consultants of Boston and Tufts University School of Medicine, Boston, Massachusetts.

[2] Retina Consultants of Houston, Houston, Texas.

[3] Oxford Eye Hospital, University of Oxford, Oxford, United Kingdom.

[4] CHU de Bordeaux – Université Bordeaux 2, Bordeaux, France.

[5] Cole Eye Institute, Cleveland, Ohio.

[6] Wilmer Eye Institute, Johns Hopkins University, Baltimore, Maryland.

[7] University of Cologne, Cologne, Germany.

[8] Wills Eye Hospital, Philadelphia, Pennsylvania.

[9] Nagoya City University, Nagoya, Japan.

[10] Regeneron Pharmaceuticals Inc., Tarrytown, New York.

[11] Bayer HealthCare, Berlin, Germany.

[12] Department of Neurology, Heinrich-Heine-Universität Düsseldorf, Germany.

[13] Medical University of Vienna, Vienna, Austria.

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G.D.Y. and N.S., incorporating the advice of a panel of academic and physician experts, developed the initial proposal for the VIEW 1 study design. The study design of both studies was further developed and finalized by the academic authors and clinical and statistical authors from Regeneron Pharmaceuticals and Bayer HealthCare (sponsors). The sponsors conducted the trials and together with the investigators gathered the data. Study conduct and analyses were supervised by the Study Steering Committees and the sponsors. The Writing Committee consisting of authors J.S.H., D.M.B., V.C., and U.S.-E. (subteam of VIEW Steering Committees) along with G.D.Y. composed the first draft of the paper, which was critically revised and finalized by the input of all coauthors. The Writing Committee members and all other authors met authorship criteria. All coauthors had full and unrestricted access to the data and decided to publish the paper vouching for the accuracy and completeness of the reported data.

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Correspondence:
Ursula Schmidt-Erfurth, MD, Department of Ophthalmology, Medical University of Vienna, Waehringer Guertel 18-20, A-1090 Vienna, Austria. E-mail: ursula.schmidt-erfurth@meduniwien.ac.at.

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Page 132

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	Attorney Docket	REGN-008CIPCON2
	First Named Inventor	YANCOPOULOS, GEORGE D.
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	Examiner Name	LOCKARD, JON MCCLELLAND
	Title: "*Use of a VEGF Antagonist to Treat Angiogenic Eye Disorders*"	

Sir:

Applicants submit herewith documents which may be material to the examination of this application and in respect of which there may be a duty to disclose in accordance with 37 C.F.R. §1.56. This submission is not intended to constitute an admission that any document referred to therein is "prior art" for this invention unless specifically designated as such. A listing of the documents is shown on enclosed Form PTO/SB/08A and a copy of the cited document is attached.

The Examiner is requested to make the documents listed on the enclosed PTO/SB/08A of record in this application. Applicants would appreciate the Examiner initialing and returning the initialed copy of form PTO/SB/08A, indicating the documents cited therein have been considered and made of record herein.

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Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

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By: /Karl Bozicevic, Reg. No. 28,807/
Karl Bozicevic, Reg. No. 28,807

BOZICEVIC, FIELD & FRANCIS LLP
201 Redwood Shores Parkway, Suite 200
Redwood City, CA 94065
Telephone: (650) 327-3400
Direct: (650) 833-7735
Facsimile: (650) 327-3231

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96387
Regeneron - Bozicevic, Field & Francis
201 REDWOOD SHORES PARKWAY
SUITE 200
REDWOOD CITY, CA 94065

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U.S. PATENT DOCUMENTS					
Examiner Initial*	Cite No.	Patent Number Number-Kind Code (*if known*)	Issue Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
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	1	MITRA et al., "Review of anti-vascular endothelial growth factor therapy in macular edema secondary to central retinal vein occlusions" Expert Review in Ophthalmo, Taylor & Francis, GB (January 1, 2011) 6(6):623-629	
	2	OLIVERA et al., "VEGF Trap R1R2 suppresses experimental corneal angiogenesis" European Journal of Ophthalmology (January 1, 2010) 20(1):48-54	
	3	Regeneron Pharmaceuticals Inc., "VEGF Trap-Eye Final Phase 2 Results in Age-related Macular Degeneration Presented at 2008 Retina Society Meeting" (September 28, 2008) (XP-002770952)	

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EXPERT REVIEWS

Review of anti-vascular endothelial growth factor therapy in macular edema secondary to central retinal vein occlusions

Expert Rev. Ophthalmol. 6(6), 623–628 (2011)

Arijit Mitra and Peck-Lin Lip*

The Birmingham and Midland Eye Centre, City Hospital, Dudley Road, Birmingham, B18 7QH, UK
**Author for correspondence*
Tel.: +1 215 076 600
Fax: +1 214 406 428
plip@doctor.org.uk

Central retinal vein occlusion (CRVO) is a common retinal vascular disorder with potential risk of blindness. CRVO can be categorized into two distinct entities – non-ischemic and ischemic. Visual prognosis depends on the type of retinal vein occlusion, its severity, degree of retinal ischemia or macular edema (ME) and development of complications. The two most frequent complications of CRVO are persistent ME and neovascularization. Until recently, there has been no effective treatment for ME in CRVO. The introduction of anti-VEGF therapy has altered treatment options for this disease entity. This article aims to review the effect of anti-VEGF drugs in promoting the resolution of edema and improving vision in patients with ME in CRVO.

Keywords: anti-VEGF • macular edema • retinal vein occlusions • treatment

Epidemiology

Retinal vein occlusion is one of the most common retinal vascular disorders, with no particular ethnic preference. The Beaver Dam Eye study found that the overall 15-year cumulative incidence of retinal vein occlusion (RVO) was 2.3% and associations with RVO were noted for age, glaucoma, higher serum creatinine/phosphorus levels, lower serum ionized calcium levels, evidence of retinal focal arteriolar narrowing and the use of barbiturates [1]. The Blue Mountains Eye study observed that the prevalence for each age-specific participant was as follows: 0.7% in individuals younger than 60 years of age; 1.2% in those aged between 60 and 69 years; 2.1% in those aged between 70 and 79 years of age; and 4.6% in those aged 80 years or over [2]. They found no significant sex difference in prevalence.

Prognosis

Approximately 81% of the patients with central RVO (CRVO) are of the non-ischemic, and only 19% are of the ischemic type. However, ischemic CRVO has poorer visual prognosis and the cumulative probability of the disease converting from the non-ischemic to the ischemic form is 9.4 and 12.6% at 6 and 18 months, respectively [3]. The Central Vein Occlusion study showed that 65% of patients with initial visual acuity of 20/40 or better maintained their visual acuity, while patients with intermediate initial acuity (20/50 to 20/200) showed a variable outcome, with only 19% improving to better than 20/50 and 37% having a final visual acuity worse than 20/200. Patients who had poor visual acuity at the first visit (<20/200) had an 80% chance of having a visual acuity less than 20/200 at the final visit, whether ischemic or non-ischemic initially [4]. Macular edema (ME) is one of the common causes of visual loss in CRVO. Iris neovascularization and neovascular glaucoma develop in 40–85% of eyes affected by ischemic CRVO, but in only 5% of non-ischemic eyes [5–7].

Clinical presentation & diagnosis

CRVO is classically characterized by optic disc swelling, increased venous dilatation and tortuosity, widespread deep and superficial hemorrhages, cotton wool spots, retinal edema, and capillary nonperfusion. A number of clinical and fluorescein angiographic features can help to distinguish between ischemic and non-ischemic

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CRVO. Ischemic CRVO is more severe, and is associated with profound visual loss (visual acuity worse than 20/200), severe clinical signs and a marked afferent pupillary defect. However, during the early acute phase of CRVO, such differentiation can be less distinct and a combination of functional tests may be required to achieve a more accurate diagnosis to aid the management plan [8]. Iris neovascularization develops in approximately 35% of eyes with a risk of neovascular glaucoma, unless they are treated vigorously with panretinal photocoagulation. As a general rule, this risk of iris neovascularization is higher if the area of retinal ischemia (retinal nonperfusion as determined by fluorescein angiogram) is >10 disc diameters [9]. Hypertension, hyperlipidemia, diabetes mellitus and glaucoma are the main risk factors associated with CRVO [2,7,10].

Treatment options

There is no current standard treatment for CRVO in an acute setting. Medical or ocular interventions are not effective in reversing the pathological changes of retinal occlusion once it has occurred. The management of RVO is more appropriately aimed at identifying causable and treatable systemic or local risk factors, and the recognition and management of sight-threatening complications. The two main ocular complications are neovascularization and ME. The former is a complication of ischemic CRVO only and can lead to neovascular glaucoma of painful blind eye. Many other therapies for the treatment for CRVO with ME (CRVO-ME) have been tried in recent years, with varying degrees of success. A definite benefit from panretinal photocoagulation to prevent neovascular glaucoma has been shown by the Central Vein Occlusion study [9]. Macular grid laser photocoagulation had its value in treating ME in branch RVO but not in CRVO [9]. Other medical or surgical therapies that have been explored but failed to achieve the desired outcome or were associated with undesirable complications were laser-induced chorioretinal venous anastomosis, intravitreal administration of recombinant tissue plasminogen activator, isovolemic hemodilution therapy, oral pentoxifylline, hyperbaric oxygen therapy, radial optic neurotomy, vitrectomy with or without internal limiting membrane peeling and direct injection of recombinant tissue plasminogen activator into the lumen of a retinal vein via retinal vein cannulation [11–18].

Intravitreal triamcinolone acetonide doses of 4 mg/0.1 ml used as a nonlicensed agent with anti-inflammatory properties has been widely used for many years with variable success in CRVO-ME [19]. The SCORE study treated participants with non-ischemic CRVO-ME with either 1 or 4 mg intravitreal triamcinolone injections repeated every 4 months, or observation alone. Both treatment doses were associated with a fivefold increase in the odds of achieving a 15-letter gain in visual acuity at 12 months ($p = 0.001$) [20]. However, its short-acting properties and incidence of complications, such as raised intraocular pressure (IOP) and lens opacity, had led to its use mainly as a second-line therapy [19].

Recently, an alternative longer acting steroid, dexamethasone implant (Ozurdex), had been extensively studied and gained licensing for its efficacy in treating CRVO-ME. The Ozurdex trial compared a single dexamethasone implant, at a dose of 0.7 or 0.35 mg, with a sham implant, in adults with branch RVO (BRVO)-ME and CRVO-ME of 6 weeks to 9 months' duration (ischemic vs non-ischemic status not specified) [21]. The percentage of eyes with CRVO-ME achieving ≥15 letters improvement in visual acuity was significantly higher in both Ozurdex groups at day 30 and day 60 than in the sham group ($p < 0.001$). The greatest response was 29% at day 60. In the 0.7-mg group, 22% gained ≥15 letters improvement at 6 months but this was not significantly different from the sham group of 18% improvement. There were no statistically significant differences between the 0.7- and 0.35-mg groups at follow-up visits. Ocular hypertension was reported to be significantly higher in the Ozurdex groups compared with the sham group ($p \leq 0.002$), and peaked at day 60. The percentage of eyes in the Ozurdex groups that required IOP-lowering medication was 6% at the beginning, increasing to 24% at 6 months into the study, and no changes were seen in the sham group. The percentage that required surgical glaucoma filtration surgery was 0.63% (five out of 798 patients). The incidence of side effects were similar, although lower compared with triamcinolone agent.

More recently, several anti-VEGF drugs have shown promising and superior results in treating CRVO-ME in comparison to many other available therapies that have been tried. The aim of this review is to provide an overview of the available evidence on this topic.

Role of anti-VEGF

The increase in VEGF, a cytokine, is triggered by hypoxia in pathological conditions. Increased plasma levels of VEGF were first found in diabetic patients, and were highest among those with preproliferative and proliferative retinopathy [22,23]. Human eyes with CRVO showed evidence of intraretinal upregulated expression of VEGF mRNA [24]. Indeed, raised levels of VEGF have been reported in both the aqueous and vitreous fluid of patients with ischemic CRVO, and are responsible for the increase in vascular permeability that leads to ME [25].

Aqueous and vitreous levels of VEGF were significantly correlated with the severity of ME [26,27]. Delivering anti-VEGF antibody into the eye therefore, in theory, should help in the treatment of CRVO-ME, as has been shown in diabetic ME [28]. Intravitreal bevacizumab injections have resulted in a substantial decrease in VEGF under physiologic levels and have remained low with the loading doses of three consecutive monthly retreatments [27].

Anti-VEGF agents

Monoclonal antibodies against VEGF were first developed as an intravenous treatment for metastatic colorectal cancer [29,30]. The three available anti-VEGF agents for intravitreal use are pegaptanib (Macugen™, Eyetech/Pfizer), bevacizumab and ranibizumab (Avastin® and Lucentis, both from Genentech/Roche). Pegaptanib sodium is a 50-kDa aptamer; a pegylated modified oligonucleotide that adopts a specific 3D configuration and has a high affinity for extracellular VEGF-165 [31]. Studies have proven its effect on inhibiting pathological neovascularization and vascular leakage in rodents with induced macular choroidal neovascularization [31,32]. Ranibizumab is a shorter 48-kDa antibody fragment (κ isotype) that binds to the receptors of biologically

Table 1. Summary of evidence for intravitreal anti-VEGF pegaptanib in CRVO-ME.

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Table 1. Summary of evidence results of anti-vascular endothelial growth factor treatment on central retinal vein occlusion macular edema.

Study	Design	Treatment	Results	Ref.
CRUISE study (2010) (392 CRVO)	Ranibizumab 0.3 mg vs ranibizumab 0.5 mg vs sham	Prospective, randomized, double-masked multicenter trial	6 months; Monthly injections	BCVA gained >15 letters: R0.3/0.5 = 46.2/47.7/16.9% Mean reduction in MT: R0.3/0.5 = 504.97/523.9%	[40]
Campochiaro *et al.* (2010) (30 CRVO, 20 BRVO)	Ranibizumab 0.3 mg vs ranibizumab 0.5 mg	Prospective, randomized	2 years; 3 injections + PRN n = 2 in second-year BRVO n = 3.5 in second-year CRVO	BCVA gained >15 letters in 2 years: 39% in BRVO; 21% in CRVO (no differences in primary end points of all measures between 2 agents)	[41]
BOCC study (2010) (29 CRVO)	Ranibizumab 0.5 mg vs sham	Prospective, randomized, double-masked multicenter trial	6 months; 3 injections + PRN Mean injections = 4.3	Ranibizumab group had significant improvement in BCVA; ranibizumab gained by >16 letters, sham lost by 8 letters ($p = 0.001$)	[42]
Wroblewski *et al.* (2009) (93 CRVO)	Pegaptanib 0.3 mg vs Pegaptanib 1 mg vs sham	Prospective, randomized, double-masked, multicenter Phase II trial	30 weeks; Injection every 6 weeks for 24 weeks	BCVA gained >15 letters: A/0.3/1 = 36.39/28%, respectively ($p = 0.48$) BCVA lost >15 letters: A/0.3/1 = 9/6.3/1%, respectively ($p = 0.01$) Mean reduction in MT: A/0.3/1 = by 269.2/10.5 µm, respectively ($p < 0.001$)	[43]
Pece *et al.* (2010) (9 CRVO, 8 BRVO)	Ranibizumab 0.5 mg	Prospective, consecutive, non-comparative case series	12 months; CRVO $n = 3$ (range: 2–4) BRVO, $n = 3.6$ (range: 3–4)	BCVA gained >15 letters ($p < 0.0001$): CRVO 90%, BRVO 63% MT reduced by 350 µm in CRVO and by 275 µm in BRVO ($p < 0.0001$)	[44]
Figueroa *et al.* (2010) (18 CRVO, 28 BRVO)	Bevacizumab 1.25 mg	Prospective, nonrandomized case series	6 months; CRVO, n = 4.6 (range: 3–6) BRVO, n = 3.7 (range: 1–6)	BCVA gained >10 letters ($p < 0.001$): CRVO 44%, BRVO 67%; BCVA stable: CRVO 56%, BRVO 32% MT reduced by 210 µm in CRVO and by 219 µm in BRVO	[45]
Kriechbaum *et al.* (2008) (8 CRVO, 21 BRVO)	Bevacizumab 1 mg	Prospective, uncontrolled case series	6 months; 3 injections + PRN (n = 5.3)	BCVA gained >15 letters ($p < 0.001$); MT reduced by 172 µm ($p < 0.001$)	[46]
Spaide *et al.* (2009) (20 CRVO)	Ranibizumab 0.5 mg	Prospective, case series	12 months; 3 injections + PRN (n = 8.5)	Mean BCVA gained = 18.5 letters; MT reduced by 388.6 µm ($p < 0.001$)	[47]

A: Aflibercept 0.5 mg; B: Bevacizumab 1 mg; BCVA: Best-corrected visual acuity; BRVO: Branch retinal vein occlusion; CRVO: Central retinal vein occlusion; MT: Macular thickness; PRN: As required; R: Ranibizumab; R0.3: Ranibizumab 0.3 mg; R0.5: Ranibizumab 0.5 mg; S: Sham.

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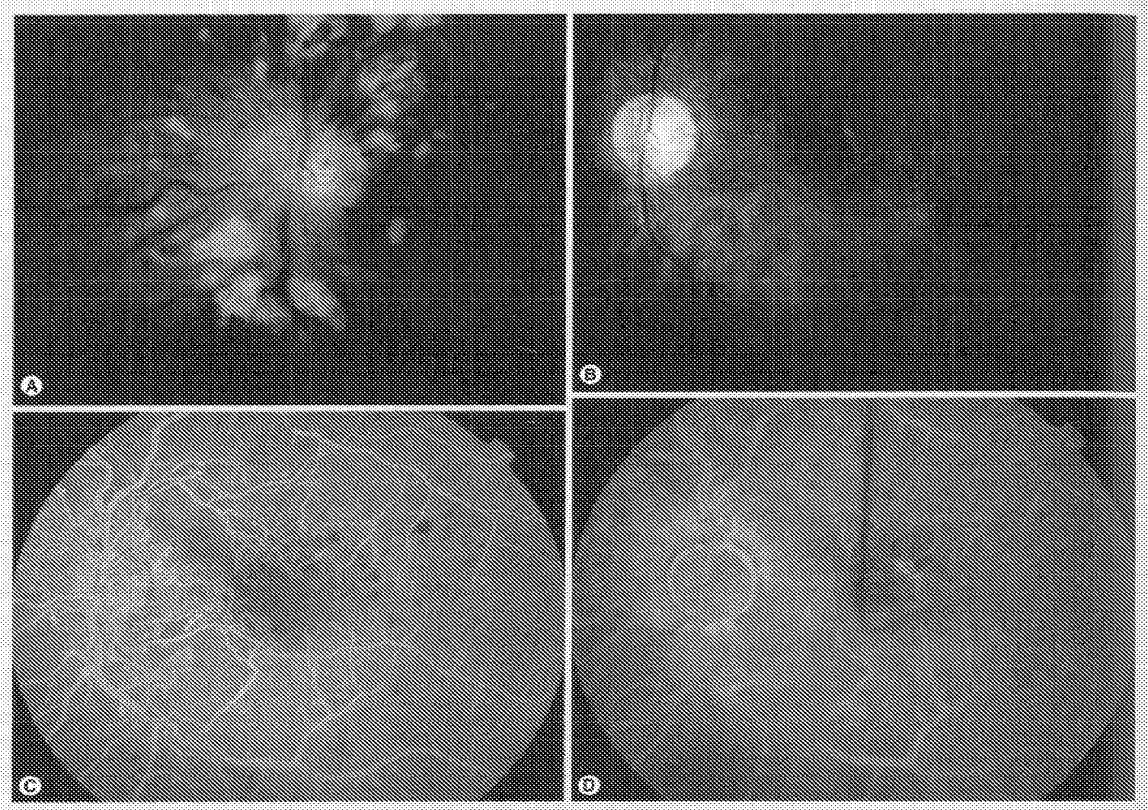

Figure 1. Resolution of ischemic central retinal vein occlusion (without macular edema) after bevacizumab injection.
(A) Patient presented with acute reduced vision (counting fingers only) and diagnostic clinical signs of ischemic central retinal vein occlusion. He received an intravitreal bevacizumab injection within 2 days of presentation. **(B)** Patient's vision recovered significantly to Snellen 6/36 after three bevacizumab injections and remained stable and unchanged for subsequent reviews (4 years of follow-up). He never developed macular edema and foveal scarring established after macular hemorrhages resolved. Laser treatment of pan-retinal photocoagulation was avoided and patient maintained normal peripheral perimeter visual field. **(C)** Fluorescein angiogram after first bevacizumab injection showed extensive ischemia with large areas of capillary drop-out. **(D)** Fluorescein angiogram after last bevacizumab injection (four in total) showed improvement of generalized perfusion.

active VEGF-A, including VEGF-110. This blocks the binding of VEGF-A to VEGR receptor (VEGFR)1 and VEGFR2 receptors on endothelial cells [33]. Bevacizumab, however, is a larger whole antibody of 149 kDa, and possesses two antigen-binding domains for its receptors Flt-1 and KDR. It binds to all isoforms of VEGF [34]. The difference in molecular masses may determine their potential difference in efficacy (studies are currently underway to further evaluate this factor) and their duration of action. Detailed safety profiles and risks of adverse effects are now available for these agents as they have been used extensively in patients for the treatment of age-related macular degeneration [35,36]. Furthermore, the incidence of raised IOP and development of lens opacity with anti-VEGF agents is negligible when compared with intravitreal steroid injections [37,38].

Evidence

Until recently, most of our clinical decisions regarding the management of CRVO-ME were based on the Central Vein Occlusion study [9]. Recently, the Cochrane Eye and Vision Group published a systematic review on anti-VEGF therapy in the management of ME secondary to CRVO [39]. They concluded that ranibizumab and pegaptanib sodium had shown promise in the short-term treatment of non-ischemic CRVO-ME. Despite the lack of any randomized trial data, many case series reported that off-label bevacizumab can be as effective as ranibizumab in treating CRVO-ME, a growing popular choice because of its low cost. Table 1 includes a summary of published randomized control trials and case series for the treatment CRVO-ME [30–47]. There were no data on anti-VEGF agents in the subgroup of ischemic CRVO with or without ME. Spaide

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et al. studied the effect of ranibizumab in patients who had previous bevacizumab or triamcinolone injections [67]. All studies had reported convincing evidence of the benefits of anti-VEGF treatments in CRVO resulting in both visual and anatomical resolution up to 1-year follow-up. Again, there were no major ocular or systemic adverse effects from many of the studies analyzed. The recognized risk with intravitreal injection procedures is severe ocular infection or endophthalmitis. Only recently have there been reports on sustained elevated IOP after anti-VEGF injections [68,69]. The incidence was low, at 3.45–6% in patients receiving multiple intravitreal anti-VEGF injections (range: 3–19 injections). There was concern over patients with pre-existing glaucoma who experienced higher rates of elevated IOP when compared with patients without (33 vs 3.1%, respectively; $p < 0.001$) [69].

Expert commentary

Who will respond?

Intact external limiting membrane

In a recent study, Wolf-Schnurrbusch *et al.* attempted to analyze the predictive factors for best-corrected visual acuity (BCVA) after anti-VEGF treatment in patients with treatment-naive CRVO-ME [29]. BCVA, ophthalmoscopy, fundus photography and spectral domain-optical coherence tomography (SD-OCT) imaging were all performed. SD-OCT was analyzed for integrity of the external limiting membrane (ELM), photoreceptor inner segments (PIS) and outer segments (POS). In total, 62 patients were treated with intravitreal bevacizumab (1.25 mg) or ranibizumab (0.5 mg). In 55%, the ELM was intact. BCVA outcome was analyzed 4 weeks after the first injection, and the study reported a mean BCVA increase of 18 ± 12 letters in eyes with intact ELM compared with 4 ± 10 letters with disturbed ELM ($p < 0.001$). In total, 36 patients (58%) showed a clinically relevant improvement of BCVA (≥5 letters) 4 weeks after the first injection. There were no differences between the two anti-VEGF agents used. The authors concluded that intact ELM in SD-OCT imaging is associated with better visual outcome after intravitreal anti-VEGF treatment in patients with ME secondary to CRVO, and suggested that indication for treatment and retreatment should be based on functional and morphologic findings, such as the deterioration of the outer retinal layers.

Ischemic or non-ischemic

It is fair to conclude that anti-VEGF therapy has been established from various studies in achieving promising visual and anatomical improvement in non-ischemic CRVO. The dilemma still holds on treating the subgroup of very ischemic CRVO-ME with profound visual loss. One is not to forget the potential advantage of the combined treatment of anti-VEGF agents with intravitreal corticosteroids, or indeed laser therapy, when one therapy alone fails to produce rapid significant improvement in vision and anatomical changes. Udaondo *et al.* reported a very small series of refractory BRVO-ME patients (n = 5) who had not responded well to bevacizumab ± triamcinolone injections initially, but did show significant improvement in BCVA and macular thickness with the addition of two injections of pegaptanib [58]. In our personal experience, we also found that combined therapy is more likely to be needed in dealing with the very ischemic subgroup of CRVO-ME patients. Interestingly, ischemic CRVO without ME seems to have the most rapid and long-lasting response from anti-VEGF treatment alone (author's experience with bevacizumab), with no more than the initial course of three injections required. We identified a small group of three patients who had early presentation and angiographic-proven ischemic CRVO, without ME. After the initial course of three intravitreal bevacizumab injections, the ischemic retinopathy was stabilized or reversed (mean: 0). Patients experienced visual and visual field improvement or stabilization, without the need for further treatment (additional sessions of anti-VEGF or steroid injections or laser therapy). Follow-up was 22 months to 4 years, with no recurrence of disease nor ocular complications.

Five-year view

The available evidence suggests that repeated early frequent treatment of CRVO-ME with the anti-VEGF agents ranibizumab, bevacizumab or pegaptanib give the best chance of achieving and stabilizing both optimal anatomical and visual outcomes in the short to medium term. There is no standard protocol regarding the optimal timing of initial treatment with different anti-VEGF agents and subsequent retreatment is yet to be formulated. The general approach from various studies suggests the initial loading dose of one injection per month for the first 3 months. The patients are then reviewed once a month and reinjections are indicated based on anatomical response. Where multiple injections are likely to be required, the effectiveness and safety over longer periods has yet to be determined. As NICE in the UK has recently recognized and approved the use of Ozurdex for treating ME secondary to CRVO and BRVO (not amenable to laser), this will likely lead to a shift in clinicians' views in choosing the intravitreal agent for treating CRVO-ME in the next 5 years. Ranibizumab has also been licenced to treat the same disease and is currently being reviewed by NICE. With more research and experience into exploring the frequency and safety of the currently available agents, it is also likely that clinicians would achieve the best protocol when dealing with CRVO-ME patients. Clinicians are indeed entering into an exciting era in treating these previously refractory cases; similar to the recent success in developing a longer lasting steroid (Ozurdex), the likelihood of another anti-VEGF agent (e.g., VEGF-Trap) may be available in 5 years time to achieve equally promising but longer effectiveness, and reduce the frequency of injections. As further studies are awaited on this subject, there is no doubt that the increases in the spectrum of indications for anti-VEGF agents will have a significant economic impact. In the UK, extensive evidence on safety and long-term results would be needed before anti-VEGF agents can be widely adopted for a select group of CRVO-ME patients.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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Key issues

- The available evidence suggests that repeated early frequent treatment of central retinal vein occlusion with macular edema (ME) with the anti-VEGF agents ranibizumab, bevacizumab or pegaptanib may improve both anatomical and visual outcomes in the short to medium term.
- Intact external limiting membrane in spectral domain-optical coherence tomography imaging is associated with better visual outcome after intravitreal anti-VEGF treatment in patients with ME secondary to central retinal vein occlusion.
- The dilemma still holds regarding treatment of the very ischemic central retinal vein occlusion subgroup with ME with profound visual loss.
- Combination therapy of anti-VEGF agents and a steroid may be required as the best option to stabilize refractory disease.

References

1. Klein R, Moss SE, Meuer SM *et al.* The 15-year cumulative incidence of retinal vein occlusion: the Beaver Dam Eye study. *Arch. Ophthalmol.* 126(4), 513–518 (2008).
2. Mitchell P, Smith W, Chang A. Prevalence and associations of retinal vein occlusion in Australia: the Blue Mountains Eye study. *Arch. Ophthalmol.* 114, 1243–1247 (1996).
3. Hayreh SS, Zimmerman MB, Podhajsky P. Incidence of various types of retinal vein occlusion and their recurrence and demographic characteristics. *Am. J. Ophthalmol.* 117(4), 429–441 (1994).
4. The Central Vein Occlusion study group. Natural history and clinical management of central retinal vein occlusion. *Arch. Ophthalmol.* 115(4), 486–491 (1997).
5. Rath EZ, Frank RN, Shin DH, Kim C. Risk factors for retinal vein occlusions: A case–control study. *Ophthalmology* 99, 509–514 (1992).
6. The Central Vein Occlusion study group. Baseline and early natural history report. *Arch. Ophthalmol.* 111, 1087–1095 (1993).
7. The Eye Disorders Case–Control study group. Risk factors for central retinal vein occlusion. *Arch. Ophthalmol.* 114, 545–554 (1996).
8. Hayreh SS. Management of central Retinal vein occlusion. *Ophthalmologica* 217, 167–188 (2003).
9. The Central Vein Occlusion study group. A randomised clinical trial of early panretinal photocoagulation for ischaemic central vein occlusion: the Central Retinal Vein Occlusion study group N Report. *Ophthalmology* 102, 1434–1444 (1995).
10. McAllister IL, Constable IJ. Laser-induced chorioretinal venous anastomosis for treatment of non-ischaemic central retinal vein occlusion. *Arch. Ophthalmol.* 113, 456–462 (1995).
11. Dodson PM, Galton DJ, Hamilton AM *et al.* Retinal vein occlusion and the prevalence of lipoprotein abnormalities. *Br. J. Ophthalmol.* 66, 161–164 (1982).
12. Everett AI, Yang SS. Venous occlusive disease: the latest in current management. *Retina* 26(6), S63–S64 (2006).
13. Hoh AE, Schaal KB, Dithmar S. Central and branch retinal vein occlusion. Current strategies for treatment in Germany, Austria and Switzerland. *Ophthalmologe* 104, 290–294 (2007).
14. Park CH, Scott AW, Fekrat S. Effect of oral pentoxifylline on cystoid macular edema associated with central retinal vein occlusion. *Retina* 27(8), 1020–1025 (2007).
15. Wright JK, Franklin B, Zant E. Clinical case report: treatment of a central retinal vein occlusion with hyperbaric oxygen. *Undersea Hyperbar. Med.* 34(5), 315–319 (2007).
16. Arevalo JF, Garcia RA, Wu L *et al.* Radial optic neurotomy for central retinal vein occlusion: results of the Pan-American Collaborative Retina study group (PACORES). *Retina* 28(8), 1044–1052 (2008).
17. Park DH, Kim IT. Long-term effects of vitrectomy and internal limiting membrane peeling for macular edema secondary to central retinal vein occlusion and hemicentral vein occlusion. *Retina* 30(1), 117–124 (2010).
18. Weiss JN, Bynoe LA. Injection of tissue plasminogen activator into a branch retinal vein in eyes with central retinal vein occlusion. *Ophthalmology* 108, 2249–2257 (2001).
19. Gewaily D, Greenberg PB. Intravitreal steroids versus observation for macular edema secondary to central retinal vein occlusion. *Cochrane Database Syst. Rev.* 1, CD007324 (2009).
20. Ip MS, Scott IU, Van Veldhuisen PC *et al.*; SCORE study research group. A randomized trial comparing the efficacy and safety of intravitreal triamcinolone with observation to treat vision loss associated with macular edema secondary to central retinal vein occlusion: the Standard Care vs Corticosteroid for Retinal Vein Occlusion (SCORE) study report 5. *Arch. Ophthalmol.* 127(9), 1101–1114 (2009).
21. Haller JA, Bandello F, Belfort R *et al.* The Ozurdex Geneva study group. Randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with macular edema due to retinal vein occlusion. *Ophthalmology* 117(6), 1134–1146 (2010).
22. Monnoto-Garcia S, Lip PL, Chan CC, Lip GY. Soluble vascular endothelial growth factor receptor (VEGFR)-2 in macular oedema – a mechanism for regulating angiogenesis? *Br. J. Ophthalmol.* 95(6), 788–792 (2011).
23. Lip PL, Chatterjee S, Caine GJ *et al.* Plasma vascular endothelial growth factor, angiopoietin-2, and soluble angiopoietin receptor tie-2 in diabetic retinopathy: effects of laser photocoagulation and angiotensin receptor blockade. *Br. J. Ophthalmol.* 88(12), 1543–1546 (2004).
24. Pe'er J, Folberg R, Itin A *et al.* Vascular endothelial growth factor upregulation in human central retinal vein occlusion. *Ophthalmology* 105(3), 412–416 (1998).
25. Noma H, Funatsu H, Mimura T, Harino S, Sone T, Hori S. Increase of vascular endothelial growth factor and interleukin-6 in the aqueous humour of patients with macular oedema and central retinal vein occlusion. *Acta. Ophthalmol.* 88(6), 646–651 (2010).
26. Noma H, Funatsu H, Mimura T, Eguchi S, Shimada K. Role of soluble vascular endothelial growth factor receptor-2 in macular oedema with central retinal vein occlusion. *Br. J. Ophthalmol.* 95(6), 788–792 (2011).
27. Funk M, Kriechbaum K, Prager F *et al.* Intraocular concentrations of growth factors and cytokines in retinal vein occlusion and the effect of therapy with bevacizumab. *Invest. Ophthalmol. Vis. Sci.* 50(3), 1025–1032 (2009).
28. Wolf-Schnurrbusch UE, Ghanem R, Rothenbuehler SP *et al.* Predictors for short-term visual outcome after anti-VEGF

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therapy of macular edema due to central retinal vein occlusion. *Invest. Ophthalmol. Vis. Sci.* 52(6), 3334–3337 (2011).

39 Homsi J, Daud AI. Spectrum of activity and mechanism of action of VEGF/PDGF inhibitors. *Cancer Control* 14(3), 285–294 (2007).

40 Los M, Roodhart JM, Voest EE. Target practice: lessons from Phase III trials with bevacizumab and vatalanib in the treatment of advanced colorectal cancer. *Oncologist* 12(8), 443–450 (2007).

41 Eyetech study group. Preclinical and Phase IA clinical evaluation of an anti-VEGF pegylated aptamer (EYE001) for the treatment of exudative age-related macular degeneration. *Retina* 22, 143–152 (2002).

42 Gragoudas ES, Adamis AP, Cunningham ET Jr, Feinsod M, Guyer DR; VEGF Inhibition Study in Ocular Neovascularization Clinical Trial Group. Pegaptanib for neovascular age-related macular degeneration. *N. Engl. J. Med.* 351(27), 2805–2816 (2004).

43 Chen Y, Wiesmann C, Fuh G *et al.* Selection and analysis of an optimized anti-VEGF antibody: crystal structure of an affinity-matured Fab in complex with antigen. *J. Mol. Biol.* 293, 865–881 (1999).

44 Kaiser PK. Antivascular endothelial growth factor agents and their development: therapeutic implications in ocular diseases. *Am. J. Ophthalmol.* 142, 660–668 (2006).

45 Jeganathan VS, Verma N. Safety and efficacy of intravitreal anti VEGF injections for age-related macular degeneration. *Curr. Opin. Ophthalmol.* 20(3), 223–225 (2009).

46 Talamino M. Systemic and ocular safety of intravitreal anti-VEGF therapies for ocular neovascular disease. *Surv. Ophthalmol.* 56(2), 95–113 (2011).

47 Jager RD, Aiello LP, Patel SC, Cunningham ET. Risks of intravitreous injection: a comprehensive review. *Retina* 24(5), 676–698 (2004).

48 Sampat KM, Garg SJ. Complications of intravitreal injections. *Curr. Opin. Ophthalmol.* 21(3), 178–183 (2010).

49 Brainbwaite T, Nanji AA, Greenberg PB. Anti-vascular endothelial growth factor for macular edema secondary to central retinal vein occlusion. *Cochrane Database Syst. Rev.* 10, CD007325 (2010).

50 Brown DM, Campochiaro PA, Singh RP *et al.*; CRUISE investigators. Ranibizumab for macular edema following central retinal vein occlusion. Six-month primary end point results of a Phase III study. *Ophthalmology* 117, 1124–1133 (2010).

51 Campochiaro PA, Hafiz G, Channa R *et al.* Antagonism of vascular endothelial growth factor for macular edema caused by retinal vein occlusions: two-year outcomes. *Ophthalmology* 117, 2387–2394 (2010).

52 Kinge B, Stordahl PB, Forsaa V *et al.* Efficacy of ranibizumab in patients with macular edema secondary to central retinal vein occlusion: results from the sham-controlled ROCC study. *Am. J. Ophthalmol.* 150, 310–314 (2010).

53 Wroblewski JJ, Wells JA, Adamis AC *et al.*; Pegaptanib in Central Retinal Vein Occlusion study group. Pegaptanib sodium for macular edema secondary to central retinal vein occlusion. *Arch. Ophthalmol.* 127(4), 374–380 (2009).

54 Pece A, Isola V, Piermarocchi S, Calori G *et al.* Efficacy and safety of anti-vascular endothelial growth factor (VEGF) therapy with intravitreal ranibizumab (Lucentis) for naive retinal vein occlusion. 1-year follow-up. *Br. J. Ophthalmol.* 95(1), 56–60 (2011).

55 Figueroa MS, Contreras I, Noval S, Arruabarrena C. Results of bevacizumab as the primary treatment for retinal vein occlusions. *Br. J. Ophthalmol.* 94, 1052–1056 (2010).

56 Kriechbaum K, Michels S, Prager F *et al.* Intravitreal avastin for macular oedema secondary to retinal vein occlusion: a prospective study. *Br. J. Ophthalmol.* 92, 518–522 (2008).

57 Spaide R, Chang LK, Klancnik JM *et al.* Prospective study of intravitreal ranibizumab as a treatment for decreased visual acuity secondary to central retinal vein occlusion. *Am. J. Ophthalmol.* 147, 298–306 (2009).

58 Adelman R, Qi Zheng Q, Mayer H. Persistent ocular hypertension following intravitreal bevacizumab and ranibizumab injections. *Br. J. Ophthalmol.* 95, 1113–1114 (2010).

59 Good T, Kimura A, Mandava N *et al.* Sustained elevation of intraocular pressure after intravitreal injections of anti-VEGF agents. *J. Ocular Pharmacol. Ther.* 26(1), 105–110 (2010).

60 Udaondo P, Garcia-Delpech S, Salom D *et al.* Intravitreal pegaptanib for refractory macular edema secondary to retinal vein occlusion. *Clin. Ophthalmol.* 5, 941–944 (2011).

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VEGF $Trap_{R1R2}$ suppresses experimental corneal angiogenesis

H. B. Oliveira[1], **T. Sakimoto**[1], **J. A. D. Javier**[1], **D. T. Azar**[1,2], **S. J. Wiegand**[3], **S. Jain**[1,2], and **J.-H. Chang**[1,2,*]

[1]The Schepens Eye Research Institute, Harvard Medical School, Boston, Massachusetts

[2]Department of Ophthalmology and Visual Sciences, University of Illinois at Chicago, Chicago, Illinois

[3]Regeneron Pharmaceuticals Inc, Tarrytown, New York

Abstract

Purpose—To determine the effect of VEGF $Trap_{R1R2}$ on bFGF-induced experimental corneal neovascularization (NV).

Methods—Control pellets or pellets containing 80 ng bFGF were surgically implanted into wild-type C57BL/6 and VEGF-LacZ mouse corneas. The corneas were photographed, harvested, and the percentage of corneal NV was calculated. The harvested corneas were evaluated for VEGF expression. VEGF-LacZ mice received tail vein injections of an endothelial-specific lectin after pellet implantation to determine the temporal and spatial relationship between VEGF expression and corneal NV. Intraperitoneal injections of VEGF $Trap_{R1R2}$ or a human IgG Fc domain control protein were administered, and bFGF pellet-induced corneal NV was evaluated.

Results—NV of the corneal stroma began on day 4 and was sustained through day 21 following bFGF pellet implantation. Progression of vascular endothelial cells correlated with increased VEGF-LacZ expression. Western blot analysis showed increased VEGF expression in the corneal NV zone. Following bFGF pellet implantation, the area of corneal NV in untreated controls was (1.05±0.12 mm^2 and 1.53±0.27 mm^2) at days 4 and 7, respectively. This was significantly greater than that of mice treated with VEGF Trap (0.24±0.11 mm^2 and 0.35±0.16 mm^2 at days 4 and 7, respectively; $p<0.05$).

Conclusions—Corneal keratocytes express VEGF after bFGF stimulation and bFGF-induced corneal NV is blocked by intraperitoneal VEGF $Trap_{R1R2}$ administration. Systemic administration of VEGF $Trap_{R1R2}$ may have potential therapeutic applications in the management of corneal NV.

Keywords

VEGF $Trap_{R1R2}$; bFGF; angiogenesis; cornea

INTRODUCTION

Corneal avascularity requires a balance between several endogenous angiogenic (including VEGF, bFGF) and anti-angiogenic (endostatin, thrombospondin-1) factors [1–4]. VEGF $Trap_{R1R2}$, a VEGF antagonist, is a soluble fusion protein combining the truncated form of the fms-like tyrosine kinase (Flt), kinase insert domain-containing receptor (KDR) and Fc

*Corresponding author: Jin-Hong Chang, Ph.D., Department of Ophthalmology and Visual Sciences, University of Illinois at Chicago, 1855 West Taylor Street, Chicago, IL 60612. Phone: (312) 413-5590, Fax: (312) 966-7770. Changr@uic.edu.

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portion of human IgG. VEGF $Trap_{R1R2}$ is designed to sequester, antagonize the VEGF and to prevent blood vessel formation [5, 6].

Angiogenesis is involved in both normal physiological processes as well as in pathological conditions; such processes and conditions include embryonic vessel formation, wound healing, tumor vascularization, rheumatoid arthritis, corneal neovascularization (NV) and diabetic retinopathy [1, 7–12]. Several angiogenic factors have been identified and characterized, including basic fibroblast growth factor (bFGF) and vascular endothelial growth factor (VEGF) [13–16]. Investigation of the relationship between bFGF and VEGF during angiogenesis and tumor progression has elucidated a synergistic effect between these two factors in the induction of angiogenesis *in vitro* [17]. Additionally, Seghezzi et al. demonstrated that bFGF induces VEGF expression in vascular endothelial cells through autocrine and paracrine mechanisms [18].

In this report, we determine whether corneal keratocytes express VEGF after bFGF stimulation and whether bFGF-induced corneal NV is blocked by intraperitoneal VEGF $Trap_{R1R2}$ administration.

MATERIALS AND METHODS

Animals

All animal studies were conducted in accordance with the Animal Care and Use Committee Guidelines of the Massachusetts Eye and Ear Infirmary and the Association for Research in Vision and Ophthalmology (ARVO) statement for the Use of Animals in Ophthalmic and Vision Research. VEGF-LacZ and C57BL/6 mice of approximately equal weights between the ages of 6–10 weeks were used.

Experimental corneal NV

bFGF pellets consist of the slow-release polymer Hydron (polyhydroxyethylmethacrylate) containing a combination of 45 ng/pellet of sucralfate (Sigma-Aldrich, St. Louis, MO) with or without 80 ng/pellet of bFGF (R&D Systems, Minneapolis, MN) and were made as previously described by Kenyon et al [19].

Briefly, a suspension of sterile saline containing the appropriate amount of recombinant bFGF and sucralfate was made and speed vacuumed for 5 minutes. Ten μl of 12% Hydron in ethanol was added to the suspension, which was then deposited onto a sterilized 15 mm^2 piece of nylon mesh (LAB Pak, Sefar America, Depew, NY) and embedded between the fibers. The resulting grid of 10 x 10 mm squares was allowed to dry on a sterile Petri dish for 60 min. The fibers of the mesh were separated under a microscope and among the approximately 100 pellets produced, 30 to 40 uniformly-sized pellets of 0.4 x 0.4 x 0.2 mm^3 were selected for implantation. All procedures were performed under sterile conditions. The pellets can be stored at −20°C for several days without loss of bioactivity.

Corneal micropocket assays were performed as described Kenyon et al, (1996) [19]. Eight weeks old mice were anesthetized by a combined ketamine and xylazine injection. Proparacaine eye drops were used for local anesthesia. Eye globes were proptosed with a jeweler's forceps. Using an operating microscope (JKH operating surgical microscope), corneas were marked with a 3 mm trephine. Corneal lamellar micropocket incisions were created parallel to the corneal plane using a modified von Graefe knife along the trephine mark. A 0.5-mm incision perpendicular to the mouse corneal surface traversing the epithelium and anterior stroma toward the center of the cornea was performed with a 1/2-in., 30-gauge needle (Becton Dickinson, Franklin Lakes, NJ). A uniformly sized hydron pellet (0.4 x 0.4 x 0.2 mm) containing 80 ng of human bFGF (R&D Systems, Minneapolis, MN)

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and 40 μg of sucrose aluminum sulfate was placed on the corneal surface at the base of the pocket with jeweler's forceps and using one arm of the forceps, the pellet was advanced to the end of the pocket. In all animals, we aimed for a 1 mm distance from the pellet to the limbus. Antibiotic ointment (Bacitracin) was then applied to the operated eye to prevent infection and to decrease surface irregularities. Corneal images were obtained perpendicular to the cornea at the pellet position to minimize the parallax as described previously by Kure et al. (2003) [20]. Two images of every pellet were obtained. The distances from limbus to pellets were measured by three independent observers, and were normalized to the overall average diameter (4.0mm).

Corneas were routinely examined and photographed. Photographs were digitized, and images were analyzed with the NIH ImageJ program.

Confocal microscopy

C57BL/6 mouse eyes were obtained on days 0, 1, 4, 7, 10, 14, and 21 after bFGF and blank pellet implantation, and were frozen in OCT compound (Baxter Scientific, Columbia, MD). Cryostat sections, 8 μm thick, were fixed in acetone for 10 min. After blocking with 1% bovine serum albumin (BSA) (Sigma-Aldrich), sections were incubated for 1 h with rat anti-CD31 antibody (Pharmingen, San Diego, CA) and goat anti-mouse VEGF antibody (R&D Systems) used at a 1:100 dilution. Secondary antibodies used were a Cy5-conjugated donkey anti-rat IgG antibody and a rhodamine-conjugated donkey anti-goat IgG antibody (both from Jackson Immunoresearch Laboratories, West Grove, PA). Sections were viewed with a Leica TCS SP2 CLSM confocal laser scanning microscope (Leica, Heidelberg, Germany).

VEGF-LacZ mice were implanted with either a bFGF pellet or a blank pellet. The mice received 8 μg/g tail vein injections of an endothelial-specific, fluorescein-conjugated lectin (lycopersicon esculentum) on days 1, 4 and 7 post-pellet implantation. Mice were then sacrificed and whole eyes were harvested and fixed in 10% neutral, buffered formalin for 24 h. The corneas were dissected and placed in blocking solution (1% BSA) for 4 h. The corneas were then incubated with a 1:200 dilution of biotin-conjugated IgG fraction of anti-β-galactosidase antibody (Rockland Immunochemicals Research Inc, Gilbertsville, PA) overnight, rinsed in PBS, and incubated with a 1:1000 dilution of rhodamine-conjugated streptavidin (Rockland) for 2 h. The specimens were rinsed in PBS and mounted on glass slides with Vectashield mounting medium for fluorescence imaging (Vector Laboratories, Burlingame, CA). Fluorescence in the perfused vessels and LacZ expression was captured using a Leica TCS SP2 CLSM confocal laser scanning microscope.

Western blot analysis for VEGF expression

Wild-type mouse corneas were collected on day 7 after bFGF pellet implantation. Corneas were sectioned, homogenized, lysed with lysis buffer, and run on 4% to 20% SDS polyacrylamide gels (Novex, San Diego, CA). Proteins were electrotransferred onto nylon membranes (Immobilon P, Millipore, Bedford, MA), blotted with 3% BSA for 30 min, and incubated for 1 h with anti-VEGF antibody (R & D system, MN, USA, cat# AF-493-NA; 1:1000 dilution). Subsequently, horseradish peroxidase donkey anti-rabbit IgG (1:20,000, GE Life Science, Piscataway, NJ) was used as secondary antibody. Human VEGF was used as a standard control (1:100).

After washing with Tris-buffered saline Tween-20 (TBST) for 15 min, immunoblots were developed with an enhanced chemiluminescence (ECL) reagent (Perkin-Elmer, Waltham, MA).

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Intraperitoneal injection of VEGF $Trap_{R1R2}$ into mouse after corneal bFGF pellet implantation

VEGF $Trap_{R1R2}$ 12.5 mg/kg or human Fc domain protein (hFc) (12.5 mg/kg; control) were intraperitoneally injected into mice immediately before bFGF pellet implantation in the cornea (n = 5 mice/group). Antibiotic ophthalmic ointment was applied after bFGF pellet implantation. Five additional mice with bFGF pellets served only as controls. The extent of corneal NV was photographed and quantified on days 4 and 7 after bFGF implantation. Subsequent experiments were performed to confirm the corneal bioavailability of VEGF $Trap_{R1R2}$ and hFc in our model by goat anti-human Fc antibody (cat # G-102-C, R & D Systems, Minneapolis, MN, USA).

RESULTS

bFGF induces VEGF expression in mouse corneas

The extent of corneal NV was assayed using bFGF pellets of 80 ng implanted into mouse corneas. New vessel growth began at day 4 post-intrastromal bFGF pellet implantation and progressed until day 21 (Figure 1).

VEGF expression was noted in the epithelium and perivascularly at day 4 (Figure 1G). The level of VEGF peaked on day 7 (Figure 1I) in the epithelium and corneal stroma, and diminished gradually by days 10, 14, and 21 (Figure 1).

Miquerol et al. generated VEGF-LacZ mice by inserting a reporter gene into the 3′ untranslated region of the endogenous VEGF gene so that VEGF and the LacZ reporter mRNA are produced from a bicistronic mRNA [21]. Using corneas from these VEGF-LacZ mice, the expression of VEGF and corneal vessels were visualized after injections of FITC-conjugated lectin into the tail vein. LacZ expression was noted in activated stromal cells on day 4 (Figure 2E) and increased on day 7 (Figure 2F) after bFGF pellet implantation.

bFGF pellet-implanted corneas were harvested and sectioned into a set of three mirror-image segments (Figure 2G and H). Lysates of these sections were analyzed by western blot analysis using an anti-VEGF antibody. Corneal segments with vascularization showed maximal VEGF expression at the area of the bFGF pellet.

Blocking of bFGF-induced corneal NV via VEGF $Trap_{R1R2}$

Mice were given a 12.5 mg/kg intraperitoneal injection of VEGF $Trap_{R1R2}$ before corneal implantation of an 80 ng bFGF pellet. Mouse corneas implanted with a bFGF pellet with or without 12.5 mg/kg intraperitoneal injection of hFc-protein were used as controls. The distance of the pellet to the limbus was measured by 3 observers for each corneal images as described in the Materials and Methods section. There were no significant difference in the distance of pellets to limbus between 3 groups (control = 1.01mm±0.17mm; hFc = 1.21mm ±0.22mm; VEGF Trap = 1.10mm±0.20mm; p=0.30). Following bFGF pellet implantation, the area of corneal NV in untreated controls was 1.05 ± 0.12 mm^2 and 1.53 ± 0.27 mm^2 at days 4 and 7, respectively. This was significantly greater than that of mice treated with VEGF $Trap_{R1R2}$ (Figures 3C and 3F; 0.24 ± 0.11 mm^2 and 0.35 ± 0.16 mm^2 at days 4 and 7, respectively; P<0.05). Corneas displayed bFGF-induced NV on day 7 in the hFc protein intraperitoneal-treated group (Figures 3B and 3D; 1.21 ± 0.07 mm^2 and 2.25 ± 0.30 mm^2 at days 4 and 7, respectively). The results are summarized in Figure 3G.

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DISCUSSION

Corneal NV usually is associated with inflammatory, infectious, degenerative, and traumatic disorders of the ocular surface. The pathological condition of corneal NV may result from the production of angiogenic factors by local epithelial cells, keratocytes, and infiltrating leukocytes [22]. During corneal NV, these angiogenic factors may directly or indirectly stimulate vascular endothelial cells to proliferate, migrate, and form new blood vessels.

Implantation of bFGF pellets in mouse corneas stimulates corneal vessel formation originating from the limbal area [19]. In this study, we investigated the role of VEGF in bFGF-induced corneal NV. Our results suggest that bFGF stimulates VEGF production in corneal keratocytes. In the corneal NV assay, vessels were visualized on day 4, peaked on day 7, and extended to day 21 following bFGF pellet implantation, with a concomitant increase in VEGF expression in the stroma. A similar experiment reported that corneas implanted with sham pellets do not induce corneal NV [23].

Cursiefen *et al.* have demonstrated that VEGF $Trap_{R1R2}$, a soluble VEGF antagonist molecule, binds VEGF-A and PlGF but not VEGF-C and VEGF-D *in vitro*, and in mice, an intraperitoneal injection of VEGF $Trap_{R1R2}$ blocked suture-induced corneal vessel formation [24]. We used similar conditions in our experiments, and show that VEGF $Trap_{R1R2}$ blocked bFGF-pellet-induced corneal NV, much like the VEGF $Trap_{R1R2}$-mediated block of suture-induced corneal NV [24].

We also used VEGF-LacZ transgenic mice to detect VEGF expression [21]. This allele allows independent translation of VEGF and LacZ from the same mRNA and reporter activity and can be detected at the single-cell level. LacZ expression was enhanced in the corneal keratocytes after bFGF pellet implantation in these VEGF-LacZ transgenic mice. The difference of the detection of VEGF expression after bFGF-pellet implantation in WT (C57BL/6) and VEGF-LacZ (129/sv) mice at day 1 may be due to different genetic backgrounds or the different antibodies used in immunostaining.

Our findings are consistent with other reports showing that bFGF-induced corneal NV may be mediated via VEGF. The expression of VEGF induced by bFGF pellet corneal implantation may not be limited to keratocytes. Seghezzi et al. have demonstrated that bFGF-induced vascular endothelial cells produce VEGF and induce corneal NV [18]. The bFGF-induced corneal NV can be partially blocked by using a neutralizing anti-VEGF antibody. Chang et al. and Cursiefen et al. have both demonstrated that VEGF also plays a role in bFGF-induced corneal lymphangiogenesis and angiogenesis [22, 25]. Corneal suture or bFGF-pellet implantation recruits neutrophils and macrophages to the wounded cornea and produce VEGF, VEGF-C, and VEGF-D which further induces corneal NV. However, information regarding the production of VEGF by resident cells (keratocytes) in corneal angiogenesis is limited.

In this report, the experiments are consistent with the hypothesis that bFGF stimulates corneal keratocytes to produce VEGF. These data suggests that experimental corneal NV using bFGF pellets in mouse corneas can be blocked by systemic administration of VEGF $Trap_{R1R2}$. In addition to its potential therapeutic applications for ocular angiogenesis, VEGF $Trap_{R1R2}$ mechanisms may lead to a better understanding of corneal NV and possibly its prevention.

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References

1. Azar DT. Corneal angiogenic privilege: angiogenic and antiangiogenic factors in corneal avascularity, vasculogenesis, and wound healing (an American Ophthalmological Society thesis). Trans Am Ophthalmol Soc. 2006; 104:264–302. [PubMed: 17471348]
2. Ambati BK, Nozaki M, Singh N, Takeda A, Jani PD, Suthar T, Albuquerque RJ, Richter E, Sakurai E, Newcomb MT, Kleinman ME, Caldwell RB, Lin Q, Ogura Y, Orecchia A, Samuelson DA, Agnew DW, St Leger J, Green WR, Mahasreshti PJ, Curiel DT, Kwan D, Marsh H, Ikeda S, Leiper LJ, Collinson JM, Bogdanovich S, Khurana TS, Shibuya M, Baldwin ME, Ferrara N, Gerber HP, De Falco S, Witta J, Baffi JZ, Raisler BJ, Ambati J. Corneal avascularity is due to soluble VEGF receptor-1. Nature. 2006; 443:993–7. [PubMed: 17051153]
3. Cursiefen C, Chen L, Saint-Geniez M, Hamrah P, Jin Y, Rashid S, Pytowski B, Persaud K, Wu Y, Streilein JW, Dana R. Nonvascular VEGF receptor 3 expression by corneal epithelium maintains avascularity and vision. Proc Natl Acad Sci U S A. 2006; 103:11405–10. [PubMed: 16849433]
4. Maharaj AS, Saint-Geniez M, Maldonado AE, D'Amore PA. Vascular endothelial growth factor localization in the adult. Am J Pathol. 2006; 168:639–48. [PubMed: 16436677]
5. Chappelow AV, Kaiser PK. Neovascular age-related macular degeneration: potential therapies. Drugs. 2008; 68:1029–36. [PubMed: 18484796]
6. Rudge JS, Holash J, Hylton D, Russell M, Jiang S, Leidich R, Papadopoulos N, Pyles EA, Torri A, Wiegand SJ, Thurston G, Stahl N, Yancopoulos GD. Inaugural Article: VEGF Trap complex formation measures production rates of VEGF, providing a biomarker for predicting efficacious angiogenic blockade. Proc Natl Acad Sci U S A. 2007; 104:18363–70. [PubMed: 18000042]
7. Velazquez OC. Angiogenesis and vasculogenesis: inducing the growth of new blood vessels and wound healing by stimulation of bone marrow-derived progenitor cell mobilization and homing. J Vasc Surg. 2007; 45(Suppl A):A39–47. [PubMed: 17544023]
8. Jakobsson L, Kreuger J, Claesson-Welsh L. Building blood vessels--stem cell models in vascular biology. J Cell Biol. 2007; 177:751–5. [PubMed: 17535968]
9. Eming SA, Brachvogel B, Odorisio T, Koch M. Regulation of angiogenesis: wound healing as a model. Prog Histochem Cytochem. 2007; 42:115–70. [PubMed: 17980716]
10. Shibuya M, Claesson-Welsh L. Signal transduction by VEGF receptors in regulation of angiogenesis and lymphangiogenesis. Exp Cell Res. 2006; 312:549–60. [PubMed: 16336962]
11. Motiejunaite R, Kazlauskas A. Pericytes and ocular diseases. Exp Eye Res. 2008; 86:171–7. [PubMed: 18078933]
12. Ejaz S, Chekarova I, Ejaz A, Sohail A, Lim CW. Importance of pericytes and mechanisms of pericyte loss during diabetes retinopathy. Diabetes Obes Metab. 2008; 10:53–63. [PubMed: 17941874]
13. Yan W, Bentley B, Shao R. Distinct Angiogenic Mediators Are Required for Basic Fibroblast Growth Factor- and Vascular Endothelial Growth Factor-induced Angiogenesis: The Role of Cytoplasmic Tyrosine Kinase c-Abl in Tumor Angiogenesis. Mol Biol Cell. 2008; 19:2278–88. [PubMed: 18353972]
14. Lee IY, Kim J, Ko EM, Jeoung EJ, Kwon YG, Choe J. Interleukin-4 inhibits the vascular endothelial growth factor- and basic fibroblast growth factor-induced angiogenesis in vitro. Mol Cells. 2002; 14:115–21. [PubMed: 12243340]
15. Poltorak Z, Cohen T, Sivan R, Kandelis Y, Spira G, Vlodavsky I, Keshet E, Neufeld G. VEGF145, a secreted vascular endothelial growth factor isoform that binds to extracellular matrix. J Biol Chem. 1997; 272:7151–8. [PubMed: 9054410]
16. Folkman J, Shing Y. Control of angiogenesis by heparin and other sulfated polysaccharides. Adv Exp Med Biol. 1992; 313:355–64. [PubMed: 1279952]
17. Ley CD, Olsen MW, Lund EL, Kristjansen PE. Angiogenic synergy of bFGF and VEGF is antagonized by Angiopoietin-2 in a modified in vivo Matrigel assay. Microvasc Res. 2004; 68:161–8. [PubMed: 15501235]

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18. Seghezzi G, Patel S, Ren CJ, Gualandris A, Pintucci G, Robbins ES, Shapiro RL, Galloway AC, Rifkin DB, Mignatti P. Fibroblast growth factor-2 (FGF-2) induces vascular endothelial growth factor (VEGF) expression in the endothelial cells of forming capillaries: an autocrine mechanism contributing to angiogenesis. J Cell Biol. 1998; 141:1659–73. [PubMed: 9647657]
19. Kenyon BM, Voest EE, Chen CC, Flynn E, Folkman J, D'Amato RJ. A model of angiogenesis in the mouse cornea. Invest Ophthalmol Vis Sci. 1996; 37:1625–32. [PubMed: 8675406]
20. Kure T, Chang JH, Kato T, Hernandez-Quintela E, Ye H, Lu PC, Matrisian LM, Gatinel D, Shapiro S, Gosheh F, Azar DT. Corneal neovascularization after excimer keratectomy wounds in matrilysin-deficient mice. Invest Ophthalmol Vis Sci. 2003; 44:137–44. [PubMed: 12506066]
21. Miquerol L, Gertsenstein M, Harpal K, Rossant J, Nagy A. Multiple developmental roles of VEGF suggested by a LacZ-tagged allele. Dev Biol. 1999; 212:307–22. [PubMed: 10433823]
22. Cursiefen C. Immune privilege and angiogenic privilege of the cornea. Chem Immunol Allergy. 2007; 92:50–7. [PubMed: 17264482]
23. Onguchi T, Han KY, Chang JH, Azar DT. Membrane type-1 matrix metalloproteinase potentiates basic fibroblast growth factor-induced corneal neovascularization. Am J Pathol. 2009; 174:1564–71. [PubMed: 19264910]
24. Cursiefen C, Cao J, Chen L, Liu Y, Maruyama K, Jackson D, Kruse FE, Wiegand SJ, Dana MR, Streilein JW. Inhibition of hemangiogenesis and lymphangiogenesis after normal-risk corneal transplantation by neutralizing VEGF promotes graft survival. Invest Ophthalmol Vis Sci. 2004; 45:2666–73. [PubMed: 15277490]
25. Chang LK, Garcia-Cardena G, Farnebo F, Fannon M, Chen EJ, Butterfield C, Moses MA, Mulligan RC, Folkman J, Kaipainen A. Dose-dependent response of FGF-2 for lymphangiogenesis. Proc Natl Acad Sci U S A. 2004; 101:11658–63. [PubMed: 15289610]

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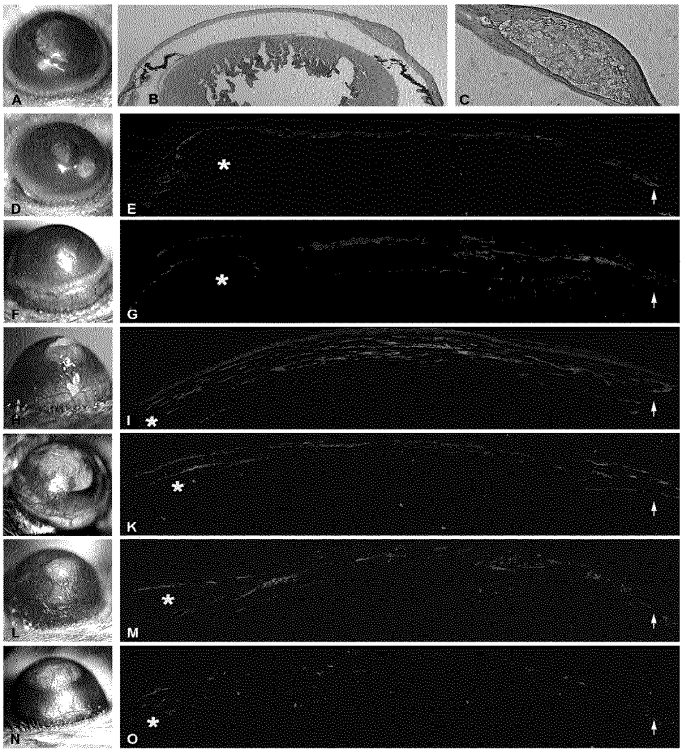

Figure 1.
Temporal and spatial relationship of VEGF expression and corneal vessel formation. Mouse corneas were implanted with a bFGF pellet and photographed by slit lamp on day 1 (D), day 4 (F), day 7 (H), day 10 (J), day 14 (L), and day 21 (N). A blank pellet was implanted as the control (A). bFGF pellet localization was shown in the transversal eye (B) and the intrastromal section (C). Sections of corneas were stained with anti-VEGF and anti-CD-31 antibodies on days 1 (E), 4 (G), 7 (I), 10 (K), 14 (M), and 21 (O). VEGF expression was noted in the corneal epithelium at day 1 (E). VEGF expression in the corneal keratocytes peaked on day 7 (I) and its expression decreased after 7 days. CD-31 localization lagged behind VEGF expression, which started on day 4 and continued until day 14. (* asterisk indicates the location of the bFGF pellet; arrows point to the limbus.) Areas of VEGF expression are stained red with anti-VEGF antibody; vascular endothelial cells are stained dark blue with anti-CD31 antibody.

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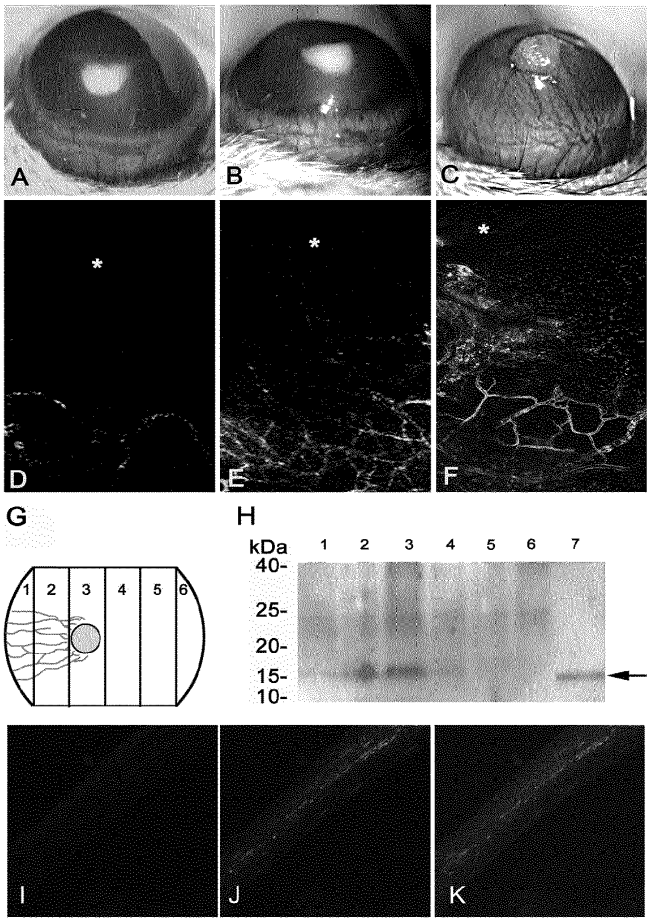

Figure 2.

VEGF expression correlated with vascular progression in the cornea. Vascular progression was induced by bFGF pellet implantation on days 1 (A), 4 (B), and 7 (C). Vascular endothelial cells were visualized by fluorescein-conjugated tomato lectin, and the progression of vessels was visualized by the VEGF-LacZ expression on days 1 (D), 4 (E), and 7 (F). LacZ expression (in red) was observed starting at day 4 and showed greater expression at day 7 (E–F). bFGF implanted corneas were divided into 6 segments as illustrated in (G) and were analyzed by Western blot analysis (H). Fifteen kDa bands (H, lanes 1 to 6) corresponding to VEGF expression in different segments (G, lanes 1 to 6) were observed. Recombinant VEGF was used as control (H, lane 7). The highest amount of VEGF was seen close to the pellet (H, lane 3) and in the segments adjacent to the pellet (H, lanes 2 and 4). There is also a lighter band noted at the limbal area closer to the pellet (H, lane 1). No VEGF expression was observed in segments away from the pellet (H, lanes 5 and 6). bFGF implanted corneas were coimmunostained with anti-VEGF antibody (I) and macrophage marker F4/80 antibody (J; merged image (K)).

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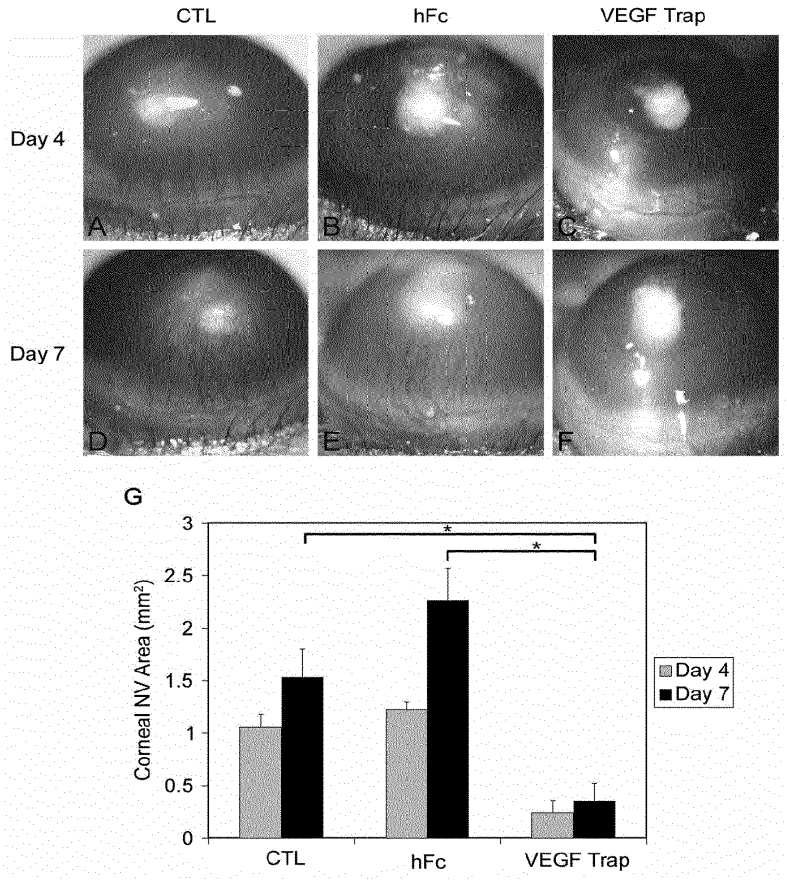

Figure 3.

VEGF-Trap$_{R1R2}$ blocks bFGF-induced corneal NV. Mice were intraperitoneally injected with VEGF Trap$_{R1R2}$ or hFc-protein before 80 ng bFGF pellet implantation. Corneal NV was photographed at day 4 (A, B, and C) and day 7 (D, E, and F). The distance of the pellet to the limbus was measured by 3 observers for each corneal images as described in the Materials and Methods section. There were no significant difference in the distance of pellets to limbus between 3 groups (control = 1.01mm±0.17mm; hFc = 1.21mm±0.22mm; VEGF Trap = 1.10mm±0.20mm; p=0.30). Enhanced corneal NV was documented in bFGF-implanted corneas with hFc-protein injection (B, E) and without peptide injection (A, D). bFGF-induced corneal NV was blocked by intraperitoneally injected VEGF Trap$_{R1R2}$ (C, F). At day 4 after bFGF pellet implantation, the areas of corneal NV in these three groups (bFGF pellet only, or combined with human Fc injection or VEGF Trap$_{R1R2}$ injection) were calculated and compared (G).

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VEGF Trap-Eye Final Phase 2 Results in Age-related Macular Degeneration Presented at 2008 Retina Society Meeting

Source Press Release
Company Regeneron Pharmaceuticals, Bayer, New York University
Tags Phase II, Protein Therapeutic, Sensory Organs
Date September 28, 2008

Regression of total active lesion caused by wet AMD reported

Scottsdale, AZ -- September 28, 2008 -- Regeneron Pharmaceuticals , Inc. (Nasdaq: REGN) and Bayer HealthCare AG announced that VEGF Trap-Eye achieved durable improvements in visual acuity and in biologic measures of neovascular disease, including retinal thickness and active choroidal neovascularization lesion size, for up to one year in a Phase 2 study in the neovascular form of Age-related Macular Degeneration (wet AMD). The results were reported today in two oral presentations at the 2008 annual meeting of the Retina Society in Scottsdale, Arizona. Slides, including data reported at the presentations, are available on the Regeneron website (regeneron.com on the Presentations Page, under the Investor Relations section).

In this double-masked Phase 2 trial, patients were initially treated with either fixed monthly or quarterly dosing for 12 weeks and then continued to receive treatment for another 40 weeks on a PRN (as needed) dosing schedule. Patients receiving monthly doses of VEGF Trap-Eye of either 2.0 or 0.5 milligrams (mg) for 12 weeks followed by PRN dosing achieved mean improvements in visual acuity versus baseline of 9.0 letters ($p<0.0001$ versus baseline) and 5.4 letters ($p<0.085$ versus baseline), respectively, at the end of one year. The proportion of patients with vision of 20/40 or better (part of the legal minimum requirement for an unrestricted driver's license in the U.S.) increased from 23 percent at baseline to 45 percent at week 52 in patients initially treated with 2.0 mg monthly and from 16 percent at baseline to 47 percent at week 52 in patients initially treated with 0.5 mg monthly. During the week 12 to week 52 PRN dosing period, patients initially dosed on a 2.0 mg monthly schedule received, on average, only 1.6 additional injections and those initially dosed on a 0.5 mg monthly schedule received, on average, 2.5 injections.

Patients receiving monthly doses of VEGF Trap-Eye of either 2.0 or 0.5 mg for 12 weeks followed by PRN dosing also achieved mean decreases in retinal thickness versus baseline of 143 microns ($p<0.0001$ versus baseline) and 125 microns ($p<0.0001$ versus baseline) at week 52, respectively.

While PRN dosing following a fixed quarterly dosing regimen (with dosing at baseline and week 12) also yielded improvements in visual acuity and retinal thickness versus baseline at week 52, the results generally were not as robust as those obtained with initial fixed monthly dosing.

"Anti-VEGF therapy has dramatically changed the treatment paradigm for wet AMD, and improvement in visual acuity is now feasible in most patients. The biggest challenge we have is that with our current drugs, the majority of patients need frequent injections into their eye to maintain their visual acuity gains," stated David M. Brown, M.D., a study investigator and a retinal specialist at The Methodist Hospital in Houston. "These study results reinforce our interest in further exploring whether continued administration of VEGF Trap-Eye on an as-needed basis after an initial period of fixed dosing can maintain a durability of effect over time in controlled Phase 3 clinical studies."

In this Phase 2 study VEGF Trap-Eye was also associated with a reduction in the size of the total active choroidal neovascular membrane (CNV), the active lesion that is the underlying cause of vision loss in patients with wet AMD. Patients initially receiving either a 2.0 mg or 0.5 mg monthly fixed dose of VEGF Trap-Eye for 12 weeks followed by PRN dosing experienced statistically significant 3.41 mm2 and 1.42 mm2 reductions in mean CNV size at 48 weeks (the final one-year analysis from the independent reading center) versus baseline, respectively. Patients in the 2.0 mg monthly cohort also achieved a statistically significant 1.75 mm2 reduction in total lesion size. A reduction in total lesion size was not seen in the cohort initially dosed with 0.5 mg monthly.

"Progression of the active CNV lesion and resulting vision impairment are inevitable consequences of untreated wet AMD. The reduction in total active CNV lesion size achieved with VEGF Trap-Eye treatment in this Phase 2 clinical study could potentially translate into clinically meaningful outcomes in the larger, controlled Phase 3 studies that are underway," stated Jason Slakter, M.D., head of the independent reading center for the study and a Clinical Professor of Ophthalmology, New York University School of Medicine, New York.

VEGF Trap-Eye was generally well tolerated and there were no drug-related serious adverse events. There was one reported case of culture-negative endophthalmitis/uveitis in the study eye, which was deemed not to be drug-related. The most common adverse events were those typically associated with intravitreal injections.

"These study results confirm the rationale for our Phase 3 clinical program for VEGF Trap-Eye in wet AMD," said George D. Yancopoulos, M.D., Ph.D., President of Regeneron Research Laboratories. "These trials are designed to optimize improvement in

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visual acuity with fixed-dosing regimens of either every 4 weeks or every 8 weeks for one year and then study how these vision improvements can be maintained with as-needed dosing in the second year."

About the Phase 2 Study in Wet AMD

In the double-masked, prospective, randomized, multi-center Phase 2 trial, 157 patients were randomized to five dose groups and treated with VEGF Trap-Eye in one eye. Two groups initially received monthly doses of 0.5 or 2.0 milligrams (mg) of VEGF Trap-Eye (at weeks 0, 4, 8, and 12) and three groups received quarterly doses of 0.5, 2.0, or 4.0 mg of VEGF Trap-Eye (at baseline and week 12). Following the initial 12-week fixed-dosing phase of the trial, patients continued to receive therapy at the same dose on a PRN dosing schedule based upon the physician assessment of the need for re-treatment in accordance with pre-specified criteria. Patients were monitored for safety, retinal thickness, and visual acuity. The primary endpoint results from the fixed dosing period were presented at the 2007 Retina Society conference in September 2007. Week 32 results were presented at the 2008 Association for Research in Vision and Ophthalmology annual meeting in April 2008.

About the Phase 3 Program in Wet AMD

Regeneron and Bayer HealthCare initiated a Phase 3 global development program for VEGF Trap-Eye in wet AMD in August 2007. In two Phase 3 trials, the companies are evaluating VEGF Trap-Eye dosed 0.5 mg every 4 weeks, 2 mg every 4 weeks, or 2 mg every 8 weeks (following three monthly doses) in direct comparison with ranibizumab (Lucentis ®, a registered trademark of Genentech , Inc.) administered 0.5 mg every 4 weeks according to its U.S. label during the first year of the studies. PRN dosing will be evaluated during the second year of each study. The VIEW1 study is currently enrolling patients in the United States and Canada and the VIEW2 study is currently enrolling patients in Europe, Asia Pacific, Japan, and Latin America. The companies are collaborating on the global development of VEGF Trap-Eye for the treatment of wet AMD, diabetic eye diseases, and other eye diseases and disorders. Bayer HealthCare will market VEGF Trap-Eye outside the United States, where the companies will share equally in profits from any future sales of VEGF Trap-Eye. Regeneron maintains exclusive rights to VEGF Trap-Eye in the United States.

About VEGF Trap-Eye

Vascular Endothelial Growth Factor (VEGF) is a naturally occurring protein in the body whose normal role is to trigger formation of new blood vessels (angiogenesis) to support the growth of the body's tissues and organs. It has also been associated with the abnormal growth and fragility of new blood vessels in the eye, which lead to the development of wet AMD. The VEGF Trap-Eye is a fully human, soluble VEGF receptor fusion protein that binds all forms of VEGF-A along with the related Placental Growth Factor (PlGF). VEGF Trap-Eye is a specific and highly potent blocker of these growth factors. Blockade of VEGF, which can prevent abnormal blood vessel formation and vascular leak, has proven beneficial in the treatment of wet AMD.

About Wet AMD

Age-related Macular Degeneration (AMD) is a leading cause of acquired blindness. Macular degeneration is diagnosed as either dry (nonexudative) or wet (exudative). In wet AMD, new blood vessels grow beneath the retina and leak blood and fluid. This leakage causes disruption and dysfunction of the retina creating blind spots in central vision, and it can account for blindness in wet AMD patients. Wet AMD is the leading cause of blindness for people over the age of 65 in the U.S. and Europe.

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Confirmation Number:	8014
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First Named Inventor/Applicant Name:	George D. YANCOPOULOS
Customer Number:	96387
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	Confirmation No.	8014
	Filing Date	March 28, 2017
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	Examiner Name	LOCKARD, JON MCCLELLAND
	Title: "*Use of a VEGF Antagonist to Treat Angiogenic Eye Disorders*"	

Sir:

Applicants submit herewith documents which may be material to the examination of this application and in respect of which there may be a duty to disclose in accordance with 37 C.F.R. §1.56. This submission is not intended to constitute an admission that any document referred to therein is "prior art" for this invention unless specifically designated as such. A listing of the documents is shown on enclosed Form PTO/SB/08A and a copy of the cited documents are attached.

The Examiner is requested to make the documents listed on the enclosed PTO/SB/08A of record in this application. Applicants would appreciate the Examiner initialing and returning the initialed copy of form PTO/SB/08A, indicating the documents cited therein have been considered and made of record herein.

Statements

☐ **No statement**

☐ **PTA Statement under 37 CFR § 1.704(d)(1):** Each item of information contained in the information disclosure statement filed herewith:

(i) Was first cited in any communication from a patent office in a counterpart foreign or international application or from the Office, and this communication was not received by any individual designated in § 1.56(c) more than thirty days prior to the filing of the information disclosure statement; or

(ii) Is a communication that was issued by a patent office in a counterpart foreign or international application or by the Office, and this communication was not received by any individual designated in § 1.56(c) more than thirty days prior to the filing of the information disclosure statement.

☒ **IDS Statement under 37 CFR § 1.97(e)(1):** 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; or

☐ **IDS Statement under 37 CFR § 1.97(e)(2):** 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 § 1.56(c) more than three months prior to the filing of the information disclosure statement.

Fees

☒ No fee is believed to be due.

☐ The appropriate fee set forth in 37 C.F.R. §1.17(p) accompanies this information disclosure statement.

The Commissioner is hereby authorized to charge any underpayment of fees up to a strict limit of $3,000.00 beyond that authorized on the credit card, but not more than $3,000.00 in additional fees due with any communication for the above referenced patent application, including but not limited to any necessary fees for extensions of time, or credit any overpayment of any amount to Deposit Account No. 50-0815, order number REGN-008CIPCON2.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: 2 August 2017

By: /Karl Bozicevic, Reg. No. 28,807/
Karl Bozicevic, Reg. No. 28,807

BOZICEVIC, FIELD & FRANCIS LLP
201 Redwood Shores Parkway, Suite 200
Redwood City, CA 94065
Telephone: (650) 327-3400
Direct: (650) 833-7735
Facsimile: (650) 327-3231

UNITED STATES PATENT AND TRADEMARK OFFICE

UNDER SECRETARY OF COMMERCE FOR INTELLECTUAL PROPERTY AND
DIRECTOR OF THE UNITED STATES PATENT AND TRADEMARK OFFICE

August 16, 2017

BOZICEVIC, FIELD & FRANCIS LLP
201 REDWOOD SHORES PARKWAY, SUITE 200
REDWOOD CITY, CA 94065
US

Dear Sir/Madam,

Your refund request for 15471506 in the amount of $140.00 has been denied.

Applicant filed an ADS on March 28, 2017 concurrently with the declaration so the ADS set the inventorship, there were typographical errors. The inventor's name is listed as Geroge D. Yancopoulos on the ADS, but as George D. Yancopoulos on the signed declaration.

Once an application data sheet or the inventor's oath or declaration is filed in a nonprovisional application, any correction of inventorship must be pursuant to 37 CFR 1.48.

37 CFR 1.48(f) provides for corrections to the name of an inventor (such as changing to a married name, changing a nickname to a full name, or a legal name change), typographical or transliteration, or to the order of inventors.

The surcharge under 37 CFR 1.16(f) for the late filing of the oath or declaration was required. The surcharge was charged to counsel's deposit account in accordance with the authorization to charge any additional fees required under 37 CFR 1.16 that was included on filing of the application. While the inventor's oath or declaration may be postponed until the application is otherwise in condition for allowance in accordance with amended 37 CFR 1.53(f) (effective September 16, 2012 for applications filed on or after September 16, 2012), the surcharge under 37 CFR 1.16(f) must be paid on filing or in response to a notice to file missing parts if the inventor's oath or declaration is not included with the application on filing. See "Changes To Implement the Inventor's Oath or Declaration Provisions of the Leahy-Smith America Invents Act," 77 FR 48775, 48787 (August 14, 2012).

Applicant Submitted a request for Corrected Filing Receipt on June 8, 2017, requesting thecorrect spelling of the first Inventors name from **Geroge D. Yancopoulos**, and changing it to **George D. Yancopoulos**.

Sincerely,

Darlene A Lyon
OPAP
703-756-1148

Electronically Filed

REQUEST FOR CORRECTION OF INVENTORSHIP UNDER 37 C.F.R. § 1.48(f) Address to: Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Attorney Docket No.	REGN-008CIPCON2
	Confirmation No.	8014
	First Named Inventor	YANCOPOULOS, GEORGE D.
	Application Number	15/471,506
	Filing Date	March 28, 2017
	Group Art Unit	1647
	Examiner Name	LOCKARD, JON MCCLELLAND
	Title: *"Use of a VEGF Antagonist to Treat Angiogenic Eye Disorders"*	

Sir:

Pursuant to 37 C.F.R. § 1.48(f), Applicants respectfully request that the application be amended to correct the inventorship of the application.

The undersigned, pursuant to the provisions in 37 C.F.R. § 1.41, hereby requests that the inventorship of the above-identified patent application be corrected to update the name of inventor --Geroge D. Yancopoulos-- to "**George D. Yancopoulos**." The incorrect spelling of inventor George D. Yancopoulos was listed in error. A Supplemental Application Data Sheet is submitted herewith referencing the requested correction.

The fee of $140.00 pursuant to 37 C.F.R. § 1.17(i) is included herewith. The Commissioner is hereby authorized to charge any additional fees under 37 C.F.R. § 1.20, which may be required by this paper, or to credit any overpayment, to Deposit Account No. 50-0815 order number REGN-008CIPCON2.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: August 31, 2017

By: /Karl Bozicevic, Reg. No. 28,807/
Karl Bozicevic
Registration No. 28,807

Bozicevic, Field & Francis LLP
201 Redwood Shores Parkway, Suite 200
Redwood City, California 94065
Telephone: (650) 327-3400
Direct: (650) 833-7735
Facsimile: (650) 327-3231

PTO/AIA/14 (11-15)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

SUPPLEMENTAL ADS

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	REGN-008CIPCON2
	Application Number	15/471,506
Title of Invention	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS	

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

Secrecy Order 37 CFR 5.2:

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

Inventor Information:

Inventor 1 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	~~Geroge~~ George	D.	YANCOPOULOS	

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

City	Yorktown Heights	State/Province	NY	Country of Residence	US

Mailing Address of Inventor:

Address 1	c/o Regeneron Pharmaceuticals, Inc.		
Address 2	777 Old Saw Mill River Road		
City	Tarrytown	**State/Province**	NY
Postal Code	10591	**Country**	US

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

Correspondence Information:

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

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

Customer Number	96387		
Email Address	docket@bozpat.com	Add Email	Remove Email

Application Information:

Title of the Invention	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS		
Attorney Docket Number	REGN-008CIPCON2	**Small Entity Status Claimed**	☐
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	1	**Suggested Figure for Publication (if any)**	1

PTO/AIA/14 (11-15)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

SUPPLEMENTAL ADS

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	REGN-008CIPCON2
	Application Number	15/471,506
Title of Invention	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS	

Filing By Reference:

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

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

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

Publication Information:

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

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

Representative Information:

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

Please Select One:	◉ Customer Number	○ US Patent Practitioner	○ Limited Recognition (37 CFR 11.9)
Customer Number	96387		

Domestic Benefit/National Stage Information:

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

Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
15/471,506	Continuation of	14972560	2015-12-17

SUPPLEMENTAL ADS

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	REGN-008CIPCON2
	Application Number	15/473,506
Title of Invention	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS	

Prior Application Status	Patented			Remove	
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
14972560	Continuation of	13940370	2013-07-12	9254338	2016-02-09

Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
13940370	Continuation in part of	PCT/US2012/020855	2012-01-11

Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
PCT/US2012/020855	Claims benefit of provisional	61432245	2011-01-13

Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
PCT/US2012/020855	Claims benefit of provisional	61434836	2011-01-21

Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
PCT/US2012/020855	Claims benefit of provisional	61561957	2011-11-21

Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add** button.

Foreign Priority Information:

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

Remove

Application Number	Country[i]	Filing Date (YYYY-MM-DD)	Access Code[i] (if applicable)

Additional Foreign Priority Data may be generated within this form by selecting the **Add** button.

SUPPLEMENTAL ADS

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	REGN-008CIPCON2
	Application Number	15/471,506
Title of Invention	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS	

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

☐ This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.

NOTE: By providing this statement under 37 CFR 1.55 or 1.78, this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA.

SUPPLEMENTAL ADS

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	REGN-008CIPCON2
	Application Number	15/471,506
Title of Invention	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS	

Authorization or Opt-Out of Authorization to Permit Access:

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

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

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

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

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

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

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

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

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

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

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

PTO/AIA/14 (11-15)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

SUPPLEMENTAL ADS

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	REGN-008CIPCON2
	Application Number	15/471,506
Title of Invention	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS	

Applicant Information:

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

Applicant 1

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

Clear

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

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

Name of the Deceased or Legally Incapacitated Inventor:

If the Applicant is an Organization check here. ☒

Organization Name	REGENERON PHARMACEUTICALS, INC.		
Mailing Address Information For Applicant:			
Address 1	777 Old Saw Mill River Road		
Address 2			
City	Tarrytown	**State/Province**	NY
Country	US	Postal Code	10591
Phone Number		Fax Number	
Email Address			

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

Assignee Information including Non-Applicant Assignee Information:

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

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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

SUPPLEMENTAL ADS

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	REGN-008CIPCON2
	Application Number	15/471,906
Title of Invention	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS	

Assignee 1

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

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

Organization Name	REGENERON PHARMACEUTICALS, INC.

Mailing Address Information For Assignee including Non-Applicant Assignee:

Address 1	777 Old Saw Mill River Road		
Address 2			
City	Tarrytown	**State/Province**	NY
Country i	US	Postal Code	10591
Phone Number		Fax Number	
Email Address			

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

Signature:

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

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

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

Signature	/Karl Bozicevic, Reg. No. 28,807/			Date (YYYY-MM-DD)	~~2017-03-28~~ 2017-08-31
First Name	Karl	Last Name	Bozicevic	Registration Number	28,807

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

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Approved for use through 04/30/2017. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

SUPPLEMENTAL ADS

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	REGN-008CIPCON2
	Application Number	15/471,506
Title of Invention	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS	

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

Privacy Act Statement

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

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

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

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

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

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

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

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

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

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

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

Electronic Patent Application Fee Transmittal					
Application Number:	15471506				
Filing Date:	28-Mar-2017				
Title of Invention:	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS				
First Named Inventor/Applicant Name:	George D. YANCOPOULOS				
Filer:	Karl Bozicevic/Kimberly Zuehlke				
Attorney Docket Number:	REGN-008CIPCON2				
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:					
PETITION FEE- 37 CFR 1.17(H) (GROUP III)		1464	1	140	140
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**

Electronic Acknowledgement Receipt	
EFS ID:	30240185
Application Number:	15471506
International Application Number:	
Confirmation Number:	8014
Title of Invention:	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS
First Named Inventor/Applicant Name:	George D. YANCOPOULOS
Customer Number:	96387
Filer:	Karl Bozicevic/Kimberly Zuehlke
Filer Authorized By:	Karl Bozicevic
Attorney Docket Number:	REGN-008CIPCON2
Receipt Date:	31-AUG-2017
Filing Date:	28-MAR-2017
Time Stamp:	14:37:28
Application Type:	Utility under 35 USC 111(a)

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Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Request under Rule 48 correcting inventorship	REGN-008CIPCON2_2017-08-31_Petition.pdf	25453 b34c4cc68346e6c207c93bcb2dc516f1ad043d55	no	1
Warnings:					
Information:					
2	Application Data Sheet	REGN-008CIPCON2_2017-08-31_supp_ADS_1.pdf	152722 a2751ddc510c502c15b0d78af29289bc33bc2f98	no	9
Warnings:					
Information:					
This is not an USPTO supplied ADS fillable form					
3	Fee Worksheet (SB06)	fee-info.pdf	30896 fd48e82f4e1908c87bffe993e56c57e00ee0028d	no	2
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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
15/471,506	03/28/2017	1647	2220	REGN-008CIPCON2	26	2

CONFIRMATION NO. 8014

REPLACEMENT FILING RECEIPT

96387
Regeneron - Bozicevic, Field & Francis
201 REDWOOD SHORES PARKWAY
SUITE 200
REDWOOD CITY, CA 94065

Date Mailed: 09/06/2017

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

Inventor(s)

George D. YANCOPOULOS, Yorktown Heights, NY;

Applicant(s)

REGENERON PHARMACEUTICALS, INC., Tarrytown, NY

Assignment For Published Patent Application

REGENERON PHARMACEUTICALS, INC., Tarrytown, NY

Power of Attorney: The patent practitioners associated with Customer Number 96387

Domestic Priority data as claimed by applicant

This application is a CON of 14/972,560 12/17/2015 PAT 9669069
which is a CON of 13/940,370 07/12/2013 PAT 9254338
which is a CIP of PCT/US2012/020855 01/11/2012
which claims benefit of 61/432,245 01/13/2011
and claims benefit of 61/434,836 01/21/2011
and claims benefit of 61/561,957 11/21/2011

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

Permission to Access Application via Priority Document Exchange: Yes

Permission to Access Search Results: Yes

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

If Required, Foreign Filing License Granted: 09/05/2017

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 15/471,506**

Projected Publication Date: Not Applicable

Non-Publication Request: No

Early Publication Request: No

Title

USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS

Preliminary Class

424

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

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Title 37, Code of Federal Regulations, 5.11 & 5.15

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201 REDWOOD SHORES PARKWAY
SUITE 200
REDWOOD CITY, CA 94065
UNITED STATES

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Application	Document	Mailroom Date	Attorney Docket No.
15471506	APP.FILE.REC	09/06/2017	REGN-008CIPCON2

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PATENT APPLICATION INFORMATION RETRIEVAL SYSTEM

INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	15/471,506
				Filing Date	March 28, 2017
				First Named Inventor	YANCOPOULOS, GEORGE D.
				Art Unit	1647
				Examiner Name	LOCKARD, JON MCCLELLAND
Sheet	1	of	1	Attorney Docket Number	REGN-008CIPCON2

U.S. PATENT DOCUMENTS

Examiner Initial*	Cite No.	Patent Number Number-Kind Code (*if known*)	Issue Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1				

U.S. PATENT APPLICATION PUBLICATIONS

Examiner Initial*	Cite No.	Publication Number **Number-Kind Code** (*if known*)	Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
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FOREIGN PATENT DOCUMENTS

Examiner Initial*	Cite No.	Foreign Document Number Country Code-Number-Kind Code (*if known*)	Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T
	1					

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T
	1	CENTER FOR DRUG EVALUATION AND RESEARCH APPLICATION NUMBER: 21-756 MEDICAL REVIEW(S) (December 17, 2004) <URL:https://www.accessdata.fda.gov/drugsatfda_docs/nda/2004/21-756_Macugen_medr.pdf>	
	2	CENTER FOR DRUG EVALUATION AND RESEARCH BLA APPLICATION NUMBER: 125156 MEDICAL REVIEW, (June 2006) <URL:https://www.accessdata.fda.gov/drugsatfda_docs/nda/2006/125156s000_Lucentis_MedR.pdf>	

Examiner Signature		Date Considered	

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

(9)

引用非特許文献

特許出願の番号	特願２０１６－２０２１６９
作成日	平成３０年　２月２３日
作成者	馬場　亮人　　４０４３　４Ｕ００
発明の名称	血管新生眼疾患を処置するためのＶＥＧＦアンタゴニストの使用

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
21-756

MEDICAL REVIEW(S)

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Medical Officer's Review of NDA 21-756
Labeling Review

NDA 21-756	Submission: December 10, 2004 Review Completed: December 13, 2004
Proposed Tradename:	Macugen
Generic Name:	pegaptanib sodium
Sponsor:	Eyetech Pharmaceuticals 3 Time Square, 12th Floor New York, New York, 10036
Pharmacologic Category:	VEGF Inhibitor
Proposed Indication:	The treatment of the neovascular form of age-related macular degeneration
Dosage Form and Route of Administration:	intravitreal injection
Submitted:	Draft Labeling

Reviewer Comments: *Reviewer recommended additions are underlined in red. Recommended deletions are located in the margins.*

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8 Draft Labeling Page(s) Withheld

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Manufactured by:

Gilead Sciences, Inc
650 Cliffside Drive
San Dimas, CA 91773

For:

Eyetech Pharmaceuticals, Inc.
Three Times Square
New York, NY 10036

Pfizer Inc.
235 E.42nd St.
New York, NY 10017

Comments/Recommendations:

The sponsor has accepted all of the changes proposed by the division. The label is recommended for approval.

Jennifer D. Harris, M.D.
Medical Officer

cc: NDA 21-756
HFD-550/Div Files
HFD-550/CSO/Puglisi
HFD-520/CHEM
HFD-550/PHARM/ZChen
HFD-550/MO/Harris
HFD-550/SMO/Chambers

NDA 21-756 Macugen Final Label

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/s/

Jennifer Harris
12/16/04 09:51:37 AM
MEDICAL OFFICER

Wiley Chambers
12/16/04 12:07:05 PM
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Medical Officer's Review of NDA 21-756
NDA Amendment (2nd year study data)

NDA 21-756	Submission: October 7, 2004 Review Completed: October 27, 2004
Proposed Tradename:	Macugen
Established Name:	pegaptanib sodium
Sponsor:	Eyetech Pharmaceuticals 3 Time Square, 12th Floor New York, New York, 10036
Pharmacologic Category:	VEGF Inhibitor
Proposed Indication:	The treatment of the neovascular form of age-related macular degeneration
Dosage Form and Route of Administration:	intravitreal injection

Submitted:

The sponsor has submitted draft safety and efficacy tables for the 2nd year data for this two year study. The results of the 1st year data were submitted in the original NDA application. Full study reports including, case report forms, case report tabulations, subgroup analysis, etc have not been provided. This review is based on an incomplete database for the 2nd year data, however, enough information has been provided to adequately label the product at this time.

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Background

At baseline (week 0), patients in each study (EOP1003 and EOP1004) were randomized to one of four treatment groups (0.3 mg pegaptanib, 1 mg pegaptanib, 3 mg pegaptanib or sham injections once every 6 weeks).

At the 54 week time point, patients in the active therapy arms were re-randomized on a 1:1 basis to either discontinue or continue treatment for a further 48 weeks. Patients receiving sham injections were re-randomized on a 1:1:1:1:1 basis to discontinue the masked treatment, to continue on study receiving one of the 3 active treatments, or to continue on sham therapy.

Patients who were randomized to stop treatment were permitted to resume therapy if they had benefited from treatment in the first year and had lost at least 2 lines of vision after discontinuation.

The patient populations for the 2nd year of study were defined as follows:

Cohort 1 - all patients re-randomized to continue the same treatment.
Cohort 2 – all patients re-randomized to discontinue treatment.
Cohort 3 – all sham patients re-randomized to active dose or sham

For the purposes of the review, special attention have been given to patients in cohort 1 since this will give a true picture of the long term safety and efficacy of pegaptanib sodium treatment.

Patient Evaluation Groups – 2nd Year

Populations	N	N	N	N
Randomized	265	264	252	272
Intent-to-Treat [1]	265	264	252	272
Safety [2]	258	256	245	265

[1] Patients who were re-randomized at week 54, regardless of their eligibility for the study
[2] Patients who received at least one study treatment

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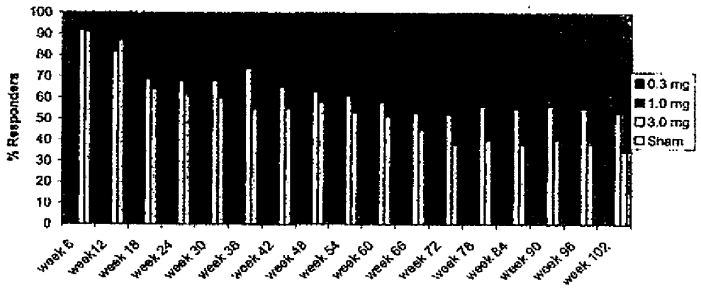
Efficacy Analysis

Responder Analysis – ITT Population– Study 1004

	0.3 mg N=66	1.0mg N=66	3.0 mg N=62	Sham N=53
Loss < 15 letters at week 102	40 (61%)	37 (56%)	33 (53%)	18 (34%)
Loss ≥ 15 letters at week 102	26 (39%)	29 (44%)	29 (47%)	35 (66%)
p-value	[redacted]	[redacted]	[redacted]	

Responder Analysis by Week - Study EOP1004



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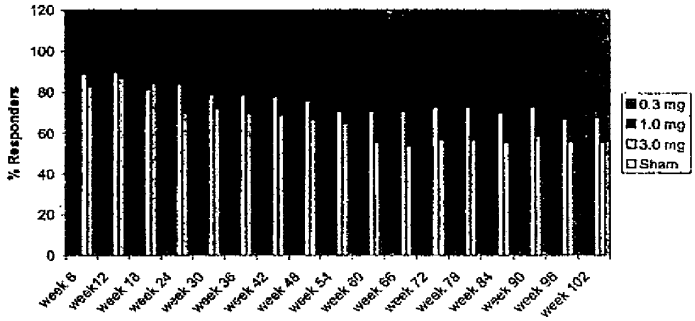
Responder Analysis – ITT Population– Study 1003

	0.3 mg N=67	1.0 mg N=67	3.0 mg N=63	Sham N=54
Loss < 15 letters at week 102	38 (57%)	46 (72%)	43 (68%)	30 (56%)
Loss ≥ 15 letters at week 102	29 (43%)	19 (28%)	20 (32%)	24 (44%)
p-value	*0.98*	*0.1*	*0.23*	

Responder Analysis by Week - Study EOP1003



Reviewer's Comments:

The statistically significant findings are highlighted in the table. The efficacy analysis in this review is based on a responder analysis of all patients who lost < 15 letters of visual acuity at week 102. This provides a means of direct comparison of the second year data to the first year data that was submitted in the original NDA.

Based on the same Hochberg multiple comparison procedure used to analyze the first year data, Study 1004 demonstrates efficacy for all active doses of pegaptanib sodium at week 102. However, this effect is not replicated in study 1003 which does not show efficacy for any of the active doses.

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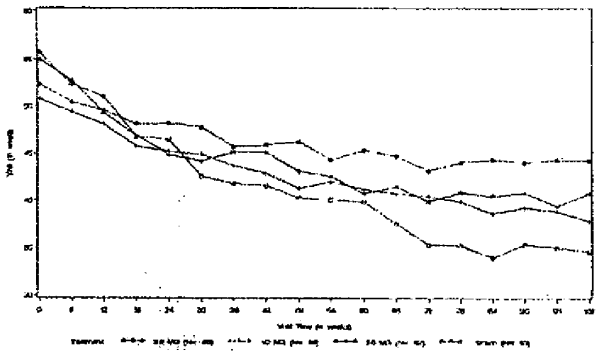
EOP1004: Mean Visual Acuity Over Time ITT (LOCF)



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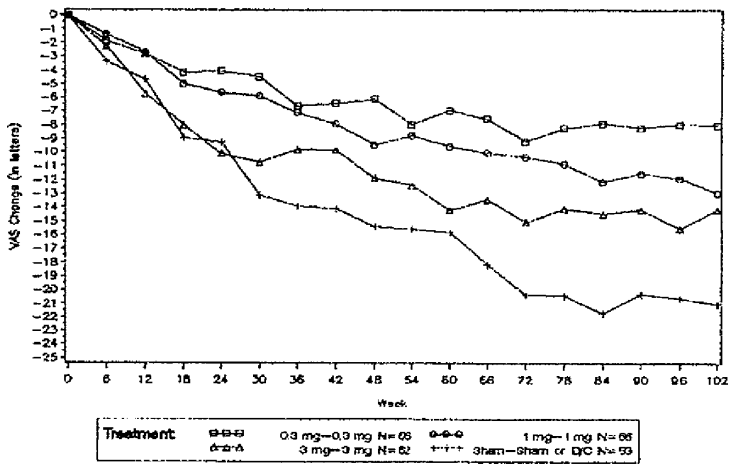
EOP1004 Mean Changes in Visual Acuity (LOCF), Baseline to Week 102



Number of On-Study PDT Treatments Received in the 2nd Year　Study EOP1004

	0.3 mg-0.3mg N=66	1 mg-1mg N=66	3mg-3mg N=62	Sham-sham or d/c N=53
No of PDT treatments	8	14	6	18

6

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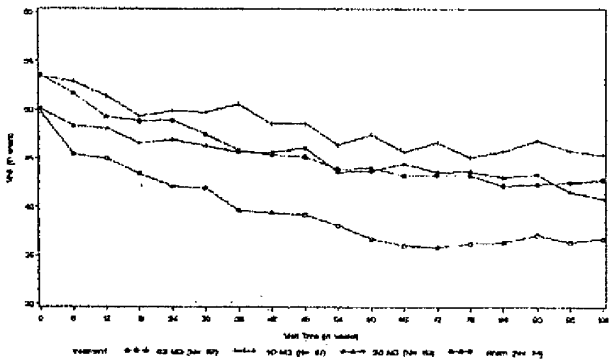
EOP1003: Mean Visual Acuity Over Time ITT (LOCF)



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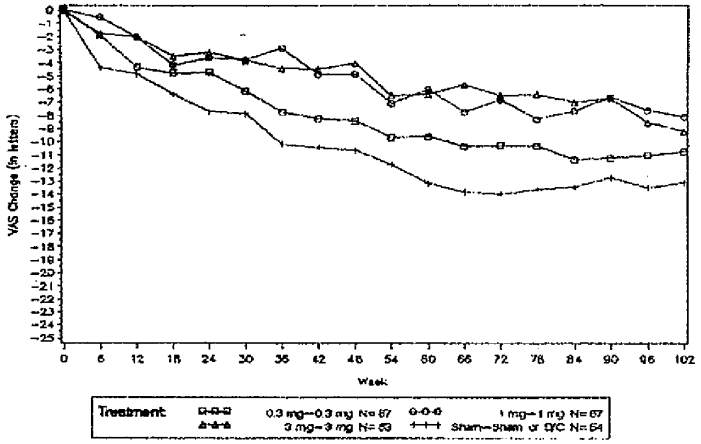
EOP1003 Mean Changes in Visual Acuity (LOCF), Baseline to Week 102



Number of On-Study PDT Treatments Received in the 2nd Year – Study EOP1003

	0.3 mg-0.3mg N=67	1 mg-1mg N=67	3mg-3mg N=63	Sham-sham or d/c N=54
No of PDT treatments	1	6	2	3

Reviewer's Comments:

Patients in all pegaptanib treatment groups as well as the sham group show a slower rate of vision loss in the 2nd year of study than in the 1st year for both studies EOP1004 and EOP1003. There appears to be stabilization of vision during the second year of treatment in the 0.3 mg and 3 mg treatment groups for study EOP1004. This

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stabilization is also seen in Study EOP1003 for the 0.3 mg and 1 mg pegaptanib groups as well as patients in the sham group.

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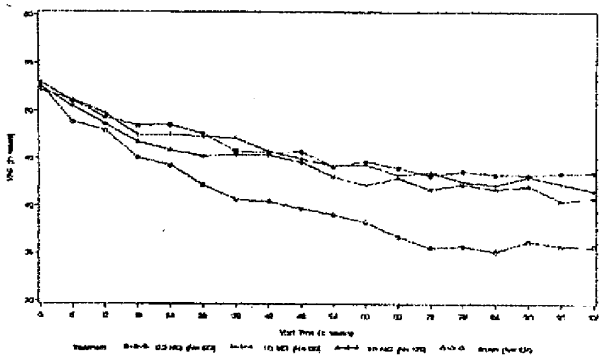
Combined Studies: Mean Visual Acuity Over Time – ITT (LOCF)



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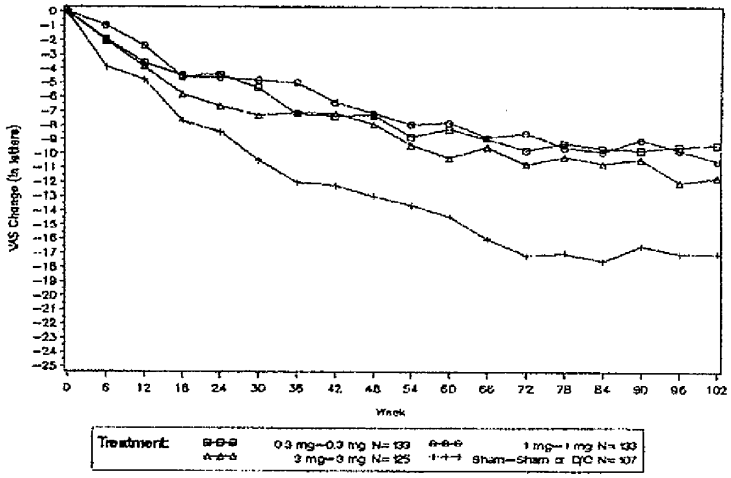
EOP1004 & EOP1003 Mean Changes in Visual Acuity (LOCF), Baseline to Week 102



Number of On-Study PDT Treatments Received in the 2nd Year – Combined Studies

	0.3 mg-0.3mg N=133	1 mg-1mg N=133	3mg-3mg N=125	Sham-sham or d/c N=107
No of PDT treatments	9	16	8	21

Reviewer's Comments:

The rate of vision loss in the combined data set is similar for all active treatment groups. The results for all treatment groups including sham demonstrate a progressive vision loss throughout the first year of treatment followed by a plateau effect in the second year. Overall, there is less vision loss in the pegaptanib treatment groups as compared to

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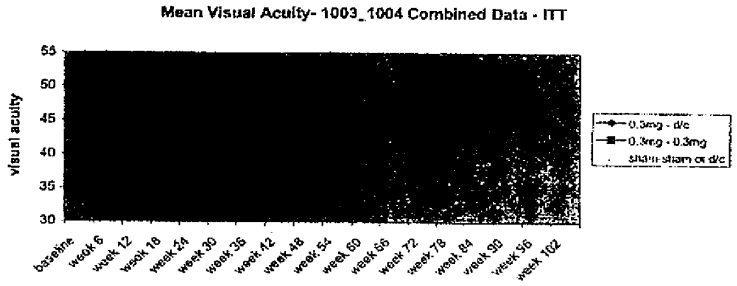
sham, however there is minimal differentiation demonstrated between the three doses of pegaptanib studied.

The following section of the review has been done to address the issue of the need for continuing injections of pegaptanib sodium after the 1st year of treatment Based on the results of the responder analysis, the was no demonstration of efficacy for the 0.3 mg dose during the 2nd year of the study based on replicative trials. However, there may still be a reason to continue injections after the first year of treatment despite the lack of demonstrated efficacy. Theoretically, further injections may be needed to maintain the positive visual acuity effects gained during the 1st year of treatment. The questions was addressed by evaluating those patients who were in the 0.3mg group during the 1st year of study and then subsequently discontinued treatment or remained on the 0.3 mg dose.

The three patient populations analyzed were:

0.3mg-0.3mg: patients who were on 0.3mg for the 1st and 2nd years
0.3mg-sham: patients who were on 0.3mg during the 1st year and were re-randomized to sham during the 2nd year.
Sham-sham or d/c: patients who were in the sham group during the 1st year and re-randomized to sham or to discontinuation of treatment during the second year



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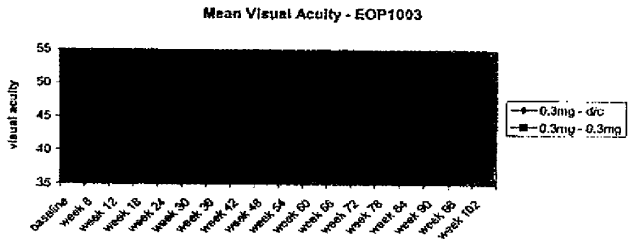

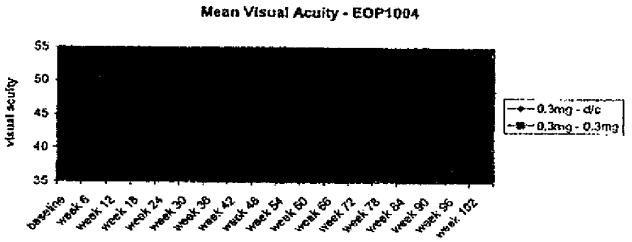

Reviewer's comments:

The mean visual acuity results for study EOP1003 appear to favor the 0.3mg-d/c group in study EOP1003 However, the separation between the two groups during the first year of treatment may be artificial since both groups are receiving the same dose. In study EOP1004, this separation is not seen and the results appear to favor the 0.3mg-0.3mg group. For the combined data set, the results are equivocal concerning the need for further injections beyond the first year of treatment.

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Safety Analysis

Number of Patients discontinued Cohort 1

	0.3 mg	1 mg	3 mg	Sham
Study EOP 1004	N=66	N=66	N=62	N=26
	18 (27%)	14 (21%)	13 (21%)	1 (4%)
Study EOP 1003	N=67	N=67	N=63	N=27
	9 (13%)	9 (13%)	8 (13%)	3 (11%)

Reasons for Discontinuation from Treatment Cohort 1 – Study EOP1004 and EOP1003

Number of patients	0.3 mg N=133	1.0 mg N=133	3.0mg N=125	Sham N=53
Death	1 (1%)	1 (1%)	0	0
Adverse event	5 (4%)	2 (2%)	4 (3%)	2 (4%)
Protocol violation	0	0	0	0
Investigator/sponsor decision	2 (2%)	1 (1%)	4 (3%)	0
Patient request	13 (10%)	16 (12%)	12 (10%)	2 (4%)
Lost to follow-up	1 (1%)	1 (1%)	0	0
Other	5 (4%)	2 (2%)	1 (1%)	0

Reviewer's Comments:
The majority of patients were reported as discontinued due to patient request. This may be indicative of adverse experiences associated with the drug that were intolerable to the patient. Case report forms have not been provided in this submission which are needed to adequately evaluate the reasons for discontinuation.

First and Second Year Adverse Events Reported in > 1% of Subjects (Cohort 1)– Safety Population – Studies EOP1003 and EOP1004

Number of subjects System organ class and preferred term	0.3 mg N=128	1 mg N=126	3 mg N=120	Sham N=51
Eye Disorders				
Punctate keratitis	54 (42%)	50 (40%)	50 (42%)	23 (45%)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cataract	42 (33%)	46 (37%)	50 (42%)	19 (37%)
Visual acuity reduced	41 (32%)	32 (25%)	34 (28%)	17 (33%)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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Number of subjects System organ class and preferred term	0.3 mg N=128	1 mg N=126	3 mg N=120	Sham N=51
[redacted]				
Macular degeneration	19 (15%)	20 (16%)	17 (14%)	12 (24%)
Eye discharge	18 (14%)	16 (13%)	14 (12%)	9 (18%)
Eye irritation	18 (14%)	18 (14%)	14 (12%)	7 (14%)
Abnormal sensation in eye	17 (13%)	17 (13%)	12 (10%)	8 (16%)
Conjunctival hemorrhage	16 (13%)	14 (11%)	8 (7%)	7 (14%)
Vision blurred	16 (13%)	14 911%)	12 (10%)	8 (16%)
Eye redness	15 (12%)	12 (10%)	17 (14%)	7 (14%)
Retinal hemorrhage	15 (12%)	17 (13%)	13 (11%)	6 (12%)
Eye pruritus	14 (11%)	10 (8%)	21 (18%)	8 (16%)
Lacrimation increased	14 (11%)	24 (19%)	17 (14%)	55 (15%)
[redacted]				
Photophobia	11 (9%)	11 (9%)	10 (8%)	5 (10%)
[redacted]				
Dry eye	10 (8%)	13 (10%)	13 (11%)	7 (14%)
Vitreous detachment	10 (8%)	13 (10%)	8 (7%)	7 (14%)
[redacted]				
Conjunctival hyperemia	7 (5%)	7 (6%)	6 (5%)	3 (6%)
[redacted]				
Eyelid edema	5 (4%)	10 (8%)	11 (9%)	26 (7%)
Posterior capsule opacification	5 (4%)	1 (1%)	4 (3%)	2 (4%)
[redacted]				
Corneal dystrophy	4 (3%)	3 (2%)	2 (2%)	2 (4%)
Corneal epithelium defect	4 (3%)	5 (4%)	8 (7%)	4 (8%)
Eyelid ptosis	4 (3%)	3 (2%)	4 (3%)	2 (4%)
[redacted]				
Corneal abrasion	3 (2%)	4 (3%)	5 (4%)	3 (6%)
[redacted]				
Keratitis	2 (2%)	3 (2%)	2 (2%)	3 (6%)
[redacted]				
Mydriasis	2 (2%)	2 (2%)	0	1 (2%)
Pupillary reflex impaired	2 (2%)	1 (1%)	1 (1%)	2 (4%)

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Number of subjects System organ class and preferred term	0.3 mg N=128	1 mg N=126	3 mg N=120	Sham N=51
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Retinal exudates	3 (2%)	2 (2%)	0	1 (2%)
Retinal Scar	3 (2%)	2 (2%)	1 (1%)	1 (2%)
Blood and Lymphatic system disorders				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Thrombocythemia	0	2 (2%)	0	2 (4%)
Cardiac disorders				
Atrial fibrillation	3 (2%)	3 (2%)	2 (2%)	1 (2%)
Arrhythmia	1 (1%)	4 (3%)	1 (1%)	1 (2%)
Cardiac failure congestive	3 (2%)	2 (2%)	1 (1%)	4 (8%)
Bradycardia	1 (1%)	2 (2%)	2 (2%)	4 (8%)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Myocardial infarction	0	1 (1%)	2 (2%)	1 (2%)
Myocardial ischemia	0	2 (2%)	1 (1%)	0
Atrioventricular block	0	0	2 (2%)	1 (2%)
Cardiomegaly	0	2 (2%)	0	1 (2%)
Ear and Labyrinth				
Vertigo	4 (3%)	8 (6%)	2 (2%)	14 (4%)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cerumen impaction	1 (1%)	2 (2%)	0	3 (1%)
Endocrine Disorders				
Acquired hypothyroidism	0	1 (1%)	3 (3%)	4 (1%)
Hyperthyroidism	0	0	2 (2%)	2 (1%)
Gastrointestinal disorders				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Constipation	3 (2%)	6 (5%)	2 (2%)	1 (2%)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abdominal pain	3 (2%)	4 (3%)	1 (1%)	1 (2%)
General disorders and administration site conditions				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Edema peripheral	4 (3%)	2 (2%)	4 (3%)	2 (4%)
Asthenia	2 (2%)	2 (2%)	2 (2%)	1 (2%)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infections and infestations				

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Number of subjects System organ class and preferred term	0.3 mg N=128	1 mg N=126	3 mg N=120	Sham N=51
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Influenza	12 (9%)	5 (4%)	6 (5%)	5 (10%)
Urinary tract infection				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sinusitis	3 (2%)	5 (4%)	6 (5%)	3 (6%)
Gastroenteritis viral	2 (2%)	1 (1%)	3 (3%)	2 (4%)
[redacted]	[redacted]	[redacted]	[redacted]	0
Injury, poisoning and procedural complications				
Post procedural pain	3 (2%)	4 (3%)	3 (3%)	1 (2%)
[redacted]	[redacted]	[redacted]	[redacted]	0
Skin laceration	2 (2%)	3 (2%)	3 (3%)	2 (4%)
Abrasion	3 (2%)	0	2 (2%)	3 (6%)
[redacted]	[redacted]	[redacted]	[redacted]	0
Metabolism and nutrition disorders				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders				
Back pain	7 (5%)	8 (6%)	8 (7%)	5 (10%)
Arthralgia	8 (6%)	4 (3%)	4 (3%)	3 (6%)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Osteoarthritis	2 (2%)	4 (3%)	2 (2%)	1 (2%)
[redacted]	[redacted]	[redacted]	[redacted]	0
Muscle cramp	2 (2%)	0	3 (3%)	1 (2%)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Neoplasms				
Basal cell carcinoma	2 (2%)	4 (3%)	2 (2%)	2 (4%)
Prostate cancer	2 (2%)	1 (1%)	2 (2%)	1 (2%)
[redacted]	[redacted]	[redacted]	[redacted]	0
Nervous system disorders				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Psychiatric disorders				

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Number of subjects System organ class and preferred term	0.3 mg N=128	1 mg N=126	3 mg N=120	Sham N=51
Depression	6 (5%)	8 (6%)	4 (3%)	1 (2%)
[redacted]				
Renal and urinary disorders				
[redacted]				
Reproductive System				
[redacted]				
Respiratory, thoracic and mediastinal disorders				
Nasopharyngitis	15 (12%)	17 (13%)	20 (17%)	7 (14%)
[redacted]				
Cough	8 (6%)	5 (4%)	6 (5%)	4 (8%)
Pharyngitis	5 (4%)	3 (2%)	2 (2%)	2 (4%)
[redacted]				
Dyspnea	2 (2%)	4 (3%)	7 (6%)	2 (4%)
Emphysema	2 (2%)	1 (1%)	1 (1%)	2 (4%)
Epistaxis	2 (2%)	2 (2%)	2 (2%)	1 (2%)
[redacted]				
Pulmonary embolism	2 (2%)	0	0	1 (2%)
Rhinorrhea	3 (2%)	1 (1%)	1 (1%)	1 (2%)
Skin and subcutaneous tissue disorders				
[redacted]				
Cutis laxa	3 (2%)	2 (2%)	0	1 (2%)
Skin lesion	3 (2%)	0	1 (1%)	1 (2%)
Skin cysts	3 (2%)	0	0	1 (2%)
Vascular disorders				
[redacted]				
Hypertension aggravated	4 (4%)	5 (4%)	3 (3%)	3 (6%)
Hypotension	3 (2%)	4 (3%)	2 (2%)	1 (2%)
[redacted]				

Reviewer's comments:
Similar types of adverse events are seen in this combined second year data compared to the first year data as shown in the original NDA review. There are no new adverse events identified in this submission. Adverse events seen more frequently in the 0.3 mg group versus sham are highlighted. The majority of the most frequently occurring adverse events (i.e. >10%) in the drug group are those commonly seen after intraocular procedures including injections.

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First and Second Year Ocular Adverse Events > 10% and/or Events that are Considered Potentially Vision Threatening – Safety Population

Event	0.3 mg N=128	1 mg N=126	3 mg N=120	Sham N=51
Punctate keratitis	54 (42%)	50 (40%)	50 (42%)	23 (45%)
[redacted]				
Cataract	42 (33%)	46 (37%)	50 (42%)	19 (37%)
Visual acuity reduced	41 (32%)	32 (25%)	34 (28%)	17 (33%)
[redacted]				
Macular degeneration	19 (15%)	20 (16%)	17 (14%)	12 (24%)
Eye discharge	18 (14%)	16 (13%)	14 (12%)	9 (18%)
Eye irritation	18 (14%)	18 (14%)	14 (12%)	7 (14%)
Abnormal sensation in eye	17 (13%)	17 (13%)	12 (10%)	8 (16%)
Conjunctival hemorrhage	16 (13%)	14 (11%)	8 (7%)	7 (14%)
Vision blurred	16 (13%)	14 (11%)	12 (10%)	8 (16%)
Eye redness	15 (12%)	12 (10%)	17 (14%)	7 (14%)
Retinal hemorrhage	15 (12%)	17 (13%)	13 (11%)	6 (12%)
Eye pruritus	14 (11%)	10 (8%)	21 (18%)	8 (16%)
Lacrimation increased	14 (11%)	24 (19%)	17 (14%)	55 (15%)
[redacted]				
Retinal Artery Occlusion	1 (1%)	3 (2%)	0	1 (2%)
Retinal Detachment	0	4 (3%)	2 (2%)	1 (2%)

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First and Second Year Rate of Endophthalmitis for Each Cohort – Study EOP1003 and EOP1004 – Safety Population

	0.3 mg	1 mg	3 mg	Sham
2nd year data	N=258	N=256	N=245	N=265
Cohort 1	0	0	0	0
Cohort 2	0	0	0	0
Cohort 3	0	1 (2%)	3 (5%)	0
1st year data	N=295	N=301	N=296	N=298
	6 (2%)	3 (1%)	3 (1%)	0

Reviewer's Comments:
There is a lower risk of endophthalmitis seen in the 2nd year of treatment compared to the 1st year (0.5% vs. 1.4%).

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Reviewer's Comments:

During this two year study, the baseline IOP for all treatment groups remains unchanged. There does not appear to be a risk of hypotony associated with multiple penetrations of the globe over a 2 year period.

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Conclusions:

- *All active treatment groups of pegaptanib sodium show a diminished effect in the primary efficacy endpoint (number of patients who loss ≤ 15 letters of vision) at week 102.*
- *Visual acuity appears to stabilize in the second year of the study for the 0.3 mg treatment group in replicative studies; however, this phenomenon is also seen in the sham treatment group.*
- *The effectiveness of 0.3mg pegaptanib sodium is less in the second year than in the first.*
- *The need for continued injections every 6 weeks with 0.3 mg pegaptanib sodium cannot be definitively determined from this database.*
- *No new safety concerns were identified in the second year data. The majority of adverse events identified continue to be those commonly seen with intraocular procedures including intravitreous injections.*
- *There was a lower risk of endophthalmitis seen in the 2nd year of treatment compared to the 1st year (0.5% vs. 1.4%).*

Recommendations:

The original conclusions of the NDA review remain unchanged. Pegaptanib sodium 0.3% is approvable from a clinical perspective for the treatment of the neovascular form of age-related macular degeneration. The labeling should reflect the diminished efficacy demonstrated in the second year of the study.

Jennifer D. Harris, M.D.
Medical Officer

cc: NDA 21-756
HFD-550/Div Files
HFD-550/CSO/Puglisi
HFD-520/CHEM
HFD-550/PHARM/Chen
HFD-550/MO/Harris
HFD-550/SMO/Chambers

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/s/

Jennifer Harris
12/7/04 09:07:57 AM
MEDICAL OFFICER

Wiley Chambers
12/7/04 04:20:25 PM
MEDICAL OFFICER

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CLINICAL REVIEW

Medical Officer's Review of NDA 21-756

Proprietary Name:	**Macugen**
Tradename:	**pegaptanib sodium injection**
Applicant:	**Eyetech Pharmaceuticals** **500 Seventh Avenue, 18th Floor** **New York, New York 10018**
NDA Drug Classification:	**1P**
Proposed Indication:	**The treatment of the neovascular form of age-related macular degeneration.**
Date of Submission:	**March 18, 2004**
Date of Review:	**July 27, 2004**
Reviewer:	**Jennifer Harris, M.D.**

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CLINICAL REVIEW

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Clinical Review for NDA 21-756

Executive Summary

I. Recommendations

A. Recommendation on Approvability

NDA 21-756 is approvable for the treatment of the neovascular form of age-related macular degeneration pending the receipt and review of the 120-day safety update; revised drug product specifications and satisfactory labeling.

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

It is recommended that the sponsor conduct studies postmarketing to address the possible neurotropic effects of pegaptanib sodium. This was raised as a concern in the advisory committee meeting.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

AMD is the leading cause of blindness in developed countries with approximately 15 million people with the disease in the United States. AMD is characterized as a progressive degenerative disease of the macula. There are two forms of AMD: neovascular and non-neovascular. The non-neovascular form of AMD is more common and leads to a slow deterioration of the macula with a gradual loss of vision over a period of years. The neovascular form of the disease is responsible for the majority of cases of severe vision loss and is due to proliferation of abnormal blood vessels behind the retina. These blood vessels leak blood and fluid into the retina, which results in visual abnormalities. The development of these abnormal blood vessels is due in part to the activity of VEGF (vascular endothelial growth factor) and its inhibition is expected to impact on the onset and/or severity of vision loss associated with the proliferation of abnormal blood vessels.

Macugen (pegaptanib sodium injection) has been developed by Eyetech, Pharmaceuticals for the treatment of the neovascular form of age-related macular

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degeneration (AMD). In vitro studies have suggested that pegaptanib binds to VEGF and inhibits its binding to cellular receptors. Macugen's anti-VEGF activity is expected to inhibit abnormal blood vessel proliferation and therefore decrease the vision loss associated with the neovascular form of AMD.

Macugen is administered as an intravitreal injection which is dosed every six (6) weeks. It has been study in approximately 966 patients during the clinical development program. During the two phase 3 trials approximately 295 patients received the 0.3 mg dose, 301 patients received the 1mg dose and 296 patients received the 3 mg dose.

B. Efficacy

The submitted studies in NDA 21-756 are sufficient to establish efficacy for the use of pegaptanib sodium 0.3 mg in the treatment of the neovascular form of age-related macular degeneration. The two phase 3 studies show replicative results in the ability of pegaptanib sodium to reduce the risk of vision loss in patients with neovascular AMD by approximately 15% when administered every six weeks compared to sham.

C. Safety

The majority of safety concerns raised in the review of this application are likely attributed to the procedure required to administer pegaptanib sodium and not to the drug product itself. The majority of adverse events seen in the database are those commonly seen with intraocular procedures including intravitreous injections. There is concern raised in this database over the rate of endophthalmitis. This event is most likely due to contamination during the procedure itself and not to the drug product since most cases were infectious in nature. The labeling will need to reflect the risk of this administration related adverse event and the importance of the use of sterile technique. This will allow for physicians and patients to be adequately informed about this risk and steps to take to minimized its occurrence.

D. Dosing

Adequate dose ranging studies were conducted during drug development. The 0.3 mg dose of pegaptanib sodium has been demonstrated to be safe and effective in two controlled phase 3 trials. The dosing interval (every 6 weeks) chosen by the applicant was not varied during the development program, therefore there is no clinical data available to assess the adequacy of this dosing interval.

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CLINICAL REVIEW

Executive Summary Section

E. Special Populations

The sponsor has adequately evaluated gender effects on both the safety and efficacy outcomes. Sub-group analyses did not reveal any difference in the primary efficacy endpoint between males and females. The safety profile seen in male and females is similar. The types and rates of adverse events seen in the two groups are consistent.

The trials for this indication were conducted in a population that was overwhelmingly elderly and white. This is reflective of the population which is mostly affected by this disease and does not reflect an issue with recruitment. The number of patients outside of this demographic were too small to make any definitive conclusion about the safety and efficacy; however, based on a subset analysis it does not appear that there are any age, race or ethnicity effects.

Pediatric trials have not been conducted for this drug. The indication being sought is for age-related macular degeneration which is a disease seen exclusively in the adult population.

The demographics of the patients enrolled in the trial during the development program for this product are representative of the targeted population. There is no additional data need from other populations.

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Clinical Review

I. Introduction and Background

AMD is the leading cause of blindness in developed countries with approximately 15 million people with the disease in the United States. AMD is characterized as a progressive degenerative disease of the macula. There are two forms of AMD: neovascular and non-neovascular. The non-neovascular form of AMD is more common and leads to a slow deterioration of the macula with a gradual loss of vision over a period of years. The neovascular form of the disease is responsible for the majority of cases of severe vision loss and is due to proliferation of abnormal blood vessels behind the retina. These blood vessels leak blood and fluid into the retina, which results in visual abnormalities. The development of these abnormal blood vessels is due in part to the activity of VEGF (vascular endothelial growth factor) and its inhibition is expected to impact on the onset and/or severity of vision loss associated with the proliferation of abnormal blood vessels.

Macugen (pegaptanib sodium injection) has been developed for the treatment of the neovascular form of age-related macular degeneration (AMD). In vitro studies have suggested that pegaptanib binds to VEGF and inhibits its binding to cellular receptors. Macugen's anti-VEGF activity is expected to inhibit abnormal blood vessel proliferation and therefore decrease the vision loss associated with the neovascular form of AMD.

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

Proprietary Name:	Macugen
Tradename:	pegaptanib sodium
Sponsor:	Eyetech Pharmaceuticals 500 Seventh Avenue, 18th Floor New York, New York 10018
NDA Drug Classification:	1P
Pharmacologic Category	Vascular Endothelial Growth Factor (VEGF) Inhibitor
Proposed Indication:	The treatment of the neovascular form of age-related macular degeneration.
Dosage Form and Route of Administration	Intravitreal Injection

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CLINICAL REVIEW

Clinical Review Section

B. State of Armamentarium for Indication(s)

Macugen (pegaptanib sodium injection) has been developed for the treatment of the neovascular form of age-related macular degeneration (AMD). Currently, there is only one treatment approved for use in AMD. Photodynamic therapy (PDT) with verteporfin is approved for patients with the predominantly classic form of AMD.

C. Important Milestones in Product Development

Milestones leading up to this NDA submission:

4/26/01 – End of Phase 2 Meeting
1/18/01 – Fast Track Designation Granted

8/27/04 – Advisory Committee Meeting

A decision was made to convene an advisory committee meeting for pegaptanib to present the efficacy and safety findings contained in the NDA. This was due to the fact that this drug product is the first in its class that will potentially be approved for this indication. Additionally, the route/regimen and frequency of administration (repeated intravitreal injections) required for this drug product is atypical for any currently approved ophthalmic drug products.

The advisory committee concluded that efficacy had been demonstrated for the use of pegaptanib sodium in the treatment of neovascular age-related macular degeneration. Overall, the committee concluded that the product was safe, however, there were recommendations to monitor for longer-term effects and to educate physicians concerning injection procedures to minimized the rate of endophthalmitis.

D. Other Relevant Information

Pegaptanib Sodium is a new molecular entity. It has not been approved for marketing in or outside of the United States at any time by any sponsor and has not been withdrawn from marketing for any reason.

E. Important Issues with Pharmacologically Related Agents

There are no other drugs in this pharmacologic class currently marketed for ophthalmic use. There are products in this class currently under investigation. There have been no additional issues raised with this class of agents outside of those identified in this NDA review.

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II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

Composition of Macugen (pegaptanib sodium injection) 0.3 mg/90 µL[a]

Name of Ingredients	Reference to Standards	Function	Solution Composition mg/mL	Unit Dosage Composition 0.3 mg/90 µL	Percent (w/v)
Pegaptanib Sodium	In-house standard	Drug substance	3.47[b]	0.3 mg[b]	0.3[b]
Monobasic Sodium Phosphate Monohydrate	USP	pH buffering agent	0.77	0.069 mg	0.077
Dibasic Sodium Phosphate Heptahydrate	USP	pH buffering agent	1.2	0.11 mg	0.12
Sodium Chloride	USP	Tonicity adjuster	9.0	0.8 mg	0.9
Hydrochloric Acid	NF	pH adjuster	As needed[c]	As needed[c]	
Sodium Hydroxide	NF	pH adjuster	As needed[c]	As needed[c]	--
Water for Injection	USP	Diluent	q.s.	q.s.	--
Nitrogen	NF	Processing aid/inert atmosphere	q.s.	q.s.	--
Total Volume			1 mL	90 µL	

[a] Quantities are calculated
[b] Based on a theoretical potency of 100% for pegaptanib sodium with no overage. The actual weight varies according to the actual potency of pegaptanib sodium used. Compositions calculated based on oligonucleotide moiety
[c] For pH adjustment

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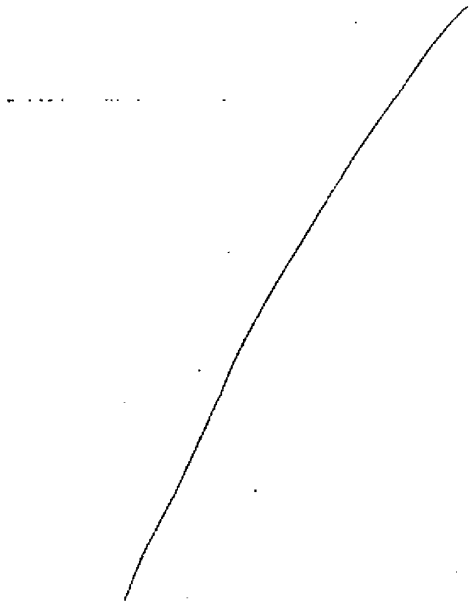
CLINICAL REVIEW

Clinical Review Section

Analytical Specification for Macugen Injection, 0.3 mg



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III. Human Pharmacokinetics and Pharmacodynamics

A. Pharmacokinetics

PK characteristics:

- Following intravitreous administration, pegaptanib is systemically available, and displays non-linear pharmacokinetics at or doses above 1 mg. At 2 mg/eye and 3 mg/eye dose treatment groups, plasma pegaptanib concentrations increased disproportionately with dose.
- Mean terminal elimination half-life of pegaptanib is 10 days with individual values ranging from 2 to 19 days. During repeated dosing when administered every 4 or 6 weeks, pegaptanib accumulation is minimal/negligible, if any.
- Pegaptanib metabolism is not fully characterized, however, it is expected to be metabolized by nucleases to shorter chains of nucleotides. Because of its molecular structure, typical P450 drug-drug interactions are not expected. However, pharmacodynamic interactions with patients taking anti-hypertensive or IOP lowering agents have not been studied.
- Renal impairment (<70 mL/min CrCL) results in significant decrease in pegaptanib clearance.

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B. **Pharmacodynamics**

Pharmacodynamic evaluations have not been studied for this drug product.

IV. Description of Clinical Data and Sources

A. **Overall Data**

This review is based on the results of the applicant supported trials for AMD conducted under IND 56,503. Two phase 3 safety and efficacy trials were submitted to support the indication currently being sought by the applicant. In addition, the results of four early phase 1/2 dose ranging and safety trials were also submitted.

This NDA was submitted in Common Technical Document (CTD) format in electronic and paper media (angiograms only) for review.

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[redacted] CLINICAL REVIEW

Clinical Review Section

B. Tables Listing the Clinical Trials

Protocol	Design	Dose	Patients Treated	Study Assessments
Studies in Age-related Macular Degeneration (AMD)				
Controlled AMD Trials				
EOP1003	Phase 2/3 multi-center, randomized, sham-injection controlled, double masked, dose finding	Intravitreous injections of either 0.3, 1 or 3 mg pegaptanib sodium/eye or sham every 6 weeks for 54 weeks	622 patients 50 years of age active subfoveal CNV secondary to exudative AMD	BCVA, Fluorescein angiography and fundus photography, AEs, IOP, laboratory parameters, vital signs, PDT administration, local ocular events
EOP1004	Phase 2/3 multi-center, randomized, sham-injection controlled, double masked, dose finding	Intravitreous injections of either 0.3, 1 or 3 mg pegaptanib sodium/eye or sham every 6 weeks for 54 weeks	586 patients 50 years of age active subfoveal CNV secondary to exudative AMD	BCVA, Fluorescein angiography and fundus photography, AEs, IOP, laboratory parameters, vital signs, PDT administration, local ocular events, PK, QOL
Uncontrolled AMD Trials				
NX109-01	Phase 1, multi-center, open label escalating dose, dose finding	Single intravitreous injection of either 0.25, 0.5, 1, 2 or 3 mg pegaptanib sodium/ eye	15 patients 50 years of age with exudative AMD	DLT, AEs, vital signs, BCVA, IOP, laboratory parameters, immune response, PK parameters, local ocular events
EOP1006	Phase 1/2, multi-center, open label, multiple dose in patients without PDT	Total of 3 consecutive intravitreous injections of 3 mg pegaptanib sodium/eye, 28 days apart	10 patients 50 years of age with subfoveal CNV secondary to exudative AMD	BCVA, AEs, IOP, laboratory parameters, vital signs, DLT, PK parameters, immune response, local ocular events

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EOP1001	Phase 1/2, multi-center, open label, multiple dose in patients following PDT administration	Total of 3 intravitreous injections of 3 mg pegaptanib sodium/ eye, 28 days apart	11 patients 50 years of age with predominantly classic subfoveal CNV secondary to exudative AMD	BCVA, AEs, IOP, laboratory parameters, vital signs, DLT, PK parameters, immune response, requirement for PDT administration, local ocular events
EOP1006	Phase 2 multi-center, randomized, multiple dose, open label cohort	Intravitreous injections of 3 mg pegaptanib sodium/ eye every 6 weeks for 54 weeks	37 patients 50 years of age with subfoveal CNV secondary to exudative AMD (Study is ongoing in 147 patients)	AE, local ocular event, IOP, laboratory parameters, vital signs, PK parameters, immune response
Development Trials for Additional Indications				
Studies in Diabetic Macular Edema (DME)				
EOP1002	Phase 1/2, multi-center, multiple dose open label,	Intravitreous injections of 3 mg pegaptanib sodium/ eye every 6 weeks for 12 to 30 weeks	10 patients 18 years of age with clinically significant DME	AEs, BCVA, laboratory parameters, IOP, retinal thickening, local ocular events
EOP1005	Phase 2, multi-center, randomized, sham-injection controlled, double-masked, dose finding	Intravitreous injections of either 0.3, 1.0 and 3 mg pegaptanib sodium/ eye or sham every 6 weeks for 12 to 30 weeks	169 patients 18 years of age with clinically significant DME (Study is ongoing)	Retinal thickening, BCVA, AEs, IOP, laboratory parameters, local ocular events, need for laser at 12 weeks
Studies in Von Hippel-Lindau Disease (VHL)				
EOP1003	Phase 1/2, open-label, non-randomized, pilot	Intravitreous injections of 3 mg pegaptanib sodium/ eye every 6 weeks for 30 to 54 weeks	5 patients 18 years of age with severe ocular VHL tumors	BCVA, macular thickening, fluorescein leakage, disease progression, AEs, local ocular events, IOP

CNV = Choroidal neovascularization; PDT = Photodynamic therapy with verteporfin; DLT = Dose limiting toxicity; AE = Adverse event; BCVA - Best corrected visual acuity; IOP = intraocular pressure, PK = Pharmacokinetics; QOL = quality of life.

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C. Postmarketing Experience

There is no postmarketing experience with this drug Macugen is not approved in any other country.

D. Literature Review

This product is a new molecular entity developed by the applicant. There is no data in the published literature pertinent to this drug product other than that submitted by the applicant.

V. Clinical Review Methods

A. How the Review was Conducted

This review evaluated the results of the two phase 3 trials submitted by the applicant. Each individual study was evaluated in depth to determine if the data supported the primary efficacy endpoint. The integrated safety and efficacy database was finally evaluated to determine the overall risk/benefit profile for this drug product.

B. Overview of Materials Consulted in Review

This review was based on data submitted by the sponsor submitted in Common Technical Document (CTD) format in electronic and paper media (angiograms only) for review.

C. Overview of Methods Used to Evaluate Data Quality and Integrity

DSI was requested to investigate four of the clinical sites in the phase 3 studies. The audits have not been competed at this time. The results will be reviewed for any data integrity issues once completed.

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

These studies were conducted in accordance with the International Conference on Harmonization (ICH) Guidelines for Good Clinical Practice (GCPs), the Declaration of Helsinki (as amended in Tokyo, Venice, Hong Kong, South Africa and Scotland), and in compliance with relevant regulations for informed consent and protection of subject rights in the country of conduct.

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Before initiation of the study, the protocol and the patient informed consent provisions were reviewed and approved by the appropriate ethics committees (EC) or institutional review boards (IRB) for each of the centers involved in the study. The studies began only after receiving written approval from each EC/IRB.

E. Evaluation of Financial Disclosure

Eyetech has certified that [redacted]

[redacted] Dr [redacted] and Dr [redacted] were certified to hold financial interests with the sponsor however these interests were not significant as defined in 21 CFR 54.2(b). Both were investigators for [redacted] Dr. [redacted] enrolled [redacted] and Dr. [redacted] enrolled [redacted]. The number of patients enrolled by these investigators were to small to have any impact on the outcome of the phase 3 study.

VI. Integrated Review of Efficacy

A. Brief Statement of Conclusions

The submitted studies in NDA 21-756 are sufficient to establish efficacy for the use of pegaptanib sodium 0.3 mg in the treatment of the neovascular form of age-related macular degeneration. The two phase 3 studies show replicative results in the ability of pegaptanib sodium to reduce the risk of vision loss in patients with neovascular AMD when administered every six weeks compared to sham.

B. General Approach to Review of the Efficacy of the Drug

The submitted phase 3 studies (EOP1003 and EOP1004) were reviewed independently to determine if the results of each trial demonstrated efficacy for the primary efficacy endpoint. The primary efficacy end point for each trial was a responder analysis of the proportion of patients who loss less than 15 letters of visual acuity from baseline (doubling of the visual angle) at 54 weeks. This analyses was done for two populations which represent ends of the data spectrum to evaluate the robustness of the results; an all randomized patient population with last-observation-carried-forward (LOCF) and the per-protocol population with observed cased only.

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C. **Detailed Review of Trials by Indication**

Proposed Indication: The treatment of the neovascular form of age-related macular degeneration.

Study 1 – Study EOP1003

Title: A Phase 2/3 Randomized, Double-Masked, Controlled, Dose-Ranging, Multi-Center Comparative Trial, in Parallel Groups, to Establish the Safety and Efficacy of Intravitreous Injections of Pegaptanib Sodium (Anti-Vascular Endothelial Growth Factor [VEGF] Pegylated Aptamer) Given Every 6 Weeks for 54 Weeks, in Patients with Exudative Age- Related Macular Degeneration (AMD)

Objective: The objective of this study was to establish the safe and efficacious dose of pegaptanib sodium when given as an intravitreous injection (0.3 mg, 1 mg or 3 mg/eye) compared with control sham injections every 6 weeks over a 54-week period (9 treatments) in patients with subfoveal choroidal neovascularization (CNV) secondary to AMD.

Study Design: This was a randomized, double masked, controlled, dose-ranging, multi-center, comparative, Phase 2/3 trial, in parallel groups. The study was conducted internationally in Europe, Israel, Australia, South America and North America. The study has a 2 year duration with two randomization steps and is ongoing. Data from the first year on study are included in this report.

Clinical sites – Study EOP1003

Center Number	Principal Investigator	Center Location	Number of Subjects
Australia			
114	Andrew Chang, MD	Syndey	7
64	Jennifer Arnold, MD	Parramatta	34
65	Ian Constable, MD	St. Nedlands	12
66	Paul Mitchell, MD	Westmead	8
73	Robyn Guymer, MD	East Melbourne	16
131	Mark Gillies, MD	Sydney	12
Austria			
67	Michael Stur, MD	Vienna	11
116	Anton Haas, MD	Graz	4
Belgium			

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CLINICAL REVIEW

Clinical Review Section

Center Number	Principal Investigator	Center Location	Number of Subjects
113	Anita Leys, MD	Leuven	38
Brazil			
70	Michel Fuzi, MD	Sao Paulo	7
108	Marcos de Avila, MD	Sector Burgeno	6
112	Carlos Moreira, MD	Curitiba	3
134	Jaco Lavinsky	Porto Alegre	5
Chile			
71	Jose Manuel Lopez, MD	Santago	7
Colombia			
104	Francisco Rodriguez, MD	Colombia	18
Czech Republic			
119	Ivan Fiser, MD	Prague	11
Denmark			
72	Michael Larsen, MD	Herlev	9
France			
74	Francois Koenig, MD	Lyon	2
75	Gisele Soubrane, MD	Creteil	25
76	Jean-Francois Korobelnik, MD	Bordeau	5
78	Alain Gaudric, MD	Paris	3
Germany			
79	Stefan Dithmar, MD	Heidelberg	10
80	Daniel Pauleikhoff, MD	Munstser	1
81	Ulrike Schneider, MD	Tubingen	6
82	Peter Wiedemann, MD	Leipzig	14
83	B Kirchhof, MD	Koln	8
Hungary			
122	Ilaliko Suveges, MD	Budapest	3
137	Jozsef Gyory, MD	Veszprem Korhaz	3
Israel			
84	Anat Loewenstein, MD	Tel-Aviv	11
85	Irit Rosenblatt, MD	Petach Tikva	11
103	Ayala Pollack, MD	Rehovot	7
Italy			
86	Rosario Brancato, MD	Milano	6
87	Francesco Bandello, MD	Udine	16
88	Felice Cardillo Piccolino, MD	Torino	10
89	Lfonso Giovannini, MD	Torrette Ancona	18
123	Ugo Merchini	Firenze	8
Poland			
127	Krystna Pcoold, MD	Poznan	5
128	Jozef Kaluzny, MD	Bydgoszcz	5
Portugal			
93	Jose Cunha-Vaz, MD	Coimbia	25
Spain			
94	Marta Figueroa, MD	Madrid	7
136	Jose Ruiz Moreno, MD	Alicante	10
95	Jordi Mones, MD	Barcelona	14
Switzerland			
98	Constantin Pournaras, MD	Geneva	2
99	Leonides Zografos, MD	Lausanne	1

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Center Number	Principal Investigator	Center Location	Number of Subjects
The Netherlands			
91	August Deutman, MD	Nijmegen	7
92	Reiner Schlingemann, MD	Amsterdam	15
United Kingdom			
100	Iain Chisholm, MD	Southampton	14
101	Noemi Lois, MD	Scotland	9
102	Usha Chakravarthy, MD	Belfast	18
130	Phil Hykin, MD	London	15
United States			
143	David Chow, MD	Illinois	4
144	K. Bailey Freund, MD	New York	4
145	Alexander Eaton, MD	Florida	15
146	Philip M. Falcone, MD	Connecticut	4
147	Patrick Higgins, MD	New Jersey	9
148	Keye Wong, MD	Florida	9
149	Matthew Thornus, MD	Missouri	-
153	Leonard Joffe, MD	Arizona	16
154	Jeffrey Heier, MD	Massachusettes	21
156	John Thompson, MD	Maryland	-
Canada			
151	Murray Erasmus, MD	Saskatoon	-
155	Raul Garcia, MD	Saskatchewan	8

Reviewer's Comment:
The agency prefers patients to be randomized with at least ten patients per arm per center in multicenter trials so that interaction between centers can be evaluated.

Leonard Joffe, MD is also an investigator for study EOP1004 and enrolled 5 patients. This is the only overlap in principle investigators for the two phase three trials.

First Randomization
The trial had a parallel group design. At study entry, patients were allocated to one of the four treatment arms according to a stratified randomization system. The treatment groups were:
Arm A: pegaptanib sodium 0.3 mg intravitreous injection every 6 weeks for 48 weeks
Arm B: pegaptanib sodium 1 mg intravitreous injection every 6 weeks for 48 weeks
Arm C: pegaptanib sodium 3 mg intravitreous injection every 6 weeks for 48 weeks
Arm D: sham intravitreous injection every 6 weeks for 48 weeks

Patients were stratified by center and the following factors:
- Type of lesion (visible classic CNV area divided by total lesion area); defined as predominantly classic (>50% classic CNV), minimally classic (1-49% classic CNV), or occult with no classic (0% classic CNV)
- Whether the patient had received prior PDT therapy (one treatment maximum)

Second Randomization
At one year (54 weeks), patients were re-randomized for a total study period of 102 weeks.

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Patients who were treated with pegaptanib sodium during the first year were re-randomized at week 54 in a ratio of 1:1 to either stop therapy (no further treatment) or to continue with the same dose and dosing regimen of pegaptanib sodium.

Patients who were receiving sham injections during the first year were re-randomized at week 54 in a ratio of 1:1:1:1:1 to either stop therapy, continue with sham injections or to continue on study receiving one of the three pegaptanib sodium doses.

Study Population – Inclusion and Exclusion Criteria

Inclusion Criteria
Ophthalmic Inclusion Criteria

1. BCVA in the study eye between 20/40 and 20/320, and better than or equal to 20/800 in the fellow eye.
2. Subfoveal CNV, secondary to AMD, with a total lesion size (including blood, scar/atrophy and neovascularization) of <12 total disc areas, of which at least 50% had to be active CNV.
3. Any subretinal hemorrhage could comprise no more than 50% of total lesion size.
4. For patients with minimally classic and occult with no classic CNV, there had to be the presence of subretinal hemorrhage (but comprising no more than 50% of the lesion) and/or lipid and/or documented evidence of 3 or more lines of vision loss (ETDRS or equivalent) during the previous 12 weeks.
5. Clear ocular media and adequate pupillary dilatation to permit good-quality stereoscopic fundus photography.
6. Intraocular pressure (IOP) of 23 mmHg or less.
7. PDT with verteporfin was permitted in this protocol only for patients with predominantly classic lesions determined by the investigator, and additionally they had to meet the criteria described in the product label (eligibility for PDT was confirmed retrospectively by the IRC). All PDT therapies given during the study were scheduled to occur within a 5- to 10-day window prior to treatment so that the study injection occurred after the period of photosensitivity, and any angiograms required by this protocol would be used to confirm eligibility for any subsequent PDT treatments wherever possible in order to minimize the number of additional angiograms required.

General Inclusion Criteria

1. Patients of either gender, aged >50 years.
2. Performance status ≤ 2 according to Eastern Cooperative Oncology Group (ECOG) scale.
3. Normal electrocardiogram (ECG) or clinically non-significant changes.
4. Women had to be using two forms of effective contraception, be post-menopausal for at least 12 months prior to study entry, or be surgically sterile. If the woman was of child-bearing potential, a serum pregnancy test was performed within 48 hours prior to treatment and the result made available prior to treatment initiation. The two forms of

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effective contraception had to be implemented during the study and continue for at least 60 days following the last dose of test medication.

5. Adequate hematological function: hemoglobin >10g/dL, platelet count >130 x 109/L and white blood cell count (WBC) >3.8 x 109/L.
6. Adequate renal function: serum creatinine and blood urea nitrogen (BUN) within 2 x the upper limit of normal (ULN) of the institution.
7. Adequate liver function: serum bilirubin < 1.5 mg/dL, and gamma glutamyl transferase (GGT), alanine amino transferase (ALT/SGOT), aspartame amino transferase (AST/SGPT), and alkaline phosphatase within 2 x ULN of the institution.
8. Written informed consent.
9. Ability to return for all study visits.

Exclusion Criteria:

1. Previous subfoveal thermal laser therapy.
2. Any subfoveal scarring or atrophy, and no more than 25% of the total lesion size could be made up of scarring or atrophy.
3. More than one prior PDT with verteporfin was not permitted. In addition, patients could not have received their one prior PDT within less than eight weeks or more than 13 weeks prior to the baseline angiography/photography for the study. Patients could have their first "on study" PDT (if eligible) after baseline angiography/photography, but at least 5 days prior to the first study treatment.
4. Significant media opacities, including cataract, that might interfere with visual acuity, assessment of toxicity or fundus photography. Patients could not be entered if there was a likelihood that they would require cataract surgery within the following 2 years.
5. Presence of other causes of CNV, including pathologic myopia (spherical equivalent of 8 diopters or more, or axial length of 25mm or more), the ocular histoplasmosis syndrome, angioid streaks, choroidal rupture and multifocal choroiditis.
6. Any intraocular surgery within 3 months, or extrafoveal/juxtafoveal laser within 2 weeks, of study entry.
7. Previous posterior vitrectomy, or scleral buckling surgery.
8. Previous or concomitant therapy with another investigational agent, including PDT with verteporfin for lesions other than predominantly classic (i.e., currently not approved in the majority of participating countries) to treat AMD, except multivitamins and trace minerals.
9. Presence of pigment epithelial tears or rips.
10. Any of the following underlying diseases:
    - Diabetic retinopathy
    - History or evidence of severe cardiac disease, e.g., New York Heart Association (NYHA) Functional Class III or IV, myocardial infarction within 6 months, ventricular tachyarhythmia's requiring ongoing treatment or unstable angina
    - History or evidence of peripheral vascular disease
    - Clinically significant impaired renal or hepatic function
    - Stroke (within 12 months of study entry)
    - Acute ocular or periocular infection
11. Previous therapeutic radiation to the eye, head, or neck.

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12. Any treatment with an investigational agent in the past 60 days for any condition.
13. Known serious allergies to the fluorescein dye used in angiography (and indocyanine green if used) or to the components of the pegaptanib sodium formulation.

Primary Efficacy Variable
The primary efficacy endpoint was the proportion of patients losing <15 letters of VA from baseline to 54 weeks (responders).

Secondary Efficacy Endpoints:
- Proportion of patients gaining >15 letters of VA from baseline to 54 weeks
- Proportion of patients gaining >0 letter of VA from baseline to 54 weeks
- Mean change in VA from baseline to 6, 12 and 54 weeks

Other Planned Efficacy Endpoints:
- Change in VA from baseline, prior to every treatment from baseline to 54 weeks
- Proportion of patients with Snellen Equivalent equal to or worse than 20/200 in the study eye at baseline, 6 weeks, 12 weeks and 54 weeks post baseline
- Change in total lesion size in disc areas from baseline to 30 weeks and 54 weeks
- Change in total CNV size in disc areas from baseline to 30 weeks and 54 weeks
- Change in CNV leak size in disc areas from baseline to 30 weeks and 54 weeks
- Proportion of patients with progression in lesion subtype from baseline to 54 weeks (pure occult to minimally classic or predominantly classic, and minimally classic to predominantly classic)
- Proportion of patients receiving PDT at any time during the course of the study.

Safety Endpoints
- All AEs, whether deemed related to treatment or not
- All serious adverse events (SAEs), whether deemed related to treatment or not
- All laboratory abnormalities, whether deemed clinically relevant or not
- A loss of 20 letters of vision on the ETDRS chart between consecutive treatments

Safety assessments included documentation of local ocular events in the study eye such as diffuse retinal hemorrhage; acute cataract; increase in IOP; retinal detachment, acute retinal arterial or venous occlusions; and sterile or infectious endophthalmitis. If there was an adverse event relating to the fellow eye, it was captured on the AE page of the CRF.

Protocol Defined Analysis Populations

Safety Population: consisted of all patients who received at least one treatment, regardless of their eligibility for the study.
Intent-To-Treat Population: all randomized patients who received double-masked treatment and who had complete baseline vision assessments.

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Per-Protocol Population: patients in the ITT population who did not experience any major violations of the protocol or of ophthalmic inclusion/exclusion criteria which could have had an impact on VA, for example cataract removal, were included in the per-protocol population. Additionally patients without post-baseline VA assessments were excluded.
All-randomized Population: Included all patients randomized to take part in the study, regardless of whether they received the study treatment or not.
Week 54 observed patient population: included patients from the ITT population who also had week 54 VA data (whether or not they were still receiving study treatment).

Reviewer's Comment: *This is not a true intent-to-treat population as defined. A true intent-to-treat population is defined as all randomized patients regardless of whether treatment was received or if baseline visual assessments were completed.*

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Study Flow Chart - Assessments and Timing – Study EOP1003

	BL	Randomization 1									Randomization 2							
Week	-1	0	6	12	18	24	30	36	42	48	54	60	66	72	78	84	90	96
Treatment number		1	2	3	4	5	6	7	8	9	1	2	3	4	5	6	7	8
Informed consent	X																	
Medical history	X																	
Ophthalmic history	X																	
Pregnancy test	X																	
Randomization	X										X							
Pegaptanib sodium or sham injection		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Efficacy																		
Refraction and VA (ETDRS)	B		S	S	S	S	B	S	S	S	B	S	S	S	B	S	S	S
Color fundus photographs[1]	B[2]						B				B				B			
Fluorescein angiogram[1]	B[2]						B				B				B			
ICG/OCT[3]	B										B							
Safety																		
Physical examination[4]	X																	
Adverse events / serious adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Intraocular pressure[5]	B	S[6]	S[6]	S[6]	S[6]	S[6]	B[6]	S[6]	S[6]	S[6]	B[6]	S[6]	S[6]	S[6]	B[6]	S[6]	S[6]	S[6]
Ophthalmic examination	B	S[6]	S[6]	S[6]	S[6]	S[6]	B[6]	S[6]	S[6]	S[6]	B[6]	S[6]	S[6]	S[6]	B[6]	S[6]	S[6]	S[6]
Vital signs	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory tests	X		X	X	X	X	X	X	X	X	X[8]	X[8]	X[8]	X[8]	X[8]	X[8]	X[8]	X[8]
ECG	X																	
Telephone safety check[7]		X	X	X	X	X	X	X	X	X	X[8]	X[8]	X[8]	X[8]	X[8]	X[8]	X[8]	X[8]

B = Assessment on both eyes
BL = Baseline, performed within 7 days of first treatment
S = Assessment on study eye only
EW = Early withdrawal (prior to Week 102)
[1] Sent to [redacted] for efficacy and safety assessments
[2] Reviewed by Eligibility and Classification Quality Assurance Team (ECQAT) for eligibility and randomization stratification
[3] Some selected sites performed optional indocyanine green angiograms (ICG) or optical coherence tomography (OCT), but no analyses of data were performed
[4] Physical examination performed post baseline only if indicated
[5] Applanation tonometry at baseline and for confirmation of IOP>30 mmHg
[6] Before treatment, at least 30 minutes after treatment and 1 week after treatment
[7] Telephone safety check carried out 3 days post treatment
[8] Treated (active or sham) patients only

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Subject Disposition and Demographics – Study EOP1003

Treatment	Patients Randomized and Treated (N=612)	Patients Discontinued (n=53)
0.3 mg	151	11
1 mg	155	13
3 mg	153	17
Sham	153	12

Discontinued Patients and Reason – Study EOP1003

Patient	Treatment	Reason	Study day
064-012	Sham	Died	342
098-002	Sham	Died	35
130-013	Sham	Died	273
145-018	Sham	Died	350
064-019	Sham	Patient request/frustrated with vision	376
084-010	Sham	Patient request/requested other treatment options	68
085-007	Sham	Patient request/pain on injection	332
102-009	Sham	Patient request/refused further injections	294
087-014	Sham	Worsening ocular hemorrhage	391
093-018	Sham	Osteoarticular pain	355
154-026	Sham	Colon cancer	137
089-016	Sham	Personal/economic problems-noncompliant with visits	428
075-005	0.3 mg	Patient request/pain on injection	130
081-005	0.3 mg	Patient request/refused further injections	378
087-010	0.3 mg	Patient request/palpitations prior to injection	57
123-010	0.3 mg	Patient request/cannot attend follow-up visits	248
154-001	0.3 mg	Patient request/refused further injections	35
154-017	0.3 mg	Patient request/poor health-unable to make visits	213
089-019	0.3 mg	Endophthalmitis	385
100-002	0.3 mg	Investigator decision/Transient ischemic attack	39
123-002	0.3 mg	Protocol deviation/noncompliant with visits	404
108-007	0.3 mg	Died	312
136-011	0.3 mg	Died	130
064-014	1 mg	Patient request/frustrated with vision	377
065-010	1 mg	Patient request/frustrated with vision	217
070-001	1 mg	Patient request/refused further injections	376
073-008	1 mg	Patient request/visit schedule too rigorous	27
073-014	1 mg	Patient request/developed cataract 2° to injection/had surgery	344
084-009	1 mg	Patient request/refused further injections	76
075-028	1 mg	Pulmonary embolism	260
083-002	1 mg	Poor health/pneumonia	137
101-010	1 mg	Adverse event/shortness of breath-suspected pulmonary embolism	252
102-026	1 mg	Adverse event/ refused further injections(watery eyes)	90

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Patient	Treatment	Reason	Study day
104-001	1 mg	panuveitis	217
130-001	1 mg	Died	358
136-005	1 mg	Died	281
075-006	3 mg	Patient request/travel problems	453
089-018	3 mg	Patient request/no improvement in vision	419
108-004	3 mg	Patient request/refused further injections	169
113-015	3 mg	Patient request/refused further participation	134
123-005	3 mg	Patient request/refused further treatment	440
155-004	3 mg	Patient request/spouse died	135
082-006	3 mg	Cerebrovascular accident	271
089-015	3 mg	metastatic lung cancer	248
092-012	3 mg	Angina pectoris	294
095-003	3 mg	Adverse event/worsening general condition	475
122-002	3 mg	Adverse event/lung cancer	260
085-001	3 mg	Died	202
104-011	3 mg	Died	195
119-012	3 mg	Died	341
093-028	3 mg	Investigator/sponsor decision-worsening AMD	214
147-003	3 mg	Investigator/sponsor decision/abnormal EKG	48

Demographics – Safety Population – Study EOP1003

		0.3 mg (N=151)	1 mg (N=155)	3 mg (N=153)	Sham (N=153)
Gender					
Male		69 (46%)	68 (44%)	60 (39%)	57 (37%)
Female		82 (54%)	87 (56%)	93 (61%)	96 (63%)
Race					
White		143 (95%)	148 (95%)	145 (95%)	144 (94%)
Asian		0	1 (1%)	1 (1%)	1 (1%)
Black		0	1 (1%)	0	1 (1%)
Hispanic		7 (5%)	5 (3%)	7 (5%)	5 (3%)
Other		1 (1%)	0	0	2 (1%)
Age					
Mean		74.9	74.5	75.4	74.9
Range		53-90	53-90	53-89	52-92
Smoking status					
Yes		24 (16%)	15 (10%)	15 (10%)	14 (9%)
% Classic AMD	≥ 50%	35 (23%)	40 (26%)	39 (25%)	39 (25%)
	1% - 49%	60 (40%)	57 (37%)	55 (36%)	52 (34%)
	0%	56 (37%)	58 (37%)	59 (39%)	62 (41%)
Prior PDT with verteporfin		6 (4%)	10 (6%)	6 (4%)	4 (3%)
ETDRS Vision					
Mean		53	50.9	50.1	51.3
Range		11-75	22-77	22-76	21-75

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Reviewer's comments:
The overwhelming majority of patients enrolled in this trial were older white adults. This is reflective of the population which is mostly affected by this disease and does not reflect an issue with recruitment. The between group demographics, however, were well balanced for all baseline characteristics.

Efficacy Analysis

Primary Efficacy Results – All Randomized Patients LOCF – Study 1003

Number of Patients (%)		0.3 mg N= 153	1 mg N= 158	3 mg N= 155	Sham N= 156
Responders[1]	Baseline				
	Month 3	134 (87.6%)	146 (92.4%)	136 (87.7%)	130 (83.3%)
	Month 6	127 (83%)	137 (86.7%)	128 (82.6%)	112 (71.8%)
	Month 9	117 (76.5%)	126 (79.8%)	125 (80.7%)	105 (67.3%)
	Month 12	[redacted]	[redacted]	108 (69.7%) p=0.06	93 (59.6%)

[1] Patients who lost < 15 letters of vision. Note: Patients who lost < 15 letters of vision from baseline to 54 weeks is the primary efficacy endpoint

Primary Efficacy Results – PP population observed cases only– Study 1003

Number of Patients (%)		0.3 mg	1 mg	3 mg	Sham
Responders[1]	Month 3	122 (87.8%) *N=139*	131 (92.9%) *N= 141*	122 (86.5%) *N= 141*	120 (82.8%) *N= 145*
	Month 6	110 (85.3%) *N= 129*	125 (86.8%) *N= 144*	116 (82.3%) *N= 141*	101 (69.7%) *N= 145*
	Month 9	103 (78.3%) *N= 131*	115 (79.9%) *N= 144*	110 (79.1%) *N= 139*	93 (66%) *N= 141*
	Month 12	[redacted] *N= 133*	[redacted] *N= 139*	90 (66.7%) *N = 135*	82 (58.6%) *N= 140*

[1] Patients who lost < 15 letters of vision. Note: Patients who lost < 15 letters of vision from baseline to 54 weeks is the primary efficacy endpoint
[2] 3 mg dose was omitted from statistical analysis prior to unmasking data

Reviewer's Comments:
There were no interim analyses for safety or efficacy performed during the clinical trial. The statistically significant findings are highlighted in the table. The bolded entries indicate a trend for efficacy although statistical significance was not reached. Based on the Hochberg multiple comparison procedure defined in

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the protocol, both the 0.3 mg and 1 mg doses demonstrate efficacy in this trial. There is approximately a 15% treatment effect for both doses.

Primary Efficacy Results – Sensitivity Analyses – Study 1003

Worst Case Analysis	N=153	N=158	N=155	N=156
Responders[1]	104 (68%)	109 (69%)	93 (60%)	96 (61.5%)
p-value	0.15	0.11	-	-
Week 54 Observed population	N=139	N=144	N=139	N=142
Responders[1]	103 (74%)	109 (76%)	93 (67%)	82 (58%)
p-value	0.005	0.003	-	-

[1] Patients who lost < 15 letters of vision from baseline to 54 weeks – primary efficacy endpoint
[2] 3 mg dose was omitted from statistical analysis prior to unmasking data

Number of Patients Receiving On-Study PDT Treatment in the Study Eye – ITT Population – Study EOP1003

Number of patients		0.3 mg N=150	1 mg N=154	3 mg N=153	Sham N=152
All patients					
PDT treatment	Yes	17 (11%)	19 (12%)	20 (13%)	19 (13%)
Predominantly Classic CNV		n=35	n=39	n=39	n=39
PDT Treatment	Yes	14 (40%)	15 (38%)	16 (41%)	13 (33%)
Minimally Classic CNV		n=59	n=57	n=55	n=52
PDT Treatment	Yes	2 (3%)	3 (5%)	3 (5%)	5 (10%)
Occult CNV		n=56	n=58	n=59	n=61
PDT Treatment	Yes	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Pairwise Comparison		0.3 mg vs. sham	1 mg vs. sham	3 mg vs. sham.	
		p=0.68	p=1.0	p=0.92	

Number of On-Study PDT Treatments Received in The Study Eye – ITT population – Study EOP1003

Number of patients	0.3 mg N=150	1 mg N=154	3 mg N=153	Sham N=152
Total number of PDT treatments	n=28	n=36	n=41	n=32
Predominantly classic CNV	23 (82%)	30 (83%)	35 (85%)	20 (63%)
Minimally classic CNV	3 (11%)	4 (11%)	5 (12%)	10 (31%)
Occult CNV	2 (7%)	2 (6%)	1 (2%)	2 (6%)

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Reviewer's Comments:

The number of patients receiving PDT treatments during the trial as well as the number of treatments received are consistent across the treatment groups. Therefore the efficacy demonstrated in the 0.3 mg and 1 mg groups does not appear to have been confounded by the adjunctive PDT treatment received by the patients in the trial.

It is noted that a small percentage of patients with minimally classic or occult CNV received PDT treatment. PDT treatment is not approved for these indications and is in violation of the study protocol. However, due the small numbers, this does not have any impact on the final efficacy results.

Responder Analysis for PDT Treatment Interaction – Study 1003

Number of Patients (%) who never received PDT before or during the study		0.3 mg N= 131	1 mg N= 132	3 mg N= 127	Sham N= 127
Responders[1]	Month 3	116 (88.6%)	123 (93.2%)	114 (89.8%)	106 (83.5%)
	Month 6	110 (84%)	117 (88.6%)	109 (85.8%)	92 (72.4%)
	Month 9	102 (78%)	109 (82.6%)	105 (82.7%)	85 (67%)
	Month 12	97 (74%)	103 (78%)	92 (72.4%)	78 (61.4%)

[1] Patients who lost < 15 letters of vision.

Number of Patients (%) who only received PDT before the study		0.3 mg N= 2	1 mg N= 5	3 mg N= 6	Sham N= 4
Responders[1]	Month 3	1 (50%)	5 (100%)	6 (100%)	3 (75%)
	Month 6	2 (100%)	5 (100%)	4 (66.7%)	3 (75%)
	Month 9	2 (100%)	5 (100%)	5 (83.3%)	3 (75%)
	Month 12	2 (100%)	3 (60%)	5 (83.3%)	3 (75%)

[1] Patients who lost < 15 letters of vision.

Number of Patients (%) who only received PDT during the study		0.3 mg N= 16	1 mg N= 17	3 mg N= 20	Sham N= 25
Responders[1]	Month 3	13 (81.3%)	15 (88.2%)	14 (70%)	21 (84%)
	Month 6	12 (75%)	11 (64.7%)	13 (65%)	17 (68%)
	Month 9	9 (56.3%)	8 (47%)	13 (65%)	17 (68%)
	Month 12	9 (56.3%)	9 (53%)	10 (50%)	12 (48%)

[1] Patients who lost < 15 letters of vision.

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Number of Patients (%) who received PDT before and during the study		0.3 mg N=4	1 mg N=4	3 mg N=2	Sham N=0
Responders[1]	Month 3	4 (100%)	3 (75%)	2 (100%)	0
	Month 6	3 (75%)	4 (100%)	2 (100%)	0
	Month 9	4 (100%)	4 (100%)	2 (100%)	0
	Month 12	4 (100%)	4 (100%)	1 (50%)	0

[1]Patients who lost < 15 letters of vision

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Additional Efficacy Analyses

	baseline	week 6	week 12	week 18	week 24	week 30	week 36	week 42	week 48	week 54
0.3 mg	53	52	49.7	49.3	48.7	47.7	47.2	46.5	46.1	45.4
1 mg	50.9	53.3	50.2	48.5	49	48	47.3	46.4	46.7	44.9
3 mg	50.1	47.6	47.3	46.5	46.6	46.1	45.6	45.3	45.2	42.9
sham	51.3	48	45.9	44.4	42.9	42.2	41.2	40.4	40	38.5

Reviewer's Comments:
The rate of vision loss in the 0.3 mg and 1 mg groups is similar. This vision loss does not appear to plateau which would suggest that there may be continued vision loss despite therapy. This will be further analyzed after the results of the 2 years data is available.

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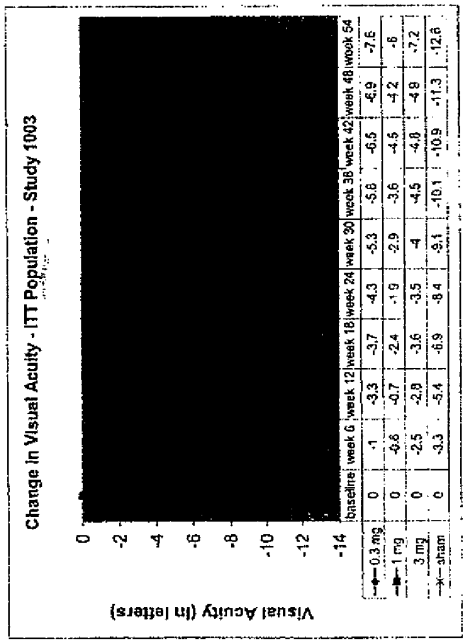

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Mean Total Lesion Size, CNV Size and Leak Size - Study 1003

	0.3 mg n=150	1 mg n=154	3 mg n=153	Sham N=152
Total Lesion size[1]				
Baseline	3.9	3.7	3.7	4.0
Week 30	4.9	4.7	5.1	5.5
Week 54	5.6	5.6	6.0	6.4
Total CNV Size[1]				
Baseline	3.1	3.2	3.2	3.5
Week 30	3.9	3.9	4.3	4.8
Week 54	4.7	4.6	5.0	5.7
Total Leak Size[1]				
Baseline	3.4	3.3	3.3	3.5
Week 30	4.1	3.4	4.2	4.9
Week 54	4.5	3.9	4.4	5.1

[1] size given in DA (disc area)

Reviewer's Comments:
The increase in the total lesion size at week 54 does appear to be less in all of the drug groups compared to sham. Clinically this correlates with the vision results which demonstrate that there is less visual loss in the drug groups compared to sham. However, none of the doses evaluated appear to be able to inhibit the lesion growth.

Vision Gain – Study EOP1003

		0.3 mg n=150	1 mg n=154	3 mg n=153	Sham N=152
Number of Patients (%)					
Vision gain ≥ 15 letters[1]	Yes	6 (4%)	10 (6%)	7 (5%)	5 (3%)
	p-value	0.93	0.49	-	-
Vision gain ≥ 0 letters[2]	Yes	49 (33%)	59 (38%)	60 (39%)	42 (28%)
	p-value	0.38	0.08	-	-

[1] patients who gained ≥ 15 letters of vision from baseline to 54 weeks
[2] patients who gained ≥ 0 letters of vision from baseline to 54 weeks
[3] 3 mg dose was omitted from statistical analyses prior to unmasking data

Reviewer's Comments:
There is only a small percentage of patients in each treatment group that show a clinically meaningful increase in vision and the difference seen between the groups is not statistically significant . This is expected based on the disease process being studied.

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CLINICAL REVIEW

Clinical Review Section

Responder analyses based on baseline characteristics for study EOP1003

Reviewers Comments:

The white vs. non-white treatment groups are grossly imbalanced (N= 292 vs. N= 17). This is expected due to the indication being studied. There is no evidence that overall efficacy is derived from any one subgroup in any treatment arm.

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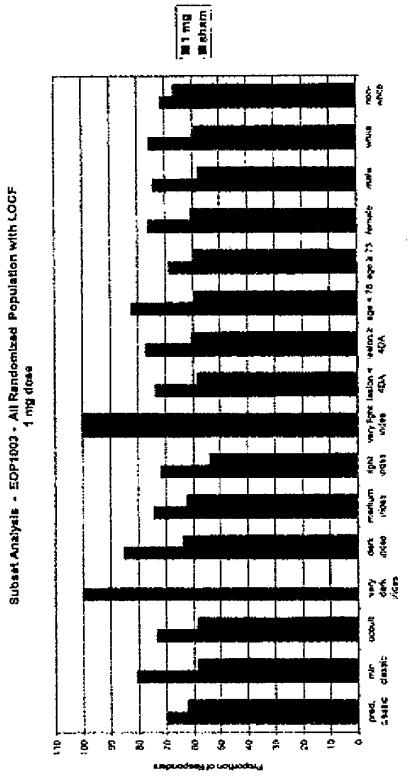

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Study 2 – Study EOP1004

Title: Same as Study EOP1003
Objective: Same as Study EOP1003
Study Design: Same as Study EOP1003. This study was conducted in North America.

Clinical sites – Study EOP1004

Center Number	Principal Investigator	Center Location	Number of Patients
01	Julia Halter, MD	Baltimore, MD	4
02	Michael Klein, MD	Portland, OR	6
03	Daniel F. Martin, MD	Atlanta, GA	-
04	Gary Fish, MD	Dallas TX	6
05	Allen Ho, MD	Philadelphia, PA	11
06	Scott D. Pendergast, MD	Lakewood, OH	33
07	Christine Gonzales, MD	Los Angeles, CA	30
08	Antonia Capone, MD	Royal Oak, MI	23
09	Jorge Arroyo, MD	Boston, MA	8
10	Steve Sanislo, MD	Menlo Park, CA	9
12	Richard Rosen, MD	New York, NY	6
13	Dean Eliot, MD	Detroit, MI	1
14	Jean Daniel Arbour, MD	Montreal, Quebec	-
15	Robert Avery, MD	Santa Barbara, CA	3
17	Paul Bernstein, MD	Salt Lake City, UT	7
18	Francis Cangemi, MD	Belleville, NJ	6
19	David Boyer, MD	Beverly Hills, CA	22
20	Sandy Brucker, MD	Philadelphia, PA	12
21	Herbert Cantrill, MD	Minneapolis, MN	20
22	Gaetano Barille, MD	New York, NY	-
23	Steven Charles, MD	Memphis, TN	5
24	Thomas A. Ciuilla, MD	Indianapolis, IN	-
25	Thomas Connor, MD	Milwaukee, WI	8
26	Brian P. Conway, MD	Charlottesville, VA	13
27	Alan F. Cruess, MD	Kingston, ON	-
28	John a. Wells, III, MD	Columbia, SC	15
29	Thomas Friberg, MD	Pittsburgh, PA	10
30	Richard Garfinkel, MD	Chevy Chase, MD	10
31	Bert Glaser, MD	Chevy Chase, MD	1
32	W. Sanderson Grizzard, MD	Tampa, FL	14
33	Barry Taney, MD	Fort Lauderdale, FL	8
34	Howard Cummings, MD	Knoxville, TN	17
35	Henry Hudson, MD	Tucson, AZ	25
36	Sharon Fekrat, MD	Durham, NC	14
37	Mark W. Johnson, MD	Ann Arbor, MI	2
38	Baruch Kuppermann, MD	Irvine, CA	1
40	Hilel Lewis, MD	Cleveland, OH	9

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Center Number	Principal Investigator	Center Location	Number of Patients
41	Jennifer Lim, MD	Los Angeles, CA	7
43	Naresh Mandava, MD	Aurora, CO	4
44	H. Richard McDonald, MD	San Francisco, CA	12
45	William Mieler, MD	Houston TX	3
46	Mohit Nanda, MD	Santa Ana, CA	7
47	Robert Leonard, MD	Oklahoma City, OK	8
48	Elias Reichel, MD	Boston, MA	13
49	Philip Rosenfeld, MD	Miami, FL	9
50	Ronald Wilson, MD	New Orleans, LA	18
51	Nelson Sabates, MD	Kansas City, MO	12
52	Vincent Deramo, MD	Great Neck, NY	8
53	M. Madison Shusher, MD	Winston-Salem, NC	7
54	Scott Sneed, MD	Phoenix, AZ	14
55	Glen Stoller, MD	Rockville Center, NY	8
56	Paul Tornambe, MD	Poway, CA	3
57	Michael Varenhorst, MD	Wichita, KS	13
58	Lloyd Wilcox, MD	Concord, NH	1
60	Marco Zarbin, MD	Newark, NJ	-
61	Patricia Harvey, MD	Toronto, ON	-
62	David Tom, MD	Hamden, CT	15
110	Alice T. Lyon, MD	Chicago, IL	3
115	David J. Weissgold, MD	Burlington, CT	8
140	Dennis Marcus, MD	Augusta, GA	2
141	John Wroblewski, MD	Hagerstown, MD	15
142	Leonard Joffe, MD	Tucson, AZ	5
39	Brian Leonard, MD	Ottawa, ON	6
42	David Maberley, MD	Vancouver, BC	12
59	Geoff Williams, MD	Calgary, AB	5

Reviewer's Comment:
The agency prefers patients to be randomized with at least ten patients per arm per center in multicenter trials so that interaction between centers can be evaluated.

Leonard Joffe, MD is also an investigator for study EOP1003 and enrolled 16 patients. This is the only overlap in principle investigators for the two phase three trials.

Inclusion/Exclusion Criteria - Same as Study EOP1003

Safety and Efficacy Endpoints - Same as Study EOP1003

Study Schedule Same as Study EOP1003. In addition, plasma samples for nested pharmacokinetic (PK) study was conducted at week 6 and week 18.

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Subject Disposition and Demographics

Treatment	Patients Randomized and Treated (N=578)	Patients Discontinued (n=60)
0.3 mg	144	12
1 mg	146	17
3 mg	143	20
Sham	145	11

Discontinued Patients and Reason – Study EOP1004

Patient	Treatment	Reason	Study Day
007-033	0.3 mg	Investigator decision/pt too frogile s/p hip replacement surgery	231
009-005	0.3 mg	Patient request/felt vision was getting worse	148
017-008	0.3 mg	Patient request/transportation issues	378
019-026	0.3 mg	Patient request/recovery time too long	205
021-010	0.3 mg	Patient died	231
032-002	0.3 mg	Patient request/withdrew consent	126
034-013	0.3 mg	Lost to follow-up	85
041-003	0.3 mg	Patient request/did not what to continue	288
042-001	0.3 mg	Adverse event/endophthalmitis	63
048-002	0.3 mg	Patient died	185
050-012	0.3 mg	Patient died	140
055-017	0.3 mg	Adverse event/subretinal hemorrhage, retinal detachment	95
007-015	1 mg	Lost to follow-up	217
008-018	1 mg	Patient died	228
015-002	1 mg	Patient died	301
019-009	1 mg	Patient request/no longer wants to participate	465
019-033	1 mg	Move to nursing home	306
020-007	1 mg	Patient request/withdrew consent	358
033-006	1 mg	Patient died	62
036-017	1 mg	Unable to return for visits	343
041-001	1 mg	Patient died	187
043-001	1 mg	Adverse event/subretinal & vitreous hemorrhage	452
050-009	1 mg	Patient request/does not want tx from new PI	260
050-021	1 mg	Patient died	323
055-014	1 mg	Lost to follow-up	205
057-004	1 mg	Patient request/poor health	299
059-006	1 mg	Patient died	101
062-006	1 mg	Patient request/withdrew consent	165
062-009	1 mg	Patient request/anxiety	126
006-002	3 mg	Patient request/withdrew consent	377
006-010	3 mg	Patient died	372
015-003	3 mg	Patient request/moving to another state	130

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Patient	Treatment	Reason	Study Day
017-006	3 mg	Patient request/not able to follow-up	377
017-007	3 mg	Investigator decision/poor clinical response	383
019-007	3 mg	Alzheimer's – unable to follow protocol	378
021-005	3 mg	Patient request/study not helping vision	166
026-003	3 mg	Patient died	256
030-001	3 mg	Investigator decision/missed injection due to retinal detachment	210
030-009	3 mg	Patient request/withdrew consent	393
033-009	3 mg	Patient request/withdrew consent	401
034-011	3 mg	Patient died	116
042-009	3 mg	Patient request/withdrew consent	378
046-008	3 mg	Patient request/family illness	356
050-004	3 mg	Patient request/move out of state	378
050-013	3 mg	Patient request/ does not want tx from new PI	251
052-006	3 mg	Adverse event/myocardial infarction, cerebral hemorrhage	36
052-011	3 mg	Patient request/failure to respond to treatment	308
053-006	3 mg	Patient request/general health reasons	127
062-010	3 mg	Adverse event/retinal detachment	300
004-007	Sham	Patient request/did not feel study was helping	84
012-001	Sham	Patient request/felt injections were making eyes worse	126
017-001	Sham	Patient request/refused further injection	378
019-004	Sham	Patient request/vision loss	173
021-012	Sham	Patient died	335
028-021	Sham	Patient request/vision loss	276
035-021	Sham	Adverse event/acute congestive heart failure	128
040-003	Sham	Patient died	328
049-013	Sham	Patient request/withdrew consent	238
052-007	Sham	Patient request/progressive loss of vision	133
023-001	Sham	Investigator decision/no injection for 12 weeks	241

Demographics – Safety Population – Study EOP1004

	0.3 mg (N=144)	1 mg (N=146)	3 mg (N=143)	Sham (N=145)
Gender				
Male	64 (44%)	68 (47%)	45 (31%)	63 (43%)
Female	80 (56%)	78 (53%)	98 (69%)	82 (57%)
Race				
White	140 (97%)	143 (98%)	141 (99%)	140 (97%)
Asian	2 (1%)	0	0	0
Black	0	0	0	0
Hispanic	2 (1%)	2 (1%)	2 (1%)	4 (3%)
Other	0	1 (1%)	0	1 (1%)

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Age					
Mean		78	76.5	77.1	76.7
Range		58-92	52-92	56-97	55-89
Smoking status					
Yes		14 (10%)	15 (10%)	15 (10%)	15 (10%)
% Classic AMD	≥ 50%	37 (26%)	38 (26%)	41 (29%)	37 (26%)
	1%-49%	51 (35%)	51 (35%)	50 (35%)	50 (34%)
	0%	56 (39%)	57 (39%)	52 (36%)	58 (40%)
Prior PDT with verteporfin		18 (13%)	20 (14%)	20 (14%)	16 (11%)
ETDRS Vision					
Mean		52.5	50.5	52.1	54
Range		23-74	19-73	14-73	27-74

Reviewer's comments:
The overwhelming majority of patients enrolled in this trial were older white adults. This is reflective of the population which is mostly affected by this disease and does not reflect an issue with recruitment. The between group demographics, however, were well balanced for all baseline characteristics.

Efficacy Analysis

Primary Efficacy Results – All Randomized Patients LOCF – Study 1004

Number of Patients (%)		**0.3 mg N= 144**	**1 mg N= 147**	**3 mg N= 147**	**Sham N= 148**
Responders[1]	Month 3	125 (86.8%)	118 (80.3%)	121 (82.3%)	115 (77.7%)
	Month 6	118 (81.9%)	106 (72.1%)	102 (69.4%)	85 (57.4%)
	Month 9	106 (73.6%)	108 (73.5%)	103 (70.1%)	78 (52.7%)
	Month 12	[redacted]	98 (66.7%) p=0.03	91 (61.9%) p=0.13	79 (53.4%)

[1] Patients who lost < 15 letters of vision. Note: Patients who lost < 15 letters of vision from baseline to 54 weeks is the primary efficacy endpoint

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Primary Efficacy Results – PP population observed cases only– Study 1004

Number of Patients (%)		0.3 mg	1 mg	3 mg	Sham
Responders[1]	Month 3	122 (87.4%) *N=140*	114 (81.4%) *N=140*	110 (81.5%) *N=135*	104 (77%) *N=135*
	Month 6	112 (82.4%) *N=136*	96 (72.2%) *N=133*	91 (67.4%) *N=135*	77 (58.8%) *N=131*
	Month 9	94 (74.6%) N=126	94 (75.2%) *N= 125*	90 (70.9%) *N=127*	70 (53.4%) *N=131*
	Month 12	[redacted] *N=131*	85 (66.9%) p=0.06 *N=127*	70 (57.4%) p=0.59 *N=122*	69 (53.9%) *N=128*

[1] Patients who lost < 15 letters of vision Note: Patients who lost < 15 letters of vision from baseline to 54 weeks is the primary efficacy endpoint

Reviewer's Comments:
There were no interim analyses for safety or efficacy performed during the clinical trial. The statistically significant findings are highlighted in the table. The bolded entries indicate a trend for efficacy although statistical significance was not reached. Based on the Hochberg multiple comparison procedure defined in the protocol, only the 0.3 mg dose demonstrates efficacy in this trial. There is approximately a 15% treatment effect seen.

Primary Efficacy Results – Sensitivity Analyses – Study 1004

Worst Case Analysis	N=144	N=147	N=147	N=148
Responders[1]	89 (61.8%)	89 (60.5%)	73 (49.7%)	87 (58.8%)
p-value	0.27	0.76	0.36	-
Week 54 Observed population	N=132	N=131	N=125	N=133
Responders[1]	89 (67%)	89 (68%)	73 (58%)	72 (54%)
p-value	0.01	0.032	0.5	-

[1] Patients who lost < 15 letters of vision from baseline to 54 weeks – primary efficacy endpoint

Number of Patients Receiving On-Study PDT Treatment in the Study Eye – ITT Population – Study EOP1004

Number of patients		0.3 mg N=144	1 mg N=146	3 mg N=143	Sham N=144
All patients					
PDT treatment	Yes	32 (22%)	36 (25%)	37 (26%)	43 (30%)
Predominantly Classic		n=37	n=38	n=41	n=37

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CNV					
PDT Treatment	Yes	24 (65%)	23 (61%)	24 (59%)	25 (68%)
Minimally Classic CNV		n=51	n=51	n=50	n=49
PDT Treatment	Yes	5 (10%)	12 (24%)	8 (16%)	13 (27%)
Occult CNV		n=144	n=146	n=143	n=144
PDT Treatment	Yes	3 (5%)	1 (2%)	5 (10%)	5 (9%)
Pairwise Comparison		0.3 mg vs. sham	1 mg vs. sham	3 mg vs. sham	
		p=0.05	p=0.22	p=0.26	

Number of On-Study PDT Treatments Received in The Study Eye – ITT population – Study EOP1004

Number of patients	0.3 mg N=144	1 mg N=146	3 mg N=143	Sham N=144
Total number of PDT treatments	n=56	n=72	n=73	n=94
Predominantly classic CNV	42 (75%)	45 (63%)	48 (66%)	59 (63%)
Minimally classic CNV	10 (18%)	26 (36%)	18 (25%)	27 (29%)
Occult CNV	4 (7%)	1 (1%)	7 (10%)	8 (9%)

Reviewer's Comments:

The overall number of patients receiving PDT treatments during the trial as well as the number of treatments received are significantly less in the 0.3 mg group versus sham. Therefore, the efficacy demonstrated in the 0.3 mg does not appear to have been confounded by the adjunctive PDT treatment received by the patients in the trial. The lack of PDT treatments in the 0.3 mg group may be supportive of the efficacy of the drug.

It is noted that a small to moderate percentage of patients with minimally classic or occult CNV received PDT treatment. PDT treatment is not approved for these indications and is in violation of the study protocol.

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Responder Analysis for PDT Treatment Interaction– Study 1004

Number of Patients (%) who never received PDT before or during the study		0.3 mg N= 101	1 mg N= 99	3 mg N= 99	Sham N= 93
Responders[1]	Month 3	87 (86.1%)	83 (83.8%)	86 (86.9%)	74 (79.6%)
	Month 6	80 (79.2%)	77 (77.8%)	70 (70.7%)	57 (61.3%)
	Month 9	74 (73.2%)	75 (75.8%)	72 (72.7%)	52 (55.9%)
	Month 12	65 (64.4%)	70 (70.7%)	65 (65.7%)	54 (58%)

[1] Patients who lost < 15 letters of vision.

Number of Patients (%) who only received PDT before the study		0.3 mg N= 5	1 mg N= 8	3 mg N= 5	Sham N= 4
Responders[1]	Month 3	4 (80%)	5 (62.5%)	5 (100%)	3 (75%)
	Month 6	4 (80%)	2 (25%)	5 (100%)	3 (75%)
	Month 9	3 (60%)	5 (62.5%)	3 (60%)	2 (50%)
	Month 12	4 (80%)	3 (37.5%)	3 (60%)	2 (50%)

[1] Patients who lost < 15 letters of vision.

Number of Patients (%) who only received PDT during the study		0.3 mg N= 25	1 mg N= 28	3 mg N= 29	Sham N= 39
Responders[1]	Month 3	22 (88%)	21 (75%)	20 (69%)	30 (77%)
	Month 6	22 (88%)	18 (64%)	16 (57.2%)	19 (48.7%)
	Month 9	18 (72%)	17 (60.7%)	15 (51.7%)	18 (46.2%)
	Month 12	18 (72%)	16 (57.1%)	15 (51.7%)	18 (46.2%)

[1] Patients who lost < 15 letters of vision.

Number of Patients (%) who received PDT before and during the study		0.3 mg N= 13	1 mg N= 12	3 mg N= 14	Sham N= 12
Responders[1]	Month 3	12 (92.3%)	9 (75%)	10 (71.4%)	8 (66.7%)
	Month 6	12 (92.3%)	9 (75%)	11 (78.6%)	6 (50%)
	Month 9	11 (84.6%)	11 (91.7%)	13 (93%)	6 (50%)
	Month 12	10 (76.9%)	9 (75%)	8 (57.1%)	5 (41.7%)

[1] Patients who lost < 15 letters of vision.

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[redacted]

CLINICAL REVIEW

Clinical Review Section

Visual Acuity - iTT Population - Study EOP1004

	baselin e	week 6	week 12	week 18	week 24	week 30	week 36	week 42	week 48	week 54
0.3 mg	52.5	50.5	49.4	47.9	47.5	46.8	45.8	45.2	45	44.2
1 mg	50.5	48.7	46.8	45.3	44.1	42.9	42.9	42	41.5	41.9
3 mg	52.1	50.1	46.8	45.3	43.1	41.9	41.6	40.8	39.7	39.6
sham	54	49.2	46.7	43.7	42.4	39.5	38.7	37.8	37.1	35.6

Reviewer's Comments:

The rate of vision loss in the 0.3 mg is slightly less than in the other treatment groups. This vision loss does not appear to plateau which would suggest that there is there may be continued vision loss despite therapy. This will be analyzed after the results of the 2 years data is available.

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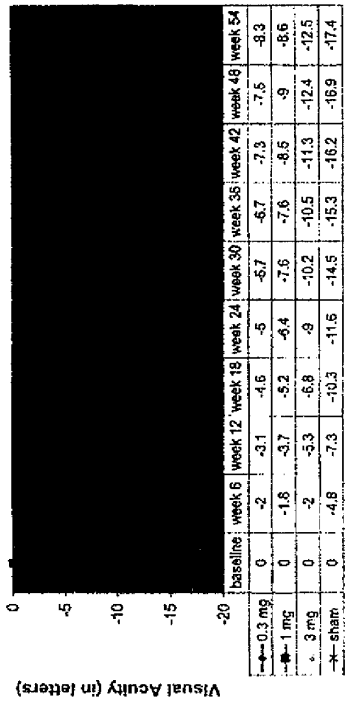
Change in Visual Acuity - ITT Population - Study 1004



	baseline	week 6	week 12	week 18	week 24	week 30	week 36	week 42	week 48	week 54
0.3 mg	0	-2	-3.1	-4.6	-5	-5.7	-6.7	-7.3	-7.5	-8.3
1 mg	0	-1.8	-3.7	-5.2	-6.4	-7.5	-7.6	-8.5	-9	-8.6
3 mg	0	-2	-5.3	-6.8	-9	-10.2	-10.5	-11.3	-12.4	-12.5
sham	0	-4.8	-7.3	-10.3	-11.6	-14.5	-15.3	-16.2	-16.9	-17.4

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Mean Total Lesion Size, CNV Size and Leak Size – Study 1004

	0.3 mg n=144	1 mg n=146	3 mg n=143	Sham N=144
Total Lesion size[1]				
Baseline	3.6	4.4	3.6	4.4
Week 30	5	5.4	5.3	5.8
Week 54	5.5	6	6.3	7
Total CNV Size[1]				
Baseline	3.1	3.8	3.2	3.9
Week 30	4	4.5	4.2	5
Week 54	4.7	5	5	5.8
Total Leak Size[1]				
Baseline	3.2	3.6	3.5	3.7
Week 30	3.8	3.9	4.2	4.9
Week 54	4.1	4	4.9	5.2

[1] size given in DA (disc area)

Reviewer's Comments:

The increase in the total lesion size, total lesion size and total leak size at week 54 appears to be less in the 0.3 mg group compared to sham. Clinically this correlates with the vision results which demonstrate that there is less visual loss in the drug groups compared to sham.

Vision Gain – Study EOP1004

		0.3 mg n=144	1 mg n=146	3 mg n=143	Sham N=144
Number of Patients (%)					
Vision gain ≥ 15 letters[1]	Yes	12 (8%)	10 (7%)	6 (4%)	1 (1%)
	p-value	0.005	0.01	0.04	-
Vision gain ≥ 0 letters[2]	Yes	49 (34%)	51 (35%)	33 (23%)	25 (17%)
	p-value	0.0006	0.002	0.17	-

[1] patients who gained ≥ 15 letters of vision from baseline to 54 weeks
[2] patients who gained ≥ 0 letters of vision from baseline to 54 weeks

Reviewer's Comments:
There is only a small percentage of patients in each treatment group that show a clinically meaningful increase in vision. This is expected based on the disease process being studied.

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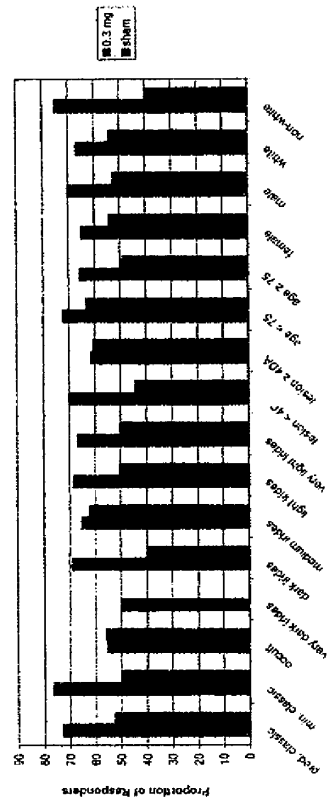
Responder analyses based on baseline characteristics for study EOP1004

Subset Analysis - EOP1004 - All Randomized Population with LOCF



Reviewers Comments:

The white vs non-white treatment groups are grossly imbalanced (N= 263 vs. N= 9). This is expected due to the indication being studied. There is no evidence that overall efficacy is derived from any one subgroup in any treatment arm.

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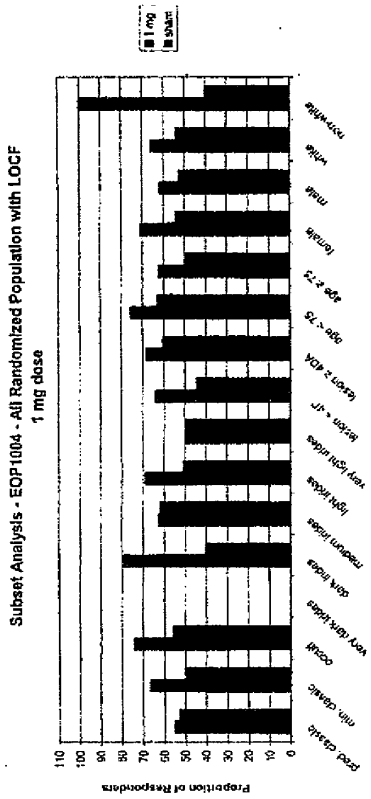
[redacted]

CLINICAL REVIEW

Clinical Review Section



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D. Efficacy Conclusions

The submitted studies in NDA 21-756 are sufficient to establish efficacy for the use of pegaptanib sodium 0.3 mg in the treatment of the neovascular form of age-related macular degeneration. The two phase 3 studies show replicative results in the ability of pegaptanib sodium to reduce the risk of vision loss in patients with neovascular AMD by approximately 15% when administered every six weeks compared to sham.

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VII. Integrated Review of Safety

A. Brief Statement of Conclusions

The majority of safety concerns raised in the review of this application are likely attributed to the procedure required to administer pegaptanib sodium and not the drug product itself. The majority of adverse events seen in the database are those commonly seen with intraocular procedures including intravitreous injections. There are no signals noted in the database submitted to raise a concern over the unacceptable safety of this drug product. However, there is considerable concern raised over the rate of endophthalmitis seen in these trials. Since the cases reported were, in fact, infectious in nature (not sterile), this event is most likely due to contamination during the procedure itself and not the drug product. The injection procedure used to administer this drug product may require refinement before the safety profile is considered acceptable.

B. Description of Patient Exposure

In the overall development program, almost all patients received doses of either 0.3, 1 or 3 mg of pegaptanib sodium as intravitreous injections. A small number of patients received doses of 0.25 mg (3 patients), 0.5 mg (3 patients), or 2 mg (3 patients).

Number of Patients per Treatment Group in Completed cohorts in the Pegaptanib Sodium Development Program

Number of Patients	0.3 mg	1 mg	3 mg	Sham injection
Controlled exudative AMD, all patients	295	301	296	298
Non-controlled exudative AMD, all patients[1]	0	3	61	0
DME Patients[2], EOP1002	0	0	10	0
Overall Total	295	304	367	298

[1]Includes 0.25 mg, 0.5 mg and 2 mg doses from study NX109-01. [2] Only the completed cohort from study EOP1006 is included. [3] Study EOP1005 is not included as it is ongoing and has not been unmasked.

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Number of Injections Administered

Total number of injections	0.3 mg	1 mg	3 mg	Sham injection
Studies 1003 and 1004 AMD	2478	2568	2499	2557
Phase 1/2 exudative AMD studies	0	3	62	0
Study 1006[1] exudative AMD	0	0	218	0
Study 1002[2] DME	0	0	53	0

*Includes 0.25 mg, 0.5 mg and 2 mg doses from study NX109-01. [1] Only the completed cohort is included; [2] Study EOP1005 is not included as it is ongoing and has not been unmasked.

Almost 1000 patients have been treated at or above the recommended dose (0.3 mg) for beyond 1 year at the time of NDA filing.

Number (%) of Patients per Treatment Group Receiving the Specified Number Number of Study Treatments in the Week 54 Cohort of Studies EOP1003 and EOP1004

Number of Treatments*	0.3 mg N=295	1 mg N=301	3 mg N=296	All Doses N=892	Sham N=298
1	4(1)	2(1)	3(1)	9(1)	2(1)
2	1(0)	3(1)	1(0)	5(1)	1(0)
3	7(2)	3(1)	4(1)	14(2)	3(1)
4	4(1)	4(1)	2(1)	10(1)	5(2)
5	2(1)	2(1)	5(2)	9(1)	1(0)
6	5(2)	5(2)	7(2)	17(2)	7(2)
7	8(3)	10(3)	12 (4)	30 (3)	3(1)
8	37(13)	23(8)	35(12)	95(11)	28(9)
9	227(77)	249(83)	227(77)	703(79)	248(83)
Total number of treatments	2478	2568	2499	7545	2557
Mean	8.4	8.5	8.4	8.5	8.6
SD	1.5	1.4	1.4	1.4	1.3
Median	9.0	9.0	9.0	9.0	9.0
Range	1-9	1-9	1-9	1-9	1-9

* Pegaptanib sodium intravitreous injection or sham treatment

C. **Methods and Specific Findings of Safety Review**

All safety data were reported for the safety patient population which included all patients who had received at least one study drug injection. Only data relating to the first year of study treatment were analyzed for this review. This included all adverse events up to 6 weeks after the week 48 injection for all patients who received an injection at week 48 or

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378 days post the first injection for all other patients. For patient deaths, the cut-off date for inclusion in this report on the first part of the study was within 42 days (6 weeks) of the week 48 injection.

Overall Summary of Adverse Events – Safety Population – Studies EOP1003 and EOP1004

Number of Patients (%)	0.3 mg n=295	1 mg n=301	3 mg n=296	Sham N=298
Patients with at least one AE	286 (97%)	286 (95%)	288 (97%)	283 (95%)
Patients with at least one ophthalmic AE (study eye)	269 (91%)	270 (90%)	270 (91%)	254 (85%)
Patients with at least one SAE	55 (19%)	50 (17%)	64 (22%)	45 (15%)
Patients with an AE leading to treatment interruption or study discontinuation	7 (2%)	5 (2%)	10 (3%)	7 (2%)

Adverse Events Reported in ≥ 1% of Subjects in Any Treatment Group – Safety Population – Studies EOP1003 and EOP1004

Number of subjects System organ class and preferred term	0.3 mg N=295	1 mg N=301	3 mg N=296	Sham N=298
Blood and lymphatic system disorders				
Anemia NOS	2 (1%)	5 (2%)	12 (4%)	8 (3%)
Cardiac disorders				
Arrhythmia NOS	1 (<1%)	3 (1%)	5 (2%)	0 (0%)
Atrial fibrillation	4 (1%)	2 (1%)	2 (1%)	7 (2%)
Bradycardia NOS	2 (1%)	1 (<1%)	4 (1%)	2 (1%)
Myocardial infarction	3 (1%)	2 (1%)	2 (1%)	3 (1%)
Coronary artery disease NOS	1 (<1%)	0 (0%)	1 (<1%)	3 (1%)
Ear and labyrinth disorders				
[redacted]				
Endocrine disorders				
Acquired hypothyroidism	0 (0%)	2 (1%)	4 (1%)	1 (1%)
Eye disorders				
[redacted]				
Visual acuity reduced	82 (28%)	58 (19%)	62 (21%)	82 (28%)
Cataract	64 (22%)	78 (26%)	85 (29%)	68 (23%)
[redacted]				

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Number of subjects System organ class and preferred term	0.3 mg N=295	1 mg N=301	3 mg N=296	Sham N=298
[redacted]				
Abnormal sensation in eye	23 (8%)	21 (7%)	26 (9%)	30 (10%)
[redacted]				
Lacrimation increased	25 (8%)	31 (10%)	29 (10%)	30 (10%)
Macular degeneration	25 (8%)	31 (10%)	29 (10%)	36 (12%)
[redacted]				
Eye irritation	22 (7%)	24 (8%)	29 (10%)	20 (7%)
Photophobia	22 (7%)	21 (7%)	30 (10%)	23 (8%)
[redacted]				
Eye pruritus	22 (7%)	18 (6%)	27 (9%)	23 (8%)
Eye redness	21 (7%)	23 (8%)	19 (6%)	21 (7%)
[redacted]				
Vitreous detachment	12 (4%)	23 (8%)	14 (5%)	14 (5%)
Conjunctival edema	12 (4%)	16 (5%)	18 (6%)	13 (4%)
Corneal epithelium disorder	13 (4%)	15 (5%)	17 (6%)	18 (6%)
Corneal epithelium defect	10 (3%)	8 (3%)	18 (6%)	14 (5%)
[redacted]				
Eyelid edema	7 (2%)	12 (4%)	17 (6%)	13 (4%)
Conjunctival hyperemia	7 (2%)	8 (3%)	8 (3%)	9 (3%)
Retinal exudates	6 (2%)	3 (1%)	0 (0%)	6 (2%)
[redacted]				
Corneal dystrophy	4 (1%)	6 (2%)	6 (2%)	2 (1%)
[redacted]				
Eyelid ptosis	3 (1%)	5 (2%)	8 (3%)	6 (2%)
Keratitis	4 (1%)	7 (2%)	8 (3%)	9 (3%)
[redacted]				
Ocular hypertension	4 (1%)	7 (2%)	7 (2%)	6 (2%)
Posterior capsule opacification	2 (1%)	3 (1%)	4 (1%)	2 (1%)
Pupillary reflex impaired	3 (1%)	2 (1%)	2 (1%)	5 (2%)
Retinal artery embolism	4 (1%)	1 (0%)	2 (1%)	2 (1%)
[redacted]				
Arcus lipoides	1 (<1%)	1 (<1%)	3 (1%)	1 (<1%)
Eye allergy	1 (<1%)	0 (0%)	2 (1%)	3 (1%)
Eyelid margin crusting	1 (<1%)	1 (<1%)	2 (1%)	3 (1%)
Macular edema	1 (<1%)	2 (1%)	3 (1%)	4 (1%)
[redacted]				
Retinal scar	1 (<1%)	2 (1%)	4 (1%)	7 (2%)
Erythema of eyelid	0 (0%)	1 (<1%)	4 (1%)	3 (1%)

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Number of subjects System organ class and preferred term	0.3 mg N=295	1 mg N=301	3 mg N=296	Sham N=298
Corneal scar	0 (0%)	1 (<1%)	1 (<1%)	3 (1%)
Iris adhesions	0 (0%)	1 (<1%)	3 (1%)	0 (0%)
Maculopathy	0 (0%)	3 (1%)	3 (1%)	1 (<1%)
Uveitis NOS	0 (0%)	4 (1%)	1 (<1%)	0 (0%)
Gastrointestinal disorders				
Nausea	13 (4%)	7 (2%)	16 (5%)	13 (4%)
Diarrhea NOS	8 (3%)	4 (1%)	9 (3%)	6 (2%)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Constipation	7 (2%)	5 (2%)	9 (3%)	5 (2%)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gastrooesophageal reflux disease	7 (2%)	3 (1%)	2 (1%)	6 (2%)
Abdominal pain NOS	3 (1%)	2 (1%)	1 (0%)	3 (1%)
Hiatus hernia	1 (<1%)	0 (0%)	3 (1%)	1 (<1%)
Abdominal pain upper	0 (0%)	1 (<1%)	3 (1%)	1 (<1%)
Diverticulitis NOS	0 (0%)	1 (<1%)	4 (1%)	4 (1%)
General disorders and administration site conditions				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fall	2 (1%)	1 (<1%)	5 (2%)	2 (1%)
Pyrexia	4 (1%)	5 (2%)	0 (0%)	2 (1%)
Influenza like illness	1 (<1%)	4 (1%)	0 (0%)	2 (1%)
Malaise	1 (<1%)	1 (<1%)	3 (1%)	0 (0%)
Asthenia	0	1 (<1%)	4 (1%)	2 (1%)
Immune system disorders				
Drug hypersensitivity	2 (1%)	2 (1%)	5 (2%)	3 (1%)
Seasonal allergy	2 (1%)	0 (0%)	5 (2%)	6 (2%)
Infections and infestations				
Upper respiratory tract infection NOS	13 (4%)	10 (3%)	12 (4%)	11 (4%)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Influenza	10 (3%)	8 (3%)	7 (2%)	13 (4%)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sinusitis NOS	6 (2%)	3 (1%)	10 (3%)	7 (2%)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lower respiratory tract infection NOS	2 (1%)	1 (<1%)	2 (1%)	3 (1%)
Herpes zoster	1 (<1%)	2 (1%)	4 (1%)	2 (1%)
Respiratory tract infection NOS	1 (<1%)	2 (1%)	2 (1%)	8 (3%)
Tooth abscess	1 (<1%)	3 (1%)	3 (1%)	5 (2%)
Tooth caries NOS	1 (<1%)	2 (1%)	3 (1%)	3 (1%)
Bladder infection NOS	0 (0%)	4 (1%)	0 (0%)	8 (3%)
Ear infection NOS	0 (0%)	1 (<1%)	4 (1%)	3 (1%)
Hordeolum	0 (0%)	1 (<1%)	2 (1%)	3 (1%)
Injury, poisoning and procedural complications				
Periorbital haematoma	7 (2%)	5 (2%)	5 (2%)	7 (2%)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post procedural pain	4 (1%)	2 (1%)	2 (1%)	4 (1%)
Skin laceration	3 (1%)	3 (1%)	2 (1%)	4 (1%)

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Number of subjects System organ class and preferred term	0.3 mg N=295	1 mg N=301	3 mg N=296	Sham N=298
Corneal erosion	1 (0%)	1 (<1%)	3 (1%)	1 (<1%)
Muscle strain	0 (0%)	1 (<1%)	2 (1%)	3 (1%)
Investigations				
[redacted]				
Weight increased	2 (1%)	3 (1%)	6 (2%)	3 (1%
Weight decreased	1 (<1%)	2 (1%)	6 (2%)	1 (<1%)
Gamma-glutamyltransferase increased	1 (<1%)	0 (0%)	0 (0%)	3 (1%)
Metabolism and nutrition disorders				
Hypercholesterolemia	7 (2%)	10 (3%)	3 (1%)	9 (3%)
Dehydration	2 (1%)	2 (1%)	3 (1%)	4 (1%)
[redacted]				
Hyperlipidaemia NOS	3 (1%)	2 (1%)	2 (1%)	4 (1%)
Hypokalaemia	3 (1%)	1 (<1%)	3 (1%)	4 (1%)
Musculoskeletal and connective tissue disorders				
Arthralgia	13 (4%)	12 (4%)	11 (4%)	17 (6%)
Back pain	11 (4%)	10 (3%)	8 (3%)	14 (5%)
[redacted]				
Pain in limb	2 (1%)	7 (2%)	6 (2%)	6 (2%)
Arthritis NOS aggravated	1 (<1%)	2 (1%)	6 (2%)	4 (1%)
Osteoarthritis NOS	1 (<1%)	5 (2%)	3 (1%)	1 (<1%)
Osteoporosis NOS	1 (<1%)	2 (1%)	4 (1%)	6 (2%)
Localized osteoarthritis	0 (0%)	4 (1%)	3 (1%)	2 (1%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)				
Basal cell carcinoma	4 (1%)	2 (1%)	4 (1%)	5 (2%)
Prostate cancer NOS	2 (1%)	2 (1%)	1 (<1%)	3 (1%)
Skin carcinoma NOS	4 (1%)	0 (0%)	1 (<1%)	2 (1%)
Lung cancer stage unspecified (excl metastatic tumours to lung)	0 (0%)	0 (0%)	3 (1%)	1 (<1%)
Nervous system disorders				
[redacted]				
Dizziness	7 (2%)	7 (2%)	9 (3%)	7 (2%)
[redacted]				
Carpal tunnel syndrome	2 (1%)	1 (<1%)	0 (0%)	4 (1%)
[redacted]				
Syncope	0 (0%)	3 (1%)	4 (1%)	3 (1%)
Psychiatric disorders				
Depression	11 (4%)	7 (2%)	10 (3%)	11 (4%)
[redacted]				
Anxiety	2 (1%)	8 (3%)	3 (1%)	9 (3%)
Confusional state	3 (1%)	2 (1%)	0 (0%)	1 (<1%)
Renal and urinary disorders				
[redacted]				
Renal failure NOS	0 (0%)	1 (<1%)	1 (<1%)	3 (1%)
Respiratory, thoracic and mediastinal disorders				
Nasopharyngitis	19 (6%)	23 (8%)	27 (9%)	19 (6%)
[redacted]				

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Number of subjects System organ class and preferred term	0.3 mg N=295	1 mg N=301	3 mg N=296	Sham N=298
[redacted]				
Chronic obstructive airways disease	2 (1%)	1 (<1%)	2 (1%)	3 (1%)
Dyspnea NOS	3 (1%)	3 (1%)	8 (3%)	4 (1%)
Epistaxis	3 (1%)	2 (1%)	3 (1%)	2 (1%)
Pharyngitis	3 (1%)	2 (1%)	5 (2%)	5 (2%)
[redacted]				
Chronic obstructive airways disease exacerbated	1 (<1%)	4 (1%)	2 (1%)	2 (1%)
Pulmonary congestion	0 (0%)	2 (1%)	3 (1%)	2 (1%)
Skin and subcutaneous tissue disorders				
[redacted]				
Cutis laxa	3 (1%)	2 (1%)	2 (1%)	3 (1%)
Rash NOS	3 (1%)	7 (2%)	3 (1%)	3 (1%)
Vascular disorders				
Hypertension NOS	14 (5%)	26 (9%)	29 (10%)	22 (7%)
[redacted]				
Hypotension NOS	1 (<1%)	2 (1%)	4 (1%)	0 (0%)

Reviewer's comments:
Adverse events seen more frequently in the 0.3 mg group versus sham are highlighted. The majority of the most frequently occurring adverse events (i.e. >10%) in the drug group are those commonly seen after intraocular procedures including injections. Anterior chamber inflammation, vitreous floaters, vitreous opacities and increased intraocular pressure are reported at a much higher rate in the drug groups than in the sham arm. This may be due to the lack of intraocular penetration in the sham group, however, a drug effect cannot be ruled out.

Discussion of Vision Threatening Adverse Events:

Endophthalmitis

Endophthalmitis was experienced by 12 pegaptanib sodium-treated patients; no cases occurred in the sham-treated patients. Four (4) additional events of endophthalmitis were reported in pegaptanib sodium-treated patients in the ongoing controlled studies as of the data cutoff date of 26 September 2003. All 16 cases occurred in the study eye and occurred within one week of injection.

The injection procedure as originally described in the study protocols was revised in a protocol amendment to reduce the risk of endophthalmitis.

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The amendment required use of:
1. sterile preparation and drape similar to that used for routine intraocular surgery, and
2. use of either pre-injection topical ophthalmic antibiotic drops for three days prior to the injection OR a 10 mL povidone iodine flush immediately prior to injection.

Three of the sixteen (3/16) cases of endophthalmitis occurred after the amendment was distributed to the sites.

Reviewer's Comments:

The rate of endophthalmitis seen in the phase three trials is much higher than expected for an intravitreal injection. It is approximately 10 fold higher than the rate seen in cataract surgery. This calls in to question the appropriateness of the technique used to administer this drug. Despite the change in the injection procedure instituted to reduce the risk of endophthalmitis there is still a significant risk of this adverse event.

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Listing of Patients with Endophthalmitis

Patient ID	Sex/ Age	Dose Group	Injections Prior to SAE	Onset Post Last Injection	Baseline VA	VA Before Event	VA After Event	Latest VA Wk 54	Outcome	Culture
EOP1003/1004 Week 54 Cohort										
1003 - 073-015	F/81	3 mg	8	4 days	20/100	20/63	20/125	20/125	d/c'd due to Patient request	Coagulase negative Staph
1003 - 089-019	F/69	0.3 mg	4	4 days	20/320	20/800	<20/800	<20/800	d/c'd due to AE	Staph epidermidis
1003 -102-033	F/76	0.3 mg	2	4 days	20/100	20/160	20/100	20/125	Cont't	Coagulase positive Staph
1003 -113-012	F/81	1 mg	5	2 days	20/100	20/50	20/63	20/50	Cont't	Negative
1003 -143-006	F/86	0.3 mg	2	4 days	20/125	20/200	20/320	20/125	Cont't	Coagulase negative Staph
1003 - 145-013	M/85	3 mg	6	7 days	20/125	20/400	20/400	20/640	Cont't	Micrococcus species
1004 -025-001	M/73	0.3 mg	7	3 days	20/40	20/50	20/200	20/80	Cont't	Coagulase negative Staph
1004 -026-009	F/69	1 mg	2	3 days	20/80	20/80	20/200	20/200	Cont't	Coagulase negative Staph
1004 -034-020	M/80	0.3 mg	1	4 days	20/200	20/200	20/400	20/500	Cont't	Staphy epidermidis
1004 - 042-001	M/77	0.3 mg	1	4 days	20/63	20/63	20/800	20/800	d/c'd due to AE	Staph lugdunensis
1004 -054-018	F/73	1 mg	1	2 days	20/80	20/80	20/100	20/125	Cont't	Negative
1004 - 057-014	M/78	3 mg	5	5 days	20/250	20/320	20/250	20/320	Cont't	Negative
EOP1003/1004 Year 2										
1004-025-005	F/81	masked	10	1 day	20/63	20/160	20/200	20/160 Wk 78	Cont't	Negative
1004-035-001	M/74	masked	13	4 days	20/160	20/80	20/100	20/160 Wk 103	d/c'd due to AE	Coagulase negative Staph
1004 - 048-017	F/78	masked	9	5 days	20/80	20/250	20/320	20/320 Wk 84	d/c'd due to AE	Negative
EOP1005 Ongoing										
1005-015-001	F/59	masked	1	3 days	20/80	20/63	20/125	20/160 Wk 30	d/c'd due to AE	Negative

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Retinal Detachment

The incidence of study eye retinal detachment in the first 54 weeks of Studies EOP1003 and EOP1004 was 0.6% (5/892) in the combined pegaptanib sodium and 0.3% (1/298) in the sham groups One patient received 0.3 mg, 2 patients received 1 mg, and 2 patients received 3 mg pegaptanib sodium.

The onset of these events did not correlate with the number of treatments received, since the detachments occurred after the third (two patients), fourth, six or eighth injection. The event onset varied from 7 to 137 days after the last injection. Two of the patients had detachments that were exudative/hemorrhagic in nature, which may have been secondary to the underlying disease process; these detachments did not have a rhegmatogenous component. The detachment of a third patient was attributed to proliferative vitreoretinopathy and contracture of the retina.

Retinal Tear

Four of 892 patients (0.4%) receiving pegaptanib sodium (2 receiving 0.3 mg; 2 receiving 3 mg) and 1/298 (0.3%) receiving sham treatment experienced a retinal tear in the study eye during the first 54 weeks of Studies EOP1003 and EOP1004. In all 5 cases, the tear was diagnosed at the study visit one week postinjection

For the 4 patients who were receiving active treatment, the tears occurred after the second, fifth, or sixth (two patients) injection. Four patients were treated with laser photocoagulation and one received no treatment. None of the patients progressed to retinal detachment and none discontinued treatment due to this event. There were no retinal tears in the fellow eye.

Traumatic Cataracts

Five patients developed a traumatic cataract during the first 54 weeks of Studies EOP1003 and EOP1004, all of which were iatrogenic in nature. In 4 of these patients there was contact and/or penetration of the lens with the intravitreous injection needle; two of these events occurred on the same day at the same investigational site (1003-093). In the fifth patient, an anterior chamber paracentesis was performed due to increased IOP after an intravitreous injection, and the paracentesis needle punctured the anterior lens capsule. All of these patients subsequently had a cataract extraction, and all but one continued in the study; the remaining patient requested to be withdrawn from the study after cataract surgery.

Retinal Artery Occlusion

Central retinal artery occlusion (CRAO) in the study eye during the first 54 weeks of Studies EOP1003 and EOP1004 was seen in 4 patients, 1 receiving 0.3 mg pegaptanib

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sodium and 3 receiving 1 mg. All 4 cases were transient closures of the central artery which were associated with increased IOP immediately following an injection. All were treated with, and resolved after, paracentesis. These events occurred after the first, third or sixth injection. All events resolved without sequelae and all 4 patients continued in the study.

In addition to the 4 study eye cases described above, one patient receiving pegaptanib sodium 1mg presented with a CRAO in the fellow eye 28 days after the first injection. The patient was treated with paracentesis and acetazolamide.

Deaths

Twenty-five deaths were recorded in the Week 54 cohort of Studies EOP1003 and EOP1004, 19 in patients receiving pegaptanib sodium and 6 patients receiving sham. The incidence of death in all pegaptanib sodium treated patients in the Week 54 cohort of Studies EOP1003 and EOP1004 was 2.1%, with the rate in sham-treated patients from these studies being 2.0%.

Number (%) of Deaths in the Week 54 Cohort of Studies EOP1003 and EOP1004

	0.3 mg	1 mg	3 mg	Sham
	N=295	N=301	N=296	N=298
EOP1003 Wk 54 Cohort	2/151(1.3)	2/155(1.3)	3/153(2.0)	4/153(2.6)
EOP1004 Wk 54 Cohort	3/144(2.1)	6/146(4.1)	3/143(2.1)	2/145(1.4)

Death Listing in Pegaptanib Sodium Studies by Treatment Group

Patient Identifier	Age/ Gender	Trt Group	Study Day of Death	Last Trt to Death (Days)	Cause(s) of Death (Investigator Term)
Week 54 Cohort of Studies EOP1003 and EOP1004					
EOP1003-108-007	82/M	0.3 mg	312	17	Myocardial Infarction
EOP1003-136-011	80/F	0.3 mg	130	11	Brain Hemorrhage
EOP1004-021-010	68/M	0.3 mg	231	20	Cardiac Arrest
EOP1004-048-002	69/M	0.3 mg	185	17	Abdominal Aortic Aneurysm
EOP1004-050-012	76/M	0.3 mg	140	54	Acute Myeloid Leukemia
EOP1003-130-001	75/F	1 mg	358	22	Heart Attack
EOP1003-136-005	74/M	1 mg	281	31	Stroke
EOP1004-008-018	85/M	1 mg	228	19	Anemia
EOP1004-015-002	76/F	1 mg	307	34	Pneumonia; Worsening Chronic Bronchiectasis; Worsening Mycobacterium Avium Complex Pneumonia
EOP1004-033-006	86/F	1 mg	62	20	Aortic Stenosis, Cardiopulmonary Arrest

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EOP1004-041-001	81/F	1 mg	187	55	Renal failure; Septicemia;
EOP1004-050-021	82/M	1 mg	323	48	Poorly Differentiated Large Cell Lung Cancer
EOP1004-059-006	75/M	1 mg	101	17	Metastatic Cancer
EOP1003-074-002	89/F	3 mg	183	183	Ischemic Cerebral Vascular Accident
EOP1003-104-011	75/M	3 mg	195	27	Massive Gastric Bleeding
EOP1003-085-001	82/F	3 mg	227	64	Pneumonia
EOP1004-006-010	85/F	3 mg	372	36	Renal Failure
EOP1004-026-003	81/F	3 mg	256	47	Cardiac Arrest; Necrotic Bowel
EOP1004-034-011	85/F	3 mg	116	30	Cardiac Arrest
EOP1003-064-012	82/M	Sham	342	3	Myocardial Infarction; Emphysema
EOP1003-098-002	79/M	Sham	35	35	Acute Myeloid Leukemia
EOP1003-130-013	83/F	Sham	273	63	Bronchopneumonia
EOP1003-145-018	72/M	Sham	350	87	Metastatic Lung Cancer; Multiple Blood Clots
EOP1004-021-012	80/F	Sham	335	79	Bladder Cancer
EOP1004-040-003	76/F	Sham	328	27	Pelvic mass
Deaths Other than in Week 54 Cohort of Studies EOP1003 and EOP1004*					
EOP1005-024-011	80/F	masked	52	10	Acute Myocardial Infarction
EOP1004-141-010**	82/F	0.3 mg	393	58	Gastric Cancer
EOP1003-071-005**	90/M	1 mg	471	136	Cardiorespiratory Arrest
EOP1004-036-017	81/M	1 mg	431	95	Myocardial infarction
EOP1000-006-001	85/F	3 mg	74	18	Myocardial Infarction
EOP1002-HUD-02	73/F	3 mg	67	26	Multisystem Organ Failure
EOP1003-093-005**	74/M	3 mg	401	61	Septic Shock; Intestinal Necrosis
EOP1003-119-012**	75/M	3 mg	381	47	Probable Ischemic Heart Disease
EOP1003-093-018	93/M	Sham	355	142	Pulmonary Embolism
EOP1004-006-034**	84/F	3 mg	415	121	Acute Respiratory Failure
*Study treatment for patients in EOP1003 and EOP1004 given for the Week 54 period					
** No study treatment after Week 54					

Reviewer's Comments:

The death rate in the pooled phase 3 studies is consistent across the treatment groups. The 2% death rate is likely due to the population studied in these trials and not due to the drug or procedure.

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[redacted]

CLINICAL REVIEW

Clinical Review Section

Study Eye IOP – Safety population – Study EOP1003

Study Eye IOP - Safety population - Study EOP1003

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[redacted] CLINICAL REVIEW

Clinical Review Section

Study Eye IOP – Safety population – Study EOP1004

Among patients receiving pegaptanib sodium, 9% (0.3 mg), 13% (1 mg) and 15% (3 mg) underwent paracentesis for the treatments of increased intraocular pressure, while no sham-treated patient did. A total of 12% of patients in the 0.3 mg pegaptanib sodium group, 14% in the 1 mg group, and 19% in the 3 mg group received a concomitant medication for increased IOP on one ore more injection days.

Reviewer's Comments:

The is an expected increase in IOP which occurs post injection in all of the drug treatment groups. The increase in IOP is consistent across drug groups. During the first year of the study, the baseline IOP for all drug groups appears to remain unchanged. There is no trend of hypotony due to multiple penetrations of the globe over the year of treatment.

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Concomitant PDT Use

Number (%) of Patients with and Ocular Adverse Events >10% and/or Events that May Have a Significant Effect on Vision in the Study Eye by PDT Use – Study EOP1003 & EOP1004 – Safety Population

Event		0.3 mg	1 mg	3 mg	All Doses	Sham
PDT after 1st injection	Yes	N=51	N=56	N=59	N=166	N=64
	No	N=244	N=245	N=237	N=726	N=234
Eye Pain	PDT	[redacted]	23 (41%)	22 (37%)	67 (40%)	25 (39%)
	No PDT		74 (30%)	83 (35%)	232 (32%)	58 (25%)
Punctate Keratitis	PDT		19 (34%)	17 (29%)	54 (33%)	12 (19%)
	No PDT		72 (29%)	81 (34%)	232 (32%)	67 (29%)
Vitreous Floaters	PDT		22 (39%)	15 (25%)	54 (33%)	6 (9%)
	No PDT		81 (33%)	88 (37%)	240 (33%)	17 (7%)
Visual Acuity Reduced	PDT		15 (27%)	14 (24%)	43 (26%)	27 (42%)
	No PDT		32 (13%)	38 (16%)	123 (17%)	44 (19%)
Anterior Chamber Inflammation	PDT		12 (21%)	14 (24%)	42 (25%)	5 (8%)
	No PDT		30 (12%)	25 (11%)	86 (12%)	12 (5%)
Cataract	PDT		7 (13%)	16 (27%)	34 (20%)	9 (14%)
	No PDT		54 (22%)	53 (22%)	147 (20%)	45 (19%)
Visual Disturbance NOS	PDT		6 (11%)	16 (27%)	30 (18%)	9 (14%)
	No PDT		33 (13%)	24 (10%)	87 (12%)	24 (10%)
Vitreous Opacities	PDT		11 (20%)	8 (14%)	30 (18%)	6 (9%)
	No PDT		45 (18%)	40 (20%)	135 (19%)	23 (10%)
Photophobia	PDT		5 (9%)	9 (15%)	20 (12%)	7 (11%)
	No PDT		16 (7%)	20 (8%)	52 (7%)	16 (7%)
Vision Blurred	PDT		6 (11%)	5 (8%)	20 (12%)	5 (8%)
	No PDT		18 (7%)	12 (5%)	46 (6%)	9 (4%)
Corneal Edema	PDT		2 (4%)	5 (8%)	14 (8%)	14 (6%)
	No PDT		21 (9%)	32 (14%)	71 (10%)	16 (7%)
Retinal Hemorrhage	PDT		8 (14%)	3 (5%)	14 (8%)	6 (9%)
	No PDT		20 (8%)	16 (7%)	43 (6%)	19 (8%)
Endophthalmitis	PDT	1 (2%)	0	0	1 (1%)	0
	No PDT	5 (2%)	3 (1%)	3 (1%)	11 (2%)	0
Retinal Detachment	PDT	0	1 (2%)	0	1 (1%)	0
	No PDT	1 (0%)	1 (0%)	2 (1%)	4 (1%)	0

Reviewer's Comments:
Those adverse events occurring at a higher rate in the group administered PDT during treatment are highlighted. There was an increased risk of the majority of ocular adverse events which occur in >10% of the population as well the majority of events considered vision threatening when concomitant PDT was administered.

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Clinical Laboratory Evaluations, Vital Signs, ECG's

Number (%) of Patients with Laboratory Test Abnormalities Meeting the Primary Criteria Occurring at an Incidence of > 1% in Any Treatment Group, Without Regard to Baseline in the Week 54 Cohort of Studies EOP1003 an EOP1004

Laboratory Test	Units	Primary Criteria	0.3 mg	1 mg	3 mg	All Doses	Sham
Hematology			N=293	N=299	N=293	N=885	N=295
Hemoglobin	g/dL	<0.8xBL	3(1)	6(2)	10(3)	19(2)	7(2)
Platelets	10E9/L	< 75	5 (2)	0	0	5 (1)	1 (0)
Neutrophils (Abs)	10E6/L	> 1 5xULN	5 (2)	1 (0)	6 (2)	12 (1)	5 (2)
Eosinophils (Abs)	10E6/L	>1.5x ULN	8(3)	4(1)	2(1)	14(2)	12(4)
Eosinophils	%	>1.5x ULN	11(4)	7(2)	5(2)	23(3)	20(7)
Liver Function			N=295	N=301	N=296	N=892	N=298
GGT	IU/L	>3xULN	5(2)	6(2)	11(4)	22(2)	4(1)
Renal Function			N=295	N=301	N=296	N=892	N=298
BUN	µ MOL/L	>1.3xULN	10(3)	11(4)	12(4)	33(4)	7(2)
Creatinine	µ MOL/L	>1.3xULN	8(3)	10(3)	9(3)	27(3)	11(4)
Electrolytes			N=295	N=301	N=296	N=892	N=298
Potassium	MMOL/L	>1.1xULN	6(2)	8(3)	14(5)	28(3)	8(3)
Carbon dioxide	MMOL/L	< 0.9xLLN	1 (0)	5 (2)	4 (1)	10 (1)	2 (1)
		> 1.1xULN	5 (2)	4 (1)	7 (2)	16 (2)	4 (1)
Phosphorus	MMOL/L	>1.1xULN	3(1)	3(1)	8(3)	14(2)	5(2)

N=No patients evaluable for laboratory tests
BL=Baseline
ULN=Upper limit of normal

Reviewer's Comments:
There are no dose dependent changes in laboratory values noted.

Vital Signs – Studies EOP1003 & EOP1004 – Safety Population

Reviewer's Comments:
There were no clinically significant changes in diastolic or systolic BP, temperature or pulse in any of the treatment groups during the first year of this study.

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CLINICAL REVIEW

Clinical Review Section

D. Adequacy of Safety Testing

The database submitted in this NDA is adequate to assess the safety profile of pegaptanib sodium.

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E. **Summary of Critical Safety Findings and Limitations of Data**

The majority of safety concerns raised in the review of this application are likely attributed to the procedure required to administer pegaptanib sodium and not the drug product itself. The majority of adverse events seen in the database are those commonly seen with intraocular procedures including intravitreous injections. There is concern raised in this database over the rate of endophthalmitis. This event is most likely due to contamination during the procedure itself and not the drug product since most cases were infectious in nature. The labeling will need to reflect the risk of this administration related adverse event and the importance of the use of sterile technique. This will allow for physicians and patients to be adequately informed about this risk and steps to take to minimized its occurrence.

VIII. Dosing, Regimen, and Administration Issues

Adequate dose ranging studies were conducted during drug development. The 0.3 mg dose of pegaptanib sodium has been demonstrated to be safe and effective in two controlled phase 3 trials. The dosing interval (every 6 weeks) chosen by the applicant was not varied during the development program, therefore there is no clinical data available to assess the adequatcy of this dosing interval.

IX. Use in Special Populations

A. **Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation**

The sponsor has adequately evaluated gender effects on both the safety and efficacy outcomes. Sub-group analyses did not reveal any difference in the primary efficacy endpoint between males and females. The safety profile seen in male and females is similar. The types and rates of adverse events seen in the two groups are consistent

B. **Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy**

The trials for this indication were conducted in a population that was overwhelmingly elderly and white. This is reflective of the population which is mostly affected by this disease and does not reflect an issue with recruitment. The number of patients outside of this demographic were too small to make any

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definitive conclusion about the safety and efficacy, however based on a subset analysis it does not appear that there is any age, race or ethnicity effects.

C. Evaluation of Pediatric Program

Pediatric trials have not been conducted for this drug. The indication being sought is for age-related macular degeneration which is a disease seen exclusively in the adult population.

D. Comments on Data Available or Needed in Other Populations

The demographics of the patients enrolled in the trial during the development program for this product are representative of the targeted population. There is no additional data need from other populations.

X. Conclusions and Recommendations

A. Conclusions

The submitted studies in NDA 21-756 are sufficient to establish efficacy for the use of pegaptanib sodium 0.3 mg in the treatment of the neovascular form of age-related macular degeneration. The two phase 3 studies show replicative results in the ability of pegaptanib sodium to reduce the risk of vision loss in patients with neovascular AMD when given every six weeks compared to sham.

B. Recommendations

NDA 21-756 is approvable from a clinical perspective the treatment of the neovascular form of age-related macular degeneration pending the receipt and review of the 120-day safety update, labeling and revised drug product specifications.

XI. Appendix

A. Other Relevant Materials

The labeling for this drug product will be contained in a separate M.O. review.

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/s/

Jennifer Harris
9/16/04 10:02:05 AM
MEDICAL OFFICER

Wiley Chambers
9/17/04 07:40:06 AM
MEDICAL OFFICER

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引用非特許文献

特許出願の番号	特願２０１６－２０２１６９
作成日	平成３０年　２月２３日
作成者	馬場　亮人　　４０４３　４Ｕ００
発明の名称	血管新生眼疾患を処置するためのＶＥＧＦアンタゴニストの使用

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CENTER FOR DRUG EVALUATION AND RESEARCH

BLA APPLICATION NUMBER:

125156

MEDICAL REVIEW

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Medical Officer's Review #3 – Labeling and Postmarketing Commitment

Application Type	BLA
Submission Number	125156
Primary Reviewer	Rhea Lloyd, M.D.
Date of Labeling Submission	June 28, 2006
Date of Postmarketing Commitment Submission	June 29, 2006
Date of Labeling Review	June 29, 2006
Name	Lucentis (ranibizumab injection)
Applicant	Genentech, Inc. 1 DNA Way South San Francisco, CA 94080 650-225-1558

Submitted
The applicant has submitted labeling based on previous review, internal discussions and correspondence between the applicant and the Office of Antimicrobial Products with revisions to Section 12.2. In the second sentence of paragraph 2, the word "months" was capitalized. In the last sentence of paragraph 2, the phrase, [redacted] was replaced by "Foveal retinal thickness data."

Also submitted, as agreed during the 29 June 2006 teleconference between the Agency and the applicant, are the following additional Postmarketing Commitments:

1. Submit the final Clinical Study Report from Study FVF3689g by 30 June 2008.
2. Provide safety and efficacy data from a 2-year adequate and well-controlled clinical trial of a mutually acceptable design exploring multiple dosing frequencies of Lucentis. The timelines are outlined below:

Protocol Submission:	14 November 2008
Study Start:	21 September 2009
Final Clinical Study Report:	1 April 2013

Reviewer's Comment:
Acceptable.

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7 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

✓ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Medical- 1044

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Recommendations
It is recommended that BLA 125156 be approved with the labeling contained in this review.

The application supports the safety and effectiveness of Lucentis (ranibizumab injection) for the treatment of ヒト neovascular ヒト age related macular degeneration.

Rhea A. Lloyd, M.D.
Medical Officer, Ophthalmology

cc: William Boyd, MD
Wiley Chambers, MD
Janice Soreth, MD
Mark Goldberger, MD, MPH

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Deputy Division Director Review

Application Type	BLA
Submission Number	125156
Established Name	Ranibizumab injection
Trademark	Lucentis
Therapeutic Class	Vascular endothelial growth factor (VEGF) inhibitor
Applicant	Genentech, Inc. 1 DNA Way South San Francisco, CA 94080 650-225-1558

Proposed Dosing Regimen
Lucentis is to be administered as an intravitreal injection 0.5 mg (0.05 mL) every one to three months.

Indication
Treatment of [redacted] neovascular [redacted] age related macular degeneration

Intended Population
Adults with neovascular (wet) age-related macular degeneration

Formulation

Ingredients	[redacted]	Reference to Standard or Specification
Ranibizumab	Active ingredient	
α,α-trehalose dehydrate	[redacted]	
histidine HCl		Ph. Eur.
[redacted]		USP and Ph. Eur.
Polysorbate 20		NF and Ph. Eur.
Water for Injection		USP and Ph. Eur.

[a] Target fill volume of [redacted] per vial.

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EXECUTIVE SUMMARY

Recommendation on Regulatory Action
Lucentis (ranibizumab injection) with the labeling changes listed in this review is recommended for approval for the treatment of [redacted] neovascular [redacted] age related macular degeneration.

The applicant, Genentech Inc. has conducted three adequate and well-controlled studies, FVF2598g, FVF3192g, and FVF2587g which demonstrated statistically and clinically significant differences in the proportion of subjects who lose fewer than 15 letters in best corrected vision at 12 months compared with sham treatment.

Recommendation on Postmarketing Actions
Risk Management Activity
No post marketing risk management activity beyond the usual collection of adverse events is recommended.

Required Phase 4 Commitments

[redacted]

Other Phase 4 Requests
There are no other Phase 4 requests.

Summary

Established Name	ranibizumab injection
(Proposed) Trade Name	Lucentis 0.5 mg
Therapeutic Class	vascular endothelial growth factor (VEGF) inhibitor
Route of Administration	intravitreal injection

Age Related Macular Degeneration (AMD) is clinically manifest in two distinct forms: the non-exudative (dry) or the exudative (wet) form of the disease. The etiology of the disease is such that new abnormal blood vessels proliferate from the choriocapillaris through defects in the Bruch's membrane under the retinal pigment epithelium (RPE), forming neovascular membranes. These new vessels leak serous fluid and may give rise to serous and hemorrhagic detachment of the RPE and neurosensory retina and may stimulate fibrous disciform scarring with subsequent loss of central vision.

Neovascular AMD is characterized by CNV in the macular region. Vascular endothelial growth factor-A (VEGF-A) has been observed in surgically excised human fibrovascular lesions. It is

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reasonable to suggest that active forms of VEGF-A are targets for therapeutic intervention in neovascular AMD.

Efficacy
The three phase 3 studies submitted, Study FVF2598g, Study FVF2587g, and Study FVF3192g were designed to demonstrate the safety and efficacy of Lucentis (ranibizumab injection) in the treatment of neovascular AMD. All three studies were prospective, multicenter, randomized, double-masked, parallel group. Study FVF2598g and FVF3192g had sham controls, and Study FVF2587g had an approved photodynamic therapy as a control. All three studies demonstrated clinically and statistically significant differences between ranibizumab and the control arm. The effectiveness of dosing every three months appeared to be only one third as effective as monthly injections. Based on the population studied, there does not appear to be any difference in Lucentis' effect based on age, race, ethnicity or iris color.

Safety
The population studied was predominantly elderly and white which is representative of the population usually affected by age-related macular degeneration. The demographics of the patient population do not reflect problems with recruitment.

The most common adverse events identified are conjunctival hemorrhage, eye pain, increased intraocular pressure, retinal disorder and vitreous floaters. These adverse events are often associated with intravitreal injections.

Dosing Regimen and Administration
The sponsor has performed adequate dose ranging and dose frequency studies of Lucentis (ranibizumab injection). Lucentis has been proven safe and effective when administered as an intravitreal injection 0.5 mg/0.05 mL once monthly. This dosing regimen achieved and sustained a statistically significant difference in the proportion of patients who lost 15 letters of vision compared to baseline relative to the control group. When Lucentis is dosed every three months, it appears that 2/3 of the effectiveness is lost.

Drug-Drug Interactions
In Study FVF2587g, Lucentis (ranibizumab) was dosed with verteporfin PDT. Significant inflammation was observed when Lucentis was administered 7 days following PDT, but not when dosed at intervals longer than 7 days. No drug-drug interaction analyses were performed.

Special Populations
Subgroup analyses did not reveal any differences in the safety or efficacy with respect to age, sex, baseline visual acuity, CNV lesion type, lesion size, or prior laser photocoagulation. The population studied for this indication was predominantly elderly and white, reflective of the population most affected by this disease. The number of patients outside of this demographic group was too small to draw any definitive conclusion regarding the safety and efficacy. No pediatric trials were conducted for this drug as age-related macular degeneration is a disease seen only in adults.

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INTRODUCTION AND BACKGROUND

Product Information

Established Name	ranibizumab injection
(Proposed) Trade Name	Lucentis 0.5 mg
Therapeutic Class	vascular endothelial growth factor (VEGF) inhibitor
Route of Administration	intravitreal injection
Chemical Class	VEGF Inhibitor
Indication	Treatment of neovascular (wet) age-related macular degeneration

Currently Available Treatment for Indications
There are currently two approved drug products for the treatment of age related macular degeneration – Visudyne (verteporfin for injection) and Macugen (pegaptanib sodium injection). Visudyne was approved under NDA 21-119 on April 12, 2000, for the treatment of patients with predominantly classic subfoveal choroidal neovascularization due to age-related macular degeneration. Macugen was approved under NDA 21-756 on December 17, 2004, for the treatment of neovascular (wet) age-related macular degeneration.

Availability of Proposed Active Ingredient in the United States
Ranibizumab is a new molecular entity and has not been marketed in the United States.

SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

CMC (and Product Microbiology, if Applicable)
Formulation

Ingredients	[redacted] Amount		Reference to Standard or Specification
Ranibizumab	[redacted]	Active ingredient	
α, α-trehalose dehydrate	[redacted]		
histidine HCl	[redacted]		Ph. Eur.
[redacted]	[redacted]		USP and Ph. Eur.
Polysorbate 20	[redacted]		NF and Ph. Eur.
Water for Injection	[redacted]		USP and Ph. Eur.

[1] Target fill volume o. [redacted] per vial.

Genentech intends to use a life-cycle approach for setting ranibizumab specifications. This life-cycle approach will use interim acceptance criteria based upon the limited data available at the time of submission. Since campaign-to-campaign variation can be larger than the variation within a campaign, Genentech proposes a post-approval commitment for re-evaluating the

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interim acceptance criteria after three commercial post-approval campaigns (consisting of a minimum of – additional lots). The re-evaluation is expected to take place within two years after approval but will ultimately depend on the currently unknown manufacturing schedule for ranibizumab Drug Substance.

Lucentis Drug Product Release and Shelf-Life Specifications.

Test Code	Test Name	Acceptance Criteria	Release	Shelf-life

Animal Pharmacology/Toxicology

There were no significant findings in the pharmacology/toxicology reviews which would affect the clinical outcome.

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DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

Sources of Clinical Data

This review is based on the primary reviews from the Clinical, Pharmtox, Product Quality, Biopharm and Statistical staff and results of the applicant supported trials for AMD conducted under BBIND . — Three phase 3 safety and efficacy trials were submitted to support the indication currently being sought by the applicant. In addition, the results of four phase 1/2 dose ranging and safety trials were also submitted. This NDA was submitted in electronic format as a hybrid CTD (i.e., CTD structure with PDF tables of contents), according to ICH and FDA guidelines for electronic submissions.

Tables of Clinical Studies

Study	Design (Sites)	Population	Control	No. of Enrolled Subjects	Treatment Frequency and Duration	Ranibizumab Dose(s)
FVF2587g	Randomized, double-masked, double-sham active treatment-controlled (US, Europe, Australia)	Subjects with predominantly classic subfoveal neovascular AMD	Verteporfin PDT (+sham injection)	423	Intravitreal injection q month, max. 24 injxns over 2 yrs, or verteporfin PDT q3mos as needed	0.3 mg (n=140); 0.5 mg (n=140), sham injection (n=143)
FVF2598g	Randomized, double-masked, sham-controlled (US)	Subjects with minimally classic or occult subfoveal neovascular AMD	Sham injection	716	Intravitreal injection q mo., max. 24 injxns over 2 years	0.3 mg (n=238), 0.5 mg (n=240), sham injection (n=238)
FVF3192g	Randomized, double-masked, sham-controlled (US)	Subjects with recurrent subfoveal CNV with or without classic CNV secondary to AMD	Sham injection	184	Intravitreal injection q month for 3 doses (Day 0, Month 1, Month 2) followed by doses q 3 months (Mos. 5, 8, 11, 14, 17, 20 and 23)	0.3 mg 0.5 mg sham injection (Target: 61-62 subjects per group)
FVF2508g	Extension (US)	Subjects with neovascular AMD who completed a Genentech Phase 1/2 ranibizumab study	None	70	Intravitreal injections every 28 days (± 5 days) through October 2006 or until 30 days after product launch	0.5 mg (n=66)
FVF2425g	Randomized, open-label, multiple-dose escalating regimens	Subjects with neovascular AMD	None	39	Intravitreal injections at 2- or 4-week intervals, max. of 5, 7 or 9 total injections	0.3 mg to 1.0 mg escalating regimen with 7 total injxns (n=9); 0.3mg to 2.0 mg

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Study	Design (Sites)	Population	Control	Enrolled	Duration	Ranibizumab Dose(s)
	(US)				over 16 weeks	escalating regimen with 9 total injxns (n=10); 0.3 mg to 2.0 mg escalating regimen with 5 total injxns (n=10)
FVF2128g	Randomized, open-label, dose-escalation (US)	subjects with classic neovascular AMD	Usual care[c]	64	Intravitreal injections q 4 weeks, maximum of 8 total injections over 28 weeks, or usual care with crossover to ranibizumab treatment after 14 weeks	0.3 mg (n=25), 0.3 mg initial dose escalated to 0.5 mg for subsequent doses 9n=28), usual care (n=11)
FVF1770g	Open-label, single-dose escalation (US)	Subjects with neovascular AMD	None	27	Single intravitreal injection	0.05 mg (n=6), 0.15 mg (n=6), 0.30 mg (n=6), 0.50 mg (n=7), 1.0 mg (n=2)
FVF2428g	Randomized, single-masked, sham-controlled, combination treatment (US)	Subjects with predominantly classic neovascular AMD	Verteporfin PDT (+sham injection)	162	Intravitreal injection q month, max. 24 injxns over 2 years, in combination with verteporfin PDT q3mos, as needed	0.5 mg (n=106), sham injection (n=56)
CRFB002A 1201	Open-label (Japan)	Subjects with subfoveal CNV secondary to AMD	None	Target 84	Intravitreal injections every month	0.3 mg 0.5 mg (Target: 42 subjects per group)
CRFB002B 2201	Open-label (Europe)	Subjects with occult or predominantly classic subfoveal CNV secondary to AMD	Verteporfin PDT	32	Intravitreal injections every month in combination with verteporfin PDT	0.5 mg (n=30)

Review Strategy
This review relies primarily on the results of the three Phase 3 trials submitted by the applicant.

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The submitted clinical study reports, clinical protocols and literature reports related to trials FVF2598g and FVF2587g were reviewed. The application is in electronic format as a hybrid CTD (i.e., CTD structure with PDF tables of contents), according to ICH and FDA guidelines for electronic submissions.

Data Quality and Integrity
There is no evidence that Phase 3 studies reviewed in this BLA were not conducted in accordance with acceptable clinical ethical standards.

There were no significant problems identified Division of Scientific Investigations (DSI) audits that are likely to affect the data quality. The case report forms for the three studies were provided by Genentech, and these were reviewed for completeness and quality.

Compliance with Good Clinical Practices
The studies were conducted in accordance with the International Conference of Harmonization E6 Guidelines for Good Clinical Practice (GCPs), the Declaration of Helsinki and in compliance with relevant local and national regulations for informed consent and protection of subject rights in the country of conduct.

Before initiation of the study, the original protocol, all protocol amendments, the informed consent documents and all supportive information were reviewed and approved by the appropriate ethics committees (EC) or institutional review boards (IRB) for each of the centers involved in the study. The studies began only after receiving written approval from each EC/IRB.

Financial Disclosures
The applicant has adequately disclosed financial arrangements with clinical investigators as recommended in the FDA guidance for industry on *Financial Disclosure by Clinical Investigators*.

There is no evidence suggesting problems with the integrity of the submitted data.

CLINICAL PHARMACOLOGY

Pharmacokinetics – *See primary reviews.*

Pharmacodynamics – *See primary reviews.*

Exposure-Response Relationships
The retina is the site of disease in neovascular AMD. Therefore, systemic ranibizumab concentrations after intravitreal administration are not expected to correlate with efficacy.

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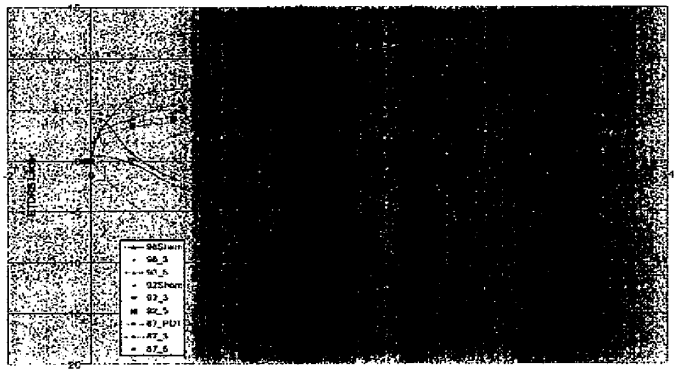
INTEGRATED REVIEW OF EFFICACY

The study designs of the three Phase 3 studies are included in the Primary Medical Officer's Review. Additional analyses and cross comparisons between studies are presented below. It is recognized that there are potential risks in comparing across studies. With respect to treatment by an intravitreal route of administration, these studies utilized essentially the same population.



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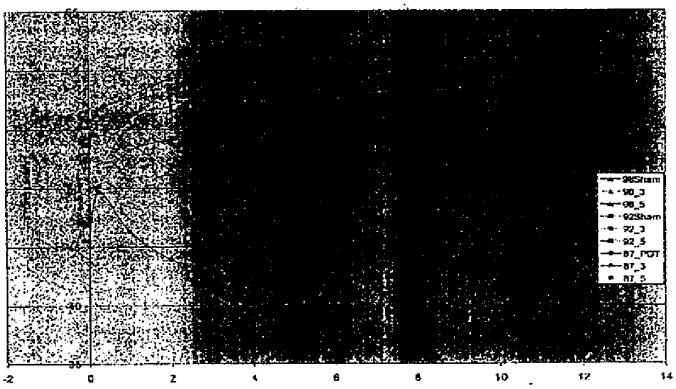

The 0.5 dose was consistently more effective than the 0.3 dose and each were more effective than the control group. The slope of the best fit line between month 3 and month 12 demonstrated a two thirds reduced effect of ranibizumab when the product was administered every three months compared to monthly treatments. The month 3-12 slopes for sham were -.87, -.85, -.84. The month 3-12 slopes for the 0.5 dose monthly were +.23 and +.26. The month 3-12 slope for the q3month injections was -.56. For the q3month injection, this becomes a 5 letter loss over the 9 month period

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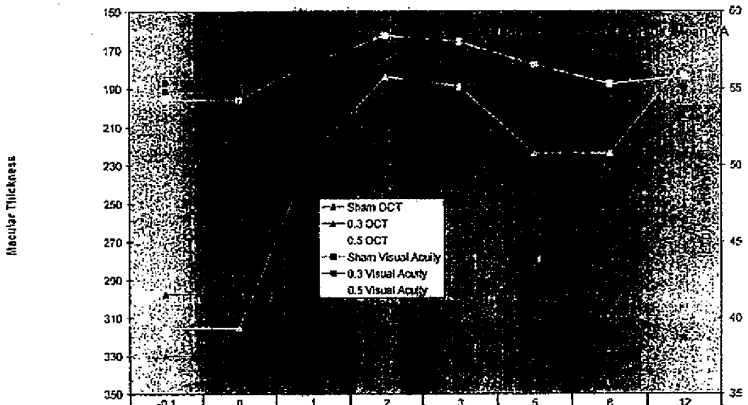

	-0.1	0	1	2	3	6	9	12
Sham OCT	297	297	317	312	312	278	272	251
0.3 OCT	330	330	213	183	192	214	231	205
0.5 OCT	315	315	223	184	189	224	224	175
Sham Visual Acuity	55	55	50	49	49	44	41	39
0.3 Visual Acuity	55	55	56	57	58	58	58	55
0.5 Visual Acuity	54	54	57	58	58	57	55	56

Noted above, there is no correlation between OCT and visual acuity. Treatment with ranibizumab results in a thinner macula even when the visual acuity decreases. The month 12 values illustrate this point. At month 12 for the ranibizumab 0.5 group, the mean macular thickness has its lowest value; however the visual acuity is at its worst.

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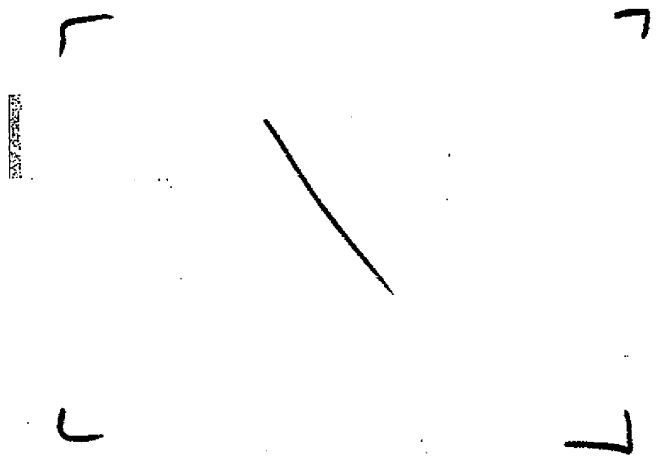

This graph illustrates that a substantially larger proportion of patients treated with ranibizumab injection develop thinner maculae and have improved visual acuity. While there is not a direct correlation between visual acuity and macular thickness over the course of this study, there is a general tendency for patients treated with ranibizumab to do both. For any individual patient, there is no significant correlation between macular thickness and visual acuity.

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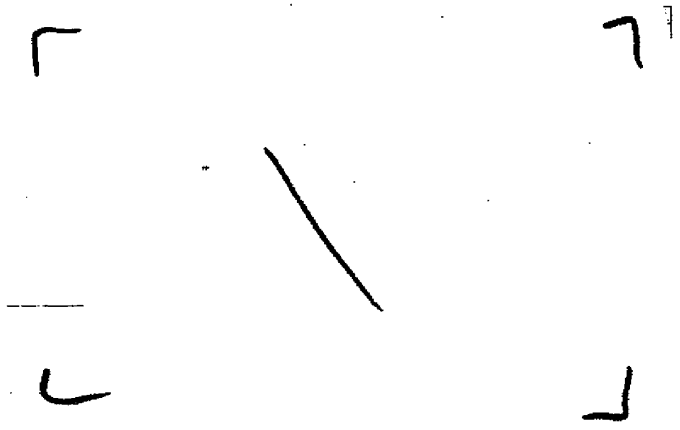

This graph presents a comparison between a change in OCT and the visual acuity at the next visit. Although not shown, data looks very similar for predictions of visual acuity at visits after the next visit. The graph illustrates that macular thickness is not predictive of visual acuity at later visits.

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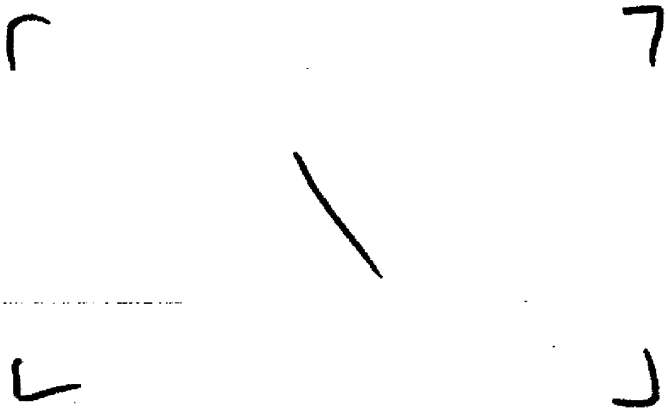

This graph illustrates the variation in visual acuity for any given macular thickness. While it is expected that thicker maculae will ultimately lead to poor vision, within the time frames of this study, there is no direct correlation between visual acuity and macular thickness. As a general rule, it appears that macular thickness below 200 often leads to better vision.

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An attempt was made to see if OCT criteria or vision loss criteria might have aided in the decision to treat patients with Lucentis. Although no formal criteria have been defined for normality of OCT, an increase in 100 microns might be considered the smallest change reliably available to use as a basis for treatment. In addition, although a 15 letter loss is the smallest clinically significant change, a single line change (5 letters) is commonly reported for safety parameters and was therefore investigated as a small visual acuity change. The results are listed below:

Percentage of Patients Meeting particular OCT or Vision Loss Criteria

OCT Increased by at least 100 or Vision Loss by 5 or more letters

	Month 2	Month 3	Month 5	Month 8	Month 12
Sham	64%	53%	75%	75%	78%
0.3	19%	38%	51%	54%	59%
0.5	5%	30%	43%	54%	54%

OCT Increased by at least 100

	Month 2	Month 3	Month 5	Month 8	Month 12
Sham	22%	11%	22%	17%	14%
0.3	0%	5%	16%	16%	11%
0.5	0%	0%	16%	16%	8%

Vision Loss by 5 or more letters

	Month 2	Month 3	Month 5	Month 8	Month 12
Sham	50%	47%	69%	69%	75%
0.3	19%	35%	41%	46%	59%
0.5	5%	30%	38%	54%	51%

OCT Increased by at least 100 with no loss of 5 or more letters

	Month 2	Month 3	Month 5	Month 8	Month 12
Sham	14%	6%	6%	6%	3%
0.3	0%	3%	11%	8%	0%
0.5	0%	0%	5%	0%	3%

As noted from the table, even a change as small as 100 microns or loss of 5 letters is not likely to have led to additional treatments and if used as the sole criteria would have resulted in fewer treatments than once every three months.

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Efficacy Conclusions

The submitted pivotal studies in BLA 125156 Lucentis (ranibizumab injection) demonstrate the efficacy for the use of ranibizumab 0.5-mg in the treatment of neovascular age-related macular degeneration.

The submitted phase 3 studies both demonstrate a clinically significant treatment effect of ranibizumab [redacted] and 0.5-mg compared to sham and Verteporfin PDT, respectively, for the primary efficacy endpoint, the proportion of subjects with a loss of fewer than 15 letters in the best corrected visual acuity score at Month 12 compared with baseline.

Macular thickness is not predictive of current or future visual acuity, although macular thickness above 200 µm and particularly greater than 400 µm is associated with poorer vision. Ranibizumab is capable of doing more than just thinning the macula and vision may be lost in spite of a thin macula.

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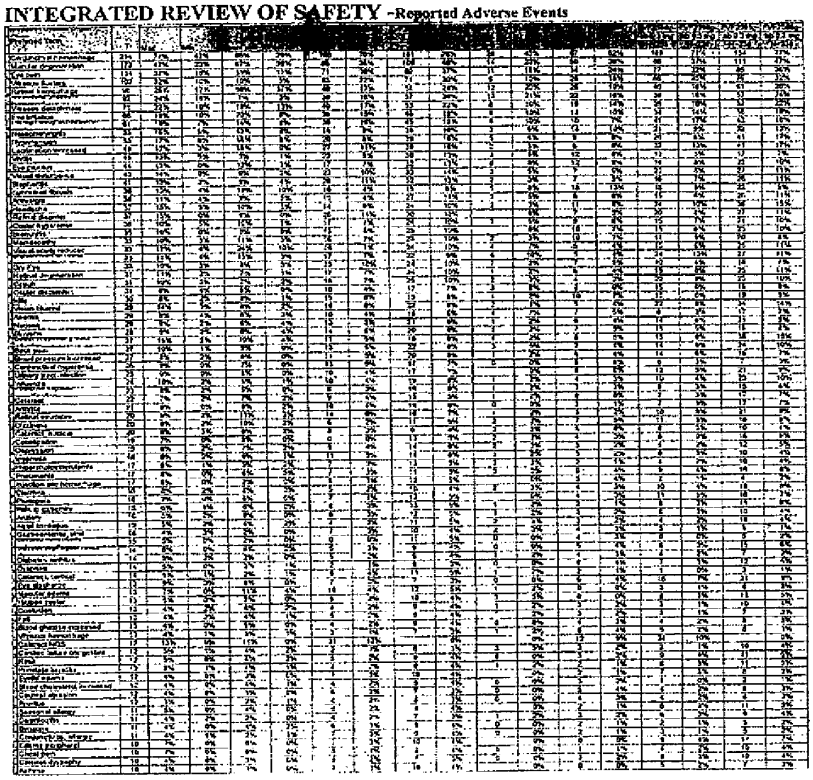
INTEGRATED REVIEW OF SAFETY -Reported Adverse Events



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Immunogenicity

Serum samples for the evaluation of immunoreactivity to ranibizumab were obtained from subjects at screening and prior to study drug administration at Months 6 and 12. The assay demonstrated immunoreactivity in a small percentage of subjects in all three treatment groups prior to initial administration of study drug, possibly due to preexisting anti-Fab antibodies.

The assay indicated positive results in a small percentage of subjects in all three treatment groups prior to initial administration of study drug, possibly due to preexisting anti-Fab antibodies. All three treatment groups had increases in positive results during the treatment period.

Immunoreactivity to Ranibizumab in the First Treatment Year- Safety Evaluable Subjects

Visit	[redacted]	[redacted]	[redacted]	FVF5287g Ranibizumab		
	[redacted]	[redacted]	[redacted]	[redacted]	0.5 mg N=137	0.5 mg N=140
Screening	5/215 (2.3%)	6/215 (2.8%)	7/218 (3.2%)	8/131 (6.1%)	12/125 (9.6%)	7/123 (5.7%)
Month 6	19/201 (9.5%)	15/211 (7.1%)	17/207 (8.2%)	6/114 (5.3%)	11/120 (9.2%)	10/116 (8.6%)
Month 12	20/206 (9.7%)	22/222 (9.9%)	26/219 (11.9%)	7/125 (5.6%)	9/123 (7.3%)	16/129 (12.4%)

Note: Table entries are numbers of subjects with positive immunoreactivity over numbers of subjects with evaluable samples. LTR=0.7 log titer.

Exploratory subgroup analyses based on immunoreactivity to ranibizumab were performed to determine whether the appearance of immunoreactivity was related to key safety and efficacy outcomes. The analysis population was divided into three subgroups: subjects who had a negative or missing test result at screening and negative post-baseline results, subjects who had a negative or missing test result at screening but at least one positive post-baseline result, and subjects who had a positive test result at screening. Visual acuity outcomes and the occurrence of intraocular inflammation and autoimmune adverse events were examined by treatment group for each immunoreactivity subgroup. No clinically relevant differences between immunoreactivity subgroups were identified in study FVF2598g.

In Study FVF5287g, with regard to intraocular inflammation adverse events, proportionately more ranibizumab-treated subjects who were immunoreactive at some timepoint experienced intraocular inflammation events than subjects who were never immunoreactive. Twenty- eight percent (5 of 18) of ranibizumab-treated subjects who were immunoreactive during treatment only and thirty-two percent of subjects (6 of 19) who were immunoreactive at baseline experienced inflammation adverse events in the study eye, compared with 10% of ranibizumab-treated subjects (23 of 230) who were never immunoreactive. Of the 12 verteporfin PDT-treated subjects who were immunoreactive at some timepoint, none experienced an intraocular inflammation adverse event.

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Intraocular Inflammation in Subjects with Immunoreactivity Based on the Initial and Confirmatory Assays (.) Studies FVF2428g, FVF2587g, FVF3192g (First Treatment Year) and FVF2598g (2-Year Treatment Period)
Safety Evaluable Subjects

Study	Treatment Group	[redacted]	[redacted]	[redacted]	Study Visit of Intraocular Inflammation Diagnosis
FVF2428g	Verteporfin PDT + sham	91103	34 / Month 1	1.200	No CRF found	---
	Verteporfin PDT + Ranibizumab 0.5 mg	91308	- 7 / Screening	0.884	No CRF found	
			366 / Month 12	0.767		
FVF2587g	Verteporfin PDT	319001	386 / Month 12	0.797	No	---
		334008	-12 / Screening	1.130	No	
			190 / Month 6	0.902	No	
		401002	-8 / Screening	1.820	No CRF found	
			186 / Month 6	1.780		
			361 / Month 12	1.800		
	Ranibizumab 0.3 mg	321003	-7 / Screening	0.945	Yes – Vitritis	Screening and Month 1
		334003	176 / Month 6	2.300	Yes – Iritis	Month 4 [2]
		337012	-26 / Screening	0.938	Yes – Iritis	Month 5 [3]
		351004	344 / Month 12	2.190	No	---
		352006	-10 / Screening	2.070	No	---
			180 / Month 6	1.890	No	---
			362 / Month 12	1.860	No	---
		403003	-1 / Screening	0.910	No	---
	Ranibizumab 0.5mg	306020	174 / Month 6	1.530	Yes – Vitritis	Months 1 and 2
			362 / Month 12	1.850		
		337009	364 / Month 12	1.270	No	---
		342007	174 / Month 6	2.450	Yes – Iritis, Vitritis	Month 11 [4]
			360 / Month 12	3.060		
		346001	182 / Month 6	1.260	No	---
			361 / Month 12	1.770		
		389001	-28 / Screening	1.240		
			182 / Month 6	0.993	Yes – Uveitis [5]	Month 7
			365 / Month 12	0.952		
FVF2598g	Sham	102008	183 / Month 6	1.230	No	---
			358 / Month 12	2.090		

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Study	Treatment Group	[illegible]	[illegible]	[illegible]	[illegible]	Study Visit of Intraocular Inflammation Diagnosis
			463 / Barly term.	2.060		
		116002	723 / Month 24	2.560	No	
		139004	-28 / Screening	2.100	Yes – Iritis	Day 7
			176 / Month 6	2.060		
			358 / Month 12	2.170		
			729 / Month 24	2.340		
		150005	181 / Month 6	0.864	No	---
			393 / Month 12	0.863		
		182003	355 / Month 12	0.903	No	---
	Ranibizumab 0.3mg	101021	361 / Month 12	1.850	No CRF found	
			719 / Month 24	1.810		
		110004	728 / Month 24	1.490	No	---
		112002	716 / Month 24	0.866	No	---
		125007	183 / Month 6	0.918	No	---
		141009	721 / Month 24	1.270	No	
		143001	-13 / Screening	3.550	Iritis	Month 2
			177 / Month 6	3.740		
		146001	714 / Month 24	1.080	No	
		149006	364 / Month 12	3.150	Iritis	Month 15 [6]
			717 / Month 24	2.120		
		159013	360 / Month 12	2.000	No	
			724 / Month 24	1.890		
		165002	-21 / Screening	0.910	No	
			175 / Month 6	0.993		
			368 / Month 24	0.793		
		170010	365 / Month 12	2.770	No CRF found	
			715 / Month 24	2.800		
		177006	358 / Month 12	1.870	Iritis	Day 7
			717 / Month 24	1.850		
	Ranibizumab 0.5 mg	102001	722 / Month 24	0.922	No	
		104002	719 / Month 24	1.140	No	
		106002	722 / Month 24	1.130	No	
		122002	359 / Month 12	1.630	No	
			723 / Month 24	1.770		
		124003	722 / Month 24	0.782	No	
		126001	174 / Month 6	1.700	No	
			357 / Month 12	2.040		
			727 / Month 24	1.480		
		141008	181 / Month 6	1.570	No	
			362 / Month 12	1.940		
			726 / Month 24	2.340		

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Study	Treatment Group	[illegible]	[illegible]	[illegible]	[illegible]	Study visit of Intraocular Inflammation Diagnosis
		141013	715 / Month 24	2.610	Vitritis	Day 0
		143010	722 / Month 24	2.440	No	
		152004	522 / Early Term.	0.752	No	
		153006	183 / Month 6	1.900	No	
			365 / Month 12	1.530		
			718 / Month 24	2.070		
		159017	716 / Month 24	0.780	No	
		167002	717 / Mont 24	1.230	No CRF found	
		188005	717 / Month 24	1.250	No	
FVF3192g	Sham	534001	-7 / Screening	2.520	Vitritis	Month 1
	Ranibizumab 0.5 mg	507018	357 / Month 12	0.875	No	
		522002	367 / Month 12	1.530	No	

1 In Study FVF2428g, intravitreal injections (sham or ranibizumab 0.5 mg) were given every month and verteporfin PDT every 3 months.
2 Iritis diagnosed 1 day after Month 4 injection.
3 Iritis diagnosed day of injection. Injection was not held.
4 No resolution of uveitis noted in CRFs submitted.
5 Uveitis diagnosed 3 days post Month 7 injection. Serious AE led to treatment discontinuation in Month 9.
6 Treatment discontinued.

The Immunoreactivity Assay still requires refinement (see Product Quality Review). Based on this assay, Titers above 3 were associated with Intraocular Inflammation in 100% of cases.

Thromboembolic Events

Serious Adverse Events Potentially Related to Systemic VEGF Inhibition during the First Treatment Year: Studies FVF2598g and FVF2587g

Type of Adverse Event	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	Ranibizumab 0.5 mg (N=140)
TOTAL *	2 (0.8%)	8 (3.4%)	9 (3.8%)	3 (2.1%)	4 (2.9%)	8 (5.7%)
Hypertension events	0	1 (0.4%)	0	0	0	0
Arterial thromboembolic events	2 (0.8%)	5 (2.1%)	8 (3.3%)	2 (1.4%)	2 (1.4%)	4 (2.9%)
Non-ocular hemorrhages	0	1 (0.4%)	0	0	2 (1.5%)	3 (2.1%)
Other potentially associated events	0	1 (0.4%)	1 (0.4%)	1 (0.7%)	1 (0.7%)	1 (0.7%)

Note: Multiple occurrences of the same type of event for a subject were counted once in the overall incidence.

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I concur with the Medical Officer's assessment that there is a trend in the occurrence of serious adverse events potentially related to systemic VEGF inhibition noted at Month 12, but not at 24 months, particularly in the ranibizumab 0.5-mg dose group. This includes trends in serious arterial thromboembolic events and, to a lesser extent, in serious non-ocular hemorrhages (but not in serious hypertension or proteinuria).

The sponsor applied the Antiplatelet Trialists' Collaboration (APTC) classification (Antiplatelet Trialists' Collaborations 1994) to the adverse events which mitigates some of these issues by focusing on a more restricted but well-defined spectrum of serious adverse events: vascular deaths (including deaths of unknown cause), nonfatal myocardial infarction, nonfatal ischemic stroke, and nonfatal hemorrhagic stroke.

APTC Arterial Thromboembolic Events during the First Treatment Year: Studies FVF2598g and FVF2587g

Type of Adverse Event	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Pooled Ranibizumab 0.5 mg N=379
TOTAL [a]	2 (0.8%)	3 (1.3%)	5 (2.1%)	3 (2.1%)	3 (2.2%)	6 (4.3%)	11 (2.9%)
Vascular deaths	0	1 (0.4%)	1 (0.4%)	1 (0.7%)	1 (0.7%)	2 (1.4%)	3 (0.8%)
Nonfatal myocardial infarction	1 (0.4%)	1 (0.4%)	1 (0.4%)	1 (0.7%)	1 (0.7%)	3 (2.1%)	4 (1.1%)
Nonfatal ischemic stroke	1 (0.4%)	1 (0.4%)	3 (1.3%)	1 (0.7%)	1 (0.7%)	1 (0.7%)	4 (1.1%)
Nonfatal hemorrhagic stroke	0	0	0	0	0	0	0

Note: Arterial thromboembolic events, defined according to the Antiplatelet Trialists' Collaboration classification (1994), are presented.

When applying the APTC classification to the serious adverse events, there is an overall trend in the ranibizumab 0.5-mg dose group compared to subjects in other treatment groups, but this is only a trend, the numbers are small and it does not hold up for the 24 month data.

Human Carcinogenicity
No studies have been conducted.

Special Safety Studies
Safety analysis was based on an evaluation of other safety parameters, as well, which included visual acuity (best corrected), intraocular pressure, ocular signs by slit lamp examination and indirect ophthalmoscopy the results of which are included throughout the safety review.

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Withdrawal Phenomena and/or Abuse Potential
Not applicable. This is not a therapeutic class with known abuse potential or apparent withdrawal potential.

Human Reproduction and Pregnancy Data
There are no adequate and well-controlled studies in pregnant women. There was no inadvertent exposure to the product in pregnant women during the development program.

Assessment of Effect on Growth
The intended population for this product is adults with age-related macular degeneration, a disease that does not exist in the pediatric age group. This application contains no pediatric data.

Overdose Experience
This product has minimal overdose potential and no studies were performed. Planned initial single doses of ranibizumab injection 1.0 mg were associated with clinically significant intraocular inflammation in 2 of 2 patients injected. With an escalating regimen of doses beginning with initial doses of ranibizumab injection 0.3 mg, doses as high as 2.0 mg were tolerated in 15 of 20 patients.

Postmarketing Experience
This product has not yet been marketed.

ADDITIONAL CLINICAL ISSUES

Dosing Regimen and Administration
The sponsor has performed adequate dose ranging studies during the drug development program. Lucentis (ranibizumab) 0.5 mg dose has been demonstrated to be safe and effective in two Phase 3 clinical trials. The dosing interval in the two pivotal Phase 3 trials was once monthly resulting in the improvement and maintenance of visual acuity and function, and for the reduction of vascular leakage and retinal edema, in patients with neovascular (wet) age-related macular degeneration.

Drug-Drug Interactions
No important drug-drug interactions have been identified.

Special Populations
The sponsor has adequately evaluated gender effects on both the safety and efficacy outcomes. Subgroup analyses did not reveal any differences in the primary efficacy endpoint between males

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and females. The safety profiles seen in males and females, including the types and rates of adverse events, are similar.

Trials for this indication were conducted in a population that was overwhelmingly elderly and Caucasian. This is reflective of the population in which age-related macular degeneration occurs and does not reflect a problem with study enrollment.

Pediatrics
The applicant requested a waiver of the pediatric study requirements for the original Biologics License Application. The waiver was requested because the disease under study age-related macular degeneration does not occur in the pediatric age group.

Advisory Committee Meeting
Not applicable. No Advisory Committee Meeting will be held regarding this application.

Literature Review
The medical reviewer conducted a PubMed electronic literature search to supplement the submitted review of the relevant literature. There was no significant new information found in the published literature.

Postmarketing Risk Management Plan
No postmarketing risk management plan has been submitted.

Other Relevant Materials
Comments received from DDMAC and the Office of Drug Safety have been incorporated in the labeling review as appropriate.

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_____ § 552(b)(5) Deliberative Process

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OVERALL ASSESSMENT

Conclusions

The submitted studies in BLA 125156 are sufficient to establish efficacy for the use of ranibizumab 0.5 mg injection in the treatment of the neovascular age-related macular degeneration. The phase 3 studies demonstrate replicative results in the ability of ranibizumab to stabilize and prevent vision loss in patients with neovascular macular degeneration when give intravitreally every month when compared to sham and verteporfin PDT treatment. A clinically significant effective is still present if Lucentis is administered once every three months after the first four doses.

Recommendation on Regulatory Action

BLA 125156 is recommended for approval from a clinical perspective for [redacted] patients with neovascular (wet) age-related macular degeneration.

Recommendation on Postmarketing Actions

Risk Management Activity

Not applicable. No postmarketing risk management activity is recommended at this time.

Required Phase 4 Commitments

[redacted]

Wiley A. Chambers, MD
Deputy Division Director
Division of Anti-Infective and Ophthalmology Products

cc: Rhea Lloyd
William Boyd
Janice Soreth
Mark Goldberger

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Clinical Team Leader Labeling Review
(Medical Officer's Review #2)

Application Type	BLA
Submission Number	125156
Primary Reviewer	Rhea Lloyd, M.D.
Clinical Team Leader	William M. Boyd, M.D.
Letter Date	December 29, 2005
Stamp Date	December 30, 2005
Date of Labeling Submission	June 13, 2006
Date of Labeling Review	June 13, 2006
Established Name	Ranibizumab injection
Trademark	Lucentis
Therapeutic Class	Vascular endothelial growth factor (VEGF) inhibitor
Applicant	Genentech, Inc. 1 DNA Way South San Francisco, CA 94080 650-225-1558

Submitted

Submitted is revised labeling based on previous review, discussion between the applicant and the Deputy Division Director on June 12, 2006, and input from the Study Endpoints and Label Development (SEALD) Team.

In this submission, the applicant has accepted all requested changes to the package insert.

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_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Medical- 3046

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Recommendations

It is recommended that BLA 125156 be approved with the labeling revisions listed in this review.

The application supports the safety and effectiveness of Lucentis (ranibizumab injection) for the treatment of ⊏ ― ⊐ neovascular ⊏ ― ⊐ age related macular degeneration

William M. Boyd, M.D.
Clinical Team Leader

MAC 6/28/06

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CLINICAL REVIEW

Application Type	BLA
Submission Number	125156
Submission Code	Original
Letter Date	December 29, 2005
Stamp Date	December 30, 2005
PDUFA Goal Date	June 30, 2006
Reviewer Name	Rhea A. Lloyd, MD
Review Completion Date	June 21, 2006
Established Name	Ranibizumab injection
(Proposed) Trade Name	Lucentis
Therapeutic Class	Vascular endothelial growth factor (VEGF) inhibitor
Applicant	Genentech, Inc. 1 DNA Way South San Francisco, CA 94080 650-225-1558
Priority Designation	1P

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Proposed Dosing Regimen

Lucentis is to be administered as an intravitreal injection 0.5 mg (0.05 mL) once a month or once every three months after the initial — monthly injections.

Proposed Indication

[redacted]

Intended Population

Adults with neovascular (wet) age-related macular degeneration

Formulation

Ingredient	[redacted]	Reference to Standard or Specification
Ranibizumab	[redacted] Active ingredient	
α, α-trehalose dehydrate	[redacted]	
histidine HCl		Ph. Eur.
[redacted]		USP and Ph. Eur.
Polysorbate 20		NF and Ph. Eur.
Water for Injection		USP and Ph. Eur.

[redacted] Target fill volume of [redacted] per vial.

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Original BLA
Rhea A. Lloyd, MD
125156
Lucentis (ranibizumab injection)

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Original BLA
Rhea A. Lloyd, MD
125156
Lucentis (ranibizumab injection)

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

From a clinical perspective, Lucentis (ranibizumab injection) with the labeling changes listed in this review is recommended for approval for the treatment of patients with neovascular (wet) age-related macular degeneration

The applicant, Genentech, conducted two adequate and well-controlled Phase 3 studies, FVF2598g and FVF2587g which demonstrate statistical and clinical significance on the primary efficacy endpoint (i.e., the proportion of subjects who lose fewer than 15 letters in best corrected vision at 12 months compared with baseline).

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

No post marketing risk management activity is necessary.

1.2.2 Required Phase 4 Commitments

1. Develop and validate assays to detect and characterize immune responses to ranibizumab:

   A. Develop and validate a confirmatory assay capable of detecting both IgG and IgM isotype responses.

   B. Develop and validate an assay to detect neutralizing anti-ranibizumab antibodies.

   The assay methodology and validation reports will be provided by September 28, 2007.

2. To characterize further the immune response to ranibizumab, serum samples collected in studies FVF2587g, FVF2598g, FVF3192g will be assayed using the validated methods described above in Postmarketing Commitment 1.— The data obtained will be analyzed to discover and evaluate any association between immunoreactivity and dosing frequency as well as any potential impact of immunoreactivity on efficacy or safety outcomes.

   Date of submission of protocol and statistical analysis plan: February 28, 2007

   Date of submission of final study report: September —, 2008

   The need for an additional clinical study will be determined based on the results from the analysis described above.

1.2.3 Other Phase 4 Requests

There are no other Phase 4 requests.

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1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Established Name	ranibizumab injection
(Proposed) Trade Name	Lucentis 0.5 mg
Therapeutic Class	vascular endothelial growth factor (VEGF) inhibitor
Route of Administration	intravitreal injection

Age-related macular degeneration (AMD) is a common cause of severe and irreversible vision loss in older adults. AMD is clinically manifest in two distinct forms: the non-exudative (dry) or the exudative (wet) form of the disease. Though the exudative (wet) form represents approximately 10% of AMD cases, it is responsible for 80-90 % of the vision loss due the vascular leakage associated with the characteristic choroidal neovascularization. An estimated 150,000 new cases of neovascular AMD are diagnosed each year in the United States. As the median age of the population increases, it is likely that ophthalmologists will encounter increasing numbers of patients with AMD.

The etiology of the disease is such that new abnormal blood vessels proliferate from the choriocapillaris through defects in the Bruch's membrane under the retinal pigment epithelium (RPE), forming neovascular membranes. These new vessels leak serous fluid and may give rise to serous and hemorrhagic detachment of the RPE and neurosensory retina and may stimulate fibrous disciform scarring, with subsequent loss of central vision.

Neovascular AMD is characterized by CNV in the macular region. Vascular endothelial growth factor-A (VEGF-A) has been observed in surgically excised human fibrovascular lesions. VEGF-A is alternatively spliced and post-translationally cleaved to generate multiple active forms, of which at least two have been observed in excised human CNV lesions. An increase in VEGF-A expression has been noted in experimental models of CNV in rodents. In addition, transgenic mice with increased VEGF-A expression in photoreceptors or retina pigment epithelium developed neovascularization reminiscent of CNV seen in humans with neovascular AMD. These results suggest that active forms of VEGF-A are reasonable targets for therapeutic intervention in neovascular AMD.
Ranibizumab is a recombinant humanized antibody Fab fragment that neutralizes VEGF as a therapeutic intervention in neovascular AMD.

1.3.2 Efficacy

Study FVF2598g and Study FVF2587g, were designed to demonstrate the safety and efficacy of Lucentis (ranibizumab injection) in the treatment of neovascular AMD. Both study designs were prospective, multicenter, randomized, double-masked, parallel group. Study FVF2598g had an inactive control and Study FVF2587g had an approved therapy as a control.

Study FVF2598g met its primary endpoint and all of the secondary endpoints for the first treatment year. The primary endpoint was met with nearly 95% of ranibizumab-treated subjects maintaining or improving vision at 12 months, compared with 62% of sham-treated subjects ($p < 0.0001$ for each of the ranibizumab groups vs. the sham-injection group). Visual acuity results assessed at a starting test distance of 2 meters were 1-2 letters better than those assessed at a starting test distance of 4 meters. The robustness of the primary endpoint and key secondary

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endpoint results was demonstrated by the consistent results from sensitivity analyses. The treatment benefit of ranibizumab on visual acuity was also consistent across the subgroups evaluated.

Study FVF2587g met its primary efficacy objective for the first treatment year. The primary efficacy objective was met with approximately 94% of subjects treated with 0.3 mg ranibizumab and 96% of subjects treated with 0.5 mg ranibizumab maintaining or improving vision at Month 12, compared with approximately 64% of verteporfin PDT–treated subjects ($p \leq 0.0001$ for superiority for each of the ranibizumab groups vs. the verteporfin PDT group). The 1-year results demonstrated a beneficial effect of ranibizumab on visual acuity. Visual acuity results based on assessment at a starting test distance of 4 meters were 1-2 letters better than those based on assessment at a starting test distance of 2 meters. The robustness of the results of the primary efficacy endpoint was demonstrated by the consistent results from sensitivity analyses. The treatment benefit of ranibizumab on visual acuity was also consistent across the subgroups evaluated.

1.3.3 Safety

The population studied was predominantly elderly and white which is representative of the population usually affected by age-related macular degeneration. The demographics of the patient population do not reflect problems with recruitment.

Based on the population studied, there does not appear to be any difference in Lucentis' effect based on age, race, ethnicity or iris color.

The most common adverse events identified are conjunctival hemorrhage, eye pain, increased intraocular pressure, retinal disorder and vitreous floaters. These adverse events are often associated with intravitreal injections.

1.3.4 Dosing Regimen and Administration

The sponsor has performed some dose ranging and dose frequency studies of Lucentis (ranibizumab injection). Lucentis (ranibizumab injection) has been proven safe and effective when administered as an intravitreal injection 0.5 mg/0.05 mL once monthly. This dosing regimen achieved and sustained a statistically significant difference in the proportion of patients who lost 15 letters of vision compared to baseline relative to the control group.

The sponsor also performed a Phase 3 trial, Study FVF3192g in which Lucentis (ranibizumab injection) was administered as an intravitreal injection 0.5 mg/0.05 mL once monthly for 3 months and then every three months. The 12-month results show that Lucentis achieved statistical significance in the primary efficacy endpoint. Study FVF3192g is reviewed in more detail in another review.

1.3.5 Drug-Drug Interactions

In Study FVF2587g, Lucentis (ranibizumab injection) was dosed with (separated by 1 week) verteporfin PDT. No drug-drug interaction analyses were performed.

1.3.6 Special Populations

There were no statistically significant differences in demographic data, diagnoses, or baseline lesion characteristics between treatment groups within each study.

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Subgroup analyses did not reveal any differences in the primary efficacy endpoint with respect to age, sex, baseline visual acuity, CNV lesion type, lesion size, or prior laser photocoagulation. The safety profile was also similar in each of these groups.

The population studied for this indication was predominantly elderly and white, reflective of the population most affected by this disease. The number of patients outside of this demographic group was too small to draw any definitive conclusion regarding the safety and efficacy. There do not appear to have been any race or ethnicity effects.

No pediatric trials were conducted for this drug. Age-related macular degeneration is a disease seen only in adults.

The demographics of the patients enrolled in the trial during the development program for this product are representative of the targeted population. There is no additional data need from other populations.

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2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Established Name	ranibizumab injection
(Proposed) Trade Name	Lucentis 0.5 mg
Therapeutic Class	vascular endothelial growth factor (VEGF) inhibitor
Route of Administration	intravitreal injection
Chemical Class	New molecular entity

Proposed Indication

→ adults with neovascular (wet) age-related macular degeneration

Formulation

Ingredients	Amount per [redacted]	Function	Reference to Standard or Specification
Ranibizumab	[redacted]	Active ingredient	
α, α-trehalose dehydrate	[redacted]		Ph. Eur.
histidine HCl			
[redacted]			USP and Ph. Eur.
Polysorbate 20			NF and Ph. Eur.
Water for Injection			USP and Ph. Eur.

[a] Target fill volume of [redacted] per vial.

The release and shelf-life specifications for the Certificate of Analysis (C of A) testing of Lucentis Product are presented above. Shelf-life criteria for tests that are part of the stability program are only listed where they differ from the release criteria. Otherwise, the shelf-life criteria are identical to the release criteria. All release and shelf-life testing for the Lucentis Product is performed at Novartis Pharma Stein AG.

Genentech intends to use a life-cycle approach for setting ranibizumab specifications. This life-cycle approach will use interim acceptance criteria based upon the limited data available at the time of submission. Since campaign-to-campaign variation can be larger than the variation within a campaign, Genentech proposes a post-approval commitment for re-evaluating the interim acceptance criteria after three commercial post-approval campaigns (consisting of a minimum of [redacted] additional lots). The re evaluation is expected to take place within two years after approval, but will ultimately depend on the currently unknown manufacturing schedule for ranibizumab Drug Substance.

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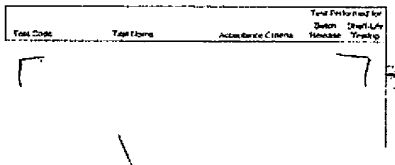
Lucentis Drug Product Release and Shelf-Life Specifications.



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Lucentis (ranibizumab injection) is a new molecular entity and is not currently marketed in the United States nor has it been marketed or withdrawn from the market in any other country.

2.2 Currently Available Treatment for Indications

There are currently two approved drug products for the treatment of age related macular degeneration – Visudyne (verteporfin for injection) and Macugen (pegaptanib sodium injection).

Visudyne was approved under NDA 21-119 on April 12, 2000, for the treatment of patients with predominantly classic subfoveal choroidal neovascularization due to age-related macular degeneration.

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Macugen was approved under NDA 21-756 on December 17, 2004, for the treatment of neovascular (wet) age-related macular degeneration.

2.3 Availability of Proposed Active Ingredient in the United States

Ranibizumab is a new molecular entity and has not been marketed in the United States.

2.4 Important Issues With Pharmacologically Related Products

There have been no additional safety concerns raised with pharmacologically related products other than those discussed within this review.

2.5 Presubmission Regulatory Activity

Ranibizumab was evaluated in six clinical studies in neovascular AMD: two Phase I studies (FVF2425g and FVF1770g), two Phase I/II studies (FVF2428g and FVF2128g), and two Phase 3 studies (FVF2598g and FVF2587g).

On October 6, 1999, Genentech submitted the Investigational New Drug application (IND) for ranibizumab. Study FVF1770g was the first clinical trial performed to evaluate the safety, tolerability, pharmacokinetics, and activity of a single-dose intravitreal injection of ranibizumab. Study FVF2128g was a dose escalation study evaluating the safety, tolerability, pharmacokinetics, and activity of multidose intravitreal injections of ranibizumab. Study FVF2425g evaluated the safety, tolerability and pharmacokinetics of escalating multiple-dose intravitreal injections of ranibizumab. Study FVF2428g evaluated the safety, tolerability and efficacy of multiple-dose intravitreal injections of ranibizumab in combination with verteporfin photodynamic therapy (PDT).

A Type C Meeting was held on February 2, 2002, in which Genentech received FDA guidance on the requirements for a clinical development program to support the licensure of ranibizumab. In addition, the Agency informed Genentech that reproductive/developmental toxicology studies for bevacizumab (the full-length antibody counterpart of ranibizumab) could be cross-referenced in the Ranibizumab Biologics License Application (BLA) in lieu of conducting separate reproductive/developmental toxicology studies with ranibizumab.

On October 31, 2002 an End-of-Phase 2 Meeting was held in which Genentech presented its plans for the Phase 3 clinical program in AMD. The sponsor incorporated many, but not all of FDA recommendations into the Phase 3 protocols, including the testing of two ranibizumab dose groups (0.3 mg and 0.5 mg) in addition to a control. The most notable differences included the use of 2 meter testing instead of 4 meter testing and the use of sham injections. The Agency agreed that the BLA could be filed and reviewed based on the 1-year safety and efficacy data from each Phase 3 study; though these studies would remain masked and controlled for 2 years.

Study FVF2598g was initiated March 19, 2003. Study FVF2587g was initiated May 20, 2003. On September 21, 2005, Genentech discussed with the FDA the clinical portions of the BLA at a pre-BLA teleconference. The majority of ranibizumab studies have been sponsored by

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Genentech in the United States, with the exception of Study FVF2587g, which was co-sponsored by Novartis and included sites outside of the United States, and Studies CRFB002B2201 and CRFB002A1201, which are Novartis-sponsored trials. See table in section 4.2 for a complete list of studies..

2.6 Other Relevant Background Information

There is no other relevant background information.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

The application is approvable from a CMC perspective (see Product Review).

3.2 Animal Pharmacology/Toxicology

There were no significant findings in the pharmacology/toxicology reviews which would affect the clinical outcome.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

This review is based on the results of the applicant supported trials for AMD conducted under BBIND —. Phase 3 safety and efficacy trials were submitted to support the indication currently being sought by the applicant. In addition, the results of four phase 1/2 dose ranging and safety trials were also submitted.

This NDA was submitted in electronic format as a hybrid CTD (i.e., CTD structure with PDF tables of contents), according to ICH and FDA guidelines for electronic submissions.

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4.2 Tables of Clinical Studies

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Study	Phase	Design (Sites)	Population	Control	No. of Enrolled Subjects	Treatment Frequency and Duration	Ranibizumab	[illegible]
PIVOTAL PHASE 3 TRIALS								
FVF2587g [illegible]	3	Randomized, double-masked, double-sham,[a] active treatment-controlled (US, Europe, Australia)	Subjects with predominantly classic subfoveal neovascular AMD	Verteporfin PDT (+sham injection)	423	Intravitreal injection q month, max. 24 injxns over 2 yrs, or verteporfin PDT q3mos as needed	0.3 mg (n=140), 0.5 mg (n=140), sham injection (n=143)	Ongoing[b]
FVF2598g [illegible]	3	Randomized, double-masked, sham-controlled (US)	Subjects with minimally classic or occult subfoveal neovascular AMD	Sham injection	716	Intravitreal injection q mo., max. 24 injxns over 2 years	0.3 mg (n=238), 0.5 mg (n=240), sham injection (n-238)	Ongoing[b]
ADDITIONAL PHASE 3 TRIALS								
FVF3192g [illegible]	3b	Randomized, double-masked, sham-controlled (US)	Subjects with recurrent subfoveal CNV with or without classic CNV secondary to AMD	Sham injection	184	Intravitreal injection q month for 3 doses (Day 0, Month 1, Month 2) followed by doses q 3 months (Mos. 5, 8, 11, 14,	0.3 mg 0.5 mg sham injection (Target: 61-62 subjects per group)	Ongoing

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Study	Phase	Design (Sites)	Population	Control	No. of Enrolled Subjects	Treatment Frequency and Duration	Ranibizumab Dose(s)	Status
						17, 20 and 23)		
FVF2508g	Extension	Extension (US)	Subjects with neovascular AMD who completed a Genentech Phase 1/2 ranibizumab study	None	70	Intravitreal injections every 28 days (± 5 days) through October 2006 or until 30 days after product launch	0.5 mg (n=66)	Ongoing
FVF3442g [redacted]	Extension	Extension open-label (US)	Subjects with subfoveal CNV secondary to AMD who completed a Genentech ranibizumab study	Ranibizumab naïve	Target 600	Intravitreal injections q 30 days for up to 24 months or until 30 days after product launch	0.5 mg (Target: 600 subjects)	Ongoing

a The active ranibizumab groups also received sham PDT with saline infusions, and the verteporfin PDT group received sham intravitreal injections.
b Enrollment has been completed; the study is ongoing.
c Excludes 5 subjects in Study FVF2128g and 3 subjects in Study FVF2425g who were enrolled but discontinued from the study before Day 0.
d Standard of care as determined by the treating physician and/or investigator.
e Novartis sponsored study.

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Study	Phase	Design (Sites)	Population	Control	No. of Enrolled Subjects	Treatment Frequency and Duration	Ranibizumab Dose(s)	Status
PHASE 1 / 2 DOSE RANGING TRIALS								
FVF2425g	1	Randomized, open-label, multiple-dose escalating regimens (US)	Subjects with neovascular AMD	None	29[c]	Intravitreal injections at 2- or 4-week intervals; max. of 5, 7 or 9 total injections over 16 weeks	0.3 mg to 1.0 mg escalating regimen with 7 total injxns (n=9); 0.3mg to 2.0 mg escalating regimen with 9 total injxns (n=10); 0.3 mg to 2.0 mg escalating regimen with 5 total injxns (n=10)	Completed
FVF2128g	1/2	Randomized, open-label, dose-escalation (US)	subjects with classic neovascular AMD	Usual care[d]	64[e]	Intravitreal injections q 4 weeks, maximum of 8 total injections over 28 weeks, or usual care with crossover to ranibizumab treatment after 14 weeks	0.3 mg (n=25), 0.3 mg initial dose escalated to 0.5 mg for subsequent doses 9n=28), usual care (n=11)	Completed
FVF1770g	1	Open-label, single-dose escalation (US)	Subjects with neovascular AMD	None	27	Single intravitreal injection	0.05 mg (n=6), 0.15 mg (n=6), 0.30 mg (n=6), 0.50 mg (n=7), 1.0 mg (n=2)	Completed

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Study	Phase	Design (Sites)	Population	Control	No. of Enrolled Subjects	Treatment Frequency and Duration	Ranibizumab Dose(s)	Status
FVF2438g C-3	1/2	Randomized, single-masked, sham-controlled, combination treatment (US)	Subjects with predominantly classic neovascular AMD	Verteporfin PDT (+sham injection)	162	Intravitreal injection q month, max. 24 injcns over 2 years, in combination with verteporfin PDT q3mos, as needed	0.5 mg (n=106), sham injection (n=56)	Ongoing[3]
NOVARTIS SPONSORED TRIALS								
CRFB002A1201[1]	1/2	Open-label (Japan)	Subjects with subfoveal CNV secondary to AMD	None	Target 84	intravitreal injections every month	0.3 mg 0.5 mg (Target: 42 subjects per group)	Ongoing
CRFB002B2201[4]	2	Open-label (Europe)	Subjects with occult or predominantly classic subfoveal CNV secondary to AMD	Verteporfin PDT	32	Intravitreal injections every month in combination with verteporfin PDT	0.5 mg (n=30)	Ongoing

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4.3 Review Strategy

This review evaluates the results of two Phase 3 trials submitted by the applicant. Each individual study was evaluated in depth to determine if the data supported the primary efficacy endpoint. The integrated safety and efficacy database was finally evaluated to determine the overall risk/benefit profile for this drug product.

The submitted clinical study reports, clinical protocols and literature reports related to trials FVF2598g and FVF2587g were reviewed. The application is in electronic format as a hybrid CTD (i.e., CTD structure with PDF tables of contents), according to ICH and FDA guidelines for electronic submissions.

4.4 Data Quality and Integrity

There is no evidence that Phase 3 studies reviewed in this BLA were not conducted in accordance with acceptable clinical ethical standards.

There were no new Division of Scientific Investigations (DSI) audits completed by the time of this review. The case report forms for the three studies were provided by Genentech, and these were reviewed for completeness and quality.

Several investigators who participated in Study FVF2598g and FVF2587g were inspected by DSI within the past 24 months. [redacted], was inspected in August 2004 and given a final classification of VAI. [redacted] was inspected in March 2005 and given a final classification of NAI.

4.5 Compliance ~~with~~ Good Clinical Practices

The studies were conducted in accordance with the International Conference of Harmonization E6 Guidelines for Good Clinical Practice (GCPs), the Declaration of Helsinki and in compliance with relevant local and national regulations for informed consent and protection of subject rights in the country of conduct.

Before initiation of the study, the original protocol, all protocol amendments, the informed consent documents and all supportive information were reviewed and approved by the appropriate ethics committees (EC) or institutional review boards (IRB) for each of the centers involved in the ~~study~~. The studies began only after receiving written approval from each EC/IRB.

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4.6 Financial Disclosures

The applicant has adequately disclosed financial arrangements with clinical investigators as recommended in the FDA guidance for industry on *Financial Disclosure by Clinical Investigators*.

There is no evidence suggesting problems with the integrity of the submitted data.

5 CLINICAL PHARMACOLOGY

Pharmacokinetic and pharmacodynamic data for ranibizumab are available from six clinical studies, in which ranibizumab was administered either as a single agent or in combination with verteporfin PDT to subjects with neovascular AMD.

5.1 Pharmacokinetics

Ranibizumab is administered intravitreally for the treatment of neovascular AMD and subsequently absorbed into the systemic circulation. Attempts were made to measure systemic pharmacokinetics from serum samples. Elimination of ranibizumab from systemic circulation is believed to be absorption rate limited based on nonclinical pharmacokinetic data. In the noncompartmental pharmacokinetic analysis of serum concentration data from 10 subjects in the Phase I study FVF1770g, ranibizumab serum concentration versus time profiles were observed to decline monoexponentially and ranibizumab area under the concentration–time curve (AUC) increased in a dose-proportional manner, which suggested linear pharmacokinetics over the dose range studied. Results from these 10 subjects also indicated that ranibizumab serum concentrations following a single intravitreal ranibizumab dose of 0.3–1.0 mg/eye were lower than the concentration range of ranibizumab expected to reduce VEGF-induced endothelial cell proliferation by 50% (IC_{50}); 0.23– 0.56 nM, which is equivalent to 11–27 ng/mL, based on a molecular mass of 48 kDa for ranibizumab.

A population pharmacokinetic analysis (Study 05-1181) was conducted to summarize data obtained from five ranibizumab clinical studies: four studies in which ranibizumab was used as a single agent (Studies FVF1770g, FVF2128g, FVF2425g, and FVF2598g) and one study in which ranibizumab was administered to subjects concomitantly with verteporfin PDT (Study FVF2428g). This analysis included a total of 675 measurable ranibizumab samples from 228 subjects who received doses of ranibizumab, ranging from 0.05 to 2.0 mg/eye, either as a single dose or in a multiple-dose regimen at a frequency ranging from every 2 weeks to every month. In all studies, ranibizumab was administered intravitreally as a bolus to one study eye. Based on the final model, several covariates were correlated with population pharmacokinetic parameter estimates. Serum creatinine clearance (CrCL) was found to be the most significant covariate for apparent systemic clearance (CL/F) of ranibizumab. However, when compared with the large intersubject variability of CL/F, the effect of CrCL on CL/F was determined to have no clinical significance. Verteporfin PDT was found to decrease the elimination rate of ranibizumab from the eye. Although this finding is consistent with expected anatomical changes of a lesion following verteporfin PDT, it has no effect on ranibizumab systemic exposure. For a typical

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subject, the CL/*F* was 23.8 L/day, the apparent volume of the central compartment was 2.97 L, and the elimination rate of ranibizumab was 0.0800 day $^{-1}$. In summary, there is no covariate that affects the systemic exposure of ranibizumab with clinical significance.

5.2 Pharmacodynamics

In vitro, maximal inhibition of rhVEGF-induced proliferation of human umblical vein endothelial cells was observed at ranibizumab concentrations of approximately 1.29 nM (which is equivalent to 62 ng/mL assuming a molecular weight for ranibizumab of 48 kDa). The population pharmacokinetic model for predicted minimum vitreal ranibizumab concentration with a monthly dosing regimen of 0.3-mg ranibizumab is 12 µg/mL (range, 2.3–41 µg/mL) and above the concentrations necessary to inhibit VEGF activity.

In vivo, neovascular AMD may be associated with foveal retinal thickening as assessed by optical coherence tomography (OCT) and leakage from CNV as assessed by fluoresceinangiography.

Foveal retinal thickness was assessed using OCT in a subset of subjects in Study FVF2598g (46 of 716 subjects with a baseline evaluation) and Study FVF2587g (53 of 423 subjects with a baseline evaluation). In subjects treated with ranibizumab (pooled data from the 0.3-mg and 0.5-mg groups), on average, foveal retinal thickness decreased by Day 7 and continued to decrease through Month 12. On Day 7, the average change in Study FVF2598g was − 84 µm for ranibizumab compared with − 23 µm for the sham-injection control ($p = 0.099$). In Study FVF2587g, the average change was − 105 µm for ranibizumab compared with − 26 µm for verteporfin PDT ($p = 0.008$). At Month 12, the average change in Study FVF2598g was − 123 µm for ranibizumab compared with − 15 µm for sham-injection control ($p = 0.009$). In Study FVF2587g, the average change was − 190 µm for ranibizumab compared with − 87 µm for verteporfin PDT ($p = 0.0004$).

In subjects treated with monthly injections of ranibizumab in Studies FVF2598g and FVF2587g, the area of leakage from CNV as assessed by fluorescein angiography decreased, on average, by Month 3. In Study FVF2598g, the average change was approximately − 1.0 disc areas (DA) for subjects in both the 0.3-mg and 0.5-mg ranibizumab groups versus + 0.8 DA for those in the sham-injection control group ($p < 0.0001$). In Study FVF2587g, it was approximately − 1.3 DA for subjects in both the 0.3-mg and 0.5-mg ranibizumab groups compared with + 0.2 DA for subjects in the verteporfin PDT group ($p < 0.0001$). However, it is known that the area of leakage from CNV does not correlate with visual function.

5.3 Exposure-Response Relationships

The retina is the site of disease in neovascular AMD. Therefore, systemic ranibizumab concentrations after intravitreal administration are not expected to correlate with efficacy.

Ranibizumab systemic pharmacokinetics were characterized throughout the clinical program, including a population pharmacokinetic analysis.

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6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The proposed indication is [redacted] in patients with neovascular (wet) age-related macular degeneration.

6.1.1 Methods

The submitted Phase 3 studies (FVF2598g and FVF2587g) were reviewed independently to determine if the results of each trial demonstrated efficacy for the primary efficacy endpoint. The primary efficacy endpoint for each trial was a responder analysis of the proportion of patients who lost fewer than 15 letters of visual acuity from baseline (doubling of the visual angle) at 54 weeks. This analysis was done for two populations which represent different ranges of data to evaluate the robustness of the results; an all randomized patient population with last-observation-carried-forward (LOCF) and the per protocol population with observed cases only.

6.1.2 General Discussion of Endpoints

Visual acuity is a well-established and validated measure of visual function that has been used for decades in ophthalmology research. The methods used in this study follow methods used in clinical trials of both diabetic macular edema and AMD.

Reviewer's Comment:

In choroidal neovascularization secondary to age-related macular degeneration, a recommended endpoint is a statistically significant difference between groups in the percentage of patients with a halving of the visual angle (15 letters or more on an Early Treatment Diabetic Retinopathy visual acuity chart measured at 4 meters)

6.1.3 Study Design

6.1.3.1 Study FVF2598g

Title: A Phase 3, Multicenter, Randomized, Double-Masked, Sham Injection-Controlled Study of the Efficacy and Safety of rhuFab V2 (Ranibizumab) in Subjects with Minimally Classic or Occult Subfoveal Neovascular Age-Related Macular Degeneration.

Objectives: Primary:

- To evaluate the efficacy of intravitreal injections of ranibizumab (0.3 mg and 0.5mg) administered monthly in preventing vision loss, as measured by the proportion of subjects who lost fewer than 15 letters in visual acuity at 12 months compared with baseline
- To evaluate the safety and tolerability of intravitreal injections of ranibizumab administered monthly

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Secondary:

- To evaluate the efficacy of monthly intravitreal injections of ranibizumab in preventing vision loss as measured by the following:
  - The mean change from baseline in visual acuity over time up to 12 months
  - The proportion of subjects who gained at least 15 letters in visual acuity at 12 months compared with baseline
  - The proportion of subjects with a visual acuity Snellen equivalent of 20/200 or worse at 12 months
- To investigate the efficacy of monthly intravitreal injections of ranibizumab on vision-related functioning and well being assessed during a period of 12 months, as measured by the National Eye Institute (NEI) Visual Function Questionnaire-25 (VFQ-25)
- To evaluate the efficacy of monthly intravitreal injections of ranibizumab on the size of CNV and amount of leakage from CNV at 12 months, as assessed by fluorescein angiography

Study Design: This is a prospective, multicenter (96 sites), randomized, double-masked, sham injection-controlled trial of intravitreally administered ranibizumab.

Test Drug Schedule:

Eligible subjects were randomized in a 1:1:1 ratio to receive 0.5 mg ranibizumab, 0.3 mg ranibizumab or sham injection. Subjects received a ranibizumab or sham injection monthly (30 ± 7 days) for up to a maximum of 13 injections during the first treatment year (Day 0 to Month 12). The second treatment year of the study is ongoing. Subjects have continued to receive monthly ranibizumab or sham injections during the second treatment year with the last injection administered at Month 23. Subjects will have a final safety visit at Month 24.

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Study Design

This was a Phase 3, multicenter, randomized, double-masked, sham injection–controlled study of intravitreally administered ranibizumab. Approximately 720 subjects with primary or recurrent subfoveal CNV secondary to AMD who have minimally classic or occult lesions were enrolled.

Consented subjects participated in a screening period lasting up to 28 days to determine eligibility. Fluorescein angiograms were sent to a central reading center to determine CNV classification for study eligibility. Eligible subjects were randomized in a 1:1:1 ratio to receive 0.5 mg of ranibizumab, 0.3 mg of ranibizumab, or a sham injection. Randomization was stratified by the visual acuity score at Day 0 (≤ 54 letters [approximately worse than 20/80] vs. ≥ 55 letters [approximately 20/80 or better] based on the ETDRS chart and assessment at a starting distance of 2 meters), by type of CNV (minimally classic CNV vs. occult CNV without classic component), and by study center. A dynamic randomization scheme was used to obtain approximately a 1:1:1 ratio among the treatment groups. Subjects received a ranibizumab or sham injection monthly for 23 months of treatment (24 injections). Only one eye was chosen as the "study eye." Only the study eye received intravitreal injections of ranibizumab or a sham injection.

After careful review of data, including 12-month data from this ongoing study, Genentech believed that it was in the best interest of subjects randomized to the sham-injection group to

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cross over to receive ranibizumab. Specifically, subjects randomized to the sham-injection group who had not completed their Month 23 visit (last possible injection visit) would cross over to receive monthly injections of 0.5 mg ranibizumab for the remainder of the treatment period upon approval of the current protocol amendment (dated 9 September 2005) and Informed Consent Form by the site Institutional Review Board (IRB). Subjects who had discontinued the study and/or treatment were excluded from the crossover.

A minimum of two investigators per study site was required to fulfill the masking requirements of this study. At least one investigator was designated the evaluating physician, who was masked to the treatment assignment and conducted all ocular assessments. At least one other investigator was designated the injecting physician, who was unmasked to the treatment assignment and performed the ranibizumab/sham preparation, but was masked to study drug dose (0.3 mg vs. 0.5 mg of ranibizumab). Once the designated roles were determined, the roles could not be switched at any time during the conduct of the study. The injecting physicians (and designated unmasked assistants, if needed) were not permitted to be involved in the conduct of the study in any other manner and could not communicate with any other personnel or subjects regarding the treatment assignment.

Subjects had scheduled monthly visits throughout the study for the evaluation of safety and efficacy. Subjects had either the first injection of intravitreal ranibizumab or a sham injection by the injecting physician on Day 0 and underwent safety and eye assessments by the evaluating physician (e.g., indirect ophthalmoscopy and slit lamp examination) 7 days after the first injection. At subsequent visits (every month), the subject had a safety evaluation by the evaluating physician prior to study drug injection. The monthly visits were scheduled every 30 days relative to Day 0. Subjects were contacted by the site personnel 2 days after each injection to elicit reports of any decrease in vision, eye pain, unusual redness, or any other new ocular symptoms in the study eye. Subjects were also asked whether they had taken the prescribed self-administered post-injection antimicrobials. Subjects will have a final safety visit at Month 24.

Study Treatment
Ranibizumab was administered in a multiple-dose regimen of either 0.3 mg or 0.5 mg of ranibizumab every month (Day 0-Month 23) for a total of 24 injections. Sham injections were given monthly or until the subjects crossed over, and then 0.5 mg ranibizumab was to be administered monthly during the crossover period for the remainder of the treatment period. The cross over was to be implemented upon approval of the current protocol amendment and Informed Consent Form by the site's IRB. If verteporfin PDT had been given in the study eye within the last 28 days, then the ranibizumab/sham injection was held.

Study Population
Inclusion Criteria

Subjects had to meet the following inclusion criteria to be eligible for study entry:

1. Age ≥ 50 years
2. Active primary or recurrent subfoveal CNV lesions secondary to AMD in the study eye, as defined in the following table.

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Table 6.1.3.1-2 - Definitions of Terms Pertaining to AMD Inclusion Criteria

Term	Definition
Active	Any of the following: 1) Exhibiting a ≥ 10% increase in lesion size, as determined by comparing a fluorescein angiogram performed within 1 month preceding Day 0, inclusive, with a fluorescein angiogram performed within 6 months preceding Day 0, inclusive; or 2) Resulting in a visual-acuity loss of ≥ 1 Snellen line (or equivalent) and occurring at any time within the prior 6 months; or 3) Subretinal hemorrhage associated with CNV within 1 month preceding Day 0
Primary	Newly diagnosed and previously untreated
Recurrent	Previously diagnosed and regressed but currently presenting with a new, active component
Subfoveal	Including the center of the fovea within the boundaries of the CNV
CNV lesion	A contiguous area of abnormal tissue in the macula that encompasses angiographically documented CNV with possible additional components of subretinal hemorrhage, blocked fluorescence not from hemorrhage, serous detachment of the retinal pigment epithelium, and fibrosis
AMD	Clinical and/or angiographic signs consistent with AMD (e.g., drusen, retinal pigment epithelial changes, choroidal neovascularization) with no other likely etiologic explanations for the degenerative changes

3. Lesions with occult CNV or with some classic CNV component were permissible. However, if classic CNV (well-demarcated hyperfluorescence boundaries in the early phase of the fluorescein angiogram) was present, the area of classic CNV had to be < 50% of the total lesion size.
4. Total area of CNV (including both classic and occult components) encompassed within the lesion ≥ 50% of the total lesion area.
5. Total lesion area ≤ 12 disc areas (DA) in size
6. Best corrected visual acuity, using ETDRS charts, of 20/40 to 20/320 (Snellen equivalent) in the study eye

   Only one eye was assessed in the study. If both eyes were eligible, the one with the better visual acuity was selected for treatment and study unless, based on medical reasons, the investigator deemed the other eye the more appropriate candidate for treatment and study.

Exclusion Criteria

Subjects who met any of the following exclusion criteria were ineligible for study entry:

a. **Prior/Concomitant Treatment**
   1. Prior treatment with verteporfin, external-beam radiation therapy, or transpupillary thermotherapy (TTT) in the study eye
   2. Treatment with verteporfin in the non-study (fellow) eye less than 7 days preceding Day 0
   3. Previous participation in a clinical trial (for either eye) involving anti-angiogenic drugs (Pegaptanib, Ranibizumab, anecortave acetate, protein kinase C inhibitors, etc.)

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4. Previous intravitreal drug delivery (e.g., intravitreal corticosteroid injection or device implantation) in the study eye
5. Previous subfoveal focal laser photocoagulation in the study eye
6. Laser photocoagulation (juxtafoveal or extrafoveal) in the study eye within 1 month preceding Day 0
7. History of vitrectomy surgery in the study eye
8. History of submacular surgery or other surgical intervention for AMD in the study eye
9. Previous participation in any studies of investigational drugs within 1 month preceding Day 0 (excluding vitamins and minerals)

b. **Lesion Characteristics**
1. Subretinal hemorrhage in the study eye that involved the center of the fovea, if the size of the hemorrhage was either ≥ 50% of the total lesion area or ≥ 1 DA in size.
2. Subfoveal fibrosis or atrophy in the study eye
3. CNV in either eye due to other causes, such as ocular histoplasmosis, trauma or pathologic myopia
4. Retinal pigment epithelial tear that involved the macula in the study eye

c. **Concurrent Ocular Conditions**
1. Any concurrent intraocular condition in the study eye (e.g., cataract or diabetic retinopathy) that, in the opinion of the investigator, either
   i. Required medical or surgical intervention during the 24-month study period to prevent or treat visual loss that may have resulted from that condition, or
   ii. If allowed to progress untreated, could likely have contributed to loss of at least 2 Snellen equivalent lines of best corrected visual acuity over the 24-month study period
2. Active intraocular inflammation (grade trace or above) in the study eye
3. Current vitreous hemorrhage in the study eye
4. History of rhegmatogenous retinal detachment or macular hole (Stage 3 or 4) in the study eye
5. History of idiopathic or autoimmune-associated uveitis in either eye
6. Infectious conjunctivitis, keratitis, scleritis, or endophthalmitis in either eye
7. Aphakia or absence of the posterior capsule in the study eye
   i. Previous violation of the posterior capsule in the study eye was also excluded unless it occurred as a result of yttrium aluminum garnet (YAG) laser posterior capsulotomy in association with prior posterior chamber intraocular lens implantation.
8. Spherical equivalent of the refractive error in the study eye that demonstrated more than -8 diopters of myopia
9. Intraocular surgery (including cataract surgery) in the study eye within 2 months preceding Day 0
10. Uncontrolled glaucoma in the study eye (defined as intraocular pressure [IOP] ≥ 30 mmHg despite treatment with anti-glaucoma medication)
11. History of glaucoma filtering surgery in the study eye
12. History of corneal transplant in the study eye

d. **Concurrent Systemic Conditions**

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1. Pre-menopausal women not using adequate contraception
    i. The following were considered effective means of contraception: surgical sterilization; use of oral contraceptives; barrier contraception with either a condom or diaphragm in conjunction with spermicidal gel; an intrauterine device; or contraceptive hormone implant or patch
2. History of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicated the use of an investigational drug or that might have affected interpretation of the results of the study or rendered the subject at high risk for treatment complications
3. Current treatment for active systemic infection

e. **Other**

1. History of allergy to fluorescein, not amenable to treatment
2. Inability to obtain fundus photographs or fluorescein angiograms of sufficient quality to be analyzed and graded by the central reading center
3. Inability to comply with study or follow-up procedures

Outcome Measures

Primary Efficacy Outcome Measures

The proportion of subjects who lost fewer than 15 letters (approximately 3 lines) in the best corrected visual acuity score at 12 months compared with baseline, based on the ETDRS visual acuity chart and assessment at a starting distance of 2 meters.

Secondary Efficacy Outcome Measures – For the First Treatment Year

- Proportion of subjects who lost fewer than 15 letters in the best corrected visual acuity score at 12 months compared with baseline, based on assessment at a starting test distance of 4 meters
- Mean change from baseline in the best corrected visual acuity score over time up to 12 months
- Proportion of subjects who gained at least 15 letters in the best corrected visual acuity score at 12 months compared with baseline
- Proportion of subjects with a visual acuity Snellen equivalent of 20/200 or worse at 12 months (legal blindness is defined as both eyes with 20/200 or worse)
- Mean change from baseline in the VFQ-25 near activities subscale score over time up to 12 months
- Mean change from baseline in the VFQ-25 distance activities subscale score over time up to 12 months
- Mean change from baseline in the VFQ-25 vision-specific dependency subscale score over time up to 12 months
- Mean change from baseline in the total area of CNV at 12 months (based on assessment by the central reading center)
- Mean change from baseline in the total area of leakage from CNV at 12 months (based on assessment by the central reading center)

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The secondary efficacy outcome measures for the second treatment year of the study are the following:

- Proportion of subjects who lose fewer than 15 letters in the best corrected visual acuity score at 24 months compared with baseline
- Mean change from baseline in the best corrected visual acuity score at 24 months
- Proportion of subjects who gain at least 15 letters in the best corrected visual acuity score at 24 months compared with baseline
- Proportion of subjects with a visual-acuity Snellen equivalent of 20/200 or worse at 24 months
- Proportion of subjects who lose fewer than 15 letters in the best corrected visual acuity score at 24 months compared with baseline, based on assessment at a starting test distance of 4 meters
- Mean change from baseline in the VFQ-25 near activities subscale at 24 months
- Mean change from baseline in the VFQ-25 distance activities subscale at 24 months
- Mean change from baseline in the VFQ-25 vision-specific dependency subscale at 24 months
- Mean change from baseline in the total area of CNV at 24 months (based on assessment by the central reading center)
- Mean change from baseline in the total area of leakage from CNV at 24 months (based on assessment by the central reading center)

Safety Outcome Measures

The safety outcome measures are the following:

- The incidence and severity of ocular adverse events
- The incidence and severity of non-ocular adverse events
- Changes and abnormalities in clinical laboratory parameters
- The incidence of serum antibodies to ranibizumab
- Changes in vital signs

Reviewer's Comment:

As noted in Section 2.5 regarding previous correspondence and meetings, the Agency does not agree with the sponsor's primary efficacy endpoint.

Visual acuity testing is recommended to be performed with at target distance of a minimum of 4 meters, not 2 meters, from the patient. This distance measure (4 meters) is recommended to minimize the potentially confounding influences of accommodation and patient positioning on the measurement.

For the purposes of this review the Agency will consider the primary efficacy endpoint as the proportion of subjects with a loss of fewer than 15 letters in the visual acuity score in the study eye at 12 months compared with baseline, based on assessments at a starting test distance of 4 meters, not 2 meters.

The VFQ-25 scale and its subscales have not been validated against actual activities of daily living.

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SAFETY PLAN

Following each injection (ranibizumab or sham), subjects were to remain at the clinic for at least 60 minutes (± 10 minutes). Finger counting was tested on each subject after each injection; hand motion and light perception was tested when necessary. Intraocular pressure was measured before and 60 minutes (± 10 minutes) after each injection. If there were no safety concerns in the 60 minutes (± 10 minutes) following an injection, the subject was to leave the clinic. If any concern or immediate toxicity was noted, the subject was to remain at the clinic and be treated according to the designated evaluating physician's clinical judgment.

Subjects were to return for a follow-up visit at Day 7 after the first injection. In addition, subjects were to be contacted by study site personnel 2 days (± 1 day) after each injection to elicit reports of any decrease in vision, eye pain, unusual redness, or any other new ocular symptoms in the study eye. Subjects were also asked whether they have taken the prescribed self-administered post-injection antimicrobials. If determined necessary by the evaluating physician, the subject was asked to return to the clinic as soon as possible for a safety assessment visit and was evaluated by the designated evaluating physician. Subjects were instructed to contact their designated evaluating physician at any time should they have health-related concerns.

Detailed ocular examinations, including indirect ophthalmoscopy, measurement of intraocular pressure, visual acuity testing, and slit lamp examination, was performed throughout the study by the designated evaluating physician. Routine hematology, chemistry, and urinalysis profiles were obtained for all subjects. In addition, blood samples for serum ranibizumab concentrations and antibodies to ranibizumab were obtained for all subjects.

Study drug administration was temporarily held for subjects who experience certain ocular events or infection events. Study drug administration was also held at a visit if the evaluating physician suspected that the lesion in the study eye had converted to predominantly classic CNV and verteporfin PDT treatment was being considered. In the event any subject developed an adverse event in the study eye that was considered by the designated evaluating physician to be severe in intensity, serious consideration was to be given to discontinuing the subject from study treatment. The investigator or Sponsor could request that a subject be withdrawn from treatment or from the study for safety reasons at any time.

Subjects who were discontinued from study treatment were to continue to undergo the scheduled monthly assessments. Subjects withdrawn from the study prior to completion were asked to return for an early termination evaluation 30 days (± 7 days) following their last injection/study visit for monitoring of all adverse events (serious and nonserious; ocular and non-ocular).

Preliminary findings from FVF2428g (see Section 1.7.4) suggest that administering the ranibizumab injections 7 days (± 2 days) after treatment with verteporfin PDT in the same eye might result in a decrease in visual acuity of ≥ 30 letters due to temporary intraocular inflammation (uveitis). Therefore, if verteporfin PDT treatment was required in the study eye, it was to be administered at least 28 days prior to ranibizumab/sham injections and no sooner than 21 days after ranibizumab/sham injections.

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A formal Data Monitoring Committee (DMC) was established to monitor subject safety. The DMC conducted semiannual reviews of unmasked safety data including serious adverse events, adverse events (ocular and non-ocular), deaths, clinically significant decreases in visual acuity, and results of ocular assessments.

Concomitant Therapy and Clinical Practice

Subjects who received prior treatment with verteporfin in the study eye were excluded from the study. Verteporfin therapy in the non-study eye less than 7 days prior to Day 0 was not permitted.

Subjects who are confirmed (by fluorescein angiography and written documentation) by the central reading center to have changed lesion classification from minimally classic/occult CNV to predominantly classic CNV could receive alternative therapies (e.g., verteporfin) in the study eye.

Pegaptanib sodium injection was not permitted in either eye due to the potential safety concern of concurrent treatment with two anti-VEGF agents.

Concurrent use of systemic anti-VEGF agents including treatment with intravitreal or intravenous Avastin was not permitted in either eye. Subfoveal laser photocoagulation in the study eye was not allowed prior to Day 0 or during study participation. Juxtafoveal or extrafoveal laser photocoagulation for AMD was not allowed in the study eye within 1 month preceding Day 0 and during study participation. Elective vitrectomy surgery was not allowed in the study eye during study participation. Transpupillary thermotherapy (TTT), external beam radiation therapy, submacular surgery, or other surgical intervention for AMD was not allowed in the study eye during study participation. Onset of glaucoma during study participation should be treated as clinically indicated. Cataract surgery in the study eye could be performed if clinically indicated and should occur ≥ 28 days after the last ranibizumab or sham injection; the next ranibizumab or sham injection will be held for ≥ 28 days following cataract surgery. At least one monthly injection was to be missed when cataract surgery in the study eye is performed.

Dose Holding and Treatment Discontinuation

Dose interruption and treatment discontinuation due to adverse events were determined using the criteria in the following Table. If any of the listed events occurred, the reason for dose holding was recorded on the Study Drug Administration Case Report Form (CRF) and, if applicable, on the Adverse Event CRF.

Table 6.1.3.1-3 Dose Holding and Treatment Discontinuation Criteria

Event	[redacted]
Intraocular inflammation	Dose was held if intraocular inflammation was ≥ 2+ in the study eye.
Visual acuity loss	Dose was held if there was a treatment-related decrease in best corrected visual acuity of ≥ 30 letters in the study eye compared with the last assessment of visual acuity prior to the most recent treatment.

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Intraocular pressure	Dose was held if IOP in the study eye was ≥ 30 mmHg. Treatment was permitted when IOP had been lowered to < 30 mmHg, either spontaneously or by treatment, as determined by the evaluating physician.
Vitreous hemorrhage	Dose was held if there was a ≥ 2+ vitreous hemorrhage and ≥ 30-letter decrease in visual acuity in the study eye compared with the last assessment of visual acuity prior to the onset of the vitreous hemorrhage. Treatment was permitted when the vitreous hemorrhage improved to <2+ or visual acuity score improved to a <30-letter decrease.
Sensory rhegmatogenous retinal break or detachment (including macular hole)	Dose was held if a retinal break was present in the study eye. Treatment may have been resumed ≥ 28 days after the retinal break had been successfully treated. Subjects with a rhegmatogenous retinal detachment or Stage 3 or 4 macular hole were discontinued from treatment for the duration of the study.
Subfoveal hemorrhage	Dose was if there was a subretinal hemorrhage involving the center of the fovea in the study eye, if the size of the hemorrhage was either ≥ 50% of the total lesion area or ≥ 2 DAs in size.
Local or systemic infection	Dose was held if any of the following were present: infectious conjunctivitis, infectious keratitis, infectious scleritis, or endophthalmitis in either eye, or if the subject was receiving treatment for a severe systemic infection.
Intraocular surgery	Dose was held if intraocular surgery had been performed in the study eye within the previous 28 days.

Analysis Populations

Randomized Subjects
These subjects were enrolled and randomized in the study. This population was used for summaries of demographics and study conduct and for most summaries of efficacy. Treatment group assignment for this population was as randomized (i.e., ITT).

Per Protocol Subjects
A subset of randomized subjects who were considered more compliant with the protocol. Treatment group assignment for this population was as randomized. This population was used for supportive analyses of visual acuity efficacy outcome measures at Month 12.

Safety Evaluable Subjects
Randomized subjects who received at least one treatment with study drug. Treatment group assignment for this population was defined as follows:

- Sham: subjects randomized to the sham-injection group who received a sham injection on Day 0
- 0.3 mg Ranibizumab: subjects randomized to receive 0.3 mg ranibizumab or subjects who were randomized to sham but received a 0.3 mg injection of ranibizumab on Day 0 in error
- 0.5 mg Ranibizumab: subjects randomized to receive 0.5 mg ranibizumab or subjects who were randomized to sham but received a 0.5 mg injection of ranibizumab on Day 0 in error.

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Efficacy Analyses

Comparisons of efficacy were performed between each ranibizumab dose group and the sham injection (control) group. All pairwise comparisons for treatment difference were performed using a statistical model that included only two treatment groups (active vs. control) at a time. For the primary efficacy endpoint, an adjustment was made for multiple treatment comparisons of each ranibizumab dose group with the control group. For secondary efficacy endpoints, adjustments for multiplicity of endpoints were made to manage the Type I error.

Primary Efficacy Endpoint. The proportion of subjects with fewer than 15 letters lost in best corrected visual acuity at 12 months compared with baseline, based on assessment at a starting test distance of 2 meters, was compared between each ranibizumab group and the sham control group using the Cochran $\chi 2$ test stratified by CNV classification at baseline and baseline visual acuity score. The test was performed at an overall significance level of 0.0497 after adjusting for interim analyses. The Hochberg-Bonferroni multiple comparison procedure was used to adjust for the two pairwise treatment comparisons. If the p-values for both comparisons were 0.0497, both ranibizumab groups were considered statistically significantly different from the sham control group. If the p-value for the comparison of one ranibizumab group with the sham control group was $p > 0.0497$, the other ranibizumab group was considered statistically significantly different from the control group only if the p-value for its comparison with the control group was 0.0497/2 (0.02485). Results of tests for treatment difference using the Cochran $\chi 2$ test stratified by the baseline visual acuity score and CNV classification entered into the IVRS at randomization were also provided as supportive analyses.

Reviewer's Comments:

For the purposes of this review the Agency will consider the primary efficacy endpoint as the proportion of subjects with a loss of fewer than 15 letters in the visual acuity score in the study eye at 12 months compared with baseline, based on assessments at a starting test distance of 4 meters, not 2 meters.

Determination of Sample Size

The sample size of 720 subjects with minimally classic or occult CNV will provide 95% power in the intent-to-treat (ITT) analysis to detect a statistically significant difference between one or both ranibizumab groups and the control group in the percentage of subjects with fewer than 15 letters lost at Month 12, assuming a rate of 65% in each ranibizumab group and 50% in the control group.

Interim Analyses

An independent DMC was established to monitor safety and study conduct and met approximately every 6 months to review unmasked safety summaries prepared by an external statistical coordinating center. Because the analyses involve visual acuity, which is the basis of the primary efficacy endpoint, each interim analysis conducted prior to the analysis of the primary efficacy endpoint will be allocated a Type I error of α=0.0001.

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Original BLA
Rhea A. Lloyd, MD
125156
Lucentis (ranibizumab injection)

Table 6.1.3.1-4

Study Flowchart: Screening, Treatment Phase Day 0 through Month 12, and Early Termination

| Study Period | Screen. | Treatment Period | | |

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Study Period	Screen	Treatment Phase														
	Day			Month												
	-28 to -1	0	7	±1	2	3	4	5	6	7	8	9	10	11	12	[illegible]
Assessment Window (Days)	—	—	±2	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	[illegible]
perception [k]																
Vital Signs [l]	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x
Concomitant Medications [m]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Concurrent ocular procedures		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse Events [n, o]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Follow-up contact [o]		x		x	x	x	x	x	x	x	x	x	x	x	x	

Note: Except as noted, all ocular assessments were to be performed on both eyes. For study drug treatment visits, all assessments must have been performed on the same day as study drug treatment.

a For subjects who withdraw from the study early. Performed 30 days (±7 days) following the last injection or study visit.
b Significant medical/surgical history, including chronic and ongoing conditions (e.g., trauma, cancer history, and ophthalmic history).
c VFQ-25 , SF-36 Health Survey, HUI questionnaire (selected sites only), and VAS should have been administered to the subject prior to the subject's completing any other study procedures.
d For women of childbearing potential.
e Performed pre-injection.
f Performed prior to dilating eyes.
g Also assessed at a starting distance of 4 meters after assessment at a starting distance of 2 meters.
h Laboratory evaluations included hematology, blood chemistry, and urinalysis
i Obtained pre-injection for both eyes and 60 minutes (±10 minutes) post injection for study eye only
j The measurement method used for a subject was to remain consistent throughout the study.
k Injecting physician was to perform within 15 minutes post-injection for study eye only.
l Performed post-injection
m Any prescription drugs or OTC preparations other than protocol-specified procedural medications (e.g., dilating drops, fluorescein dyes, etc.) and pre- and post-injection medications (e.g., proparacaine, antimicrobials) used by a subject within 7 days preceding Day 0.
n Adverse events were collected from Day 0 through the last study visit. Adverse events assessed by the evaluating physician as related to ranibizumab were followed, even after the subject's study participation was over, until the event resolved or the event was assessed as irreversible, chronic, or stable.
o Subjects were contacted 2 days (1 day) following treatment to elicit reports of any decreases in vision, eye pain, unusual redness, or any other new ocular symptoms in the study eye. Subjects were also asked whether they had taken the prescribed post-injection antimicrobials.

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Table 6.1.3.1-5 Subject Disposition

	[redacted]	[redacted]	[redacted]	Total N (%)
Randomized	238	238	240	716
Completed Month 12 [a]	212 (89.1%)	226 (95.0%)	226 (94.2%)	664 (92.7%)
Discontinued Treatment Prematurely	31 (13.0%)	10 (4.2%)	11 (4.6%)	52 (7.3%)
Discontinued Study prematurely	21 (8.8%)	6 (2.5%)	6 (2.5%)	33 (4.6%)
Safety Evaluable Population received study medication, as treated	236 (99.2%)	238 (100%)	239 (99.6%)	713 (99.6%)
Intent-to-treat Population ≥ 1 on therapy study visit	236 (99.2%)	238 (100%)	239 (99.6%)	713 (99.6%)
Per Protocol Population (for the analysis of 4 m BCVA at Month 12) No on-therapy study visits or protocol violation	176 (73.9%)	200 (84.0%)	196 (81.7%)	572 (79.9%)
Excluded from PP Population	62 (26.1%)	38 (11.8%)	44 (18.3%)	144 (20.1%)
Pharmacokinetic-Evaluable Population	218 (91.6%)	226 (95.0%)	225 (93.8%)	669 (93.4%)

a Defined as having a visual acuity score in the study eye at Month 12. Data from subjects who missed the Month 12 visit but stayed in the study for the second year were not counted.

Reviewer's Comments:

Overall, the study had good retention of subjects through Month 12. The sham injection group had significantly more discontinuations than either ranibizumab treatment group.

Two subjects in the sham group and one subject in the ranibizumab 0.5mg group did not receive any study treatment.

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Table 6.1.3.1-6 Major Protocol Deviations during the First Treatment Year Randomized Subjects

Deviation	[redacted]	Ranibizumab 0.5 mg (N=240)
Any deviation	55 (23.1%)	57 (23.9%)	62 (25.8%)
Re-randomized	0	0	1 (0.4%)
Dosing error: Overdose	0	1 (0.4%)	1 (0.4%)
Dosing Error: Procedure (injection) accident	0	1 (0.4%)	1 (0.4%)
Dosing Error: Sham injection performed	0	2 (0.8%)	1 (0.4%)
Treatment assignment unmasked [a]	1 (0.4%)	0	4 (1.7%)
Ineligible per protocol off-label PDT use	9 (3.8%)	0	0
Received PDT <21 days after a study drug injection			
Study eye	1 (0.4%)	0	0
Fellow eye	4 (1.7%)	9 (3.8%)	2 (0.8%)
Pre-treatment procedure not followed	5 (2.1%)	1 (0.4%)	4 (1.7%)
Dose-holding criteria not followed	1 (0.4%)	4 (1.7%)	1 (0.4%)
Visual acuity (4 m) not assessed at baseline: study eye	9 (3.8%)	9 (3.8%)	10 (4.2%)
Visual acuity (2 m) assessment incomplete: letters smaller than 20/20 not adequately tested			
Study eye	0	2 (0.8%)	3 (1.3%)
Fellow eye	24 (10.1%)	10 (4.2%)	13 (5.4%)
ETDRS chart with notation for 2-m testing was used	1 (0.4%)	3 (1.3%)	2(0.8%)
ETDRS charts switch usage (left eye chart vs. right eye chart)	0	0	1 (0.4%)
Slit lamp was performed after injection			
On Day 0	1 (0.4%)	2 (0.8%)	1 (0.4%)
At any visit other than Day 0	1 (0.4%)	2 (0.8%)	1 (0.4%)
Required a reader/translator's help for VFQ-25 and other questionnaires	1 (0.4%)	0	1 (0.4%)
Vital signs assessed pre-dose	7 (2.9%)	6 (2.5%)	9 (3.8%)
Inconsistent method for IOP measurement	11 (4.6%)	20 (8.4%)	22 (9.2%)

a Only study coordinators were unmasked for one case in the sham-injection group and two cases in the 0.5 mg group.

Reviewer's Comments:

There were slightly more protocol deviations in the ranibizumab 0.5 mg group.

The protocol deviations which occurred most frequently were an inconsistent method for IOP measurement, incomplete assessment of 2 m visual acuity in the fellow eye, and failure to assess 4m visual acuity at baseline.

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Table 6.1.3.1-7 Discontinued Subjects and Reason
Study FVF2598g

Study Site ID	[redacted]	[redacted]	[redacted]
S07438	101015	Subject's Decision	332
S08127	102010	AE - Worsening AMD	127
S08536	102014	AE - Pneumonia, COPD Exacerbation x 2	265
S08255	103006	AE - Worsening AMD	148
S08215	104010	Subject's Decision – no improvement in VA	284
S08165	106006	Physician's Decision – Intra Vit Kenalog given	236
S07439	112005	Randomized in error	93
S08082	119005	Lost to follow-up	36
S08239	121004	Subject's Decision / AE – mild iritis	158
S08235	124001	Subject's Decision – Never received treatment	1
S08130	125008	AE - 30 letter loss of vision – Worsened AMD	50
S08246	131011	Subject's Decision	239
S08111	133001	Subject's Condition Mandated Other Treatment	154
S08248	140001	AE – Lung lesion, elevated liver enzymes	259
S08586	141017	Randomized in error	1
S08088	142002	Subject's Decision	127
S08212	144002	AE - Worsening AMD	127
S08212	144005	Lost to follow-up	331
S08187	149003	Subject's Decision	36
S08187	149007	AE - Worsening AMD	359
S08187	149009	Subject's Decision	127
S00399	162003	Subject's Decision	8
S08133	164002	Subject's Decision	120
S08231	166001	AE - Worsening AMD	295
S00266	167008	Subject's Condition Mandated Other Treatment	309
S08146	175002	AE – Lung cancer treatment	176
S08194	176005	Subject's Decision	317
S02507	186002	Subject's Condition Mandated Other Treatment	162
S07387	187002	AE – Acute Gout	359
S08252	193004	AE - Worsening AMD	133
S08882	205002	AE - Death due to Asthma / COPD	333
[redacted]	[redacted]	[redacted]	[redacted]
S07438	101020	AE - Death – Myocardial infarction	12
S08127	102006	AE – Lymphoma	372
S08536	102015	Subject's Decision	258
S08144	110002	Subject's Decision	324
S08092	111005	AE – Severe aortic stenosis	96
S08190	120005	AE - Worsening AMD	66
S08246	131003	AE – Vulvar adenocarcinoma	210
S08189	160001	AE – Iritis	121
S00399	162002	AE – Loss of vision	100
S08084	196004	Lost to follow-up	218
[redacted]	[redacted]	[redacted]	[redacted]
S08092	111003	AE – Cardiac arrhythmia	100
S08082	119004	Subject's Decision	1
S07442	127002	Subject's Decision – Did not receive treatment	28

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[redacted]	[redacted]	[redacted]	[redacted]
S08081	130013	AE – Fractured pelvis	39
S08246	131001	AE – Stroke	244
S08246	131007	AE – Death due to small bowel infarct	178
S08238	138002	AE – Recurrent iritis	153
S08231	166002	Worsening AMD	241
S07479	173002	Non-compliance	28
S08232	181004	AE – Death – Asthma	155
S08084	196003	AE – Cough and wheezing	92

Reviewer's Comment:
The majority of subjects who discontinued treatment were in the sham-injection group. The most frequent reasons for discontinuation were worsening AMD, worsening vision, or subject's decision with no improvement in vision.

In the ranibizumab groups, adverse events related to systemic disease were the most frequent causes of treatment discontinuation. There was no pattern of non-ocular adverse event which led to discontinuation.

Table 6.1.3.1-8 Demographic Statistics by Treatment Group
Intent-to-Treat, Randomized Subjects

Demographic	[redacted] (N = [redacted])	[redacted]bizumab [redacted]mg (N = 238)	0.5 mg (N = 240)
Age (yr)			
Mean (SD)	77.0 (6.6)	77.4 (7.6)	76.8 (7.6)
Range	56–94	52–95	52–93
Age group (yr)			
50 to < 65	11 (4.6%)	13 (5.5%)	16 (6.7%)
65 to < 75	67 (28.2%)	64 (26.9%)	64 (26.7%)
75 to < 85	132 (55.5%)	130 (54.6%)	124 (51.7%)
≥ 85	28 (11.8%)	31 (13.0%)	36 (15.0%)
Sex			
Male	79 (33.2%)	85 (35.7%)	88 (36.7%)
Female	159 (66.8%)	153 (64.3%)	152 (63.3%)
Race/ethnicity			
White	231 (97.1%)	229 (96.2%)	232 (96.7%)
Asian or Pacific Islander	2 (0.8%)	3 (1.3%)	2 (0.8%)
Hispanic	5 (2.1%)	5 (2.1%)	6 (2.5%)
Other	0	1 (0.4%)	0

Reviewer's Comment:
The demographics of the treatment groups were balanced. The majority of the patients randomized and treated in this study were elderly and white.

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**Table 6.1.3.1-9 Baseline Ocular Characteristics in the Study Eye
Intent-to-Treat, Randomized Subjects**

[redacted]		Ranibizumab 0.3 mg (n=238)	Ranibizumab 0.5 mg (n=240)
Years since first diagnosis of neovascular AMD			
N	235	238	238
Mean (SD)	0.8 (1.3)	0.6 (1.6)	0.7 (1.3)
Range	0.0 – 10.9	0.0 – 18.9	0.0 - 13.3
Visual acuity at a starting test distance of 4 meters			
N	229	229	230
Number of letters (0–100)			
Mean (SD)	53.5 (14.7)	53.2 (13.6)	53.2 (14.9)
Range	0–88	0–82	0–80
≤ 54	111 (48.5%)	114 (49.8%)	110 (47.8%)
≥ 55	118 (51.5%)	115 (50.2%)	120 (52.2%)
Approximate Snellen equivalent			
Median	20/80	20/80	20/80
20/200 or worse	26 (11.4%)	28 (12.2%)	36 (15.7%)
Better than 20/200 but worse than 20/40	171 (74.7%)	172 (75.1%)	159 (69.1%)
20/40 or better	32 (14.0%)	29 (12.7%)	35 (15.2%)
Intraocular pressure (mmHg)			
N	238	238	240
Mean (SD)	14.8 (3.2)	14.8 (3.1)	14.8 (3.2)
Range	7–24	5–25	8–25
0–21	234 (98.3%)	233 (97.9%)	236 (98.3%)
22–29	4 (1.7%)	5 (2.1%)	4 (1.7%)

Reviewer's Comment:
There was no significant difference in baseline vision or intraocular pressure characteristics between the treatment groups.

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Original BLA
Rhea A. Lloyd, MD
125156
Lucentis (ranibizumab injection)

Table 6.1.3.1-10 Fluorescein Angiography and Fundus Photography Characteristics of the Study Eye at Baseline Intent-to-Treat, Randomized Subjects

Characteristics	[redacted] (n=238)	[redacted]	Ranibizumab 0.5 mg (n=240)
CNV classification			
Predominantly classic	0	1 (0.4%) [a]	1 (0.4%) [b]
Minimally classic	87 (36.6%)	86 (36.1%)	91 (37.9%)
Occult without classic	151 (63.4%)	151 (63.4%)	148 (61.7%)
Total area of lesion (DA)			
Mean (SD)	4.41 (2.48)	4.26 (2.54)	4.47 (2.62)
Range	0.20–11.75	0.10–11.80	0.25–12.00
≤ 4 DA	124 (52.1%)	134 (56.3%)	125 (52.1%)
> 4 DA	114 (47.9%)	104 (43.7%)	115 (47.9%)
Total area of CNV (DA)			
Mean (SD)	4.28 (2.41)	4.13 (2.47)	4.27 (2.51)
Range	0.20–11.75	0.02–11.80	0.12–12.00
Area of classic CNV (DA)			
Mean (SD)	0.17 (0.36)	0.16 (0.35)	0.17 (0.38)
Range	0.00–2.50	0.00–2.50	0.00–2.25
Total area of leakage from CNV plus intense progressive RPE staining (DA) [c]			
Mean (SD)	3.54 (2.47)	3.59 (2.50)	3.47 (2.63)
Range	0.00–12.85	0.00–11.95	0.00–13.50
Area of serous sensory retinal detachment or subretinal fluid (DA)			
Mean (SD)	4.45 (3.44)	4.52 (3.54)	4.50 (3.48)
Range	0.00–16.00	0.00–17.00	0.00–16.00
Occult CNV present	238 (100%)	235 (98.7%)	237 (98.8%)

a The subject was enrolled as a result of the site misinterpreting the lesion eligibility confirmation from the reading center.
b Re-categorization as predominantly classic CNV by the reading center post-randomization.
c n=220 for the sham-injection group, and n=218 for each ranibizumab group.

Reviewer's Comment:
There was no significant difference in the baseline characteristics of the CNV lesions across the treatment groups.

Approximately two- thirds of the subjects had occult lesions without any classic component in each treatment group.

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Table 6.1.3.1-11 Concurrent Ocular Procedures and Select Concomitant Medications during the First Treatment Year: Randomized Subjects

Procedure/Medication	[redacted]	Ranibizumab 0.3 mg (n = 238)	Ranibizumab 0.5 mg (n = 240)
Concurrent ocular procedures, study eye [a,b]			
PDT	25 (10.5%)	1 (0.4%)	0
Any procedure other than PDT	10 (4.2%)	14 (5.9%)	12 (5.0%)
AMD-related	8 (3.4%)	0	3 (1.3%)
Cataract	1 (0.4%)	4 (1.7%)	2 (0.8%)
Glaucoma	0	0	1 (0.4%)
Vitreoretinal disease	0	2 (0.8%)	2 (0.8%)
Other disease	1 (0.4%)	7 (2.9%)	5 (2.1%)
Concomitant ocular medications, study eye [c]			
Any medication use	183 (76.9%)	194 (81.5%)	199 (82.9%)
IOP lowering agents	23 (9.7%)	34 (14.3%)	33 (13.8%)
β-adrenoceptor blocking agents	13 (5.5%)	16 (7.6%)	17 (7.1%)
Dermatologic agents	12 (5.0%)	16 (6.7%)	19 (7.9%)
Fluoroquinolones	11 (4.6%)	12 (5.0%)	15 (6.3%)
Mild analgesics	6 (2.5%)	13 (5.5%)	15 (6.3%)
Ophthalmic preparations	36 (15.1%)	38 (16.0%)	40 (16.7%)
Pharmaceutical aids	10 (4.2%)	18 (7.6%)	17 (7.1%)
Steroids	14 (5.9%)	11 (4.6%)	16 (6.7%)
Vitamins and minerals	123 (51.7%)	145 (60.9%)	141 (58.8%)
Concomitant Non-Ocular Medications [d]			
Any medication use	236 (99.2%)	238 (100%)	238 (99.2%)
Antacids	30 (12.6%)	20 (8.4%)	20 (8.3%)
Antianemic agents	35 (14.7%)	23 (9.7%)	31 (12.9%)
Antianxiety agents	18 (7.6%)	37 (15.5%)	35 (14.6%)
Antidepressants	36 (15.1%)	43 (18.1%)	53 (22.1%)
Antihypertensive agents	38 (16.0%)	53 (22.3%)	62 (25.8%)
Antirheumatic and anti-inflammatory agents	84 (35.3%)	69 (29.0%)	80 (33.3%)
β-adrenoceptor blocking agents	71 (29.8%)	81 (34.0%)	76 (31.7%)
Bronchodilators and anti-asthmatics	20 (8.4%)	30 (12.6%)	30 (12.5%)
Calcium regulators and replenishers	80 (33.6%)	87 (36.6%)	81 (33.8%)
Diuretics	73 (30.7%)	82 (34.5%)	76 (31.7%)
Expectorants	18 (7.6%)	16 (6.7%)	8 (3.3%)
Histamine H2-receptor antagonists	29 (12.2%)	17 (7.1%)	28 (11.7%)
Hypolipidemics	104 (43.7%)	114 (47.9%)	109 (45.4%)
Mild analgesics	147 (61.8%)	143 (60.1%)	153 (63.8%)
Penicillins	13 (5.5%)	27 (11.3%)	21 (8.8%)
Steroids	60 (25.2%)	65 (27.3%)	50 (20.8%)
Supplements	45 (18.9%)	47 (19.7%)	35 (14.6%)
Vitamins and minerals	144 (60.5%)	138 (58.0%)	127 (52.9%)

a Based on data recorded on the Vertesporfin PDT CRF pages.
b Based on the procedures reported on the Concurrent Ocular Procedure CRF pages, which were designed to capture all procedures other than PDT.
c Tabulation was based on medication use reported on the Concomitant Medications CRF pages for medications used by ≥ 5% of subjects in any group.
d Tabulation was based on medications reported on the Concomitant Medications CRF pages. Only the medications satisfying any of the following criteria were presented: used by ≥ 25% of subjects in any group at

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screening, used by ≥ 30% of subjects in any group during Year 1, or with a >4% difference between sham and either ranibizumab group.

Reviewer's Comment:
In the ranibizumab 0.5 mg group, the procedures other than PDT performed were usually related to cataract surgery.

Table 6.1.3.1-12 Prior Therapies for AMD in the Study Eye Randomized Subjects

			0.5 mg (n=240)
Any prior therapy for AMD	134 (56.3%)	140 (58.8%)	137 (57.1%)
Laser photocoagulation	22 (9.2%)	13 (5.5%)	14 (5.8%)
Medication	4 (1.7%)	3 (1.3%)	3 (1.3%)
Supplements	119 (50.0%)	132 (55.5%)	125 (52.1%)
Other	8 (3.4%)	3 (1.3%)	2 (0.8%)

Reviewer's Comment:
The treatment groups were well balanced with regard to prior treatment for age-related macular degeneration. Almost twice as many patients had prior laser photocoagulation in the sham group than in the ranibizumab groups.

Table 6.1.3.1-13 Concurrent PDT and Intravitreal Steroid Treatment in the Study Eye – Randomized Subjects

			0.5 mg (n=240)
Concurrent PDT	25 (10.5%)	1 (0.4%)	0
Intravitreal steroid injection	6 (2.5%)	0	0

Reviewer's Comment:
The vast majority of on-study PDT treatments and all intravitreal steroid injections were received by those in the sham injection group.

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6.1.3.2 Study FVF2587g

Title: A Phase 3, Multicenter, Randomized, Double-Masked, Active Treatment-Controlled Study of the Efficacy and Safety of rhuFab V2 (Ranibizumab) Compared with Verteporfin (Visudyne) Photodynamic Therapy in Subjects With Predominantly Classic Subfoveal Neovascular Age-Related Macular Degeneration.

Objectives: Primary:

- To evaluate the efficacy of intravitreal injections of ranibizumab administered monthly compared with verteporfin photodynamic therapy (PDT) in preventing vision loss, as measured by the proportion of subjects who lost fewer than 15 letters in visual acuity at 12 months compared with baseline.
  - The non-inferiority of ranibizumab to verteporfin PDT was evaluated; if non-inferiority was demonstrated, then the treatment differences between ranibizumab and verteporfin PDT were also to be evaluated for superiority.
- To evaluate the safety and tolerability of intravitreal injections of ranibizumab administered monthly.

Secondary:

- To evaluate the efficacy of monthly intravitreal injections of ranibizumab in preventing vision loss as measured by the following:
  - Mean change from baseline in visual acuity over time up to 12 months
  - Proportion of subjects who gained at least 15 letters in visual acuity at 12 months compared with baseline
  - Proportion of subjects with a visual acuity Snellen equivalent of 20/200 or worse at 12 months
- To investigate the efficacy of monthly intravitreal injections of ranibizumab on vision-related functioning and well-being assessed during a period of 12 months, as measured by the National Eye Institute (NEI) Visual Function Questionnaire-25 (VFQ-25)
- To evaluate the efficacy of monthly intravitreal injections of ranibizumab on the size of classic choroidal neovascularization (CNV) and amount of leakage from CNV at 12 months, as assessed by fluorescein angiography

Study Design: Phase 3, multicenter (100 sites), randomized, double-masked, active treatment-controlled study of intravitreally administered ranibizumab compared with verteporfin PDT. Approximately 426 subjects with primary or recurrent subfoveal CNV secondary to AMD who had predominantly classic lesions were to be enrolled.

Test Drug Schedule.

Eligible subjects were randomized in a 1:1:1 ratio to receive one of the following:

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- 0.3 mg ranibizumab and sham PDT with saline infusion,
- 0.5 mg ranibizumab and sham PDT with saline infusion, or
- Sham injection of ranibizumab and active verteporfin PDT.

Verteporfin/sham PDT was administered prior to the ranibizumab/sham injection to ensure the best practice with respect to aseptic technique and to attempt to minimize the risk of infection. Subjects received a ranibizumab or sham injection monthly (30 ± 7 days) for 23 months of treatment (24 injections) and active (verteporfin) or sham (saline) PDT on Day 0 and every 3 months if needed (as determined by the assessment of fluorescein angiograms by the evaluating physician) for 21 months of treatment.

Table 6.1.3.2-1 Clinical Sites - Study FVF2587g

Site Number	Investigator Name Location Investigator Number		Verteporfin PDT N=143	Ranibizumab 0.5 mg N=140	All Subjects N=423

[redacted]

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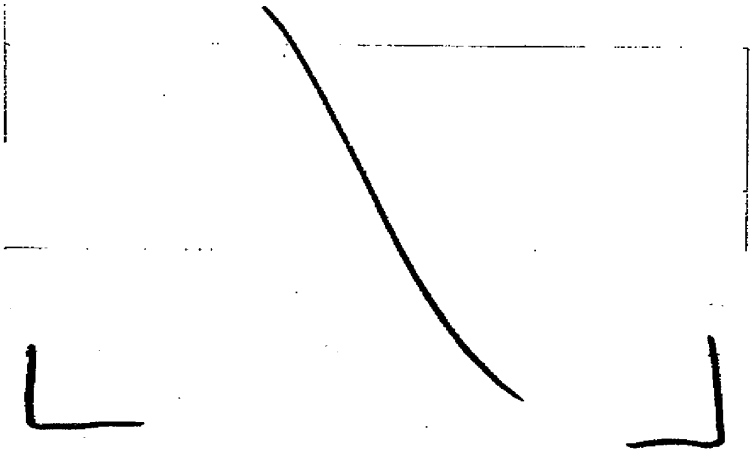

Overall Study Design

This was a Phase 3, multicenter, randomized, double-masked, active treatment controlled study of intravitreally administered ranibizumab compared with verteporfin PDT. Approximately 426 subjects with primary or recurrent subfoveal CNV secondary to AMD who had predominantly classic lesions were to be enrolled. The study was to be conducted at approximately 100 study sites. The study design was essentially the same as Study 98.

Fluorescein angiograms were sent to a central reading center to determine CNV classification for study eligibility. Eligible subjects were randomized in a 1:1:1 ratio to receive one of the following treatments:

- 0.3 mg ranibizumab and sham PDT with saline infusion,
- 0.5 mg ranibizumab and sham PDT with saline infusion, or
- Sham injection of ranibizumab and active verteporfin PDT.

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Randomization was stratified by the visual acuity score at Day 0 (≤44 letters [approximately worse than 20/125] vs. ≥45 letters [approximately 20/125 or better] based on the ETDRS chart and assessment at a starting distance of 2 meters) and by study center. Verteporfin/sham PDT was administered prior to the ranibizumab/sham injection. Subjects received a ranibizumab or sham injection monthly (30 ± 7 days) for 23 months of treatment (24 injections) and active (verteporfin) or sham (saline) PDT on Day 0 and every 3 months if needed (as determined by the assessment of fluorescein angiograms by the evaluating physician) for 21 months of treatment. To preserve masking, administration of sham PDT with saline infusion mimicked that of active verteporfin PDT, and administration of active verteporfin PDT was in accordance with the Visudyne prescribing information.

There was a minimum of two investigators per study site to fulfill the masking requirements of this study. At least one investigator was designated as the evaluating physician, who was masked to the treatment assignment and conducted all ocular assessments. At least one other investigator was designated as the injecting physician, who was unmasked to the treatment assignment and performed the ranibizumab or sham injection procedures and the active or sham PDT infusion procedures, but who was masked to the ranibizumab dose (0.3 mg or 0.5 mg).

Study Population

Inclusion/Exclusion Criteria

Essentially the same as Study 98 except that patients had predominately classic choroidal neovascularization.

Outcome Measures

Essentially the same as Study 98 except that patients had predominately classic choroidal neovascularization.

Reviewer's Comment:

As noted in Section 2.5 regarding previous correspondence and meetings, the Agency does not agree with the sponsor's primary efficacy endpoint

Visual acuity testing is recommended to be performed with at target distance of a minimum of 4 meters from the patient. This distance measure (4 meters) is recommended to minimize the potentially confounding influences of accommodation and patient positioning on the measurement.

For the purposes of this review the Agency will consider the primary efficacy endpoint as the proportion of subjects with a loss of fewer than 15 letters in the visual acuity score in the study eye at 12 months compared with baseline, based on assessments at a starting test distance of 4 meters, not 2 meters.

Study Treatments

Dosing and Administration of Ranibizumab and Sham

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Ranibizumab was administered intravitreally in a multiple-dose regimen of either 0.3 mg or 0.5mg of ranibizumab every month (Day 0-Month 23) for a total of 24 injections. Sham intravitreal injections were administered according to the same dosing schedule as ranibizumab injections: every month (Day 0 – Month 23) for a total of 24 injections. Dosing was not to occur earlier than 14 days after the previous treatment. Missed doses were not to be replaced.

Verteporfin/sham PDT was to be administered prior to the ranibizumab/sham injection to ensure the best practice with respect to aseptic technique and to attempt to minimize the risk of injection. The injecting physician(s) (and any assistants, if applicable) performing the ranibizumab/sham injections could not be involved in any other aspect of the study in any way, and could not divulge the treatment assignment to anyone. The evaluating physician(s) was responsible for all other aspects of the study except for the intravitreal injection procedure, intravenous administration of verteporfin or saline, and 689-nm (± 3 nm) diode laser irradiation of the macula. Visits for injection days had to be scheduled when both physicians were present. The subjects, all site personnel (except for the injecting physician(s) and designated site personnel needed to assist with the injection procedure), and all Sponsor personnel (with the exception of drug accountability monitors, corporate compliance staff, and finance) were masked to treatment assignment.

Dosing and Administration of Verteporfin PDT
Verteporfin PDT was to be administered every 3 months (if needed) as determined by the evaluating physician's assessment of fluorescein angiography. The injecting physician determined the spot diameter of the area to be treated. Active verteporfin PDT or sham PDT with saline infusion was only to be administered on Day 0 and, if needed, at Months 3, 6, 9, 12, 15, 18 and 21.

Dosing and Administration of Sham PDT with Saline Infusion
The sham PDT with saline infusion mimicked active verteporfin PDT and was administered in accordance with Visudyne prescribing information. On Day 0, all subjects received either active or sham PDT followed by an injection of ranibizumab or a sham injection, respectively. The injecting physician and assistant and/or pharmacist were aware of the treatment assignment. If a subject received an injection of ranibizumab, he or she received sham PDT (saline infusion followed by 689-nm [±3 nm] diode laser light dose and intensity was to be the same as those used for verteporfin PDT (i.e., light dose of 50J/cm2 at an intensity of 600 mW/cm2 administered over 83 seconds). If a subject received a sham injection, he or she received active PDT (verteporfin infusion followed by 689-nm [±3 nm] diode laser irradiation to the macula). Following Day 0, the evaluating physician determined the need for PDT every 3 months (i.e., 3, 6, 9, 12, 115, 18 and 21) based on his or her assessment of ophthalmoscopic findings and fluorescein angiography results.

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Table 6.1.3.2-3 Study Treatment Holding Criteria

Event	
Intraocular inflammation	Hold active/sham PDT and ranibizumab/sham intravitreal injection if intraocular inflammation is ≥ 2+ in the study eye.
Visual acuity loss	Hold active/sham PDT and ranibizumab/sham intravitreal injection if there is a treatment-related decrease in BCVA of ≥ 30 letters in the study eye compared with the last assessment of visual acuity prior to the most recent treatment.
Intraocular pressure	Hold active/sham PDT and ranibizumab/sham intravitreal injection if IOP in the study eye was ≥ 30 mmHg. Treatment will be permitted when IOP has been lowered to < 30 mmHg, either spontaneously or by treatment, as determined by the evaluating physician.
Vitreous hemorrhage	Hold active/sham PDT and ranibizumab/sham intravitreal injection if there is a ≥ 2+ vitreous hemorrhage and ≥ 30-letter decrease in visual acuity in the study eye compared with the last assessment of visual acuity prior to the onset of the vitreous hemorrhage. Treatment will be permitted when the vitreous hemorrhage improves to <2+ or visual acuity score improved to a <30-letter decrease.
Sensory rhegmatogenous retinal break or detachment (including macular hole)	Hold active/sham PDT and ranibizumab/sham intravitreal injection if a retinal break was present in the study eye. Treatment may be resumed ≥ 28 days after the retinal break has been successfully treated. Subjects with a rhegmatogenous retinal detachment or Stage 3 or 4 macular hole were discontinued from treatment for the duration of the study.
Subfoveal hemorrhage	Hold active/sham PDT and ranibizumab/sham intravitreal injection if there is a subretinal hemorrhage involving the center of the fovea in the study eye, if the size of the hemorrhage was either ≥ 50% of the total lesion area or ≥ 2 DAs in size.
Local or systemic infection	Hold active/sham PDT and ranibizumab/sham intravitreal injection if any of the following were present: infectious conjunctivitis, infectious keratitis, infectious scleritis, or endophthalmitis in either eye, or if the subject was receiving treatment for a severe systemic infection.
Intraocular surgery	Hold active/sham PDT and ranibizumab/sham intravitreal injection if intraocular surgery had been performed in the study eye within the previous 28 days.

In this study, no subject was to receive both active verteporfin PDT and active ranibizumab injection in the study eye. If unmasked personnel discovered that a subject randomized to receive active ranibizumab injection received active verteporfin PDT in the study eye in error, then the active ranibizumab injection for the current month was to be held and the next ranibizumab injection for the subject was to be administered no earlier than 28 days after the day on which the active verteporfin PDT was received.

Additionally, the evaluating physician could discontinue a subject from treatment for other safety reasons. If a subject missed more than two ranibizumab/sham injections in a treatment year, serious consideration was to be given by the evaluating physician and the Sponsor to withdrawing the subject from the study.

Efficacy Analyses
The primary, secondary, and most of the exploratory efficacy endpoints were analyzed for randomized subjects based on the treatment assigned at randomization. Missing data were imputed using the last-observation-carried forward (LOCF) approach.

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Comparisons of efficacy were performed between each ranibizumab dose group and the verteporfin PDT (control) group. All pairwise comparisons for assessing treatment difference were performed using a statistical method that includes only two treatment groups (ranibizumab vs. control) at a time. For the primary efficacy endpoint, an adjustment was made for multiple treatment comparisons of each ranibizumab dose group with the control group. For secondary efficacy endpoints, adjustments for multiplicity of endpoints were also made to manage the Type I error rate.

Primary Efficacy Endpoint. The primary efficacy endpoint was the proportion of subjects who lost fewer than 15 letters in BCVA score at Month 12 compared with baseline, based on assessment at a starting test distance of 2 meters. The primary efficacy endpoint was analyzed for randomized subjects based on the treatment assigned at randomization, with missing data imputed using the LOCF method. Supportive sensitivity analyses were performed as well.

For each ranibizumab dose group, non-inferiority to the control group was tested using a one-sided testing procedure (or equivalently, using a one-sided CI) and a non-inferiority limit. Subject to the procedures for controlling overall Type I error, a test for a treatment difference compared with the control group could also be performed for each dose group.

To adjust for multiple comparisons of two ranibizumab dose groups with the control group, a Hochberg-Bonferroni multiple comparison procedure was used (Hochberg 1988).

The non-inferiority limit was based on the results of the Phase 3 trials of verteporfin PDT versus placebofrom the TAP Study. The value of 0.07 is approximately one-half of the minimum estimated difference (lower limit of a two-sided 95% CI) in the proportion of subjects with predominantly classic CNV who lost fewer than 15 letters at Month 12. For subjects with predominantly classic CNV, these proportions were 0.673 for verteporfin PDT-treated subjectsand 0.393 for placebo-treated subjects, for an estimated treatment effect of 0.28 (95% CI, 0.153 to 0.407, using the normal approximation to the binomial distribution). It is also the case that 0.07 is equal to 25% of the treatment effect of verteporfin PDT versus placebo.

Laboratory Tests. Descriptive summaries of laboratory values, including changes from baseline and treatment-emergent abnormalities, were generated. The number and percentage of subjects with serum antibodies to ranibizumab at baseline and during the treatment period were tabulated.

Vital Signs and Physical Findings. Descriptive summaries of vital sign measurements and changes from baseline were generated.

Ocular Assessments. Results of the following ocular assessments were summarized by timepoint and by eye (study vs. fellow) using descriptive summaries: visual acuity, intraocular pressure, slitlamp examination, indirect ophthalmoscopy, fluorescein angiography, and fundus photography. The changes from baseline in intraocular pressure were tabulated. The presence of intraocular inflammation and vitreous hemorrhage, as determined from the slit lamp examination, were tabulated by grade (according to grading scales for flare/cells and vitreous

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hemorrhage density). The presence of retinal break or detachment as determined from indirect ophthalmoscopy was tabulated.

Determination of Sample Size

The sample size was determined based on the analysis of the primary efficacy endpoint for treatment differences between each ranibizumab dose group and the control group. The planned sample size of 426 subjects was based on calculations using the following assumptions: 1:1:1 randomization ratio (0.3 mg of ranibizumab vs. 0.5 mg of ranibizumab vs. verteporfin PDT), the Pearson $\chi 2$ test for comparison of two proportions (for each ranibizumab group vs. verteporfin PDT), and the Hochberg-Bonferroni multiple comparison procedure at an overall Type I error rate of 0.0497 (after adjustment for three planned interim safety analyses prior to the analysis of the primary efficacy endpoint). The power of the Hochberg-Bonferroni multiple comparison procedure was evaluated using Monte Carlo simulations.

The sample size of 426 subjects with predominantly classic CNV provided 96% power in the primary ITT analysis based on randomized subjects to detect a statistically significant difference between one or both ranibizumab groups and the verteporfin PDT group in the percentage of subjects who lost fewer than 15 letters in visual acuity score at Month 12, assuming a rate of 84% in each ranibizumab group and 67% in the verteporfin PDT group.

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Rhea A. Lloyd, MD
125156
Lucentis (ranibizumab injection)

Table 6.1.3.2-4
Study Flowchart: Screening, Treatment Phase Day 0 through Month 12, and Early Termination

| Study Period | Screening | Treatment Phase | | |

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Study Period	Screen	Treatment Phase														Early Term.[a]
		Day		Month												
	28 to 0	0	7	1	2	3	4	5	6	7	8	9	10	11	12	
Assessment Window (Days)	—	—	±2	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	30±7
Slit Lamp Examination[e]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Dilated binocular indirect and high-magnification ophthalmoscopy[e]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Lens status assessment		x													x	
Fundus Photography[e]	x					x[h]			x[h]			x[h]			x[h]	x
Fluorescein Angiography[e]	x					x[h]			x[h]			x[h]			x[h]	x
OCT (at selected sites)[e]		x	x	x											x	x
Laboratory Samples[e,i]	x														x	x
Serum samples for antibodies to ranibizumab and pharmacokinetic sample[e]	x								x						x	x
Intraocular pressure j[k]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Active (verteporfin) or sham (saline) photodynamic therapy (study eye only)[l]		x				x[m]			x[m]			x[m]			x[m]	
Ranibizumab administration or sham injection (study eye only)		x		x	x	x	x	x	x	x	x	x	x	x	x	
Finger count, hand motion, light perception n		x		x	x	x	x	x	x	x	x	x	x	x	x	
Vital Signs[o]	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x

h Fluorescein angiography and color fundus photography were to be performed within 7 days prior to the scheduled study visit to allow adequate time for the evaluating physician to determine if PDT was necessary.
i Laboratory evaluations included hematology, blood chemistry, and urinalysis.
j The measurement method used for a subject was to remain consistent throughout the study.
k Obtained pre-treatment for both eyes and 60 minutes (±10 minutes) post-injection for study eye only.
l Active (verteporfin) or sham (saline) PDT, if needed or required by the protocol (Day 0), were to be administered prior to ranibizumab/sham injection (all timepoints).
m Active (verteporfin) or sham (saline) PDT was administered based on need, as determined by assessment of fluorescein angiograms by the evaluating physician (Months 3, 6, 9 and 12 only).
n Injecting physician was to be performed within 15 minutes post-injection for study eye only.
o Performed post-treatment

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| Study Period | Screen | Treatment Phase | | |

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Table 6.1.3.2-4
Study Flowchart: Screening, Treatment Phase Day 0 through Month 12, and Early Termination

Study Period	Treatment Phase												Early Term.[a]
	Month												
[illegible]	[illegible]	14	15	16	17	18	19	20	21	22	23	24	
VFQ-25[b]	x	x	x			x			x			x	x
SF-36 Health Survey[b]						x						x	x
HUI (at selected sites only)[b]			x				x			x			x
VAS[b]	x	x	x				x			x			x
Review of Body Systems												x	x
Best corrected visual acuity (2 meter starting distance)[c,d]	x	x	x	x	x	x	x	x	x	x	x	x[e]	x[e]
Slit Lamp Examination[c]	x	x	x	x	x	x	x	x	x	x	x	x	x
Dilated binocular indirect and high-magnification ophthalmoscopy[c]	x	x	x	x	x	x	x	x	x	x	x	x	x
Lens status assessment												x	
Fundus Photography			x[f]			x[f]			x[f]			x	x
Fluorescein Angiography			x[f]			x[f]			x[f]			x	x

a For subjects who withdrew from the study early. Performed 30 days (±7 days) following the last injection or study visit.
b VFQ-25 (where local languages were available), SF-36 Health Survey (where local languages are available), HUI questionnaire (selected sited only), and VAS were to be administered to the subject prior to the subject's completing any other study procedures.
c Performed pre-treatment
d Performed prior to dilating eyes.
e Also assess at a starting distance of 4 meters after assessing at a starting test distance of 2 meters.
f Fluorescein angiography and color fundus photography may have been performed within 7 days prior to the scheduled study visit to allow adequate time for the evaluating physician to determine if PDT is necessary.

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Study Period	Treatment Phase												Early Termination
	Month												
	13	14	15	16	17	18	19	20	21	22	23	24	
Assessment Window (Days)	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	3/6
Contrast Sensitivity [d]												x	x
Laboratory Samples [g]												x	x
Serum antibodies to ranibizumab and serum pharmacokinetic sample [e]												x	x
Intraocular pressure [e, i]	x	x	x	x	x	x	x	x	x	x	x	x	x
Active (verteporfin) or sham (saline) photodynamic therapy (study eye only) [j]			x [k]			x [k]			x [k]				
Ranibizumab administration or sham injection (study eye only)	x	x	x	x	x	x	x	x	x	x	x		
Finger count, hand motion, light perception	x	x	x	x	x	x	x	x	x	x	x		

g Laboratory evaluations included hematology, blood chemistry, and urinalysis.
h Obtained pre-treatment for both eyes and 60 minutes (±10 minutes) post-injection for study eye only.
i The measurement method used for a subject was to remain consistent throughout the study.
j Active (verteporfin) or sham (saline) PDT, if needed, was administered prior to ranibizumab/sham injection (all timepoints).
k Active (verteporfin) or sham (saline) PDT was administered based on need, as determined by assessment of fluorescein angiograms by the evaluating physician.

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Rosa A. Lloyd, MD
125156
Lucentis (ranibizumab injection)

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Table 6.1.3.2-5 Subject Disposition
Randomized Subjects

	[redacted]	[redacted]	[redacted]
Completed Month 12 [a]	127 (88.8%)	128 (91.4%)	131 (93.6%)
Discontinued Treatment Prematurely	15 (10.5%)	14 (10.0%)	9 (6.4%)
Discontinued Study prematurely	10 (7.0%)	10 (7.1%)	5 (3.6%)
Safety Evaluable Population received study medication, as treated	143 (100%)	137 (97.9%)	140 (100%)
Intent-to-treat Population ≥ 1 on therapy study visit	143 (100%)	140 (100%)	140 (100%)
Per Protocol Population (for the analysis of 4 m BCVA at Month 12) No on-therapy study visits or protocol violation	114 (79.7%)	101 (72.1%)	103 (73.6%)
Excluded from PP Population	62 (26.1%)	38 (11.8%)	44 (18.3%)
Pharmacokinetic-Evaluable Population	136 (95.1%)	135 (96.4%)	137 (97.9%)

Note: Three subjects (301010, 345001, and 403004) in the 0.3 mg group did not receive any ranibizumab during the study.

Reviewer's Comment:
Overall, the study had good subject retention with 386 subjects completing Month 12 (91.3%).

The verteporfin PDT group (10.5%) and the ranibizumab 0.3 mg group (10.0%) had an almost equal number of subjects who discontinued treatment prior to Month 12. The ranibizumab 0.5mg group had the fewest subjects discontinue treatment at 6.4%.

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Table 6.1.3.2-6- Major Protocol Deviations during the First Treatment Year Randomized Subjects

	[redacted] (N=[redacted])	Ranibizumab 0.3 mg (N=140)	Ranibizumab 0.5 mg (N=140)
Any deviation	21 (14.7%)	36 (25.7%)	26 (18.6%)
Treatment error: incorrect treatment	2 (1.4%)	7 (5.0%)	2 (1.4%)
Treatment error: received verteporfin PDT + ranibizumab at the same visit	0	2 (1.4%)	2 (1.4%)
Treatment error: incorrect administration	1 (0.7%)	3 (2.1%)	1 (0.7%)
Treatment error: received study drug kit from Study FVF2598G	0	3 (2.1%)	0
Treatment: off-schedule verteporfin/sham PDT	0	1 (0.7%)	1 (0.7%)
Treatment assignment unmasked	2 (1.4%)	1 (0.7%)	4 (2.9%)
Pre- and post-treatment procedure not followed	4 (2.8%)	9 (6.4%)	6 (4.3%)
Treatment holding criteria not followed	2 (1.4%)	1 (0.7%)	2 (1.4%)
Open-label verteporfin PDT in fellow eye <21 days after last ranibizumab/sham injection	5 (3.5%)	7 (5.0%)	3 (2.1%)
Open-label verteporfin PDT in fellow eye <5 days after last ranibizumab/sham injection	1 (0.7%)	2 (1.4%)	1 (0.7%)
Received excluded concomitant treatment in study eye	1 (0.7%)	0	0
Cataract surgery in the study eye within <28 days of a ranibizumab/sham injection	0	4 (2.9%)	1 (0.7%)
Visual acuity (4m) not assessed at Day 0 (study eye)	2 (1.4%)	7 (5.0%)	1 (0.7%)
Visual acuity (2 m) not assessed at Day 0 (study eye)	0	1 (0.7%)	1 (0.7%)
Visual acuity (2m) assessment incomplete; unknown if vision was better than 20/20 (study eye)	0	1 (0.7%)	0
Inconsistent method for measuring IOP	2 (1.4%)	2 (1.4%)	4 (2.9%)
Vital signs assessed predose	5 (3.5%)	3 (2.1%)	5 (3.6%)

Reviewer's Comments:

The most protocol deviations occurred in the ranibizumab 0.3 mg group (25.7%) followed by ranibizumab 0.5 mg (18.6%). Treatment errors, as a group, represented the majority of the protocol deviations in the ranibizumab 0.3 mg group.

The protocol deviations which occurred most frequently were the following: pre- and post-treatment procedures were not followed, open-label verteporfin PDT was administered in the fellow eye <21 days after the last ranibizumab/sham injection and vital signs were assessed pre-dose, not post-dose.

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Table 6.1.3.2-7 Discontinued Subjects and Reason

Study FVF2587g

Study Site ID	Subject ID	[redacted]	[redacted]
S08190	301006	Subject's Decision	25
S08201	306018	AE – COPD Exacerbation, Recurrent pneumonia	106
S08586	315004	AE – Lung cancer	191
S08187	316003	AE – Perforated gastric ulcer	211
S08214	321009	AE – Glioblastoma	177
S08146	326002	Subject's Decision – Decreasing vision	272
S08541	337006	Lost to follow-up	29
S08366	360002	AE – AMD requiring Macugen injxn, fellow eye	344
S08151	361001	Subject's Decision	130
S08314	364004	AE - Physician's Decision	302
S08221	368002	AE – Myocardial infarction	239
S02891	373001	AE – Bilateral blepharoconjunctivitis	3
S09325	381008	AE – Retinal detachment	211
S09311	384007	AE – Death, Cardiac arrest	121
S09339	403002	Lost to follow-up (after Month 8)	368
		[redacted] Group	
S08190	301010	AE - Progression of AMD	1
S08220	302007	Non- compliance	271
S07441	303001	AE – Retinal detachment	58
S08214	321003	AE – Death, respiratory arrest	235
S08130	335004	AE – Blurred vision (unchanged VA)	361
S08541	337003	AE – Death, cardiac arrest	282
S07438	343005	AE – Lung cancer	278
S08222	344004	AE - Stroke	136
S08252	345001	Subject's Decision – never received treatment	7
S02201	352003	Subject's Decision – multiple medical problems	183
S08133	358003	AE - Recurrent CNVM, fellow eye	337
S08258	374003	AE – Death, viral infection	289
S09308	389003	Subject's Decision	182
S09339	403004	Physician's Decision – never received treatment	1
		[redacted] Group	
S08220	302011	Lost to follow-up	180
S08165	317004	AE – Death, Congestive Heart Failure	219
S00444	319008	Subject's Decision	31
S08222	344005	AE – Progression of CNVM	175
S08234	349006	AE – Afferent pupillary defect	357
S08224	350004	Subject's Decision	212
S08083	369001	AE – Multiple infections	225
S09311	384003	AE – Death, cardiac failure	98
S09308	389001	AE – Severe uveitis	271

Reviewer's Comments:

Treatment discontinuations occurred at about the same frequency in the verteporfin PDT (15/143) and ranibizumab 0.3 mg group(14/140). In both groups, the reasons for discontinuation were most frequently adverse events due to systemic disease.

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Table 6.1.3.1-8 Demographic Statistics by Treatment Group
Intent-to-Treat, Randomized Subjects

Demographic	[illegible]	[illegible]	Ranibizumab 0.5 mg (n = 140)
Age (yr)			
Mean (SD)	77.7 (7.8)	77.4 (7.5)	76.0 (8.6)
Range	53-95	54-97	54-93
Age group (yr)			
50 to < 65	8 (5.6%)	9 (6.4%)	14 (10.0%)
65 to < 75	35 (24.5%)	28 (20.0%)	41 (29.3%)
75 to < 85	74 (51.7%)	84 (60.0%)	64 (45.7%)
≥ 85	26 (18.2%)	19 (13.6%)	21 (15.0%)
Sex			
Male	64 (44.8%)	73 (52.1%)	75 (53.6%)
Female	79 (55.2%)	67 (47.9%)	65 (46.4%)
Race/ethnicity			
White	140 (97.9%)	137 (97.9%)	136 (97.1%)
Black	1 (0.7%)	0	1 (0.7%)
Hispanic	1 (0.7%)	3 (2.1%)	2 (1.4%)
Other	1 (0.7%)	0	0
Any prior therapy for AMD	64 (44.8%)	63 (45.0%)	58 (41.4%)
Laser photocoagulation	19 (13.3%)	23 (16.4%)	20 (14.3%)
Medication / Supplements	52 (36.4%)	49 (35.0%)	46 (32.9%)

Reviewer's Comment:

The demographics of the subjects in the study were well balanced. The predominance of white elderly adults is representative of the population affected by this disease rather than a problem with enrollment.

Approximately 40% of subjects reported prior therapy for AMD in the study eye and approximately 15% reported prior laser photocoagulation in the study eye. No subjects had prior verteporfin PDT therapy because the study excluded it.

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**Table 6.1.3.2-9 Baseline Ocular Characteristics in the Study Eye
Intent-to-Treat, Randomized Subjects**

Characteristic	[redacted]	Ranibizumab 0.5 mg (n = 140)
Years since first diagnosis of neovascular AMD		
N	142	140	140
Mean (SD)	0.4 (0.9)	0.3 (0.6)	0.3 (0.6)
Range	0.0 – 5.4	0.0 – 5.4	0.0 - 7.3
Visual acuity at a starting test distance of 4 meters			
N	141	133	139
Number of letters (0–100)			
Mean (SD)	45.1 (15.2)	47.4 (13.7)	46.4 (14.8)
Range	3-73	1-74	0-75
≤ 44	62 (44.0%)	52 (39.1%)	57 (41.0%)
≥ 45	79 (56.0%)	81 (60.9%)	82 (59.0%)
Approximate Snellen equivalent			
Median	20/125	20/100	20/125
20/200 or worse	39 (27.7%)	37 (27.8%)	35 (25.2%)
Better than 20/200 but worse than 20/40	100 (70.9%)	92 (69.2%)	98 (70.5%)
20/40 or better	2 (1.4%)	4 (3.0%)	6 (4.3%)
Intraocular pressure (mmHg)			
N	143	140	140
Mean (SD)	15.2 (3.2)	15.2 (3.7)	15.4 (3.4)
Range	3–24	9–26	9–26
0–21	136 (95.1%)	133 (95.0%)	133 (95.0%)
22–29	7 (4.9%)	7 (5.0%)	7 (5.0%)

Reviewer's Comment:
The baseline ocular characteristics of the study eye were well balanced. The mean visual acuity ranged from 45.1 to 47.4 letters (Snellen equivalent 20/100 - 20/125) at a starting test distance of 4 meters.

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Table 6.1.3.2-10 Fluorescein Angiography and Fundus Photography Characteristics of the Study Eye at Baseline Intent-to-Treat, Randomized Subjects

Characteristics	[illegible]	Ranibizumab 0.3 mg (n =140)	Ranibizumab 0.5 mg (n = 140)
CNV classification			
Predominantly classic	141 (98.6%)	134 (95.7%)	135 (96.4%)
Minimally classic	2 (1.4%)	5 (3.6%)	5 (3.6%)
Occult without classic	0	1 (0.7%)	0
Total area of lesion (DA)			
Mean (SD)	1.88 (1.40)	1.89 (1.44)	1.79 (1.54)
Range	0.07-5.75	0.12-7.20	0.05-10.00
≤ 2 DA	93 (65.0%)	98 (70.0%)	93 (66.4%)
>2 to 4 DA	34 (23.8%)	32 (22.9%)	34 (24.3%)
> 4 DA	16 (11.2%)	10 (7.1%)	13 (9.3%)
Total area of CNV (DA)			
Mean (SD)	1.48 (1.25)	1.48 (1.33)	1.31 (1.24)
Range	0.07-5.55	0.11-6.80	0.05-7.50
Area of classic CNV (DA)			
Mean (SD)	1.36 (1.13)	1.28 (1.05)	1.21 (1.12)
Range	0.07-5.55	0.00-6.40	0.05-5.30
Total area of leakage from CNV plus intense progressive RPE staining (DA)			
Mean (SD)	3.06 (1.81)	3.00 (1.92)	2.92 (2.08)
Range	0.20-8.20	0.20-11.00	0.25-9.00
Area of subretinal fluid (DA)[a]			
Mean (SD)	4.34 (2.15)	4.17 (2.43)	4.26 (2.53)
Range	0.00-9.00	0.00-14.00	0.00-12.00
Presence of occult CNV			
Absent	114 (79.7%)	107 (76.4%)	111 (79.3%)
Questionable	13 (9.1%)	12 (8.6%)	11 (7.9%)
Present	16 (11.2%)	21 (15.0%)	18 (12.9%)

a Subretinal fluid is also known as serous sensory retinal detachment. n=135 for the verteporfin PDT group, n=124 for the 0.3 mg group, and n=123 for the 0.5 mg group.

Reviewer's Comment:
There was no significant difference in the baseline characteristics of the CNV lesions across the treatment groups.

The vast majority of subjects had predominantly classic CNV lesions in each treatment group.

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6.1.4 Efficacy Findings

6.1.4.1 Study FVF2598g Efficacy Results

The efficacy analysis was based on all randomized subjects with treatment groups as assigned, the intent-to-treat population with the LOCF method used to impute missing data. Some subjects did receive a treatment for which they were not randomized. These subjects were included in an "as treated" population in the safety analyses.

Reviewer's Comment:

As noted in Section 2.5 regarding previous correspondence and meetings, the Agency does not agree with the sponsor's primary efficacy endpoint.

Visual acuity testing is recommended to be performed with at target distance of a minimum of 4 meters from the patient. This distance measure (4 meters) is recommended to minimize the potentially confounding influences of accommodation and patient positioning on the measurement.

For the purposes of this review, the Agency will consider the primary efficacy endpoint as the proportion of subjects with a loss of fewer than 15 letters in the visual acuity score in the study eye at 12 months compared with baseline, based on assessments at a starting test distance of 4 meters not 2 meters.

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STUDY FVF2598g - PRIMARY EFFICACY RESULTS

Table 6.1.4.1-1
Proportion of Subjects Losing <15 Letters in Visual Acuity for the Study Eye at 12 Months Compared with Baseline at a Starting Distance of 4 Meters:

	[redacted]	Ranibizumab 0.3mg	Ranibizumab 0.5mg
[redacted]			
N	229	229	230
Responders[c]	138 (60.3%)	213 (93.0%)	209 (90.9%)
95% CI of the % [a]	(53.9%, 66.6%)	(89.7%, 96.3%)	(87.1%, 94.6%)
Difference in % (vs. sham) [b]		32.3%	29.9%
95% CI of the difference [b]		(25.3%, 39.4%)	(22.7%, 37.1%)
[redacted]			
N	176	200	196
Responders[c]	106 (60.2%)	187 (93.5%)	181 (92.3%)
95% CI of the % [a]	(53.0%, 67.5%)	(90.1%, 96.9%)	(88.6%, 96.1%)
Difference in % (vs. sham) [b]		33.3%	32.1%
95% CI of the difference [b]		(25.3%, 41.3%)	(24.0%, 40.3%)

a. By normal approximation; b. Weighted estimates adjusting for the strata by using CMH weights; c. From Cochran Chi Square tests adjusted for the strata (p<.0001).

Reviewer's Comment:
Based on the Hochberg-Bonferroni multiple comparison procedure defined within the protocol, the ranibizumab 0.3 mg and 0.5 mg doses demonstrate efficacy in this trial. The primary efficacy endpoint result for both ranibizumab groups is strongly statistically significant at p<0.0001 for each.

There is an approximate 30% treatment effect with both ranibizumab doses. At the 12 month primary efficacy endpoint, 93% of subjects in the ranibizumab 0.3-mg group and 90.9% of subjects in the ranibizumab 0.5 mg group lost fewer than 15 letters of vision from baseline compared with 60.3% of subjects in the sham injection group.

The number of subjects considered in each group was decreased in the Per Protocol analysis because some subjects did not have baseline visual acuity tested at 4 meters.

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Table 6.1.4.1-2
Sensitivity Analysis of Visual Acuity for the Study Eye at 12 Months (Worst Outcome Imputation) at a Starting Distance of 4 Meters

	[redacted]	[redacted] 0.5 mg (N=230)
N	229	229	230
Responders	118 (51.5%)	201 (87.8%)	194 (84.3%)
95% CI of the % [a]	(45.1%, 58.0%)	(83.5%, 92.0%)	(79.7%, 89.2%)
Difference in % (vs. sham) [b]		36.2%	32.8%
95% CI of the difference [b]		(28.5%, 44.0%)	(24.8%, 40.8%)
p-value (vs. sham) [c]		<0.0001	<0.0001

a By normal approximation; b Weighted estimates adjusting for the strata by using CMH weights; c From Cochran Chi Square tests adjusted for the strata.

Reviewer's Comment:
The statistically significant demonstration of efficacy is preserved with a greater than 30% treatment effect in the worst outcome imputation – sensitivity analysis.

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SECONDARY EFFICACY ENDPOINT RESULTS

Chart 6.1.4.1-1

Mean Change in Visual Acuity from Baseline to Month 12, Starting Test Distance 2 m: Randomized Subjects
Study FVF2598g

Reviewer's Comment:
The difference in visual acuity mean change from baseline between each of the ranibizumab groups versus the sham injection group was statistically significant ($p<0.0001$) at each monthly assessment.

The Agency prefers that visual acuity testing be performed with at target distance of a minimum of 4 meters from the patient to minimize the potentially confounding influences of accommodation and patient positioning on the measurement. Visual acuity data with a starting test distance of 2 meters is presented here because visual acuity at a starting test distance of 4 meters was collected at baseline and Month 12 only in this study.

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Table 6.1.4.1-3
Study Eye Visual Acuity Comparisons between Baseline and Month 12
Starting Test Distance of 4 meters: Randomized Subjects

Efficacy Variable			Ranibizumab	
			0.3 mg (N=230)	0.5 mg (N=230)
Gain of ≥ 15 letters from baseline	Yes	14 (6.1%)	42 (18.3%)	72 (31.3%)
Loss of <30 letters from baseline	Yes	193 (84.3%)	226 (98.7%)	226 (98.3%)
Mean change in visual acuity from baseline in ETDRS letters (SD)		-11.0 (17.9)	5.4 (13.4)	6.3 (14.1)
Number of Lines VA Change from Baseline		-2.2 (3.6)	1.1 (2.7)	1.4 (3.0)

Reviewer's Comment:
The differences were all statistically significant at the p<.0001 level. There appears to be a dose effect in the gain of ≥ 15 letters of vision from baseline, though this comparison was not a planned statistical comparison.

There is a statistically significant difference between sham and ranibizumab treatment groups in the prevention of vision loss defined as a loss of <30 letters. There is a statistically significant difference in the change in visual acuity from baseline, p<0.001, though this change is not considered clinically meaningful.

Table 6.1.4.1-4
Study Eye Visual Acuity at Month 12
Starting Test Distance of 4 meters
Randomized Subjects

Efficacy Variable			Ranibizumab	
			0.3 mg (N=240)	0.5 mg (N=240)
Mean Visual Acuity in ETDRS letters (SD)		42.5 (19.1)	58.8 (17.1)	59.9 (17.9)
Snellen Equivalent VA ≤ 20/200		102 (43.0%)	29 (12.2%)	28 (11.7%)

Reviewer's Comment:
There is a clinically meaningful and statistically significant (p<.0001) difference in mean visual acuity at Month 12 in ETDRS letters between the sham and ranibizumab treatment groups of 16 letters in the 0.3-mg group and 17 letters in the 0.5-mg group.

Table 6.1.4.1-5

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Mean Change from Baseline in the Total Area of Lesion, Area of Classic CNV, and Area of Subretinal Fluid and the Proportion of Subjects with a Significant Growth of CNV in the Study Eye at 12 Months
Randomized Subjects

Change from [illegible]	[illegible]	Ranibizumab [illegible]	[illegible]
Change in the total area of lesion (DA)			
N	238	238	240
Mean (SD)	2.33 (2.89)	0.11 (2.07)	0.14 (1.97)
Difference in LS means (vs. sham) [a]		-2.21	-2.18
Change in the area of classic CNV (DA)			
N [b]	87	86	91
Mean (SD)	0.79 (2.06)	-0.22 (0.44)	-0.23 (0.61)
Difference in LS means (vs. sham) [c]		-1.02	-1.02
Change in the area of SSR detachment/subretinal fluid			
N	220	218	218
Mean (SD)	1.08 (4.57)	-2.08 (4.31)	-2.62 (3.69)
Difference in LS means (vs. sham) [a]		-3.12	-3.66
Significant growth of CNV (≥ 0.3 DD increase)			
N	238	238	240
Mean (SD)	118 (49.6%)	31 (13.0%)	39 (16.3%)
Difference in LS means (vs. sham) [a]		-36.5%	-33.5%

NOTE: The LOCF method was used to impute missing data. Strata were defined using two factors: baseline CNV classification (minimally classic vs. occult without classic) and baseline visual acuity score (2 meters, ≤ 54 vs. ≥ 55 letters).
a Based on pairwise analysis of covariance models adjusted for the two stratification factors and baseline value of the endpoint (p<.0001). b Included subjects with minimally classic CNV at baseline only. c Based on pairwise analysis of covariance models adjusted for the baseline value of the endpoint and the baseline visual acuity category.

Reviewer's Comment:
Ranibizumab groups showed statistically significant differences when compared with the sham group (p <0.0001) in the mean change from baseline to 12 months in the total lesion area, the area of classic CNV, and the area of subretinal fluid. These differences are not necessarily clinically significant.

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Table 6.1.4.1-6 Mean Change from Baseline in Retinal Thickness and Total Retinal Volume in the Study Eye at 12 Months: Randomized Subjects in the OCT Subset

Change from [redacted]	[redacted]	[redacted] mab [redacted]
Foveal retinal thickness [c] (µm)		
N	15	31
Mean (SD)	-15.1 (131.6))	-122.5 (138.7)
Difference in LS means (vs. sham) [a]		-89.9
p-value (vs. sham) [a]		0.0088
Central retinal thickness [d] (µm)		
N	10	25
Mean (SD)	-1.8 (67.1)	-139.3 (113.9)
Difference in LS means (vs. sham) [a]		-103.2
p-value (vs. sham) [a]		0.0017
Total retinal volume (mm^3)		
N	10	23
Mean (SD)	-0.07 (0.82)	-1.42 (0.99)
Difference in LS means (vs. sham) [a]		-1.40
p-value (vs. sham) [a]		<0.0001

a Based on the analysis of covariance models adjusted for baseline value of the endpoint.
b Only the measurements based on the nominal scan diameter of 6.0 mm are included.
c. Defined as the average thickness in microns of the center of the fovea based on the intersection of 6 radial line scans.
d Defined as the average retinal thickness in microns of the ecotral retinal subfield (encompassing the foveal region), which in turn is one of 9 subfields modeled after the ETDRS macular grid (central, four inner and four outer subfields).

Reviewer's Comment:
Within the subset of patients who were assessed with optical coherence tomography (OCT), the pooled ranibizumab group experienced statistically significant decreases in foveal retinal thickness, central retinal thickness and total retinal volume.

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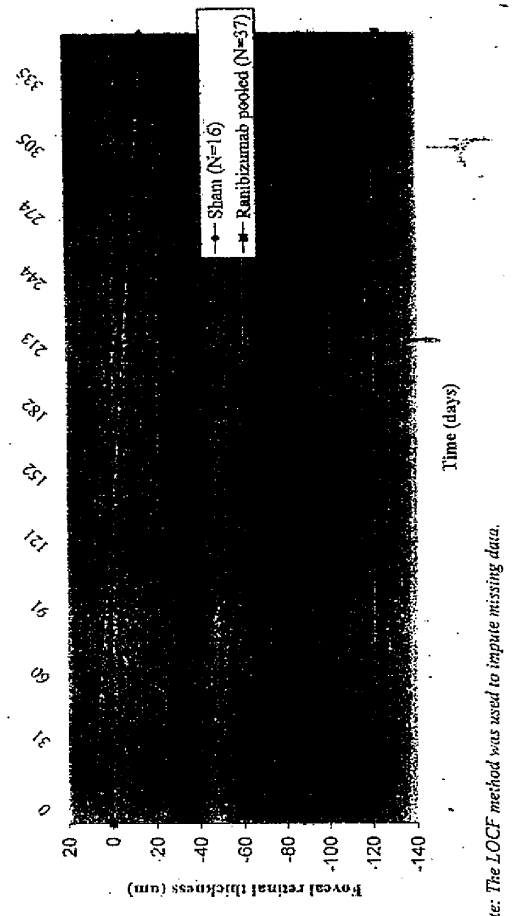
Original BLA
Rhea A. Lloyd, MD
125156
Lucentis (ranibizumab injection)

Chart 6.1.4.1-2

Mean Change from Baseline in Foveal Retinal Thickness (um) in the Study Eye: Randomized Subjects in the OCT Subset



Note: The LOCF method was used to impute missing data.

Reviewer's Comment:
There is a statistically significant difference in foveal retinal thickness (μm) between the sham-injection group and pooled ranibizumab group at Month 1 (p<0.0122) and at Month 12 p<0.0143).

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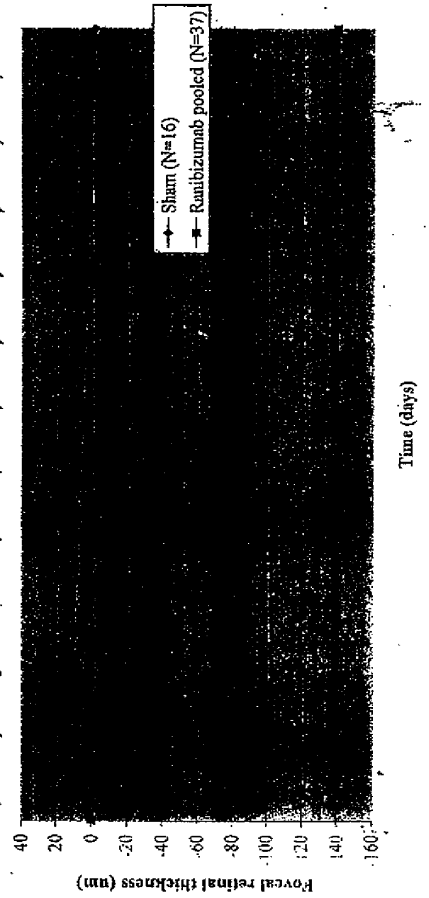
Or BLA
Rhea A. Lloyd, MD
125156
Lucentis (ranibizumab injection)

Chart 6.1.4.1-3

Mean Change from Baseline in Central Retinal Thickness (um) in the Study Eye: Randomized Subjects in the OCT Subset



Note: The LOCF method was used to impute missing data.

Reviewer's Comment:
There is a statistically significant difference in central retinal thickness (μm) between the sham-injection group and pooled ranibizumab group at Month 1 (p<0.0002) and at Month 12 p<0.0012).

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SUBGROUP ANALYSES – PRIMARY EFFICACY VARIABLE

Table 6.1.4-6 Subgroup Analysis for the Proportion Losing <15 Letters in Visual Acuity in the Study Eye at 12 Months Compared with Baseline at a Snellen Test Distance of 4 Meters: Randomized Subjects

	Age < 75 Years			Age ≥ 75 Years		
N	73	78	75	156	154	155
n (%)	47 (64.4%)	70 (93.3%)	70 (93.3%)	91 (58.3%)	143 (92.9%)	139 (89.7%)
95% CI of the %	(53.4%, 75.4%)	(87.7%, 99.0%)	(87.7%, 99.0%)	(50.6%, 66.1%)	(88.8%, 96.9%)	(84.9%, 94.5%)
Difference in % (vs. Sham)		28.9%	28.9%		34.5%	31.3%
p-value (vs. sham)		<0.0001	<0.0001		<0.0001	<0.0001
	Female			Male		
N	152	148	148	79	81	82
n (%)	90 (59.2%)	139 (93.9%)	135 (91.2%)	48 (62.3%)	74 (91.4%)	74 (90.2%)
95% CI of the %	(51.4%, 67.0%)	(90.1%, 97.8%)	(86.7%, 95.8%)	(51.5%, 73.2%)	(85.2%, 97.5%)	(83.8%, 96.7%)
Difference in % (vs. Sham)		34.7 %	32.0%		29.0%	27.9%
p-value (vs. sham)		<0.0001	<0.0001		<0.0001	<0.0001
	≤54 Letters			≥55 Letters		
N	103	110	114	126	119	116
n (%)	74 (71.8%)	104 (94.5%)	108 (94.7%)	64 (50.8%)	74 (91.4%)	74 (90.2%)
95% CI of the %	(63.2%, 80.5%)	(90.3%, 98.8%)	(90.6%, 98.8%)	(42.1%, 59.5%)	(86.6%, 96.6%)	(81.0%, 93.2%)
Difference in % (vs. Sham)		22.7 %	22.9%		40.8%	36.1%
p-value (vs. sham)		<0.0001	<0.0001		<0.0001	<0.0001

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C. BLA
Rhea A. Lloyd, MD
125156
Lucentis (ranibizumab injection)

Loss of <15 Letters from Baseline at Month 12 in the Study Eye	Sham	Ranibizumab		Sham	Ranibizumab	
		0.3 mg	0.5 mg		0.3 mg	0.5 mg
	Minimally Classic CNV at Baseline			Occult with No Classic CNV at Baseline		
N	80	85	88	149	143	141
n (%)	51 (63.8%)	79 (92.9%)	81 (92.0%)	87 (58.4%)	133 (93.0%)	127 (90.1%)
95% CI of the %	(53.2%, 74.3%)	(87.5%, 98.4%)	(86.4%, 97.7%)	(50.5%, 66.3%)	(88.8%, 97.2%)	(85.1%, 95.0%)
Difference in % (vs. Sham)		29.2 %	28.3 %		34.6 %	31.7 %
p-value (vs. sham)		<0.0001	<0.0001		<0.0001	<0.0001
	Baseline Lesion Size ≤ 4 DA			Baseline Lesion Size > 4 DA		
N	119	130	119	110	99	111
n (%)	72 (60.5%)	121 (93.1%)	81 (92.0%)	66 (60.0%)	192 (92.9%)	98 (88.3%)
95% CI of the %	(51.7%, 69.3%)	(88.7%, 97.4%)	(88.8%, 97.8%)	(50.8%, 69.2%)	(87.9%, 98.0%)	(82.3%, 94.3%)
Difference in % (vs. Sham)		32.6 %	32.8 %		32.9 %	28.3 %
p-value (vs. sham)		<0.0001	<0.0001		<0.0001	<0.0001
	With Prior Laser Photocoagulation			With No Prior Laser Photocoagulation		
N	20	12	14	209	217	216
n (%)	10 (50.0%)	12 (100.0%)	13 (92.9%)	128 (61.2%)	201 (92.6%)	196 (90.7%)
95% CI of the %	(28.1%, 71.9%)	(100%, 100%)	(79.4%, 100%)	(54.6%, 67.8%)	(89.1%, 96.1%)	(86.9%, 94.6%)
Difference in % (vs. Sham)		50.0 %	42.9 %		31.4 %	29.5 %
p-value (vs. sham)		0.0040	0.0068		<0.0001	<0.0001

Reviewer's Comment:
The approximately 30% treatment effect was maintained and was statistically significant to the p<0.0001 level in all except for a few subgroups which had small numbers of subjects. In patients with baseline visual acuity of ≤ 34 Letters, the treatment effect was approximately 22%.

There was a small number of patients in the prior laser photocoagulation subgroup (N=35). The treatment effect was higher in this subgroup with the Ranibizumab 0.3 mg dose, 50.0% (p=0.0040) than with the Ranibizumab 0.5 mg dose, 42.9% (p=0.0068).

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6.1.4.2 Study FVF2587g – Primary Efficacy Results

The efficacy analysis was based on all randomized subjects with treatment groups as assigned, the intent-to-treat population with the LOCF method used to impute missing data. Some subjects did receive a treatment for which they were not randomized.

Reviewer's Comment:

As noted in Section 2.5 regarding previous correspondence and meetings, the Agency does not agree with the sponsor's primary efficacy endpoint. Visual acuity testing is recommended to be performed with at target distance of a minimum of 4 meters from the patient. This distance measure (4 meters) is recommended to minimize the potentially confounding influences of accommodation and patient positioning on the measurement.

For the purposes of this review the Agency will consider the primary efficacy endpoint as the proportion of subjects with a loss of fewer than 15 letters in the visual acuity score in the study eye at 12 months compared with baseline, based on assessments at a starting test distance of 4 meters not 2 meters.

STUDY FVF2587g - PRIMARY EFFICACY RESULTS

Table 6.1.4.2-1
Proportion of Subjects Losing <15 Letters in Visual Acuity for the Study Eye at 12 Months Compared with Baseline at a Starting Distance of 4 Meters: Randomized Subjects

	[redacted]	[redacted]	0.5 mg n=140
N	141	133	139
Responders	93 (66%)	126 (94.7%)	136 (97.8%)
95% CI of the % [a]	(58.1%, 73.8%)	(90.9%, 98.5%)	(95.4%, 100%)
Difference in % (vs. verteporfin PDT) [b]		29.0%	32.1%
95% CI of the difference [b]		(20.4%, 37.6%)	(24.0%, 40.2%)
Non-inferiority test			
One-sided (1- α) 100% CI of the difference (vs. verteporfin PDT) [b,c]		(20.4%, –)	(23.9%, –)
p value (vs. verteporfin PDT) [d,e]		<0.0001	<0.0001

Note: Strata were defined using baseline visual acuity score (4 meters, ≤44 vs. ≥45 letters).
a By normal approximation; b Weighted estimates adjusting for the strata by using CMH weights and normal approximation of the weighted estimates; c α=0.0246.; d From normal approximation tests adjusted for the strata.; e From Cochran Chi Square tests adjusted for the strata

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Table 6.1.4.2-2
Proportion of Subjects Losing <15 Letters in Visual Acuity for the Study Eye at 12 Months Compared with Baseline at a Starting Distance of 4 Meters: Per-Protocol Subjects

	[redacted]		0.5 mg
N	114	101	103
Responders	70 (61.4%)	95 (94.1%)	100 (97.1%)
95% CI of the % [a]	(52.5%, 70.3%)	(89.4%, 98.7%)	(93.8%, 100%)
Difference in % (vs. verteporfin PDT) [b]		32.7%	35.7%
95% CI of the difference [b]		(22.6%%, 42.7%)	(26.2%, 45.2%)
Non-inferiority test			
One-sided (1- α) 100% CI of the difference (vs. verteporfin PDT) [b,c]		(23.2%, --)	(26.4%, --)
p-value (vs. verteporfin PDT) [d,e]		<0.0001	<0.0001

Note: Observed cases only. Strata were defined using baseline visual acuity score (4 meters, ≤44 vs. ≥45 letters).
a All tests and CIs are two-sided (except non-inferiority tests) and based on pairwise models. b Based on normal approximation for binomial proportions. c α=0.0246 d From normal approximation tests adjusted for the strata.; e From Cochran Chi Square tests adjusted for the strata

Reviewer's Comment:
The number of subjects considered in each group was slightly decreased because baseline visual acuity at a starting test distance of 4 meters was not obtained in all subjects.

Based on the pre-specified criteria for assessing significance, the ranibizumab 0.3 mg and 0.5 mg doses demonstrate efficacy in this trial. The primary efficacy endpoint result for both ranibizumab groups is highly statistically significant at p<0.0001 for each dose for the Intent-to-Treat and Per Protocol populations.

There is an approximate 30% treatment effect with both doses. At the 12 month primary efficacy endpoint, 94.1% of subjects in the Ranibizumab 0.3-mg group and 97.1% of subjects in the Ranibizumab 0.5-mg group lost fewer than 15 letters of vision from baseline compared with 61.4% of subjects in the verteporfin PDT group. The favorable treatment effect of each of the ranibizumab doses over the verteporfin PDT group was statistically significant, p<0.0001.

For each ranibizumab dose, the lower limit of the one-sided CI (at α=0.0246) for the difference in the percentage from the verteporfin PDT group far exceeded the pre-specified non-inferiority limit of -7%, and the non-inferiority test was statistically significant, p<0.0001.

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Table 6.1.4.2-3
Sensitivity Analysis of Visual Acuity
In the Study Eye at Month 12
(Worst Outcome Imputation) at a Starting Distance of 4 Meters

Primary [redacted] Loss of [redacted]	[redacted]	Ranibizumab [redacted]
N	141	133	139
Responders	79 (56.0%)	113 (85.0%)	122 (87.8%)
95% CI of the % [a]	(47.8%, 64.2%)	(78.9%, 91.0%)	(82.3%, 90.5%)
Difference in % (vs. Verteporfin PDT) [b]		28.9%	31.7%
95% CI of the difference [b]		(18.7%, 39.1%)	(21.9%, 41.6%)
Non-inferiority test			
One-sided (1 - α) 100% CI of the difference (vs. verteporfin PDT) [b,c]		(19.1%, --)	(22.2%, --)
p-value (vs. Verteporfin PDT) [d,e]		<0.0001	<0.0001

Note: Observed cases only. Strata were defined using baseline visual acuity score (4 meters, ≤44 vs. ≥45 letters).
a Alt tests and CIs are two-sided (except non-inferiority tests) and based on pairwise models. b Based on normal approximation for binomial proportions. c α=0.0246 d From normal approximation tests adjusted for the strata.;
e From Cochran Chi Square tests adjusted for the strata

Reviewer's Comment:
The statistically significant demonstration of efficacy is preserved in the worst outcome imputation – sensitivity analysis. The treatment effect of approximately 30% is preserved in both the intent-to-treat and per protocol populations.

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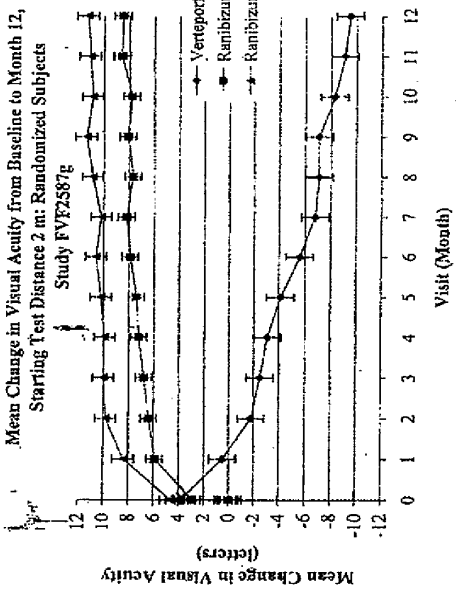
SECONDARY EFFICACY ENDPOINT RESULTS

Chart 6.1.4.2-1



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Reviewer's Comment:
The difference in mean change from baseline in visual acuity between each of the ranibizumab groups versus the verteporfin PDT group was highly statistically significant ($p<0.001$) at each monthly assessment.

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Table 6.1.4.2-4
Study Eye Visual Acuity Comparisons between Baseline and Month 12
Starting Test Distance of 4 meters
Randomized Subjects

[illegible]		[illegible]	[illegible]	[illegible] mg (N=140)
Gain of ≥ 15 letters from baseline		N=141	N=133	N=139
	Yes	15 (10.6%)	37 (27.8%)	51 (36.7%)
Loss of <30 letters from baseline		N=141	N=133	N=139
	Yes	125 (88.7%)	131 (98.5%)	139 (100%)
Mean change in visual acuity from baseline in ETDRS letters (SD)		N=141	N=133	N=139
		-8.5 (17.8)	7.2 (15.3)	11.0 (15.8)
Number of Lines VA Change from Baseline Mean (SD)		N=141	N=133	N=139
		-1.7 (3.6)	1.5 (3.1)	2.3 (3.3)

$p<.0005$ for all comparisions to sham

Reviewer's Comment:

A clinically meaningful and statistically significant gain in 15 letters of vision was noted in the 0.3 mg ranibizumab group and the 0.5 mg group, 27.8% and 36.7%, respectively when compared to the verteporfin PDT treatment group, 10.6%. There appears to be a dose effect in this increase in vision though this comparison was not a planned statistical comparison.

There is a statistically significant difference between verteporfin PDT and ranibizumab treatment groups in the prevention of vision loss of <30 letters.

There is a statistically significant difference in the change in visual acuity from baseline though this change is not considered clinically meaningful.

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Table 6.1.4-5
Study Eye Visual Acuity at Month 12
Starting Test Distance of 4 meters
Randomized Subjects

Mean Visual Acuity at Month 12 in ETDRS letters (SD)		N=143	N=139	N=140
		36.3 (16.6)	54.6 (19.1)	57.6 (18.6)
	p-value	--	<0.0001	<0.0001
Snellen Equivalent VA of 20/200 or Worse		N=143	N=139	N=140
		81 (56.6%)	32 (23.0%)	23 (16.4%)
	p-value	--	<0.0001	<0.0001

Reviewer's Comment:

There is a clinically meaningful and statistically significant difference in the mean visual acuity at Month 12 between the verteporfin PDT and ranibizumab 0.5- mg treatment group. The difference between the verteporfin PDT and ranibizumab 0.3-mg is statistically significant and approaches a clinically relevant result.

There is a statistically significant difference in the number of patients with Snellen equivalent visual acuity of 20/200 or worse between the sham and ranibizumab treatment groups.

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Table 6.1.4.2-6
Mean Change from Baseline in the Total Area of Lesion, Area of Classic CNV, and Area of Subretinal Fluid and the Proportion of Subjects with a Significant Growth of CNV in the Study Eye at 12 Months
Randomized Subjects

[illegible]	[illegible]	[illegible]	[illegible]
Change in the total area of lesion (DA)			
N	143	140	140
Mean (SD)	2.56 (3.09)	0.36 (1.06)	0.28 (1.29)
Difference in LS means (vs. verteporfin PDT) [b]		-2.20	-2.30
Change in total area of CNV [d] (DA)			
N [b]	143	140	140
Mean (SD)	1.63 (2.27)	0.20 (0.97)	0.22 (1.25)
Difference in LS means (vs. verteporfin PDT) [b]		-1.42	-1.45
Change in the area of subretinal fluid [c]			
N	135	124	123
Mean (SD)	-0.58 (4.02)	-2.68 (2.74)	-3.39 (2.90)
Difference in LS means (vs. verteporfin PDT) [b]		-2.23	-2.89
Significant growth of CNV (≥ 0.3 DD increase)			
N	143	140	140
Mean (SD)	84 (58.7%)	30 (21.4%)	38 (27.1%)
Difference in % (vs. verteporfin PDT) [e,f]		-37.3%	-31.7%

NOTE: The LOCF method was used to impute missing data. Strata were defined using baseline visual acuity score (2 meters, ≤ 44 vs. ≥ 45 letters).
a Based on t-distribution. b Based on pairwise analysis of covariance models adjusted for the stratification variable and baseline value of the corresponding endpoint. c Subretinal fluid is also known as serous sensory retinal detachment. d 95-95% of subjects had predominantly classic lesions. 85-92% of each CNV was classic in type.
e Weighted estimates adjusting for the strata by using the CMH weights and normal approximation of the weighted estimates. f Front Cochran chi square tests adjusted for the strata

Reviewer's Comment:
Ranibizumab groups showed highly statistically significant differences with the verteporfin PDT group (p <0.0001) in the mean change from baseline at 12 months in the total lesion area, total area of CNV, area of subretinal fluid and in the growth of CNV.

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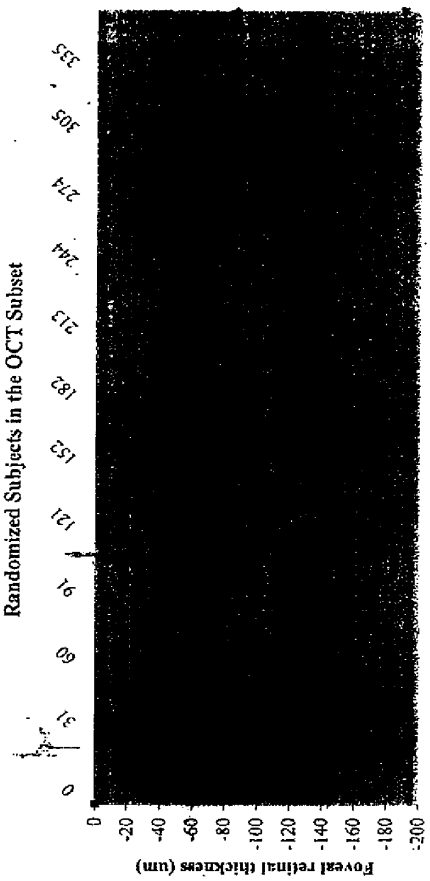
Oi BLA
Rhea A. Lloyd, MD
125156
Lucentis (ranibizumab injection)
Chart 6.1.4.2-2

Mean Change from Baseline in Foveal Retinal Thickness (um) in the Study Eye:
Randomized Subjects in the OCT Subset



Note: The LOCF method was used to impute missing data

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Reviewer's Comment:
There is a statistically significant difference in foveal retinal thickness (μm) between the verteporfin PDT group and pooled ranibizumab group at Month 1 (p<0.0045) and at Month 12 p<0.0004).

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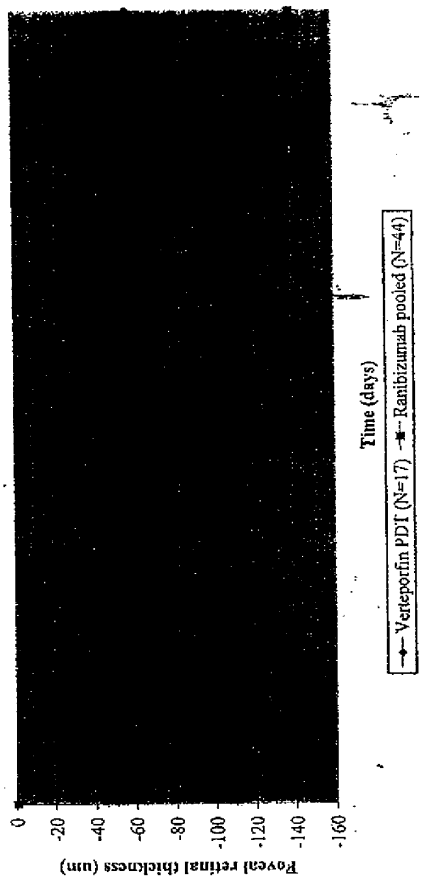
Chart 6.1.4.2-3

Mean Change from Baseline in Central Retinal Thickness (um) in the Study Eye:
Randomized Subjects in the OCT Subset



Note: The LOCF method was used to impute missing data.

Reviewer's Comment:
There is a statistically significant difference in central retinal thickness (um) between the verteporfin PDT group and pooled ranibizumab group at Month 1 (p<0.0009) and at Month 12 p<0.0527).

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SUBGROUP ANALYSES – PRIMARY EFFICACY VARIABLE

Table 6.1.4.2-7 Subgroup Analysis for the Proportion Losing <15 Letters in Visual Acuity in the Study Eye at 12 Months Compared with Baseline at a Starting Test Distance of 4 Meters: Randomized Subjects

	Age < 75 Years			Age ≥ 75 Years		
N	43	37	55	99	97	85
n (%)	26 (61.9%)	35 (91.2%)	53 (98.1%)	67 (67.7%)	91 (93.8%)	83 (97.6%)
95% CI of the %	(47.2%, 76.6%)	(91.9%, 100%)	(94.6%, 100%)	(58.5%, 76.9%)	(89.0%, 98.6%)	(94.4%, 100%)
Difference in % (vs. PDT)		35.3%	36.2%		26.1%	30.0%
	Female			Male		
N	78	64	64	63	69	75
n (%)	51 (65.4%)	61 (95.3%)	63 (98.4%)	42 (66.7%)	65 (94.2%)	73 (97.3%)
95% CI of the %	(54.8%, 75.9%)	(90.1%, 100%)	(95.4%, 100%)	(55.0%, 78.3%)	(88.7%, 99.7%)	(93.7%, 100%)
Difference in % (vs. PDT)		29.9 %	33.1%		27.5%	30.7%
	≤ 44 Letters			≥ 45 Letters		
N	65	58	60	76	75	78
n (%)	49 (75.4%)	55 (94.8%)	58 (96.7%)	44 (57.9%)	71 (94.7%)	77 (98.7%)
95% CI of the %	(64.9%, 85.9%)	(89.1%, 100%)	(92.1%, 100%)	(46.8%, 69.0%)	(89.6%, 99.8%)	(96.2%, 100%)
Difference in % (vs. PDT)		19.4 %	21.3%		36.8%	40.8%
	Occult CNV Present at Baseline			Occult CNV Absent at Baseline		
N	16	17	18	125	116	121
n (%)	7 (43.8%)	15 (88.2%)	18 (100%)	86 (68.8%)	111 (95.7%)	118 (97.5%)

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95% CI of the %	(19.4%, 68.1%)	(72.9%, 100%)	(100%, 100%)	(60.7%, 76.9%)	(92.9%, 99.4%)	(94.8%, 100%)
Difference in % (vs. PDT)		44.5 %	56.3 %		26.9 %	28.7 %
p-value (vs. PDT)		0.0067	0.0002		<0.0001	<0.0001
	Baseline Lesion Size ≤ 4 DA			**Baseline Lesion Size > 4 DA**		
N	125	124	126	16	9	13
n (%)	82 (65.6%)	117 (94.4%)	124 (98.4%)	11 (68.8%)	9 (100%)	12 (92.3%)
95% CI of the %	(57.3%, 73.9%)	(90.3%, 98.4%)	(96.2%, 100%)	(46.0%, 91.5%)	(100%, 100%)	(77.8%, 100%)
Difference in % (vs. PDT)		28.8 %	32.8 %		31.3 %	23.6 %
p-value (vs. PDT)		<0.0001	<0.0001		0.0608	0.1194
	With Prior Laser Photocoagulation			**With No Prior Laser Photocoagulation**		
N	19	19	20	122	114	119
n (%)	11 (57.9%)	19 (100.0%)	20 (100%)	82 (67.2%)	107 (93.9%)	116 (97.5%)
95% CI of the %	(35.7%, 80.1%)	(100%, 100%)	(100%, 100%)	(58.9%, 75.5%)	(89.5%, 98.3%)	(94.7%, 100%)
Difference in % (vs. PDT)		42.1 %	42.1 %		26.6 %	30.3 %
p-value (vs. PDT)		0.0015	0.0011		<0.0001	<0.0001

Note: The LOCF was used to impute missing data. The 95% CIs were based on normal approximation. p-values were from the Pearson Chi Square test.

Reviewer's Comment:

The approximately 30% treatment effect was maintained and was statistically significant to the p<0.0001 level in all except for a few subgroups likely due to the small number of subjects in those subgroups.

In patients with a baseline lesion size of > 4 disc areas, only the ranibizumab 0.3-mg dose achieved statistical significance versus verteporfin PDT, p=0.0242, perhaps due to the small number of subjects or worse disease. In this subgroup, the ranibizumab pooled group was significant with a p-value of 0.0199. Similar results were seen in the subgroups with occult CNV present at baseline and with prior laser photocoagulation.

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6.1.5 Clinical Microbiology

This is not an antimicrobial. Not applicable.

6.1.6 Efficacy Conclusions

The submitted Phase 3 studies in BLA 125156 Lucentis (ranibizumab injection) demonstrate the efficacy for the use of ranibizumab 0.5-mg in the treatment of neovascular age-related macular degeneration.

These studies both demonstrated an approximately 30% treatment effect of ranibizumab 0.3-mg and 0.5-mg compared to sham and verteporfin PDT, respectively, for the primary efficacy endpoint, the proportion of subjects with a loss of fewer than 15 letters in the best corrected visual acuity score at Month 12 compared with baseline.

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7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

The Phase 3 studies presented in this Biologics License Application, FVF2587g and FVF2598g, included 754 safety evaluable patients. In Study FVF2598g, subjects were followed monthly from Day 0 through Month 12 and received an average 12 of a total 13 possible intravitreal ranibizumab injections. The number of treatments received was slightly lower for the sham-injection group compared with the ranibizumab groups. There was no imputation of missing values due to patient discontinuation or missed visits performed in the safety data set. In Study FVF2587g, subjects were followed monthly as well. The mean number of injections in the ranibizumab and sham intravitreal injection groups was approximately 12 for each group.

Safety was assessed through the summary of ocular and non-ocular adverse events, serious adverse events, ocular assessments, deaths, laboratory test results, vital signs, and antibodies to ranibizumab. Safety analyses included all subjects who received at least one ranibizumab or sham injection. Unless specified otherwise, safety analyses were performed for the safety-evaluable subjects. Subjects were analyzed according to the actual treatment received. Safety summaries for this Clinical Study Report include data from the first treatment year.

In Study FVF2598g, the safety evaluable population was defined as randomized subjects who received at least one treatment with study drug. Treatment group assignment as follows:

- Sham: subjects randomized to the sham-injection group who received a sham injection on Day 0
- 0.3 mg Ranibizumab: subjects randomized to receive 0.3 mg ranibizumab or subjects who were randomized to sham but received a 0.3 mg injection of ranibizumab on Day 0 in error
- 0.5 mg Ranibizumab: subjects randomized to receive 0.5 mg ranibizumab or subjects who were randomized to sham but received a 0.5 mg injection of ranibizumab on Day 0 in error

In Study FVF2587g, the safety-evaluable population was defined as randomized subjects who received at least one of the following treatments: ranibizumab injection, sham intravitreal injection, active verteporfin PDT, or sham PDT with saline. Treatment groups for this population were defined according to the actual treatment received during the first treatment year.

- If a subject received only one type of active treatment (verteporfin PDT, 0.3 mg ranibizumab or 0.5 mg ranibizumab), regardless of any sham PDT or sham intravitreal injections received, the subject's treatment group was the active treatment received.
- If a subject received a combination of different active treatments, regardless of any sham PDT or sham intravitreal injections received, and one of the active treatments received

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was the treatment the subject was randomized to, the subject's treatment group was as randomized.

- If a subject received a combination of different active treatments, regardless of any sham PDT or sham intravitreal injection received, and none of the active treatments received was the treatment the subject was randomized to, the subject's treatment group was the first active treatment received.
- If a subject did not receive any active treatment but received any combination of sham PDT or sham intravitreal injection, the subject's treatment group was as randomized.

In Study FVF2598g, the most common ocular adverse events in the study eye reported more frequently in each of the ranibizumab groups than in the corresponding control groups in both studies were conjunctival hemorrhage, eye pain, increased IOP, retinal disorder, and vitreous floaters. Many of these adverse advents appear to be related to the conjunctival anesthetic or intravitreal injection procedures.

Key serious ocular adverse events of endophthalmitis, intraocular inflammation, retinal detachment, retinal tear, increased IOP, and traumatic cataract were all uncommon in ranibizumab-treated subjects (reported in < 1% of subjects for each event). Per injection rates for the serious adverse events of endophthalmitis, intraocular inflammation, retinal detachment, and traumatic cataract were all very low (≤ 0.12% per injection in each dose group).

A trend in intraocular inflammation adverse events was observed, with rates of approximately 10% 15% in the ranibizumab groups compared with rates of approximately 3% or 10% in the verteporfin PDT or sham-control groups, respectively. However, the reported intraocular inflammation adverse events were generally mild in severity. The incidence of intraocular inflammation adverse events was consistent with the results based on slitlamp examination.

As expected with a drug injected intravitreally, there was a small trend in increased IOP adverse events toward higher rates in the ranibizumab groups than in the control groups, with no difference in frequency or severity observed between the two doses. Most of these events were mild to moderate in severity.

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7.1.1 Deaths

Three deaths occurred during the first treatment year of Study FVF2598g. One subject in the 0.3 mg ranibizumab group died from a heart attack. The other two subjects were both in the ranibizumab 0.5 mg group; 1 subject died as a result of a small bowel infarct and the other died from chronic asthma / chronic obstructive pulmonary disease (COPD).

Seven deaths occurred during the first treatment year of Study FVF2587g.

Table 7.1.1-1 Deaths Occurring during Phase 3 Studies

Primary Cause of Death	[illegible]	[illegible]	[illegible]	Study FVF2587g Ranibizumab 0.3 mg N=137	Study FVF2587g Ranibizumab 0.5 mg N=140	Study FVF2587g Ranibizumab 0.5 mg N=140
Total	0	1 (0.4%)	2 (0.8%)	2 (1.4%)	3 (2.2%)	2 (1.4%)
Cardiac Arrest	0	0	0	1(0.7%)	1 (0.7%)	0
Cardiac Failure	0	0	0	0	0	1 (0.7%)
COPD	0	0	1 (0.4%)	1 (0.7%)	0	0
Myocardial infarction	0	1 (0.4%)	0			
Respiratory Arrest	0	0	0	0	1 (0.7%)	0
Small bowel infarct	0	0	1 (0.4%)			
Viral Syndrome	0	0	0	0	1 (0.7%)	0
Worsened of chronic CHF	0	0	0	0	0	1 (0.7%)

Reviewer's Comment:
There were considerably more deaths in the FVF2587g trial though there were no imbalances in the causes or association to treatment noted.

The deaths were not considered to be related to therapy.

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7.1.2 Other Serious Adverse Events

Table 7.1.2-1 Study FVF2598g
Serious Ocular Adverse Events in the Study Eye during the First Treatment Year
Safety Evaluable Subjects

Study Site ID	Subject ID	[illegible]	[illegible]	[illegible]
		Sham		
S08215	104005	30 letter loss of vision	99	None
S08087	105001	Serous hemorrhagic macular detachment	305	None
S07441	107003	Subretinal hemorrhage	63	Dose held
S08216	108006	30 letter loss of vision - Worsened CNV	246	None
S08201	118004	Cerebrovascular accident	319	None
S08130	125006	30 letter loss of vision – Worsened AMD	32	None
S08220	143005	30 letter loss of vision – Worsened AMD	239	Dose held
S08212	144002	30 letter loss of vision – Worsened AMD	94	Dose held, PDT
S08366	148001	30 letter loss of vision – Worsened AMD	155	Dose held
S08133	164002	Progression of AMD	57	Dose held, D/C study
S02796	185005	30 letter loss of vision – Worsened AMD	127	None
S02201	188006	30 letter loss of vision – Worsened AMD	62	None
		0.3 mg [illegible]		
S07348	101001	30 letter loss of vision – Worsened AMD	126	None
S08127	102005	30 letter loss of vision	122	Dose held
S08217	123002	Iridocyclitis	33	None
S06531	126002	Retinal tear	58	Dose held, Procedure
S08246	131003	30 letter loss of vision - Subretinal fibrosis	127	None
S08246	131013	Increased intraocular pressure	239	None
S08208	141014	30 letter loss of vision -Vit. hemorrhage	84	Dose held
S08220	143011	Endophthalmitis	270	Meds / Surgery
	143018	30 letter loss of vision – Worsened AMD	60	None
S08189	160001	Iridocyclitis	94	Study drug d/ced
S00399	162002	Retinal hemorrhage, Depression	15	D/C Study
S08131	179002	30 letter loss of vision – Worsened AMD	148	None
S08125	183001	30 letter loss of vision – Worsened AMD	183	None
S08165	184001	RPE Tear / Detachment	30	None
S08252	193001	Corneal abrasion	343	None
		0.5 mg [illegible]		
S07441	107008	RPE Tear / Detachment	33	Dose held
S08110	117002	Hyphema	29	Meds / AC Tap
S08246	131012	Increased intraocular pressure	183	Meds / AC Tap
S06530	138002	Iridocyclitis – Recurrent	37, 119	Study drug d/ced
S08208	141005	Accidental penetration of lens with needle during injection	69	Cataract extraction
	141016	Fat embolism, retinal artery	204	Hospitalization
S08220	143017	Uveitis	62	Study drug d/ced
S08150	15306	30 letter loss of vision – Unexplained	308	Dose held
S08083	163004	Endophthalmitis	66	Meds / Surgery
S00266	167007	Incorrect route of administration	240	Dose held

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Original BLA
Rhea A. Lloyd, MD
125156
Lucentis (ranibizumab injection)

Study Site ID	[illegible]	[illegible]	[illegible]	[illegible]
S08211	170009	Round [illegible] hole	8	Laser
S08252	193003	30 letter loss of vision – Worsened AMD	254	None
S03675	200004	30 letter loss of vision –Vitreous hemorrhage	210	None

Table 7.1.2-2 Study FVF2587g
Serious Ocular Adverse Events in the Study Eye during the First Treatment Year
Safety Evaluable Subjects

Study Site ID	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]				
S08214	321011	30 letter loss of vision – Subretinal hemorrhage	43	None
S08130	335003	30 letter loss of vision – Worsened AMD	184	None
S08222	344002	30 letter loss of vision – Unexplained	29	None
S08263	363002	30 letter loss of vision - Worsened AMD	31	None
S08255	365001	30 letter loss of vision – Worsened AMD	186, 235	None
S09325	381008	Retinal detachment	114, 189	Surgery, Study drug d/ced
[illegible]				
S07441	303001	Retinal detachment	58	Surgery, Study drug d/ced
S08215	305002	30 letter loss of vision – Worsened AMD	126,169	None
S00444	319007	Vitreous hemorrhage	276	None
S08214	321006	30 letter loss of vision – Unexplained	295	None
S08325	354006	Medication Error	302	None
S08314	364002	Incorrect injection procedure – no lidocaine admin.	358	None
[illegible]				
S08235	304005	Medication Error	367	None
S08146	326001	Occludable narrow angle	104	Iridotomy
S08596	334009	Corneal abrasion	29	Medication
S08211	339004	30 letter loss of vision – Submacular hemorrhage	95	Dose held, Surgery
S08248	340003	30 letter loss of vision – Worsened AMD	92	None
S08207	341003	Endophthalmitis	122	Dose held, Procedure
S08234	349006	Corneal abrasion	296	None
	349006	Afferent pupillary defect	357	Study drug and Study d/ced
S09308	389001	Recurrent uveitis	231,270	Study drug and Study d/ced

[1] Subject's vision fluctuated throughout study and was suspected of peaking at certain visits.

Reviewer's Comment:
The most frequent cause of a serious adverse event was the loss of 30 letters of vision which was usually due to progression of macular degeneration. The greatest number of these occurrences was in the sham- or Verteporfin PDT- treated groups, followed by the ranibizumab 0.3mg- and 0.5 mg-treated groups, respectively.

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Table 7.1.2-3 Study FVF2598g
Serious Ocular Adverse Events in the Fellow Eye during the First Treatment Year
Safety Evaluable Subjects

Study Site ID	[illegible]	[illegible]	[illegible]	[illegible]
		[illegible]		
S07847	115009	30 letter loss of vision – New CNVM	306	Surgery - TPPV
		Elevated intraocular pressure – Postop	327	Medications
S08201	118004	Visual field defect – CVA	319	Hospitalization
S08239	121007	30 letter loss of vision – New CNVM	31	None
S08130	125008	30 letter loss of vision – New CNVM	50	PDT,D/C Study
S08249	136009	30 letter loss of vision – New CNVM	92	PDT
		[illegible]		
S08218	114005	30 letter loss of vision - Worsened AMD	218	PDT
S07847	115002	30 letter loss of vision - Unexplained	160	None, resolved
S08248	140005	Retinal detachment	299	Surgery
		Recurrent retinal detachment	341	Surgery
S08194	176003	30 letter loss of vision – Worsened AMD	164	PDT
		[illegible]		
S08216	108004	30 letter loss of vision – New CNVM	66	PDT
S07439	112004	30 letter loss of vision – Unexplained	127	None, resolved

Table 7.1.2-4 Study FVF2587g
Serious Ocular Adverse Events in the Fellow Eye during the First Treatment Year
Safety Evaluable Subjects

Study Site ID	[illegible]	[illegible]	[illegible]	[illegible]
		[illegible]		
S08314	364004	Medication Error – Non-study eye injected	264	None
		[illegible]		
S08214	321006	30 letter loss of vision – Unexplained	337	None
S08214	321013	30 letter loss of vision – Subretinal hemorrhage	295	Laser tx
S08150	329008	30 letter loss of vision – Worsened AMD	85	PDT
S08133	358003	30 letter loss of vision – Recurrent CNVM	68	PDT, steroid injxn
S09326	390001	Sudden loss of vision - Blindness	337	PDT
		[illegible]		
S08220	302013	30 letter loss of vision – Worsened AMD	246	PDT
S08214	321007	30 letter loss of vision – Worsened AMD	330	Laser, steroid injxn
S08205	342003	30 letter loss of vision [1]	234	None

[1] Patient with short term memory loss, difficult to assess vision.

Reviewer's Comment:
The most frequent cause of a serious adverse event in the fellow eye was the loss of 30 letters of vision due to progression of macular degeneration in both studies regardless of treatment group.

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Table 7.1.2-5
Non-Ocular Serious Adverse Events during the First Treatment Year (Occurring in ≥ 2 Subjects in Any Group)
Safety Evaluable Subjects – Study FVF2598g and Study FVF2587g

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TOTAL [a]	39 (16.5%)	43 (18.1%)	44 (18.4%)	28 (19.6%)	20 (14.6%)	28 (20.0%)
Pneumonia	4 (1.7%)	7 (2.9%)	4 (1.7%)	2 (1.4%)	4 (2.9%)	4 (2.9%)
Diverticulitis	1 (0.4%)	2 (0.8%)	3 (1.3%)	0	0	0
Syncope	4 (1.7%)	0	1 (0.8%)	0	0	0
Coronary artery disease	4 (1.7%)	0	1 (0.4%)	0	3 (2.2%)	0
Cardiac failure, congestive	3 (1.3%)	1 (0.4%)	1 (0.4%)	3 (2.1%)	0	2 (1.4%)
Chest pain	2 (0.8%)	3 (1.3%)	0	0	0	0
Cerebrovascular accident	1 (0.4%) [b]	1 (0.4%)	3 (1.3%) [c]	0	0	0
Cellulitis	3 (1.3%)	1 (0.4%)	0	0	0	0
Hip fracture	0	3 (1.3%)	1 (0.4%)	0	0	0
Asthma	1 (0.4%)	1 (0.4%)	2 (0.8%)	0	0	0
[redacted]	2 (0.8%)	1 (0.4%)	0	1 (0.7%)	1 (0.7%)	[redacted]
Lung neoplasm, malignant	2 (0.8%)	1 (0.4%)	0	0	0	0
COPD Exacerbation	1 (0.4%)	0	2 (0.8%)	2 (1.4%)	0	3 (2.1%)
COPD	0	0	2 (0.8%)	0	0	3 (2.1%)
Abdominal pain, upper	2 (0.8%)	0	0	0	0	0
Non-cardiac chest pain	0	0	2 (0.8%)	0	0	0
Osteoarthritis	2 (0.8%)	0	0	0	0	0
Renal cell carcinoma, stage unspecified	2 (0.8%)	0	0	0	0	0
Transient ischemic attack	0	0	2 (0.8%)	0	0	0
Subdural hematoma	0	0	0	0	2 (1.5%)	0

Note: Multiple occurrences of the same event for a subject were counted once in the overall incidence. Events which occurred more frequently in the 0.5-mg group of either study are highlighted.

a Represents the number of subjects with at least one non-ocular serious adverse event. b The sham-treated subject (118004) who experienced a subacute parietooccipital CVA (reported as an ocular serious adverse event) had received a single injection of 0.5 mg ranibizumab in error approximately 8 months prior to the event. c Included one case reported as a cerebral ischemia.

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Q　.BLA
Rhea A. Lloyd, MD
125156
Lucentis (ranibizumab injection)

Reviewer's Comment:

The adverse events which were seen more frequently in the ranibizumab 0.5 mg group versus either control are highlighted.
In the FVF2590g study, serious non-ocular events were evenly distributed across the ranibizumab treated groups; but, slightly less frequent in the sham treated group.

In the FVF2587g study, serious non-ocular events occurred with approximately equal frequency in the verteporfin PDT and ranibizumab 0.5 mg treated groups. The frequency was somewhat less in the ranibizumab 0.3mg- treated group.

7.1.3 Dropouts and Other Significant Adverse Events

The case report forms of all subjects who discontinued study participation were evaluated. Refer to Table 6.1.3.1-7 and Table 6.1.3.2-7 for details.

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7.1.3.1 Overall profile of dropouts

Table 7.1.3.1-1 Subject Disposition and Reasons for Discontinuation: Randomized Subjects

	Study [illegible]					
	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Randomized	238	238	240	143	140	140
Received ranibizumab or sham injection	236 (99.2%)	238 (100%)	239 (100%)	143 (100%)	137 (97.9%)	140 (100%)
Received verteporfin or sham PDT	---	---	---	143 (100%)	137 (97.9%)	140 (100%)
Completed Month 12[a]	212 (89.1%)	226 (95.0%)	226 (94.2%)	127 (88.8%)	128 (91.4%)	131 (93.6%)
Discontinued treatment[b] prior to Month 12	31 (13.0%)	10 (4.2%)	11 (4.6%)	14 (9.8%)	13 (9.3%)	9 (6.4%)
Death	0	1 (0.4%)	1 (0.4%)	1 (0.7%)	3 (2.1%)	2 (1.4%)
Adverse Event	6 (2.5%)	3 (1.3%)	5(2.1%)	6 (4.2%)	3 (2.1%)	4 (2.9%)
Lost to follow-up	2 (0.8%)	0	0	1 (0.7%)	0	1 (0.7%)
Subject's Decision	15 (6.3%)	6 (2.5%)	4 (1.7%)	4 (2.8%)	4 (2.9%)	2 (1.4%)
Physician's Decision	2 (0.8%)	0	1 (0.4%)	1 (0.7%)	2 (1.4%)	0
Subject non-compliance	0	0	0	0	1 (0.7%)	0
Subject's condition mandated other therapeutic intervention	6 (2.5%)	0	0	1 (0.7%)	0	0

a Defined as having a visual acuity score in the study eye at Month 12. Data from subjects who missed the Month 12 visit but stayed in the study for the second year were not counted.b Two subjects were discontinued from the study at Month 12 after assessments.

Reviewer's Comment:
In both studies, the sham injection and verteporfin PDT groups had higher rates of study dropout and treatment discontinuation than the ranibizumab groups.

Approximately 50% of the treatment discontinuations were due to subject decision.

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7.1.3.2 Adverse events associated with dropouts

Treatment discontinuation and study dropout was most frequently associated with the subject's decision with no change in vision from baseline, subject's loss of vision and progression of age-related macular degeneration.

Table 7.1.3.2-1 Ocular Adverse Events in the Study Eye Leading to Discontinuation of Study or Treatment during the First Treatment Year: Safety Evaluable Subjects

MedDRA Preferred Term	Sham	[redacted]	[redacted]	[redacted]
TOTAL[a]	8 (3.4%)	3 (1.3%)	4 (1.7%)	1 (0.7%)	2 (1.5%)	4 (2.9%)
Cataract subcapsular	0	0	1 (0.4%)	0	0	0
Choroidal neovascularization	4 (1.7%)	0	0	0	0	0
Conjunctivitis allergic	0	0	1 (0.4%)	0	0	0
Conjunctivitis bacterial	0	0	0	0	0	1 (0.7%)
Corneal deposits	0	0	1 (0.4%)	0	0	0
Eye pain	0	0	1 (0.4%)	0	1 (0.7%)	0
Iritis	1	2 (0.8%)	0	0	0	0
Iridocyclitis	0	0	1 (0.4%)	0	0	1 (0.7%)
Macular degeneration	3 (1.3%)	0	0	0	0	0
Ocular hypertensia	0	0	0	0	1 (0.7%)	0
Pupillary reflex impaired	0	0	0	0	0	1 (0.7%)
Retinal detachment[b]	0	0	0	1 (0.7%)	1 (0.7%)	0
Retinal hemorrhage	2 (0.8%)	1 (0.4%)	0	0	0	0
Uveitis	0	0	1 (0.4%)	0	0	1 (0.7%)
Vision blurred	0	0	0	0	1 (0.7%)	0
Vitreous detachment	2 (0.8%)	0	0	0	0	0

Note: Multiple occurrences of the same event for a subject were counted once in the overall incidence. a Represents the number of subjects with at least one ocular adverse event in the study eye that led to discontinuation of study or treatment. b Both events were rhegmatogenous retinal detachment.

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Reviewer's Comment:

In Study FVF2598g, the adverse events which led to discontinuation of subjects in the sham-injection group were primarily related to progression of age-related macular degeneration. The adverse event which led to discontinuation in ranibizumab treated subjects most frequently in both studies was intraocular inflammation (iritis, iridocyclitis, and uveitis).

Ocular adverse events that led to discontinuation in the ranibizumab groups were generally those associated with intravitreal injections.

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Table 7.1.3.2-2 Non-Ocular Adverse Events in the Study Eye Leading to Discontinuation of Study or Treatment during the First Treatment Year: Safety Evaluable Subjects

	Study [illegible]		Study [illegible]		Study [illegible]	
TOTAL	5 (2.1%)	2 (0.8%)	5 (2.1%)	6 (4.2%)	5 (3.6%)	2 (1.4%)
Acute myocardial infarction	0	1 (0.4%)	0	0	0	0
Asthenia	0	0	0	1 (0.7%)	1 (0.7%)	0
Asthma	0	0	1 (0.4%)	0	0	0
Blood pressure increased	1 (0.4%)	0	0	0	0	0
Cardiac arrest	0	0	0	1 (0.7%)	1 (0.7%)	0
Cardiac failure	0	0	0	0	0	1 (0.7%)
Cardiac failure chronic	0	0	0	0	0	1 (0.7%)
Cardiogenic shock	0	1 (0.4%)	0	0	0	0
Cerebral infarction	0	0	0	0	1 (0.7%)	0
Cerebral ischemia	0	0	1 (0.4%)	0	0	0
Chronic obstructive pulmonary disease exacerbated	1 (0.4%)	0	0	0	0	0
Chronic obstructive pulmonary disease	1 (0.4%)	0	0	0	0	0
Cough	0	0	1 (0.4%)	0	0	0
Gastric ulcer perforation	0	0	0	1 (0.7%)	0	0
Glioblastoma	0	0	0	1 (0.7%)	0	0
Increased upper airway secretion	0	0	1 (0.4%)	0	0	0
Intestinal infarction	0	0	1 (0.4%)	0	0	0
Lung neoplasm malignant	2 (0.8%)	0	0	0	1 (0.7%)	0
Myocardial infarction	0	0	0	1 (0.7%)	0	0
Non-Hodgkin's lymphoma	0	1 (0.4%)	0	0	0	0
Non-small cell lung cancer Stage IIIb	1 (0.7%)	0	0	0	0	0
Pelvic fracture	0	0	0	0	0	1 (0.4%)
Pneumonia	1 (0.7%)	0	0	1 (0.4%)	0	0
Respiratory arrest	0	1 (0.7%)	0	0	0	0
Viral infection	0	1 (0.7%)	0	0	0	0
Wheezing	0	0	0	0	0	1 (0.4%)

Note: Multiple occurrences of the same event for a subject were counted once in the overall incidence.

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a Represents the number of subjects with at least one non-ocular adverse event in the study eye that led to discontinuation of study or treatment.

Reviewer's Comment:
No pattern of non-ocular adverse events leading to study or treatment discontinuation was noted in either study. The non-ocular adverse events reported were conditions commonly seen in an elderly population.

7.1.3.3 Other significant adverse events

Table 7.1.3.3-1 Serious Adverse Events Potentially Related to Systemic VEGF Inhibition during the First Treatment Year: Studies FVF2598g and FVF2587g

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TOTAL[a]	2 (0.8%)	8 (3.4%)	9 (3.8%)	3 (2.1%)	4 (2.9%)	8 (5.7%)
Hypertension events	0	1 (0.4%)	0	0	0	0
Arterial thromboembolic events	2 (0.8%)	5 (2.1%)	8 (3.3%)	2 (1.4%)	2 (1.4%)	4 (2.9%)
Non-ocular hemorrhages	0	1 (0.4%)	0	0	2 (1.5%)	3 (2.1%)
Other potentially associated events	0	1 (0.4%)	1 (0.4%)	1 (0.7%)	1 (0.7%)	1 (0.7%)

Note: Multiple occurrences of the same type of event for a subject were counted once in the overall incidence.

Reviewer's Comment:
In the two phase 3 studies, a small trend in the occurrence of serious adverse events potentially related to systemic VEGF inhibition was noted at Month 12, particularly in the ranibizumab 0.5-mg dose group. This reflects trends in serious arterial thromboembolic events and, to a lesser extent, in serious non-ocular hemorrhages (but not in serious hypertension or proteinuria). No imbalance in overall adverse events potentially related to systemic VEGF inhibition was observed among treatment groups.

Differing definitions, assessment methods, and reporting of arterial thromboembolic events makes there analysis challenging. The sponsor applied the Antiplatelet Trialists' Collaboration (APTC) classification (Antiplatelet Trialists' Collaborations 1994) to the adverse events which mitigates some of these issues by focusing on a more restricted but well-defined spectrum of serious adverse events: vascular deaths (including deaths of unknown cause), nonfatal myocardial infarction, nonfatal ischemic stroke, and nonfatal hemorrhagic stroke.

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Table 7.1.3.3-2 APTC Arterial Thromboembolic Events during the First Treatment Year: Studies FVF2598g and FVF2587g

Type of Adverse Event	Study FVF2598g			Study FVF2587g			Pooled Ranibizumab
	Sham	Ranibizumab		Verteporfin PDT	Ranibizumab		
	[illegible]	0.5 mg [illegible]	0.5 mg [illegible]	[illegible]	0.3 mg [illegible]	0.5 mg [illegible]	[illegible]
TOTAL [a]	2 (0.8%)	3 (1.3%)	5 (2.1%)	3 (2.1%)	3 (2.2%)	6 (4.3%)	11 (2.9%)
Vascular deaths	0	1 (0.4%)	1 (0.4%)	1 (0.7%)	1 (0.7%)	2 (1.4%)	3 (0.8%)
Nonfatal myocardial infarction	1 (0.4%)	1 (0.4%)	1 (0.4%)	1 (0.7%)	1 (0.7%)	3 (2.1%)	4 (1.1%)
Nonfatal ischemic stroke	1 (0.4%)	1 (0.4%)	3 (1.3%)	1 (0.7%)	1 (0.7%)	1 (0.7%)	4 (1.1%)
Nonfatal hemorrhagic stroke	0	0	0	0	0	0	0

Note: Arterial thromboembolic events, defined according to the Antiplatelet Trialists' Collaboration classification (1994), are presented.

Reviewer's Comment:

Applying the APTC classification to the serious adverse events, an overall trend is noted in the ranibizumab 0.5-mg dose group compared to subjects in other treatment groups. The overall frequency of such events in the ranibizumab 0.3-mg group was 6 events in 375 subjects (1.6%), 5 events in 379 subjects (1.3%) for the control groups. The overall frequency of such events in the 0.5-mg ranibizumab groups was 11 events in 379 subjects (2.9%).

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Table 7.1.3.3-3 Intraocular Inflammation in the Study Eye during the First Treatment Year Studies FVF2598g and FVF2587g: Safety Evaluable Subjects

MedDRA Preferred Terms	Study FVF2598g			Study FVF2587g		
	Sham	Ranibizumab		Verteporfin	Ranibizumab	
	N=236	0.5 mg N=[illegible]	0.5 mg N=289	[illegible]	[illegible]	0.5 mg N=140
TOTAL [a]	23 (9.7%)	26 (10.9%)	34 (14.2%)	4 (2.8%)	14 (10.2%)	21 (15.0%)
Iritis	16 (6.8%)	15 (6.3%)	15 (6.3%)	2 (1.4%)	7 (5.1%)	10 (7.1%)
Vitritis	7 (3.0%)	13 (5.5%)	22 (9.2%)	2 (1.4%)	8 (5.8%)	12 (8.6%)
Iridocyclitis	2 (0.8%)	1 (0.4%)	2 (0.8%)	0	0	4 (2.9%)
Uveitis	2 (0.8%)	0	1 (0.4%)	0	0	1 (0.7%)

Reviewer's Comment:
There was a dose dependent relationship between ranibizumab and intraocular inflammation in both studies.

In Study FVF2598g, four ranibizumab subjects had serious intraocular inflammation, two subjects in each treatment group. Two of those subjects discontinued treatment as a result. One case of serious uveitis (0.5-mg group) was treated with intravitreal antibiotics.

In Study FVF2587g, one subject in the ranibizumab 0.5 mg groups experienced a case of uveitis deemed serious. The first episode in this subject was treated with antibiotics. The second occurrence led to treatment discontinuation.

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7.1.4 Other Search Strategies

No other search strategies were used to analyze adverse events.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

The protocol adequately defined an adverse event. Each investigator evaluated study participants for adverse events, volunteered and elicited, at each intraocular-pressure check on each study visit. An Adverse Event Form was completed to document a description of the event, onset, severity, treatment required, outcome and relatedness to the use of the study medication. Checklists were not used.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The study utilized the MedDRA preferred terms for adverse event recording. The terms were sufficiently descriptive to assess adverse events expected to be experienced by the study population.

7.1.5.3 Incidence of common adverse events

Table 7.1.5.3-1

Adverse Events Occurring in ≥ 1 % of Patients during the First Treatment Year: Pooled Safety Evaluable Subjects – Study FVF2598g and Study FVF2587g

MedDRA [redacted]	[redacted]	[redacted]	[redacted]	[redacted] Patients [redacted]
Blood and Lymphatic System Disorders				
Anemia	8 (3.4%)	4 (2.8%)	11 (2.9%)	17 (4.5%)
Thrombocytopenia	0	0	3 (0.8%)	0
Cardiac Disorders				
Atrial fibrillation	5 (2.1%)	3 (2.1%)	6 (1.6%)	7 (1.8%)
Cardiac failure congestive	4 (1.7%)	4 (2.8%)	3 (0.8%)	5 (1.3%)
Coronary artery disease	5 (2.1%)	0	3 (0.8%)	4 (1.1%)
Ear and Labyrinth Disorders				
Vertigo	2 (0.8%)	5 (3.5%)	7 (1.9%)	3 (0.8%)
Endocrine Disorders				
Hypothyroidism	2 (0.8%)	2 (1.4%)	3 (0.8%)	0
Eye Disorders				
Abnormal sensation in eye	4 (1.7%)	0	6 (1.6%)	1 (0.3%)
Altered visual depth perception	3 (1.3%)	0	0	0
Anterior chamber flare	6 (2.5%)	0	7 (1.9%)	7 (1.8%)
Arcus lipoides	0	0	6 (1.6%)	7 (1.8%)
Blepharitis	14 (5.9%)	6 (4.2%)	22 (5.9%)	33 (8.7%)
Cataract	26 (11.0%)	10 (7.0%)	37 (9.9%)	43 (11.3%)
Choroidal neovascularization	27 (11.4%)	14 (9.8%)	4 (1.1%)	8 (2.1%)
Conjunctival hemorrhage	139 (58.9%)	65 (45.5%)	261 (69.6%)	255 (67.3%)
Conjunctival hyperemia	14 (5.9%)	5 (3.5%)	19 (5.1%)	22 (5.8%)
Conjunctival edema	3 (1.3%)	2 (1.4%)	4 (1.1%)	2 (0.5%)
Conjunctivitis	7 (3.0%)	0	7 (1.9%)	7 (1.8%)
Conjunctivitis, allergic	3 (1.3%)	1 (0.7%)	3 (0.8%)	9 (2.4%)
Corneal abrasion	7 (3.0%)	0	6 (1.6%)	11 (2.9%)

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Original BLA
Rhea A. Lloyd, MD
125156
Lucentis (ranibizumab injection)

Corneal dystrophy	2 (0.8%)	0	17 (4.5%)	13 (3.4%)
Cutis laxa	1 (0.4%)	0	4 (1.1%)	3 (0.8%)
Detachment of retinal pigment epithelium	30 (12.7%)	5 (3.5%)	26 (6.9%)	22 (5.8%)
Drug hypersensitivity	4 (1.7%)	6 (4.2%)	1 (0.3%)	3 (0.8%)
Dry Eye	12 (5.1%)	12 (8.4%)	15 (4.0%)	30 (7.9%)
Eye discharge	14 (5.9%)	4 (2.8%)	20 (5.3%)	13 (3.4%)
Eye hemorrhage	7 (3.0%)	0	2 (0.5%)	3 (0.8%)
Eye irritation	43 (18.2%)	8 (5.6%)	40 (10.7%)	40 (10.6%)
Eye pain	57 (24.2%)	24 (16.8%)	110 (29.3%)	105 (27.7%)
Eye pruritus	20 (8.5%)	7 (4.9%)	28 (7.5%)	29 (7.7%)
Eye swelling	4 (1.7%)	2 (1.4%)	3 (0.8%)	4 (1.1%)
Eyelid margin crusting	1 (0.4%)	0	6 (1.6%)	1 (0.3%)
Eyelid edema	4 (1.7%)	2 (1.4%)	10 (2.7%)	9 (2.4%)
Eyelid pain	1 (0.4%)	0	3 (0.8%)	6 (1.6%)
Eyelid ptosis	3 (1.3%)	0	4 (1.1%)	2 (0.5%)
Eyelids pruritis	4 (1.7%)	1 (0.7%)	2 (0.5%)	2 (0.5%)
Foreign body sensation in eyes	27 (11.4%)	15 (10.5%)	49 (13.1%)	49 (12.9%)
Glaucoma	0	2 (1.4%)	2 (0.5%)	2 (0.5%)
Injection site hemorrhage	3 (1.3%)	3 (2.1%)	8 (2.1%)	13 (3.4%)
Intraocular pressure increased	7 (3.0%)	10 (7.0%)	59 (15.7%)	61 (16.1%)
Iridocyclitis	0	0	0	4 (1.1%)
Iritis	16 (6.8%)	2 (1.4%)	22 (5.9%)	25 (6.6%)
Lacrimation increased	30 (12.7%)	6 (4.2%)	41 (10.9%)	35 (9.2%)
Macular degeneration	125 (53.0%)	89 (62.2%)	138 (36.8%)	136 (35.9%)
Macular edema	20 (8.5%)	6 (4.2%)	4 (1.1%)	10 (2.6%)
Macular scar	2 (0.8%)	1 (0.7%)	6 (1.6%)	5 (1.3%)
Maculopathy	19 (8.1%)	5 (3.5%)	15 (4.0%)	26 (6.9%)
Migraine with aura	0	2 (1.4%)	0	0
Ocular discomfort	7 (3.0%)	1 (0.7%)	20 (5.3%)	19 (5.0%)
Ocular hyperemia	16 (6.8%)	1 (0.7%)	23 (6.1%)	26 (6.9%)
Optic disc hemorrhage	3 (1.3%)	0	0	0
Optic nerve C/D ratio increased	0	2 (1.4%)	0	1 (0.3%)
Photophobia	6 (2.5%)	2 (1.4%)	6 (1.6%)	9 (2.4%)
Photopsia	13 (5.5%)	8 (5.6%)	14 (3.7%)	11 (2.9%)
Posterior capsule opacification	7 (3.0%)	2 (1.4%)	11 (2.9%)	9 (2.4%)
Punctate keratitis	6 (2.5%)	2 (1.4%)	9 (2.4%)	6 (1.6%)
Retinal degeneration	11 (4.7%)	2 (1.4%)	21 (5.6%)	23 (6.1%)
Retinal detachment	12 (5.1%)	2 (1.4%)	15 (4.0%)	8 (2.1%)
Retinal disorder	15 (6.4%)	2 (1.4%)	28 (7.5%)	33 (8.7%)
Retinal exudates	18 (7.6%)	5 (3.5%)	20 (5.3%)	17 (4.5%)
Retinal hemorrhage	101 (42.8%)	76 (53.1%)	66 (17.6%)	66 (17.4%)
Retinal edema	4 (1.7%)	0	5 (1.3%)	1 (0.3%)
Retinal pigmentation	1 (0.4%)	0	5 (1.3%)	3 (0.8%)
Retinal scar	3 (1.3%)	3 (2.1%)	5 (1.3%)	3 (0.8%)
Retinal vascular disorder	7 (3.0%)	1 (0.7%)	0	6 (1.6%)
Scleral hyperemia	3 (1.3%)	0	1 (0.3%)	1 (0.3%)
Sebaceous gland disorder	0	0	1 (0.3%)	4 (1.1%)
Subretinal fibrosis	24 (10.2%)	27 (18.9%)	33 (8.8%)	28 (7.4%)
Vision blurred	15 (6.4%)	9 (6.3%)	27 (7.2%)	24 (9.0%)

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Visual acuity reduced	23 (9.7%)	21 (14.7%)	25 (6.7%)	21 (5.5%)
Visual disturbance	14 (5.9%)	6 (4.2%)	30 (8.0%)	30 (7.9%)
Vitreous degeneration	3 (1.3%)	0	2 (0.5%)	0
Vitreous detachment	30 (12.7%)	26 (18.2%)	60 (16.0%)	59 (15.6%)
Vitreous disorder	0	0	4 (1.1%)	1 (0.3%)
Vitreous floaters	14 (5.9%)	6 (4.2%)	75 (20.0%)	78 (20.6%)
Vitreous hemorrhage	3 (1.3%)	3 (2.1%)	8 (2.1%)	8 (2.1%)
Vitritis	7 (3.0%)	2 (1.4%)	21 (5.6%)	34 (9.0%)
Gastrointestinal Disorders				
Abdominal discomfort	1 (0.4%)	0	1 (0.3%)	4 (1.1%)
Abdominal pain upper	4 (1.7%)	3 (2.1%)	0	1 (0.3%)
Colonic polyp	3 (1.3%)	1 (0.7%)	3 (0.8%)	4 (1.1%)
Constipation	0	3 (2.1%)	4 (1.1%)	4 (1.1%)
Diarrhea	12 (5.1%)	6 (4.2%)	16 (4.3%)	9 (2.4%)
Diverticulum intestinal	0	2 (1.4%)	0	0
Dyspepsia	7 (3.0%)	3 (2.1%)	5 (1.3%)	3 (0.8%)
Gastroesophageal reflux disease	6 (2.5%)	8 (5.6%)	10 (2.7%)	11 (2.9%)
Hemorrhoids	4 (1.7%)	1 (0.7%)	1 (0.3%)	4 (1.1%)
Hiatus hernia	0	2 (1.4%)	0	3 (0.8%)
Nausea	10 (4.2%)	7 (4.9%)	20 (5.3%)	19 (5.0%)
Stomach discomfort	0	3 (2.1%)	0	0
Toothache	4 (1.7%)	2 (1.4%)	3 (0.8%)	3 (0.8%)
Vomiting	2 (0.8%)	6 (4.2%)	6 (1.6%)	3 (0.8%)
General Disorders and Administration Site Conditions				
Asthenia	4 (1.7%)	3 (2.1%)	3 (0.8%)	5 (1.3%)
Chest pain	7 (3.0%)	0	7 (1.9%)	4 (1.1%)
Fatigue	4 (1.7%)	2 (1.4%)	6 (1.6%)	4 (1.1%)
Edema peripheral	9 (3.8%)	0	9 (2.4%)	7 (1.8%)
Pain	2 (0.8%)	0	4 (1.1%)	3 (0.8%)
Pyrexia	2 (0.8%)	2 (1.4%)	9 (2.4%)	5 (1.3%)
Immune System Disorders				
Drug hypersensitivity	3 (1.3%)	1 (0.7%)	4 (1.1%)	5 (1.3%)
Hypersensitivity	1 (0.4%)	3 (2.1%)	6 (1.6%)	6 (1.6%)
Seasonal allergy	2 (0.8%)	6 (4.2%)	7 (1.9%)	7 (1.8%)
Infections and Infestations				
Bronchitis	12 (5.1%)	9 (6.3%)	20 (5.3%)	23 (6.1%)
Bronchitis, chronic	0	2 (1.4%)	0	0
Cellulitis	3 (1.3%)	0	5 (1.3%)	3 (0.8%)
Cystitis	1 (0.4%)	2 (1.4%)	6 (1.6%)	8 (2.1%)
Diverticulitis	2 (0.8%)	0	7 (1.9%)	7 (1.8%)
Ear infection	2 (0.8%)	3 (2.1%)	4 (1.1%)	4 (1.1%)
Fungal infection	1 (0.4%)	0	1 (0.3%)	4 (1.1%)
Gastroenteritis, viral	5 (2.1%)	0	6 (1.6%)	11 (2.9%)
Herpes zoster	3 (1.3%)	0	10 (2.7%)	5 (1.3%)
Influenza	6 (2.5%)	1 (0.7%)	13 (3.5%)	14 (3.7%)
Kidney infection	4 (1.7%)	0	3 (0.8%)	2 (0.5%)
Localised infection	5 (2.1%)	0	3 (0.8%)	4 (1.1%)
Nasopharyngitis	23 (9.7%)	15 (10.5%)	42 (11.2%)	22 (5.8%)
Pneumonia	10 (4.2%)	5 (3.5%)	15 (4.0%)	13 (3.4%)

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[redacted]				
Sinusitis	9 (3.8%)	9 (6.3%)	20 (5.3%)	21 (5.5%)
Skin infection	3 (1.3%)	0	0	1 (0.3%)
Tooth abscess	3 (1.3%)	0	2 (0.5%)	2 (0.5%)
Tooth infection	0	0	4 (1.1%)	3 (0.8%)
Upper respiratory tract infection	15 (6.4%)	6 (4.2%)	25 (6.7%)	19 (5.0%)
Urinary tract infection	12 (5.1%)	9 (6.3%)	21 (5.6%)	18 (4.7%)
Injury, Poisoning and Procedural Complications Contrast Media Reaction				
Contusion	6 (2.5%)	5 (3.5%)	8 (2.1%)	7 (1.8%)
Excoriation	2 (0.8%)	1 (0.7%)	5 (1.3%)	5 (1.3%)
Fall	5 (2.1%)	1 (0.7%)	7 (1.9%)	8 (2.1%)
Hip fracture	0	0	4 (1.1%)	1 (0.3%)
Muscle strain	6 (2.5%)	0	4 (1.1%)	1 (0.3%)
Post procedural pain	3 (1.3%)	1 (0.7%)	1 (0.3%)	2 (0.5%)
Skin laceration	3 (1.3%)	2 (1.4%)	9 (2.4%)	4 (1.1%)
Tooth injury	0	2 (1.4%)	2 (0.5%)	0
Wrist fracture	3 (1.3%)	0	3 (0.8%)	2 (0.5%)
Investigations				
Blood cholesterol increased	4 (1.7%)	2 (1.4%)	2 (0.5%)	7 (1.8%)
Blood glucose increased	4 (1.7%)	3 (2.1%)	9 (2.4%)	8 (2.1%)
Blood pressure increased	14 (5.9%)	3 (2.1%)	18 (4.8%)	17 (4.5%)
Heart rate irregular	0	2 (1.4%)	1 (0.3%)	0
Prostate specific antigen increased	2 (0.8%)	2 (1.4%)	4 (1.1%)	4 (1.1%)
Weight decreased	3 (1.3%)	2 (1.4%)	2 (0.5%)	0
Metabolism and Nutrition Disorders				
Dehydration	0	2 (1.4%)	3 (0.8%)	1 (0.3%)
Diabetes mellitus	0	1 (0.7%)	4 (1.1%)	9 (2.4%)
Gout	3 (1.3%)	1 (0.7%)	4 (1.1%)	8 (2.1%)
Hypercholocsterolemia	5 (2.1%)	4 (2.8%)	7 (1.9%)	9 (2.4%)
Hyperlipidemia	1 (0.4%)	2 (1.4%)	4 (1.1%)	5 (1.3%)
Hypokalemia	4 (1.7%)	3 (2.1%)	7 (1.9%)	2 (0.5%)
Musculoskeletal and Connective Tissue Disorders				
Arthralgia	14 (5.9%)	9 (6.3%)	19 (5.1%)	18 (4.7%)
Arthritis	14 (5.9%)	5 (3.5%)	9 (2.4%)	12 (3.2%)
Back pain	13 (5.5%)	13 (9.1%)	22 (5.9%)	15 (4.0%)
Bone pain	0	3 (2.1%)	0	0
Bursitis	6 (2.5%)	0	1 (0.3%)	1 (0.3%)
Exostosis	0	2 (1.4%)	0	1 (0.3%)
Joint swelling	4 (1.7%)	0	3 (0.8%)	1 (0.3%)
Muscle spasms	3 (1.3%)	3 (2.1%)	6 (1.6%)	5 (1.3%)
Myalgia	0	2 (1.4%)	0	0
Neck pain	1 (0.4%)	0	4 (1.1%)	5 (1.3%)
Osteoarthritis	5 (2.1%)	0	4 (1.1%)	1 (0.3%)
Osteoporosis	0	5 (3.5%)	1 (0.3%)	4 (1.1%)
Pain in extremity	7 (3.0%)	4 (2.8%)	13 (3.5%)	10 (2.6%)
Rotator cuff syndrome	3 (1.3%)	0	0	3 (0.8%)
Shoulder pain	7 (3.0%)	1 (0.7%)	6 (1.6%)	4 (1.1%)
Neoplasms Benign, Malignant and Unspecified (Incl. Cysts and Polyps)				
Basal cell carcinoma	8 (3.4%)	2 (1.4%)	10 (2.7%)	6 (1.6%)
Seborrheic keratosis	0	2 (1.4%)	1 (0.3%)	1 (0.3%)

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Skin cancer	1 (0.4%)	0	4 (1.1%)	3 (0.8%)
Skin papilloma	0	2 (1.4%)	1 (0.3%)	1 (0.3%)
Nervous System Disorders				
Dizziness	16 (6.8%)	4 (2.8%)	14 (3.7%)	12 (3.2%)
Headache	15 (6.4%)	7 (4.9%)	35 (9.2%)	25 (6.6%)
Syncope	4 (1.7%)	3 (2.1%)	2 (0.5%)	6 (1.6%)
Transient ischemic attack	0	2 (1.4%)	0	2 (0.5%)
Psychiatric Disorders				
Anxiety	1 (0.4%)	8 (5.6%)	11 (2.9%)	11 (2.9%)
Depression	8 (3.4%)	7 (4.9%)	9 (2.4%)	12 (3.2%)
Insomnia	7 (3.0%)	2 (1.4%)	8 (2.1%)	14 (3.7%)
Renal and Urinary Disorders				
Nephrolithiasis	0	3 (2.1%)	3 (0.5%)	0
Renal cyst	0	3 (2.1%)	1 (0.3%)	0
Reproductive System and Breast Disorders				
Benign prostatic hyperplasia	1 (0.4%)	2 (1.4%)	3 (0.8%)	8 (2.1%)
Prostatitis	0	2 (1.4%)	0	1 (0.3%)
Respiratory, Thoracic and Mediastinal Disorders				
Asthma	2 (0.8%)	3 (2.1%)	8 (2.1%)	7 (1.8%)
Chronic obstructive airways disease, exacerbated	1 (0.4%)	2 (1.4%)	0	11 (2.9%)
Chronic obstructive pulmonary disease	0	1 (0.7%)	3 (0.8%)	4 (1.1%)
Cough	10 (4.2%)	8 (5.6%)	32 (8.5%)	20 (5.3%)
Dyspnea	3 (1.3%)	4 (2.8%)	10 (2.7%)	8 (2.1%)
Emphysema	0	3 (2.1%)	1 (0.3%)	2 (0.5%)
Epistaxis	0	2 (1.4%)	2 (0.5%)	1 (0.3%)
Hypoxia	3 (1.3%)	0	2 (0.5%)	0
Pharyngolaryngeal pain	1 (0.4%)	4 (2.8%)	3 (0.8%)	3 (0.8%)
Rhinitis allergic	0	2 (1.4%)	0	0
Rhinorrhea	3 (1.3%)	1 (0.7%)	7 (1.9%)	4 (1.1%)
Sinus congestion	3 (1.3%)	0	5 (1.3%)	2 (0.5%)
Skin and Subcutaneous Disorders				
Actinic keratosis	6 (2.5%)	1 (0.7%)	4 (1.1%)	1 (0.3%)
Decubitus ulcer	0	2 (1.4%)	0	0
Pruritus	2 (0.8%)	1 (0.7%)	4 (1.1%)	8 (2.1%)
Rash	9 (3.8%)	4 (2.8%)	9 (2.4%)	8 (2.1%)
Surgical and Medical Procedures				
Nasal sinus drainage	0	0	0	5 (1.3%)
Vascular Disorders				
Hypertension	23 (9.7%)	12 (8.4%)	23 (6.1%)	29 (7.7%)
Hypotension	4 (1.7%)	3 (2.1%)	3 (0.8%)	0
Orthostatic hypotension	0	2 (1.4%)	0	0

Note: Multiple occurrences of the same event in a subject were counted once in the overall incidence.

Reviewer's Comment:
The adverse events which were seen more frequently in the ranibizumab 0.5 mg group versus either control are highlighted.

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Adverse events which occurred most frequently (i.e.≥ 10%) in the study eye of the ranibizumab treatment groups were conjunctival hemorrhage, eye pain, increased IOP, retinal disorder, and vitreous floaters. Many of these adverse events are commonly associated with conjunctival anesthetic and intravitreal injection procedures.

Elevated intraocular pressure was seen in a higher percentage of subjects in the ranibizumab groups than the sham-injection group. The ranibizumab subjects were also found to use ocular hypotensive and antihypertensive agents more frequently. This trend with the use of antihypertensive agents was noted at screening as well.

Intraocular inflammation including the Med DRA preferred terms iritis, iridocyclitis, vitritis, uveitis and anterior chamber inflammation was experienced at an increased rate in ranibizumab treated subjects in both studies. In study FVF2598g, 60 of 477 subjects (12.5%) and in study FVF2587g 35 of 277 subjects (12.6%) in the ranibizumab groups experienced intraocular inflammation in the study eye. Findings from the objective slit lamp examination were consistent with occurrence of intraocular inflammation adverse events and are discussed

Table 7.1.5.3-2 Ocular Adverse Events in the Fellow Eye during the First Treatment Year Occurring in ≥ 5 % of Patients:
Safety Evaluable Population

MedDRA System Organ Class Preferred Term	[redacted]	[redacted]	Ranibizumab Pooled	0.5 mg N=379
Total [a]	168 (71.2%)	103 (72.7%)	258 (68.8%)	265 (69.9%)
Macular degeneration	60 (25.4%)	32 (22.4%)	91 (24.3%)	83 (21.9%)
Retinal hemorrhage	47 (19.9%)	26 (18.2%)	68 (18.1%)	71 (18.7%)
Vitreous detachment	31 (13.1%)	17 (11.9%)	43 (11.5%)	39 (10.3%)
Blepharitis	16 (6.8%)	6 (4.2%)	25 (6.6%)	29 (7.7%)
Cataract	10 (4.2%)	5 (3.5%)	16 (4.3%)	19 (5.0%)
Choroidal neovascularization	11 (4.7%)	6 (4.2%)	28 (7.5%)	29 (7.7%)
Dry Eye	13 (5.5%)	12 (8.4%)	12 (3.2%)	19 (5.0%)
Retinal disorder	11 (4.7%)	2 (1.4%)	17 (4.5%)	21 (5.5%)
Visual acuity reduced	18 (7.6%)	9 (6.3%)	13 (3.5%)	15 (4.0%)

Reviewer's Comment:
Ocular adverse events seen in the fellow eye during the first treatment year are those expected in this patient population.

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7.1.5.4 Common adverse event tables
Refer to Section 7.1.5.3 Incidence of Common Adverse Events

7.1.5.5 Identifying common and drug-related adverse events

Reviewer's Comment:
Intraocular inflammation which includes Med DRA preferred terms iritis, iridocyclitis, vitritis, uveitis and anterior chamber inflammation was noted to occur in a dose dependent manner in the ranibizumab treated subjects in both studies In study FVF2598g, 60 of 477 subjects (12.5%) and in study FVF2587g 35 of 277 subjects (12.6%) in the ranibizumab groups experienced intraocular inflammation in the study eye. Findings from the objective slit lamp examination were consistent with occurrence of intraocular inflammation adverse events.

Refer to Table 7.1.3.3-3 Intraocular Inflammation in the Study Eye during the First Treatment Year Studies FVF2598g and FVF2587g: Safety Evaluable Subjects for details.

7.1.5.6 Additional analyses and explorations
Not applicable. There were no additional analyses or explorations performed regarding adverse events.

7.1.6 Less Common Adverse Events
The overall safety population was not sufficiently large to identify rare events of significant concern.

7.1.7 Laboratory Findings
During clinical trials FVF2587g and FVF2598g, laboratory assessments were to be performed on all of the subjects at the Screening Visit and Month 12 or Early Termination Visit.

Reviewer's Comment:
None of the laboratory abnormalities noted were serious adverse events, led to treatment or study discontinuation.

7.1.7.1 Overview of laboratory testing in the development program
Laboratory testing during the development program was performed to determine systemic ranibizumab concentrations, immunoreactivity to ranibizumab and if any significant changes in blood chemistry, hematology or coagulation measures could be found.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values
Such analyses were not performed. Laboratory investigations were limited by the low to non-detectable ranibizumab concentrations after intravitreal injection.

7.1.7.3 Standard analyses and explorations of laboratory data
The analyses of laboratory data consisted of description of the findings.

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7.1.7.4 Additional analyses and explorations
No additional analyses and explorations were performed.

7.1.7.5 Special assessments
Laboratory abnormality adverse events were reported in less than 2% of subjects. None of the laboratory abnormalities were serious adverse events, led to treatment or study discontinuation or were considered by the investigators as study drug related.

7.1.8 Vital Signs

Vital signs were measured at the Screening Visit and at each monthly visit post treatment. Overall, on average, both ranibizumab-treated and sham-treated subjects showed little change from baseline in vital signs throughout the first treatment year. There were no meaningful between group differences in the mean change from baseline in the temperature, pulse rate and respiration rate.

Regarding blood pressure, at Month 12, the mean changes from baseline were -1.6, -0.6, and -4.4 mmHg in systolic pressure and -2.0, -1.7, and -0.5 mm Hg in diastolic pressure for the sham, 0.3-mg, and 0.5-mg groups, respectively.

Some subjects had adverse events of increased blood pressure, worsening of preexisting hypertension, or newly diagnosed hypertension during the first treatment year. There was no imbalance among treatment groups in the proportion of subjects with such adverse events (15.7% in the sham group, 13.4% in the 0.3-mg group, and 12.6% in the 0.5-mg group.)

7.1.8.1 Overview of vital signs testing in the development program
Refer to Section 7.1.1.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons
These analyses were not performed.

7.1.8.3 Standard analyses and explorations of vital signs data
These analyses were not performed.

7.1.8.4 Additional analyses and explorations
Additional analyses and explorations of vital signs data were not performed.

7.1.9 Electrocardiograms (ECGs)

Electrocardiograms were not obtained during the development program for this product.

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7.1.10 Immunogenicity

Serum samples for the evaluation of immunoreactivity to ranibizumab were obtained from subjects at screening and prior to study drug administration at Months 6 and 12. The assay demonstrated immunoreactivity in a small percentage of subjects in all three treatment groups prior to initial administration of study drug, possibly due to preexisting anti-Fab antibodies.

There was no imbalance between ranibizumab-treated and sham-treated subjects regarding immunoreactivity to ranibizumab. The assay indicated positivity in a small percentage of subjects in all three treatment groups prior to initial administration of study drug, possibly due to preexisting anti-Fab antibodies. All three treatment groups had similar increases in positivity during the treatment period.

Table 7.1.10-1 Immunoreactivity to Ranibizumab in the First Treatment Year

Screening	5/215 (2.3%)	6/215 (2.8%)	7/218 (3.2%)	8/131 (6.1%)	12/125 (9.6%)	7/123 (5.7%)
Month 6	19/201 (9.5%)	15/211 (7.1%)	17/207 (8.2%)	6/114 (5.3%)	11/120 (9.2%)	10/116 (8.6%)
Month 12	20/206 (9.7%)	22/222 (9.9%)	26/219 (11.9%)	7/125 (5.6%)	9/123 (7.3%)	16/129 (12.4%)

Note: Table entries are numbers of subjects with positive immunoreactivity over numbers of subjects with evaluable samples. LTR=0.7 log titer.

Exploratory subgroup analyses based on immunoreactivity to ranibizumab were performed to determine whether the appearance of immunoreactivity was related to key safety and efficacy outcomes. The analysis population was divided into three subgroups: subjects who had a negative or missing test result at screening and negative post-baseline results, subjects who had a negative or missing test result at screening but at least one positive post-baseline result, and subjects who had a positive test result at screening. Visual acuity outcomes and the occurrence of intraocular inflammation and autoimmune adverse events were examined by treatment group for each immunoreactivity subgroup. No clinically relevant differences between immunoreactivity subgroups were identified in study FVF2598g.

In Study FVF2587g, with regard to intraocular inflammation adverse events, proportionately more ranibizumab-treated subjects who were immunoreactive at some time point experienced intraocular inflammation events than subjects who were never immunoreactive. Twenty- eight percent (5 of 18) of ranibizumab-treated subjects who were immunoreactive during treatment only and thirty-two percent of subjects (6 of 19) who were immunoreactive at baseline experienced inflammation adverse events in the study eye, compared with 10% of ranibizumab-treated subjects (23 of 230) who were never immunoreactive. Of the 12 verteporfin PDT-treated subjects who were immunoreactive at some time point, none experienced an intraocular inflammation adverse event.

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Table 7.1.10-2 Intraocular Inflammation in Subjects with Immunoreactivity
Based on the Initial and Confirmatory Assays (ECLAs 4.FBV.8 and 4.FBV.10)
Studies FVF2428g, FVF2587g, FVF3192g (First Treatment Year) and FVF2598g (2-Year Treatment Period)
Safety Evaluable Subjects

[illegible]	[illegible]	[illegible]	Study Day / Visit [illegible]	[illegible]	Any [illegible]	[illegible]
FVF2428g	Verteporfin PDT + sham	91103	34 / Month 1	1.200	Iritis	Month 4
	Verteporfin PDT + Ranibizumab 0.5 mg	91308	-77 / Screening	0.884	No	
			366 / Month 12	0.767		
FVF2587g	Verteporfin PDT	319001	386 / Month 12	0.797	No	---
		334008	-12 / Screening	1.130	No	
			190 / Month 6	0.902	No	
		401002	-6 / Screening	1.820	No	
			186 / Month 6	1.780		
			361 / Month 12	1.800		
	Ranibizumab 0.3mg	321003	-7 / Screening	0.945	Yes – Vitritis	Screen, Month 1
		334003	176 / Month 6	2.300	Yes – Iritis	Month 4
		337012	-26 / Screening	0.938	Yes – Iritis	Month 5
		351004	344 / Month 12	2.190	No	---
		352006	-10 / Screening	2.070	No	---
			180 / Month 6	1.890	No	---
			362 / Month 12	1.860	No	---
		403003	-1 / Screening	0.910	No	---
	Ranibizumab 0.5mg	366020	174 / Month 6	1.530	Yes – Vitritis	Months 1 and 2
			362 / Month 12	1.850		
		337009	364 / Month 12	1.270	No	---
		342007	174 / Month 6	2.450	Yes – Iritis, Vitritis	Month 11
			360 / Month 12	3.060		
		346001	182 / Month 6	1.260	No	---

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Study	Treatment Group	Subject ID	Study Day / Visit of Positive Immunoreactivity Assay	Immunoreactivity Assay Log Titer	Any Intraocular Inflammation Diagnosis	Study Visit of Intraocular Inflammation Diagnosis
FVF2598g	Sham	102004	361 / Month 12	1.770		
		389001	-28 / Screening	1.240	No	---
			182 / Month 6	0.993	Yes – Uveitis [3]	Month 7
			365 / Month 12	0.952		
		102004	183 / Month 6	1.230	No	---
			358 / Month 12	2.090		
			463 / Early term.	2.060		
		116002	723 / Month 24	2.160	No	
		139004	-28 / Screening	2.100	Yes – Iritis	Day 7
			176 / Month 6	2.060		
			358 / Month 12	2.170		
			729 / Month 24	2.340		
		150005	181 / Month 6	0.864	No	---
			393 / Month 12	0.863		
		182003	355 / Month 12	0.903	No	---
	Ranibizumab 0.3mg	101021	361 / Month 12	1.850	No	
			719 / Month 24	1.810		
		110004	728 / Month 24	1.490	No	---
		112002	716 / Month 24	0.866	No	---
		125007	183 / Month 6	0.918	No	---
		141009	721 / Month 24	1.270	No	
		143001	-13 / Screening	3.550	Iritis	Month 2
			177 / Month 6	3.740		
		146001	714 / Month 24	1.080	No	
		149006	364 / Month 12	3.150	Iritis	Month 15 [4]
			717 / Month 24	2.120		
		159013	360 / Month 12	2.090	No	
			724 / Month 24	1.890		
		165002	-21 / Screening	0.910	No	
			175 / Month 6	0.993		
			368 / Month 24	0.793		

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Study	Treatment Group	Subject ID	Study Day / Visit of Positive Immunoreactivity / Assay	Immunoreactivity Assay Log Titer	Any Intraocular Inflammation Diagnosis	Study Visit of Intraocular Inflammation Diagnosis
FVF3192g	Ranibizumab 0.5 mg	170010	365 / Month 12	2.770	No	
			715 / Month 24	2.880		
		177006	358 / Month 12	1.870	Iritis	Day 7
			717 / Month 24	1.850		
		102201	722 / Month 24	0.922	No	
		104002	719 / Month 24	1.140	No	
		106002	722 / Month 24	1.130	No	
		122002	359 / Month 12	1.630	No	
			723 / Month 24	1.770		
		124003	722 / Month 24	0.782	No	
		126001	174 / Month 6	1.700	No	
			357 / Month 12	2.040		
			727 / Month 24	1.480		
		141008	181 / Month 6	1.370	No	
			362 / Month 12	1.940		
			726 / Month 24	2.340		
		141013	715 / Month 24	2.610	Vitritis	Day 0
		143010	722 / Month 24	2.440	No	
		152004	522 / Early Term.	0.752	No	
		153006	183 / Month 6	1.900	No	
			365 / Month 12	1.530		
			718 / Month 24	2.070		
		159013	716 / Month 24	0.780	No	
		167002	717 / Month 24	1.230	No	
		188005	717 / Month 24	1.250	No	
FVF3192g	Sham	534001	-7 / Screening	2.520	Vitritis	Month 1
	Ranibizumab 0.5 mg	507018	357 / Month 12	0.875	No	
		522002	367 / Month 12	1.530	No	

1 In Study FVF2428g, intravitreal injections (sham or ranibizumab 0.5 mg) were given every month and verteporfin PDT every 3 months.
2 Iritis diagnosed 1 day after Month 4 injection.

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C　　IBLA
Rhea A. Lloyd, MD
125156
Lucentis (ranibizumab injection)

3 Iritis diagnosed day of injection. Injection was not held.
4 No resolution of uveitis noted in CRFs submitted.
5 Uveitis diagnosed 3 days post Month 7 injection. Serious AE led to treatment discontinuation in Month 9.
6 Treatment discontinued.

Reviewer's Comment:
Fifty subjects in Studies FVF2428g, FVF2587g and FVF2598g had measurable immunoreactivity based upon initial and confirmatory assays. Thirteen of these subjects experienced episodes of intraocular inflammation.

In subjects with an immunoreactivity assay log titer of > 2.00, 31% experienced at least one episode of intraocular inflammation.

In subjects with an immunoreactivity assay log titer of >3.00, 100% experienced an episode of intraocular inflammation.

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7.1.11 Human Carcinogenicity

Not applicable.

7.1.12 Special Safety Studies

Safety analysis was based on an evaluation of other safety parameters, as well, which included visual acuity (best corrected), intraocular pressure, ocular signs by slit lamp examination and indirect ophthalmoscopy the results of which are included throughout the safety review.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

Not applicable. This is not a therapeutic class with known abuse potential or apparent withdrawal potential.

7.1.14 Human Reproduction and Pregnancy Data

There are no adequate and well-controlled studies in pregnant women. There was no inadvertent exposure to the product in pregnant women during the development program.

7.1.15 Assessment of Effect on Growth

The intended population for this product is adults with age-related macular degeneration, a disease that does not exist in the pediatric age group. This application contains no pediatric data.

7.1.16 Overdose Experience

This product has no overdose potential and no studies were performed.

7.1.17 Postmarketing Experience

This product has not yet been marketed.

7.2 Adequacy of Patient Exposure and Safety Assessments

The safety and exposure database for Ranibizumab included in this application is derived from 976 ranibizumab-treated subjects with neovascular age-related macular degeneration, in six clinical trials.

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

The submitted clinical study reports and clinical protocols related to the development program of ranibizumab were analyzed in this review. Proposed draft labeling and Case Report Forms for discontinued subjects in studies FVF2587g and FVF2598g were provided and reviewed. Refer to Section 4.1.

7.2.1.1 Study type and design/patient enumeration

Refer to Section 4.2 for the table of clinical studies.

7.2.1.2 Demographics

Refer to Table 6.1.3.1-9 and Table 6.1.3.2-9 Demographic Statistics by Treatment Group for Studies FVF2598g and FVF2587g.

Reviewer's Comments:

There are no remarkable differences between treatment groups in baseline demographic characteristics.

Subgroup analyses did not reveal any differences in the studies' success on the primary efficacy endpoint.

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7.2.1.3 Extent of exposure (dose/duration)

Table 7.2.1.3-1 Extent of Exposure to Study Drug or Sham Injection
Safety Evaluable Subjects

	[redacted]			[redacted]	[redacted]	[redacted]
Number of injections [a]						
Mean (SD)	11.7 (2.7)	12.4 (1.9)	12.3 (2.2)	12.0 (2.5)	12.2 (2.1)	12.1 (2.2)
Frequency						
< 10	27 (11.4%)	10 (4.2%)	15 (6.3%)	17 (11.9%)	9 (6.6%)	13 (9.3%)
10-12	55 (23.3%)	36 (15.1%)	40 (16.7%)	21 (14.7%)	29 (21.2%)	29 (20.7%)
13	154 (65.3%)	192 (80.7%)	184 (77.0%)	105 (73.4%)	99 (72.3%)	98 (70.0%)
Treatment duration (days) [b]						
Mean (SD)	332.7 (80.0)	350.6 (54.7)	346.2 (61.5)	337.1 (75.0)	346.2 (61.8)	345.6 (59.7)

a Of 13 scheduled injections from Day 0 to Month 12 visits. The verteporfin PDT group received sham injections.
b The number of days between the first and the last injection on or prior to Month 12 visit.

Reviewer's Comment:
The extent of exposure was similar between all treatment groups in each study. The vast majority of subjects received 10 or more treatment injections. The mean treatment duration ranged from 332.7 days to 350.6 days among the treatment groups.

Table 7.2.1.3-2
Extent of Exposure to Study Treatment with Verteporfin or Sham PDT
Safety Evaluable Subjects in the First Treatment Year

	[redacted]		
Number of Treatments			
Mean (SD)	3.1 (1.3)	1.9 (1.3)	1.8 (1.3)
1	18 (12.6%)	76 (55.5%)	79 (56.4%)
2	33 (23.1%)	32 (23.4%)	29 (20.7%)
3	36 (25.2%)	12 (8.8%)	19 (13.6%)
4	26 (18.2%)	5 (3.6%)	9 (6.4%)
5	30 (21.0%)	12 (8.8%)	4 (2.9%)
Treatment duration (days) [b]			
Mean (SD)	228.1 (129.0)	95.8 (129.2)	84.2 (116.3)

a Of 5 possible treatments form Day 0 to Month 12 visits. The ranibizumab groups received sham PDT.
b The number of days between the first and the last treatment on or prior to Month 12 visit.

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Table 7.2.1.3-3
Number of Study Drug or Sham Injection Treatments Held
Per Protocol-Specified Criteria During the First Treatment Year
Safety Evaluable Subjects

Injections Held	[redacted]	[redacted]	[redacted]	[redacted]	Ranibizumab 0.5 mg N=140	Ranibizumab 0.5 mg N=140
Mean	0.1 (0.4)	0.1 (0.4)	0.1 (0.4)	0.0 (0.2)	0.0 (0.2)	0.2 (0.7)
0	224 (94.9%)	227 (95.4%)	229 (95.8%)	140 (97.9%)	131 (95.6%)	129 (92.1%)
1	7 (3.0%)	9 (3.8%)	7 (2.9%)	2 (1.4%)	6 (4.4%)	6 (4.3%)
2	3 (1.3%)	0	2 (0.8%)	1 (0.7%)	0	3 (2.1%)
3	1 (0.4%)	1 (0.4%)	0	0	0	0
4	1 (0.4%)	1 (0.4%)	1 (0.4%)	0	0	0
5	0	0	0	0	0	2 (1.4%)

Reviewer's Comment:
The vast majority, more than 92% of patients in each treatment group, did not require that treatments be held due to the protocol-specified dose-holding criteria.

Table 7.2.1.3-4
Study Drug or Sham Injection Held per Protocol-Specified Criteria by Criterion Met
First Treatment Year: Safety Evaluable Subjects

Criterion	[redacted]	[redacted]	[redacted]	[redacted]	Ranibizumab 0.5 mg N=140	Ranibizumab 0.5 mg N=140
Any Treatment Held	12 (5.1%)	11 (4.6%)	10 (4.2%)	3 (2.1%)	6 (4.4%)	11 (7.9%)
Intraocular inflammation	0	2 (0.8%)	4 (1.7%)	0	1 (0.7%)	3 (2.1%)
Visual acuity loss	6 (2.5%)	1 (0.4%)	1 (0.4%)	1 (0.7%)	0	0
IOP elevation	0	0	1 (0.4%)	0	1 (0.7%)	2 (1.4%)
Vitreous hemorrhage	0	2 (0.8%)	0	0	0	0
Sensory rhegmatogenous retinal detachment / break	1 (0.4%)	1 (0.4%)	1 (0.4%)	0	1 (0.7%)	0
Subfoveal hemorrhage	5 (2.1%)	1 (0.4%)	0	2 (1.4%)	0	2 (1.4%)
Local or systemic infxn	0	4 (1.7%)	2 (0.8%)	0	2 (1.5%)	4 (2.9%)
Intraocular surgery	0	0	2 (0.8%)	0	1 (0.7%)	1 (0.7%)

Note: Tabulation was based on the 13 scheduled injections from Day 0 to Mont 12. Multiple injections that were held because of the same criterion for a given subject were counted once in the overall incidence for the criterion. Multiple occurrences of injections held in a subject were counted once in the overall incidence.

Reviewer's Comment:
Approximately 5% of subjects in each treatment group in Study FVF2598g required that at least one treatment be held due to the protocol-specified dose-holding criteria. In the sham treatment group, the reason for dose holding was most frequently visual acuity loss or subfoveal hemorrhage. In the ranibizumab treatment groups, no single criterion was met in the majority of cases.

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In Study FVF2587g, treatments were held for protocol-specified holding criteria least often in the verteporfin PDT group and most frequently in the 0.5 mg ranibizumab group. Intraocular inflammation and local or systemic infection were the most frequent criteria met in the 0.5 mg ranibizumab group.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

The medical reviewer conducted a PubMed electronic literature search to supplement the submitted review of the relevant literature. There was no significant new information found in the published litereature.

7.2.2.1 Other studies

No other studies were used to evaluate safety.

7.2.2.2 Postmarketing experience

The product has not yet been marketed. No postmarketing data were used to evaluate safety.

7.2.2.3 Literature

The applicant's literature search was complete, including important issues of safety and efficacy.

7.2.3 Adequacy of Overall Clinical Experience

The overall clinical experience was adequate.

The pivotal studies, FVF2587g and FVF2598g, were adequate and well-controlled studies which demonstrated the efficacy of ranibizumab. An adequate number of subjects from relevant demographic groups were exposed to this formulation of ranibizumab to assess potential during the development program. The study designs were appropriate.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Refer to the Pharmacology/Toxicology review for details.

7.2.5 Adequacy of Routine Clinical Testing

Routine clinical testing and monitoring of study subject was adequate to elicit adverse events.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Studies to evaluate metabolism, clearance and interaction were not performed due to the negligible systemic absorption of ranibizumab given by the intravitreal route of administration.

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7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The applicant has made adequate efforts to detect specific adverse events for ranibizumab as a biologic and a VEGF inhibitor.

Serum samples for the evaluation of immunoreactivity to ranibizumab were obtained from subjects at screening and prior to study drug administration at Months 6 and 12. The assay demonstrated immunoreactivity in a small percentage of subjects in all three treatment groups prior to initial administration of study drug, possibly due to preexisting anti-Fab antibodies. There was no imbalance between ranibizumab-treated and sham-treated subjects regarding immunoreactivity to ranibizumab. Refer to Section 7.1.10 for details. Analyses of potential side effects related to systemic VEGF inhibition focused on the incidence of hypertension, arterial thromboembolic events and non-ocular hemorrhage.

Table 7.2.7-1 Serious Adverse Events Potentially Related to Systemic VEGF Inhibition during the First Treatment Year: Studies FVF2598g and FVF2587g

[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
TOTAL[a]	2 (0.8%)	8 (3.4%)	9 (3.8%)	3 (2.1%)	4 (2.9%)	8 (5.7%)
Hypertension events	0	1 (0.4%)	0	0	0	0
Arterial thromboembolic events	2 (0.8%)	5 (2.1%)	8 (3.3%)	2 (1.4%)	2 (1.4%)	4 (2.9%)
Non-ocular hemorrhages	0	1 (0.4%)	0	0	2 (1.5%)	3 (2.1%)
Other potentially associated events	0	1 (0.4%)	1 (0.4%)	1 (0.7%)	1 (0.7%)	1 (0.7%)

Note: Multiple occurrences of the same type of event for a subject were counted once in the overall incidence.

Reviewer's Comment:

In the two phase 3 studies, a small trend in the occurrence of serious adverse events potentially related to systemic VEGF inhibition was noted, particularly in the ranibizumab 0.5-mg dose group. This reflects trends in serious arterial thromboembolic events and, to a lesser extent, in serious non-ocular hemorrhages (but not in serious hypertension or proteinuria). No imbalance in overall adverse events potentially related to systemic VEGF inhibition was observed among treatment groups.

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7.2.8 Assessment of Quality and Completeness of Data

The data presented were complete and of good quality.

7.2.9 Additional Submissions, Including Safety Update

The sponsor has submitted the following additional submissions of clinical safety and efficacy data during the review cycle. Amendments 003 and 006 were submitted in response to reviewer requests for additional analyses of the safety database. These amendments have been reviewed individually and the results incorporated into the rest of the review.

- Amendment 003 - Analysis of all of the thromboembolic adverse events in the ranibizumab trials including a comparison of risk factors and concomitant medications between patients who experienced thromboembolic events and all enrolled patients. (Submitted February 17, 2006)
- Amendment 006 – Request for information on all discontinued subjects regardless of attribution to study treatment, all serious adverse events and all adverse events occurring ≥ 1% of subjects in any treatment group for both Phase 3 studies. (Submitted March 17, 2006)
- Amendment 008 - Study FVF2598g Year 2 Data and Updated Draft Labeling (Submitted March 31 2006)

On April 28, 2006, the sponsor submitted the 120-Day Safety Update which is considered in this section. This update to the Summary of Clinical Safety includes additional safety information available from Study FVF2598g. Since the submission of the BLA, the collection and cleaning of second-treatment-year data from Study FVF2598g has been completed, and this update includes summaries based on final 2-year data from the study. No additional safety analyses are provided in the SCS update for Study FVF2587g because the trial is still ongoing, or for Study FVF2428g per prior agreement with the FDA. There are no updates to the safety analyses provided for Studies FVF2128g, FVF2425g, and FVF1770g because these trials were complete at the time of the original SCS.

All summaries presented within this report for Study FVF2598g are based on the safety-evaluable population (all subjects who received at least one ranibizumab or sham injection). In addition, subjects are grouped according to the actual treatment received, as defined from the safety analyses presented in the FVF2598g CSR Addendum. Subjects in the sham-injection group who crossed over to receive 0.5 mg ranibizumab per the sixth protocol amendment are included in the safety analyses. These subjects are included in the sham-injection group.

The original SCS included safety data from 1413 subjects, 976 of whom received treatment with ranibizumab. Of the six studies included in the SCS, Study FVF2598g was the largest with a total of 713 safety-evaluable subjects, 477 of whom received treatment with ranibizumab. As summarized in the original SCS, more than 5,800 ranibizumab injections and 2,700 sham injections were administered during the first treatment year of Study FVF2598g.

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Table 7.2.9-1 Extent of Study Drug Exposure: Study FVF2598g

[redacted]			
Original SCS			
Number of injections [a]			
Total	2765	2952	2929
Mean (SD) [b]	11.7 (2.7)	12.4 (1.9)	12.3 (2.2)
Treatment duration (days) [c]			
Mean (SD)	332.7 (80.0)	350.6 (54.7)	346.2 (61.5)
Update to SCS			
Number of injections [a]			
Total	4709	5248	5195
Mean (SD) [b]	20.0 (6.3)	22.1 (4.4)	21.7 (5.0)
Treatment duration (days) [c]			
Mean (SD)	590.1 (191.2)	651.4 (130.2)	639.9 (148.2)

a Intravitreal ranibizumab injection or sham injection b Number of injections per subject, or 24 scheduled injections during the 2-year treatment period. The summary includes ranibizumab injections received by subjects in the sham-injection group after crossover and a Month 24 injection received by Subject 144001 in the 0.5-mg group. c Number of days between the first and the last injection during the study period.

Reviewer's Comments:

The extent of study drug exposure was well balanced between the treatment groups in the first and second years of the study.

Table 7.2.9-3 Treatment and Study Discontinuations during the 2-Year Treatment Period: Safety Evaluable Subjects - Study FVF2598g

[redacted]			
Crossed over to receive 0.5 mg ranibizumab	12 (5.1%)	--	--
At Month 22	5 (2.1%)	--	--
At Month 23	7 (3.0%)	--	--
Discontinued treatment [a]	**66 (28.0%)**	**30 (12.6%)**	**32 (13.4%)**
Death	5 (2.1%)	5 (2.1%)	3 (1.3%) [b]
Adverse event	13 (5.5%)	8 (3.4%)	14 (5.9%) [b]
Lost to follow-up	2 (0.8%)	2 (0.8%)	3 (1.3%)
Subject's decision	24 (10.2%)	17 (7.1%)	13 (5.4%)
Physician's decision	1 (0.4%)	1 (0.4%)	2 (0.8%)
Subject non-compliance	1 (0.4%)	0	0
Subject's condition mandated other therapeutic intervention	23 (9.7%)	1 (0.4%)	0

a Some subjects remained in the study after treatment discontinuation.
b Three subjects discontinued from treatment because of an adverse event that resulted in death (the primary reason for study discontinuation).

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Table 7.2.9-4 Deaths during the 2-Year Treatment Period: Safety Evaluable Subjects - Study FVF2598g

[redacted]	[redacted]	[redacted]	0.5 mg (N=239)
Overall	6 (2.5%)	5 (2.1%)	6 (2.5%)
Year 1	0	1 (0.4%)	2 (0.8%)
Year 2	6 (2.5%)	4 (1.7%)	4 (1.7%)

Table 7.2.9-5 Primary Cause of Deaths that Occurred during the 2-Year Treatment Period: Study FVF2598g

Time Period	[redacted]	[redacted]	[redacted]	[redacted]	Days Since Last Study Treatment
Year 1 [1]	0.3 mg	78/F	Heart attack	12	11
	0.5 mg	78/F	Small bowel infarct	178	24
		90/F	Chronic asthma / COPD	155	2
Year 2	Sham	74/F	Unknown cause	481	3
		88/M	Congestive heart failure	724	91
		76/F	Cerebrovascular accident	673	35
		77/M	Acute or chronic renal failure	656	45
		80/M	Cerebral vascular accident; bilateral parietal lobe and cerebellum	576	31
		71/M	Acute respiratory failure	400	67
	0.3 mg	91/F	Unknown	669	99
		77/F	Complications of Non-Hodgkin's Lymphoma	752	425
		91/F	Myocardial infarction	570	23
		81/M	Pneumonia	617	47
	0.5 mg	72/M	Closed head injury resulting from automobile accident	627	57
		87/F	Stroke	667	461
		76/M	Sepsis	496	16
		85/F	Hemorrhagic cerebrovascular accident	428	14

Reviewer's Comment:
An additional 14 deaths occurred in the second treatment year. Overall, no imbalance was noted between the treatment groups in the numbers or causes of death during the 2 year treatment period. The primary causes of death were common events in this elderly population of patients.

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Table 7.2.9-6 Ocular Serious Adverse Events in the Study Eye during the 2-Year Treatment Period (Occurring in > 1 Subject Overall): Study FVF2598g

[redacted]			
Total Ocular Events in the Study Eye [a]	17 (7.2%)	20 (8.4%)	21 (8.8%)
Choroidal neovascularization	2 (0.8%)	0	0
Detachment of RPE	0	1 (0.4%)	1 (0.4%)
Endophthalmitis	0	2 (0.8%)	2 (0.8%)
IOP increased	0	1 (0.4%)	2 (0.8%)
Iridocyclitis	0	1 (0.4%)	2 (0.8%)
Macular degeneration	6 (2.5%)	1 (0.4%)	2 (0.8%)
Medication error	0	1 (0.4%)	1 (0.4%)
Retinal detachment	1 (0.4%) [b]	1 (0.4%) [c]	0
Retinal hemorrhage	4 (1.7%)	2 (0.8%)	1 (0.4%)
Retinal tear	0	1 (0.4%)	1 (0.4%)
Uveitis	0	1(0.4%)	1 (0.4%)
Visual acuity reduced	3 (1.3%)	3 (1.3%)	1 (0.4%)
Vitreous hemorrhage	2 (0.8%)	1 (0.4%)	1 (0.4%)

Note: Multiple occurrences of the same event in a subject were counted once in the overall incidence.
a Represents the number of subjects with at least one ocular adverse event in the study eye.
b Rhegmatogenous retinal detachment
c Exudative retinal detachment

Reviewer's Comment:
Generally, serious ocular adverse events occurred in a very low percentage of subjects regardless of treatment group. The results are similar to those seen in the first treatment year.

Given the numbers of intravitreal injections in each treatment group (See Table 7.2.9-1), the per-injection rates of endophthalmitis, traumatic cataract, intraocular inflammation and retinal detachment were all very low approximately ≤ 0.10% per injection in each dose group.

Conjunctival hemorrhage, increased intraocular pressure, vitreous floaters, and vitritis occurred more frequently in the ranibizumab groups than in the sham injection group.

Choroidal neovascularization, macular degeneration, retinal hemorrhage, and subretinal fibrosis, manifestations of active neovascular AMD lesions were more common in the sham-injection group than in the ranibizumab groups.

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Table 7.2.9-7 Non-Ocular Serious Adverse Events during the 2-Year Treatment Period (Occurring in > 1 Subject Overall) Study FVF2598g

Total Non-Ocular Events	73 (30.4%)	82 (34.5%)	76 (31.8%)
Abdominal pain upper	3 (1.3%)	0	0
Acute myocardial infarction	0	3 (1.3%) [b]	0
Angina unstable	0	2 (0.8%)	0
Arthritis	0	2 (0.8%)	0
Asthma	1 (0.4%)	1 (0.4%)	2 (0.8%)
Atrial fibrillation	4 (1.7%)	3 (1.3%)	5 (2.1%)
B-cell lymphoma	2 (0.8%)	0	0
Back pain	0	2 (0.8%)	0
Breast cancer	2 (0.8%)	0	0
Cardiac failure congestive	6 (2.5%)	4 (1.7%)	1 (0.4%)
Carotid artery stenosis	0	0	2 (0.8%)
Cellulitis	5 (2.1%)	1 (0.4%)	0
Cerebrovascular accident	3 (1.3%)	3 (1.3%)	6 (2.5%)
Chest pain	3 (1.3%)	4 (1.7%)	3 (1.3%)
Chronic obstructive pulmonary disease	2 (0.8%)	4 (1.7%)	4 (1.7%)
Coronary artery disease	5 (2.1%)	2 (0.8%0	4 (1.7%)
Coronary artery occlusion	1 (0.4%)	0	2 (0.8%)
Deep vein thrombosis	0	3 (1.3%)	0
Dehydration	0	1 (0.4%)	2 (0.8%)
Diverticulitis	1 (0.4%)	2 (0.8%)	4 (1.7%)
Gout	2 (0.8%)	0	0
Hip fracture	1 (0.4%)	5 (2.1%)	1 (0.4%)
Lobar pneumonia	1 (0.4%)	2 (0.8%)	0
Lumbar spinal stenosis	2 (0.8%)	0	0
Lung neoplasm malignant	3 (1.3%)	2 (0.8%)	2 (0.8%)
Myocardial infarction	4 (1.7%)	4 (1.7%)	2 (0.8%)
Non-cardiac chest pain	0	0	2 (0.8%)
Osteoarthritis	3 (1.3%)	1 (0.4%)	0
Pneumonia	4 (1.7%)	9 (3.8%)	7 (2.9%)
Renal cell carcinoma stage unspecified	2 (0.8%)	0	0
Sepsis	0	0	3 (1.3%)
Syncope	6 (2.5%)	3 (1.3%)	2 (0.8%)
Transient ischemic attack	1 (0.4%)	2 (0.850	3 (1.3%)

Note: Multiple occurrences of the same event for a subject were counted once in the overall incidence.
a Represents the number of subjects with at least one non-ocular serious adverse event.
b Includes Subject 104020 with a serious adverse event of acute myocardial infarction even though the event was removed from final study database based on a investigator correction form submitted after the completion of the FVF2598g CS.
c The sham-treated subject (118004) who experiences a subacute parietooccipital CVA (reported as an ocular serious adverse event) had received a single injection of 0.5 mg ranibizumab in error approximately 8 months prior to the event. d Includes one case reported as a cerebral ischemia.

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Reviewer's Comment:
The adverse events which were seen more frequently in the ranibizumab 0.5 mg group versus control are highlighted. The percentages of subjects with non-ocular serious adverse events were well balanced among the treatment groups and similar to those seen in the first treatment year.

Table 7.2.9-8 Ocular Adverse Events in the Study Eye that Led to Discontinuation from Study or from Treatment during the 2-Year Treatment Period: Study FVF2598g

MedDRA	[redacted]	[redacted]	[redacted]
Total [a]	15 (6.4%)	6 (2.5%)	7 (2.9%)
Choroidal neovascularization	7 (3.0%)	0	0
Conjunctivitis allergic	0	0	1 (0.4%)
Eye pain	0	0	2 (0.8%)
Glaucoma	0	0	1 (0.4%)
Hypopyon	0	0	1 (0.4%)
Indocyclitis	0	0	2 (0.8%)
Iris adhesions	0	0	1 (0.4%)
Iritis	0	3 (1.3%)	0
Macular degeneration	6 (2.5%)	0	0
Macular hole	0	1 (0.4%)	0
Maculopathy	0	1 (0.4%)	0
Retinal detachment	1 (0.4%)	0	0
Retinal hemorrhage	4 (1.7%)	1 (0.4%)	0
Retinal tear	1 (0.4%)	0	0
Uveitis	0	0	2 (0.8%)
Visual acuity reduced	2 (0.8%)	0	0
Vitreous detachment	1 (0.4%)	0	0
Vitreous floaters	0	0	1 (0.4%)
Vitritis	0	0	1 (0.4%)

Note: Multiple occurrences of the same event in a subject were counted once in the overall incidence.
a Represents the number of subjects with at least one ocular adverse event in the study eye that led to discontinuation of study or treatment.

Reviewer's Comment:
There was a larger discontinuation rate in the sham-injection group than in either ranibizumab group usually due to signs and symptoms of worsening macular degeneration.

Ranibizumab group discontinuations were caused by signs and symptoms that may be associated with intraocular inflammation. These findings are similar to those in the first treatment year.

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Table 7.2.9-9 Ocular Adverse Events in the Study Eye during the 2-Year Treatment Period (Occurring in ≥ 10% of Subjects in Any Group): Study FVF2598g

	[redacted]	[redacted]	[redacted]
Total [a]	234 (99.2%)	236 (99.2%) [a]	235 (98.3%)
Blepharitis	21 (8.9%)	26 (10.9%)	32 (13.4%)
Cataract NOS [b]	37 (15.7%)	37 (15.5%)	37 (15.5%)
Choroidal neovascularization	40 (16.9%)	1 (0.4%)	4 (1.7%)
Conjunctival hemorrhage	156 (66.1%)	184 (77.3%)	181 (75.7%)
Detachment of RPE	36 (15.3%)	27 (11.3%)	22 (9.2%)
Dry eye	15 (6.4%)	16 (6.7%)	24 (10.0%)
Eye irritation	47 (19.9%)	38 (16.0%)	46 (19.2%)
Eye pain	79 (33.5%)	86 (36.1%)	89 (37.2%)
Eye pruritus	29 (12.3%)	23 (9.7%)	32 (13.4%)
Foreign body sensation in eyes	34 (14.4%)	43 (18.1%)	45 (18.8%)
Intraocular inflammation [c]	25 (10.6%)	33 (13.9%)	43 (18.0%)
IOP increased	14 (5.9%)	57 (23.9%)	57 (23.8%)
Lacrimation increased	38 (16.1%)	41 (17.2%)	39 (16.3%)
Macular degeneration	159 (67.4%)	111 (46.6%)	109 (45.6%)
Macular edema	27 (11.4%)	6 (2.5%)	12 (5.0%)
Maculopathy	27 (11.4%)	20 (8.4%)	23 (9.6%)
Ocular hyperemia	24 (10.2%)	24 (10.1%)	24 (10.0%)
Retinal degeneration	16 (6.8%)	25 (10.5%)	24 (10.0%)
Retinal disorder	22 (9.3%)	27 (11.3%)	30 (12.6%)
Retinal exudates	25 (10.6%)	21 (8.8%)	16 (6.7%)
Retinal hemorrhage	132 (55.9%)	61 (25.6%)	58 (24.3%)
Subretinal fibrosis	37 (15.7%)	22 (9.2%)	15 (6.3%)
Vision blurred	20 (8.5%)	34 (14.3%)	22 (9.2%)
Visual acuity reduced	39 (16.5%)	26 (10.9%)	24 (10.0%)
Visual disturbance	21 (8.9%)	27 (11.3%)	33 (13.8%)
Vitreous detachment	42(17.8%)	52 (21.8%)	53 (22.2%)
Vitreous floaters	24 (10.2%)	76 (31.9%)	71 (29.7%)
Vitritis	8 (3.4%)	17 (7.1%)	30 (12.6%)

Note: Multiple occurrences of the same event in a subject were counted once in the overall incidence.
a Represents the number of subjects with at least one ocular adverse event in the study eye. b Includes the preferred terms: cataract, cataract cortical, cataract nuclear, cataract subcapsular, cataract traumatic, and lenticular opacities.
c Includes the preferred terms anterior chamber inflammation, hypopyon, iridocyclitis, iritis, uveitis and vitritis.

Reviewer's Comment:
The adverse events which were seen more frequently in the ranibizumab 0.5 mg group versus control are highlighted. Conjunctival hemorrhage, increased intraocular pressure, vitreous floaters, and vitritis occurred more frequently in the ranibizumab groups than in the sham injection group. These findings are similar to those in the first treatment year.

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Choroidal neovascularization, macular degeneration, retinal hemorrhage, and subretinal fibrosis, manifestations of active neovascular AMD lesions were more common in the sham-injection group than in the ranibizumab groups

The apparent dose dependent trend in the incidence of intraocular inflammation adverse events in the study eye was slightly increased in the 2-year treatment period data. Seven of the ranibizumab-treated subjects (1.5%) experienced at least one serious intraocular inflammation adverse event in the study eye. All of the serious intraocular inflammation adverse events were considered by the investigator to be related to study drug. Six of the seven subjects had study treatment held or discontinued from study treatment because of serious intraocular inflammation. One subject in the ranibizumab 0.5-mg group was reported to have serious uveitis and was treated with intravitreal antibiotics. The sponsor considered this adverse event a presumed case of endophthalmitis.

Elevated intraocular pressure adverse events were noted more frequently in the ranibizumab treated groups. Most events were reported as mild or moderate in severity though three ranibizumab-treated subjects had severe events. For those events that required treatment, medication was used most frequently though paracenteses and anterior chamber taps were required in eight of the 305 reported events.

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Table 7.2.9-10 Non-Ocular Adverse Events in the Study Eye during the 2-Year Treatment Period (Occurring in ≥ 5% of Subjects in Any Group):[1]Study FVF2598g

Total [a]	214 (90.7%)	228 (95.8%)	228 (95.8%)
Anemia	19 (8.1%)	17 (7.1%)	18 (7.5%)
Anxiety	7 (3.0%)	10 (4.2%)	12 (5.0%)
Arthralgia	21 (8.9%)	26 (10.9%)	27 (11.3%)
Arthritis	20 (8.5%)	17 (7.1%)	19 (7.9%)
Back pain	22 (9.3%)	24 (10.1%)	22 (9.2%)
Blood pressure increased	18 (7.6%)	16 (6.7%)	20 (8.4%)
Bronchitis	20 (8.5%)	23 (9.7%)	25 (10.5%)
Chest pain	13 (5.5%)	10 (4.2%)	9 (3.8%)
Constipation	18 (7.6%)	15 (6.3%)	13 (5.4%)
Contusion	20 (8.5%)	10 (4.2%)	9 (3.8%)
Cough	17 (7.2%)	23 (9.7%)	25 (10.5%)
Depression	16 (6.8%)	12 (5.0%)	14 (5.9%)
Diarrhea	20 (8.5%)	18 (7.6%)	10(4.2%)
Dizziness	23 (9.7%)	18 (7.6%)	11 (4.6%)
Dyspnea	6 (2.5%)	12 (5.0%)	8 (3.3%)
Edema peripheral	14 (5.9%)	17 (7.1%)	10 (4.2%)
Gastroesophageal reflux disease	12 (5.1%)	15 (6.3%)	9 (3.8%)
Headache	24 (10.2%)	36 (15.1%)	24 (10.0%)
Herpes zoster	5 (2.1%)	13 (5.5%)	10 (4.2%)
Hypercholesterolemia	11 (4.7%)	10 (4.2%)	13 (5.4%)
Hypertension	38 (16.1%)	41 (17.2%)	39 (16.3%)
Influenza	12 (5.1%)	23 (9.7%)	19 (7.9%)
Insomnia	13 (5.5%)	10 (4.2%)	14 (5.9%)
Nasopharyngitis	31 (13.1%)	32 (13.4%)	38 (15.9%)
Nausea	13 (5.5%)	21 (8.8%)	21 (8.8%)
Pain in extremity	14 (5.9%)	15 (6.3%)	13 (5.4%)
Pneumonia	13 (5.5%)	18 (7.6%)	11 (4.6%)
Sinusitis	13 (5.5%)	18 (7.6%)	20 (8.4%)
Upper respiratory tract infection	23 (9.7%)	36 (5.1%)	18 (7.5%)
Urinary tract infection	18 (7.6%)	21 (8.8%)	17 (7.1%)

Note: Multiple occurrences of the same event in a subject were counted once in the overall incidence.
a Represents the number of subjects with at least one ocular adverse event in the study eye.

Reviewer's Comment:
The adverse events which were seen more frequently in the ranibizumab 0.5 mg group versus control are highlighted. The reported adverse events during the 2-year treatment period were consistent with those seen in an elderly population and the first treatment year results.

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Reviewer's Comment:
The overall 2-year safety profile in Study FVF2598g was similar to that observed based on first-treatment-year data. The most common adverse events in the study eye observed more frequently in the ranibizumab groups than in the sham-injection group were conjunctival hemorrhage, increased intraocular pressure and vitreous floaters.

The dose dependent association of ranibizumab and intraocular inflammation noted during the first treatment year persisted in the second treatment year. Cumulative 2-year rates of reported intraocular inflammation adverse events in the study eye of 13.9% and 18.0% in the 0.3-mg and 0.5-mg ranibizumab groups compared with the sham-injection group, 10.6%. The observed intraocular inflammation adverse events were usually mild in severity and occurrence was well-balanced among the subgroups studied. Serious intraocular inflammation adverse events only occurred in the ranibizumab groups with a cumulative rate of ≤ 1.7% during the 2-year treatment period.

Table 7.2.9-11 APTC Arterial Thromboembolic Events during the 2-Year Treatment Period: Safety-Evaluable Subjects - Study FVF2598g

Event Term	[redacted]	[redacted]	0.5 mg N=239
Total	9 (3.8%)	11 (4.6%)	11 (4.6%)
Vascular deaths	4 (1.7%) [a]	3 (1.3%) [b]	3 (1.3%)
Nonfatal myocardial infarction	4 (1.7%)	6 (2.5%) [c]	3 (1.3%)
Nonfatal ischemic stroke	2 (0.8%) [d,e]	3 (1.3%) [b]	5 (2.1%) [f]
Nonfatal hemorrhagic stroke	0	0	1 (0.4%) [d]

Note: Antiplatelet Trialists' Collaboration. BMJ. 1994 Jan 8; 308(6921):81-106.
a Subject 136007 had a prior non-fatal ischemic stroke.
b Subject 101019 had a non-fatal ischemic stroke and died of an unknown cause.
c Subject 109001 had two events of MI.
d Subject 158001 had an MI and a hemorrhagic stoke, both non-fatal.
e The sham-treated subject (118004) who suffered a subacute parietooccipital lobe CVA (reported as an ocular serious adverse event) had received a single injection of ranibizumab 0.5 mg in error approximately 8 months prior to the stroke.
f Include 1 subject (200001) with cerebral ischemia who had MRI evidence of infarction I the pons and thalamus.

Reviewer's Comment:
In the second treatment year, the trend toward higher rates of APTC arterial thromboembolic events was somewhat decreased because the number of subjects who experienced events in the second treatment year was similar among the treatment groups (1 subjects [3.2%] in the sham-injection group, 8 subjects [3.4%] in the 0.3 mg ranibizumab group, and 6 subjects [2.6%] in the 0.5 mg ranibizumab group).

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7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

The trend in intraocular inflammation adverse events observed during the first treatment year was also observed through the second treatment year of Study FVF2598g, with cumulative 2-year rates of reported intraocular inflammation adverse events in the study eye of 13.9% and 18.0% in the 0.3-mg and 0.5-mg ranibizumab groups, respectively, compared with 10.6% in the sham-injection group. However, the reported intraocular inflammation adverse events were generally mild in severity. The incidence of intraocular inflammation adverse events did not differ substantially between the subgroups examined, and rates were lower in the second treatment year compared with the first treatment year. The incidence of intraocular inflammation adverse events was consistent with results based on slit lamp examination.

In Study FVF2598g, serious intraocular inflammation adverse events were observed only in the ranibizumab groups but were uncommon for both dose groups (≤ 1.7% cumulative rate over the 2-year treatment period).

The frequency of intraocular inflammation adverse events in the study eye was higher in the ranibizumab groups (10.2% in the 0.3-mg group and 15.0% in the 0.5-mg group) compared with the verteporfin PDT group (2.8%).

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

Table 7.4.1.1-1 Arterial Thromboembolic Events during the First Treatment Year: Studies FVF2598g and FVF2587g Pooled (Safety Evaluable Subjects)

Total [a]	11 (2.9%)	11 (2.9%)	15 (4.0%)
Acute Coronary Syndrome	0	1 (0.3%)	0
Acute myocardial infarction	0	1 (0.3%)	0
Angina pectoris	2 (0.5%)	3 (0.8%)	2 (0.5%)
Angina unstable	0	1 (0.3%)	0
Cerebral infarction	0	1 (0.3%)	0
Cerebral ischemia	0	0	1 (0.3%)
Cerebrovascular accident	2 (0.5%) [b]	1 (0.3%)	3 (0.8%)
Embolism	0	0	1 (0.3%)
Femoral artery occlusion	1 (0.3%)	0	0
Intestinal infarction	0	0	1 (0.3%)
Myocardial infarction	2 (0.5%)	2 (0.5%)	4 (1.1%)
Retinal artery occlusion	0	1 (0.3%)	0

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Original BLA
Rhea A. Lloyd, MD
125156
Lucentis (ranibizumab injection)

[redacted]			
Transient ischemic attack	4 (1.1%)	0	4 (1.1%)
Vascular graft occlusion	0	1 (0.3%)	0
Vascular occlusion	0	1 (0.3%)	0

a Represents the number of subjects with at least one arterial thromboembolic event
b A sham-treated subject in Study FVF2598g who experienced a subacute parietooccipital CVA (reported as an ocular serious adverse event) had received a single injection of 0.5 mg ranibizumab in error approximately 8 months prior to the event.

Reviewer's Comment:
The adverse events which were seen more frequently in the ranibizumab 0.5 mg group versus control are highlighted. The number of subjects with an arterial thromboembolic event was small in the pooled analysis of studies FVF2598g and FVF2587g. A direct relationship between ranibizumab dose and arterial thromboembolic events can not be ruled out.

A sham-treated subject in Study FVF2598g who experienced a subacute parietooccipital CVA (reported as an ocular serious adverse event) had received a single injection of 0.5 mg ranibizumab in error approximately 8 months prior to the event.

Appears This Way
On Original

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開発にあたっては、各特許権者とのライセンス等十分にご注意ください。

Table 7.4.1.1-2 Potential Risk Factors and Baseline Concomitant Medication Use for Subjects with Arterial Thromboembolic Events versus All Subjects: Studies FVF2598g and FVF2587g Pooled (Safety-Evaluable Subjects)

	Control		Ranibizumab			
			0.3 mg		0.5 mg	
	Subjects w/ ATE n=11	All Subjects n=379	Subjects w/ ATE n=11	All Subjects n=375	Subjects w/ ATE n=15	All Subjects n=[illegible]
Potential Risk Factor						
Age ≥ 75 years	8 (72.7%)	259 (68.3%)	8 (72.7%)	262 (69.9%)	12 (80.0%)	244 (64.4%)
Male	7 (63.6%)	143 (37.7%)	2 (18.2%)	156 (41.6%)	5 (33.3%)	163 (43.0%)
History of hypertension or hypertension at baseline [b]	7 (63.6%)	249 (65.7%)	9 (1.8%)	265 (70.7%)	10 (66.7%)	263 (69.4%)
History of ATE	6 (54.5%)	112 (29.6%)	8 (72.7%)	117 (31.2%)	7 (46.7%)	107 (28.2%)
History of atherosclerosis	7 (63.6%)	125 (33.0%)	9 (81.8%)	127 (33.9%)	7 (46.7%)	124 (32.7%)
History of diabetes mellitus	3 (27.3%)	46 (12.1%)	4 (36.4%)	47 (12.5%)	3 (20.0%)	59 (15.6%)
History of myocardial infarction	1 (9.1%)	29 (7.7%)	2 (18.2%)	22 (5.9%)	3 [illegible]	27 (7.1%)
History of stroke or TIA	2 (18.2%)	31 (8.2%)	3 (27.3%)	26 (6.9%)	3 (20.0%)	28 (7.4%)
History of venous thrombosis	0	9 (2.4%)	1 (9.1%)	13 (3.5%)	1 (6.7%)	13 (3.4%)
Baseline concomitant medication use						
Aspirin	6 (54.5%)	161 (42.5%)	4 (36.4%)	146 (38.9%)	7 (46.7%)	142 (37.5%)
Persantine	0	0	0	0	0	0
Anti-platelet agents	4 (36.4%)	167 (44.1%)	9 (81.8%)	168 (44.8%)	5 (33.3 %)	176 (46.4%)
Anti-coagulant agents	2 (18.2%)	27 (7.1%)	1 (9.1%)	26 (6.9%)	1 (6.7%)	18 (4.7%)
Lipid-lowering agents	4 (36.4%)	153 (40.4%)	5 (45.5%)	150 (40.0%)	3 (20.0%)	151 (39.8%)

a A sham-treated subject in Study FVF2598g who experienced a subacute parieto-occipital CVA (reported as an ocular serious adverse event) had received a single injection of 0.5 mg ranibizumab in error approximately 8 months prior to the event. b Hypertension at baseline was defined as systolic blood pressure >150 mmHg, diastolic blood pressure > 100 mmHg, or a use of a concomitant medication indicated for hypertension.

Reviewer's Comment:

For all subjects, potential risk factors for ATEs and baseline concomitant medication use were well balanced across the treatment groups in terms of percentages.

The number of subjects with ATE was small making comparisons somewhat difficult. Though subjects in the ranibizumab 0.5 mg group with an ATE did not have the highest aspirin use, their aspirin use was higher than all subjects in the ranibizumab 0.5 mg group.

Subjects with an ATE in the ranibizumab 0.5 mg group generally had potential risk factors at a higher percentage than the group as a whole.

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7.4.1.2 Combining data

Studies FVF2598g and FVF2587g were sufficiently similar to allow data to be combined by adding the numerator events and denominators of the treatment groups across the studies.

7.4.2 Explorations for Predictive Factors

A detailed discussion of the adverse events is presented in Sections 7.1.1 through 7.1.6. No clear predictive factors for a drug-related adverse event were identified.

7.4.3 Causality Determination

Due to the small number of patients, no determination of causality could be made regarding the adverse events in the Phase 3 studies.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The sponsor has performed adequate dose ranging studies during the drug development program. Lucentis (ranibizumab) 0.5 mg dose has been demonstrated to be safe and effective in two Phase 3 clinical trials. The dosing interval in the two pivotal Phase 3 trials was once monthly resulting in the improvement and maintenance of visual acuity and function, and for the reduction of vascular leakage and retinal edema, in patients with neovascular (wet) age-related macular degeneration.

8.2 Drug-Drug Interactions

No important drug-drug interactions have been identified.

8.3 Special Populations

The sponsor has adequately evaluated gender effects on both the safety and efficacy outcomes. Subgroup analyses did not reveal any differences in the primary efficacy endpoint between males and females. The safety profiles seen in males and females, including the types and rates of adverse events, are similar.

Trials for this indication were conducted in a population that was overwhelmingly elderly and Caucasian. This is reflective of the population in which age-related macular degeneration occurs and does not reflect a problem with study enrollment.

8.4 Pediatrics

The applicant requested a waiver of the pediatric study requirements for the original Biologics License Application. The waiver was requested because the disease under study age-related macular degeneration does not occur in the pediatric age group.

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8.5 Advisory Committee Meeting

Not applicable. No Advisory Committee Meeting will be held regarding this application.

8.6 Literature Review

The medical reviewer conducted a PubMed electronic literature search to supplement the submitted review of the relevant literature. There was no significant new information found in the published literature.

8.7 Postmarketing Risk Management Plan

No postmarketing risk management plan has been submitted.

8.8 Other Relevant Materials

Comments received from DDMAC and the Office of Drug Safety have been incorporated in the labeling review as appropriate.

9 OVERALL ASSESSMENT

9.1 Conclusions

The submitted studies in BLA 125156 are sufficient to establish efficacy for the use of ranibizumab 0.5 mg injection in the treatment of the neovascular age-related macular degeneration. The two Phase 3 studies provide replicative demonstration that monthly ranibizumab injections are able to stabilize and prevent vision loss in patients with neovascular macular degeneration compared to monthly sham and verteporfin PDT treatment.

9.2 Recommendation on Regulatory Action

BLA 125156 is recommended for approval from a clinical perspective for the treatment of patients with neovascular (wet) age-related macular degeneration with the labeling revisions within this review.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

Not applicable. No postmarketing risk management activity is recommended at this time.

9.3.2 Required Phase 4 Commitments

1. Develop and validate assays to detect and characterize immune responses to ranibizumab:

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A. Develop and validate a confirmatory assay capable of detecting both IgG and IgM isotype responses.

B. Develop and validate an assay to detect neutralizing anti-ranibizumab antibodies.

The assay methodology and validation reports will be provided by September 28, 2007.

2. To characterize further the immune response to ranibizumab, serum samples collected in studies FVF2587g, FVF2598g, FVF3192g will be assayed using the validated methods described above in Postmarketing Commitment . The data obtained will be analyzed to discover and evaluate any association between immunoreactivity and dosing frequency as well as any potential impact of immunoreactivity on efficacy or safety outcomes.

Date of submission of protocol and statistical analysis plan: February 28, 2007

Date of submission of final study report: September 2008.

3. The need for an additional clinical study will be determined based on the results from the analysis described above..

9.3.3 Other Phase 4 Requests

Not applicable. There are no additional Phase 4 requests.

9.4 Labeling Review

Refer to the Appendix, Section 10.2 for the medical officer's labeling review.

9.5 Comments to Applicant

There are no comments pertaining to specific deficiencies.

整理番号:SP-5349A　発送番号:092972　発送日:平成30年 3月 6日　172/E
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14 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

✓ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Medical- 6of6

Electronic Acknowledgement Receipt	
EFS ID:	32152813
Application Number:	15471506
International Application Number:	
Confirmation Number:	8014
Title of Invention:	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS
First Named Inventor/Applicant Name:	George D. YANCOPOULOS
Customer Number:	96387
Filer:	Karl Bozicevic/Kimberly Zuehlke
Filer Authorized By:	Karl Bozicevic
Attorney Docket Number:	REGN-008CIPCON2
Receipt Date:	26-MAR-2018
Filing Date:	28-MAR-2017
Time Stamp:	12:17:48
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	REGN-008CIPCON2_2018-03-26_Supp_IDS_trans.pdf	53230 9e2d9110a4c350f3e2cfa6b0c6d932d3fcda1964	no	2
Warnings:					

Information:					
2	Information Disclosure Statement (IDS) Form (SB08)	REGN-008CIPCON2_2018-03-26_Supp_IDS_SB08A.pdf	22962 34a1e53105969b09202066ec75cb96568f5b46c8	no	1
Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
3	Non Patent Literature	D9.pdf	2160139 e9e4195c672ae9ed0a526a351d6104038e2b804e	no	99
Warnings:					
Information:					
4	Non Patent Literature	D10.pdf	4911467 ef199fb6643a6e6f4a6347172a17a30b9f2d6580	no	172
Warnings:					
Information:					
			Total Files Size (in bytes):	7147798	

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.

Electronically Filed

INFORMATION DISCLOSURE STATEMENT Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450		
	Attorney Docket	REGN-008CIPCON2
	First Named Inventor	YANCOPOULOS, GEORGE D.
	Application Number	15/471,506
	Confirmation No.	8014
	Filing Date	March 28, 2017
	Group Art Unit	1647
	Examiner Name	LOCKARD, JON MCCLELLAND
	Title: "*Use of a VEGF Antagonist to Treat Angiogenic Eye Disorders*"	

Sir:

Applicants submit herewith documents which may be material to the examination of this application and in respect of which there may be a duty to disclose in accordance with 37 C.F.R. §1.56. This submission is not intended to constitute an admission that any document referred to therein is "prior art" for this invention unless specifically designated as such. A listing of the documents is shown on enclosed Form PTO/SB/08A and a copy of the cited documents are attached.

The Examiner is requested to make the documents listed on the enclosed PTO/SB/08A of record in this application. Applicants would appreciate the Examiner initialing and returning the initialed copy of form PTO/SB/08A, indicating the documents cited therein have been considered and made of record herein.

Statements

☐ **No statement**

☒ **PTA Statement under 37 CFR § 1.704(d)(1):** Each item of information contained in the information disclosure statement filed herewith:

(i) Was first cited in any communication from a patent office in a counterpart foreign or international application or from the Office, and this communication was not received by any individual designated in § 1.56(c) more than thirty days prior to the filing of the information disclosure statement; or

(ii) Is a communication that was issued by a patent office in a counterpart foreign or international application or by the Office, and this communication was not received by any individual designated in § 1.56(c) more than thirty days prior to the filing of the information disclosure statement.

☒ **IDS Statement under 37 CFR § 1.97(e)(1):** 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; or

☐ **IDS Statement under 37 CFR § 1.97(e)(2):** 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 § 1.56(c) more than three months prior to the filing of the information disclosure statement.

Fees

☒ No fee is believed to be due.

☐ The appropriate fee set forth in 37 C.F.R. §1.17(p) accompanies this information disclosure statement.

The Commissioner is hereby authorized to charge any underpayment of fees up to a strict limit of $3,000.00 beyond that authorized on the credit card, but not more than $3,000.00 in additional fees due with any communication for the above referenced patent application, including but not limited to any necessary fees for extensions of time, or credit any overpayment of any amount to Deposit Account No. 50-0815, order number REGN-008CIPCON2.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: 26 March 2018

By: /Karl Bozicevic, Reg. No. 28,807/
Karl Bozicevic, Reg. No. 28,807

BOZICEVIC, FIELD & FRANCIS LLP
201 Redwood Shores Parkway, Suite 200
Redwood City, CA 94065
Telephone: (650) 327-3400
Direct: (650) 833-7735
Facsimile: (650) 327-3231

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/471,506	03/28/2017	George D. YANCOPOULOS	REGN-008CIPCON2	8014

96387 7590 04/03/2018

Regeneron - Bozicevic, Field & Francis
201 REDWOOD SHORES PARKWAY
SUITE 200
REDWOOD CITY, CA 94065

EXAMINER	
LOCKARD, JON MCCLELLAND	

ART UNIT	PAPER NUMBER
1647	

NOTIFICATION DATE	DELIVERY MODE
04/03/2018	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):

docket@bozpat.com

Office Action Summary	Application No. 15/471,506	Applicant(s) YANCOPOULOS, GEORGE D.	
	Examiner JON M. LOCKARD	Art Unit 1647	AIA (First Inventor to File) Status No

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

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

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

Status

1)☒ Responsive to communication(s) filed on *19 May 2017*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

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

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

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

Disposition of Claims*

5)☒ Claim(s) *21-46* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *21-46* is/are rejected.

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

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

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☒ The specification is objected to by the Examiner.

11)☒ The drawing(s) filed on *28 March 2017* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

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

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

Priority under 35 U.S.C. § 119

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

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

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

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

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

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

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date *attached*.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments, and/or Claims

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

2. The Preliminary Amendment filed on 19 May 2017 has been entered in full. Claims 1-20 have been cancelled, and claims 21-46 have been added. Therefore, claims 21-46 are pending and the subject of this Office Action.

Information Disclosure Statement

3. The information disclosure statements (IDS) filed 26 May 2017, 18 July 2017, 02 August 2017 and 26 March 2018 have been considered by the examiner.

Specification

4. The disclosure is objected to because of the following informalities: An updated status of the parent nonprovisional application should be included in the first sentence of the specification. Appropriate correction is suggested.

Double Patenting

5. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the claims at issue are not identical, but at least one examined application claim is not

patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

6. A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the reference application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

7. The USPTO internet Web site contains terminal disclaimer forms which may be used. Please visit http://www.uspto.gov/forms/. The filing date of the application will determine what form should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to http://www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

8. Claims 21-46 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-5 of U.S. Patent No. 7,303,746. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the ‘746 patent are drawn to methods for treating retinal neovascularization (an

angiogenic eye disorder), comprising administering a fusion polypeptide which comprises the amino acid sequence of SEQ ID NO:16, which shares 100% sequence identity to the fusion protein of SEQ ID NO:2 (encoded by SEQ ID NO:1) of the instant application. While the '746 patent does not disclose the dosing schedules set forth in the instant claims, it is routine experimentation to optimize dosages and dosage schedules. The courts have determined that:

> "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller,* 220 F.2d 454, 454, 105 USPQ 223,235, (CCPA 1955).

Therefore, the claims are overlapping in scope.

9. Claims 21-46 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-6 of U.S. Patent No. 7,303,747. Although the conflicting claims are not identical as they differ in scope, they are not patentably distinct from each other because claims 1-6 of the '747 patent are drawn to methods for treating or ameliorating an angiogenic eye disorder, including choroidal neovascularization, vascular leak, or retinal edema, comprising administering a fusion polypeptide capable of binding endothelial growth factor (VEGF) to a patient in need thereof, wherein the fusion polypeptide comprises the amino acid sequence of SEQ ID NO:6, which shares 100% sequence identity to the fusion protein of SEQ ID NO:2 (encoded by SEQ ID NO:1) of the instant application. While the '747 patent does not disclose the dosing schedules set forth in the instant claims, it is routine experimentation to optimize dosages and dosage schedules. The courts have determined that:

> "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller,* 220 F.2d 454, 454, 105 USPQ 223,235, (CCPA 1955).

Therefore, the claims are overlapping in scope.

10. Claims 21-46 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-11 of U.S. Patent No. 7,306,799. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1-6 of the '799 patent are drawn to a method for treating an angiogenic eye disorder, including age-related macular degeneration and diabetic retinopathy, comprising administering a fusion polypeptide having the amino acid sequence set forth in SEQ ID NO:6, which shares 100% sequence identity to the fusion protein of SEQ ID NO:2 (encoded by SEQ ID NO:1) of the instant application. While the '799 patent does not disclose the dosing schedules set forth in the instant claims, it is routine experimentation to optimize dosages and dosage schedules. The courts have determined that:

> "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller,* 220 F.2d 454, 454, 105 USPQ 223,235, (CCPA 1955).

Therefore, the claims are overlapping in scope.

11. Claims 21-46 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-15 of U.S. Patent No. 7,521,049. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1-15 of the '049 patent are drawn to a method for treating an angiogenic eye disorder,

including age-related macular degeneration, diabetic retinopathy, choroidal neovascularization, vascular leak, and/or retinal edema, comprising administering a fusion polypeptide having the amino acid sequence set forth in SEQ ID NO:23, which shares 100% sequence identity to the fusion protein of SEQ ID NO:2 (encoded by SEQ ID NO:1) of the instant application. While the '049 patent does not disclose the dosing schedules set forth in the instant claims, it is routine experimentation to optimize dosages and dosage schedules. The courts have determined that:

> "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller,* 220 F.2d 454, 454, 105 USPQ 223,235, (CCPA 1955).

Therefore, the claims are overlapping in scope.

12. Claims 21-46 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-26 of U.S. Patent No. 9,254,338. Although the conflicting claims are not identical, as they recite different dosing schedules, they are not patentably distinct from each other because claims 1-26 of the '338 patent are drawn to a method for treating an angiogenic eye disorder, including age-related macular degeneration, diabetic retinopathy, choroidal neovascularization, vascular leak, and/or retinal edema, comprising administering a fusion polypeptide having the amino acid sequence set forth in SEQ ID NO:2, which shares 100% sequence identity to the fusion protein of SEQ ID NO:2 (encoded by SEQ ID NO:1) of the instant application. While the '338 patent does not disclose the dosing schedules set forth in the instant claims, it is routine experimentation to optimize dosages and dosage schedules. The courts have determined that:

> "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller,* 220 F.2d 454, 454, 105 USPQ 223,235, (CCPA 1955).

Therefore, the claims are overlapping in scope.

13. Claims 21-46 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-12 of U.S. Patent No. 9,669,069. Although the conflicting claims are not identical, as they recite different dosing schedules, they are not patentably distinct from each other because claims 1-12 of the '069 patent are drawn to a method for treating an angiogenic eye disorder, including age-related macular degeneration, diabetic retinopathy, diabetic macular edema, central retinal vein occlusion, branch retinal vein occlusion, and corneal neovascularization, comprising administering a fusion polypeptide having the amino acid sequence set forth in SEQ ID NO:2, which shares 100% sequence identity to the fusion protein of SEQ ID NO:2 (encoded by SEQ ID NO:1) of the instant application. While the '069 patent does not disclose the dosing schedules set forth in the instant claims, it is routine experimentation to optimize dosages and dosage schedules. The courts have determined that:

> "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller,* 220 F.2d 454, 454, 105 USPQ 223,235, (CCPA 1955).

Therefore, the claims are overlapping in scope.

Summary

14. No claim is 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 on Monday through Friday, 8:00 AM to 4:30 PM.

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 number for the organization where this application or proceeding is assigned is 571-273-8300.

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

/JON M LOCKARD/
Examiner, Art Unit 1647
March 29, 2018

Receipt date: 07/18/2017

INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	15/471,506
				Filing Date	March 28, 2017
				First Named Inventor	YANCOPOULOS, GEORGE D.
				Art Unit	1647
				Examiner Name	LOCKARD, JON MCCLELLAND
Sheet	1	of	1	Attorney Docket Number	REGN-008CIPCON2

U.S. PATENT DOCUMENTS

Examiner Initial*	Cite No.	Patent Number Number-Kind Code (*if known*)	Issue Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1				

U.S. PATENT APPLICATION PUBLICATIONS

Examiner Initial*	Cite No.	Publication Number **Number-Kind Code** (*if known*)	Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1				

FOREIGN PATENT DOCUMENTS

Examiner Initial*	Cite No.	Foreign Document Number Country Code-Number-Kind Code (*if known*)	Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T
	1					

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T
/J.L/	1	HEIER et al., "Intravitreal Aflibercept (VEGF Trap-Eye) in Wet Age-related macular Degeneration," Ophthalmology, 119:2537-2548 (2012	

Examiner Signature	/JON M LOCKARD/	Date Considered	03/29/2018

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CONFIRMATION NO. 8014

SERIAL NUMBER	FILING or 371(c) DATE RULE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
15/471,506	03/28/2017	424	1647	REGN-008CIPCON2

APPLICANTS
REGENERON PHARMACEUTICALS, INC., Tarrytown, NY

INVENTORS
George D. YANCOPOULOS, Yorktown Heights, NY;

**** CONTINUING DATA ***************************
This application is a CON of 14/972,560 12/17/2015 PAT 9669069
which is a CON of 13/940,370 07/12/2013 PAT 9254338
which is a CIP of PCT/US2012/020855 01/11/2012
which claims benefit of 61/432,245 01/13/2011
and claims benefit of 61/434,836 01/21/2011
and claims benefit of 61/561,957 11/21/2011

**** FOREIGN APPLICATIONS ***************************

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED ****
09/05/2017

Foreign Priority claimed ☐ Yes ☑ No 35 USC 119(a-d) conditions met ☐ Yes ☐ No Verified and Acknowledged /JON MCCLELLAND LOCKARD/ Examiner's Signature	☐ Met after Allowance Initials	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
		NY	1	26	2

ADDRESS
Regeneron - Bozicevic, Field & Francis
201 REDWOOD SHORES PARKWAY
SUITE 200
REDWOOD CITY, CA 94065
UNITED STATES

TITLE
USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS

FILING FEE RECEIVED		
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Receipt date: 03/26/2018

INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	15/471,506
				Filing Date	March 28, 2017
				First Named Inventor	YANCOPOULOS, GEORGE D.
				Art Unit	1647
				Examiner Name	LOCKARD, JON MCCLELLAND
Sheet	1	of	1	Attorney Docket Number	REGN-008CIPCON2

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U.S. PATENT APPLICATION PUBLICATIONS

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	1				

FOREIGN PATENT DOCUMENTS

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	1					

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T
/J.L/	1	CENTER FOR DRUG EVALUATION AND RESEARCH APPLICATION NUMBER: 21-756 MEDICAL REVIEW(S) (December 17, 2004) <URL:https://www.accessdata.fda.gov/drugsatfda_docs/nda/2004/21-756_Macugen_medr.pdf>	
/J.L/	2	CENTER FOR DRUG EVALUATION AND RESEARCH BLA APPLICATION NUMBER: 125156 MEDICAL REVIEW, (June 2006) <URL:https://www.accessdata.fda.gov/drugsatfda_docs/nda/2006/125156s000_Lucentis_MedR.pdf>	

Examiner Signature	/JON M LOCKARD/	Date Considered	03/29/2018

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Inventor Information for 15/471506

/J.L./

Inventor Name	City	State/Country
YANCOPOULOS, GEORGE D.	YORKTOWN HEIGHTS	NEW YORK

Appln Info | Contents | Petition Info | Atty/Agent Info | Continuity Data | Foreign Data | **Inventors** | Applicants | Address | Fees | Post Info | Pre Gra

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=> DIS HIST

     (FILE 'HOME' ENTERED AT 18:49:12 ON 29 MAR 2018)

     FILE 'MEDLINE, SCISEARCH, EMBASE, BIOSIS' ENTERED AT 18:49:22 ON 29 MAR
     2018
L1          4773 S (FLT1 OR VEGFR1 OR (VEGF (W) R1)) (P) (FLK1 OR KDR OR VEGFR2
L2            43 S L1 AND ((CHIMER? OR FUSION) (S) VEGF)
L3             0 S L2 AND ((EYE OR OCULAR OR RETINA? OR MACULAR) (S) DOSORDER)
L4             0 S L2 AND ((EYE OR OCULAR OR RETINA? OR MACULAR) (S) DISORDER)
L5           102 S L1 (P) (CHIMER? OR FUSION)
L6             2 S L5 AND ((EYE OR OCULAR OR RETINA? OR MACULAR) (S) DISORDER)
L7           700 S (VEGF (W) TRAP) AND (EYE OR OCULAR OR RETINA? OR MACULAR)
L8           572 S (VEGF (W) TRAP) (P) (EYE OR OCULAR OR RETINA? OR MACULAR)
L9           353 S (VEGF (W) TRAP) (S) (EYE OR OCULAR OR RETINA? OR MACULAR)
L10           92 S L9 AND PD<=2011
L11           47 DUP REM L10 (45 DUPLICATES REMOVED)
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Receipt date: 05/26/2017

INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	15/471,506
				Filing Date	March 28, 2017
				First Named Inventor	YANCOPOULOS, GEORGE D.
				Art Unit	N/A
				Examiner Name	N/A
Sheet	1	of	3	Attorney Docket Number	REGN-008CIPCON2

U.S. PATENT DOCUMENTS

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	1	7396664	2008-07-08	Daly et al.	

U.S. PATENT APPLICATION PUBLICATIONS

Examiner Initial*	Cite No.	Publication Number **Number-Kind Code** (*if known*)	Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1	20050163798	2005-07-28	Papadopoulos et al.	
	2	20050260203	2005-11-24	Wiegand et al.	
	3	20060058234	2006-03-16	Daly et al.	
	4	20060172944	2006-08-03	Wiegand et al.	
	5	20070190058	2007-08-16	Shams	
	6	20030171320	2003-09-11	Guyer	

FOREIGN PATENT DOCUMENTS

Examiner Initial*	Cite No.	Foreign Document Number Country Code-Number-Kind Code (*if known*)	Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T
	1	WO 2000/75319	2000-12-14	Regeneron Pharmaceuitcals, Inc.		
	2	WO 2007/022101 A2	2007-02-22	Regeneron Pharmaceuticals, Inc.		
	3	WO 2008/063932	2008-05-29	Genentech, Inc.		
	4	JP 2010-509369	2010-03-25	Genentech, Inc.	See WO 2008/063932 for English Equivalent	

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T
	1	ANONYMOUS "Lucentis (rangibizymab injection) Intravitreal Injection" pp. 103 (June 2006)	
	2	Information from ClinicalTrials.gov archive View of NCT00637377 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Wet Age-Related Macular Degeneration (AMD) (VIEW 2)" *ClinicalTrials.gov.* Web. 2010-11-30.	
	3	Charles, Steve (Guest Lecturer) "VEGF Trap Has Positive DME Data" Tenth Annual Retina Fellows Forum Jan 29 and 30, Chicago, Article Date 03/01/2010	
	4	Dixon et al., "VEGF Trap-Eye for the treatment of neobascular age-related macular degeneration" Expert Opin. Investig. Drugs (2009) 18 (10): 1-8.	
	5	DO et al., "An exploratory study of the safety, tolerability and bioactivity of a single intravitreal injection of vascular endothelial growth factor Trap-Eye in patients with diabetic macular oedema" Br J Opthamol. 93(2):144-1449 (February 2009)	

Examiner Signature		Date Considered	

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Receipt date: 05/26/2017

INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	15/471,506
				Filing Date	March 28, 2017
				First Named Inventor	YANCOPOULOS, GEORGE D.
				Art Unit	N/A
				Examiner Name	N/A
Sheet	2	of	3	Attorney Docket Number	REGN-008CIPCON2

NON PATENT LITERATURE DOCUMENTS

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	6	DO et al., "The DA VINCI Study: phase 2 primary results of VEGF Trap-Eye in patients with diabetic macular edema" Opthamology 118(9):1819-1826 (September 2011)	
	7	THE EYETECH STUDY GROUP, "Anti-Vascular Endothelial Growth Factor Therapy for Subfoveal Choroidal Neovascularization Secondary to Age-related Macular Degeneration" American Academy of Ophthamology, 110(5):979-986 (May 2003)	
	8	HEIERet al., " rhuFab V2 (anti-VEGF Antibody) for Treatment of Exudative AMD" Symposium 8:Experimental and Emerging Treatments for Choroidal Neovascularization, 10 pp (2002)	
	9	HEIER et al., "RhuFab V2 in Wet AMD - 6 Month Continued Improvement Following Multiple Intravitreal Injections" Invest Ophthalmol Vis Sci, 44:E-Abstract 972 (2003)	
	10	Information from ClinicalTrials.gov archive on the VIEW 2 study (NCT00637377) "VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD (VIEW 2)" version available and updated on 17 March 2008.	
	11	Information from ClinicalTrials.gov archive on the view of NCT00509795 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Wet Age-Related Macular Degeneration (AMD)" (12-01-2009)	
	12	Information from ClinicalTrials.gov archive on the view of NCT00789477 "DME and VEGF Trap-Eye: Investigation of Clinical Impact" (11-18-2010)	
	13	Information from ClinicalTrials.gov archive on the view of NCT00509795 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Wet Age-Related Macular Degeneration (AMD)" (01-07-2011)	
	14	KRZYSTOLIK et al., "Prevention of Experimental Choroidal NEovascularization With Intravitreal Anti-Vascular Endothelial Growth Factor Antibody Fragment" Arch Ophthamol., 120:338-346 (Mar. 2002)	
	15	Mousa and Mousa, "Current Status of Vascular Endothelial Growth Factor Inhibition in Age-Related Macular Degeneration" Biodrugs 2010; 24(3); 183-194.	
	16	NGUYEN et al., "A Phase I Study of Intravitreal Vascular Endothelial Growth Factor Trap-Eye in Patients with Neovascular Age-Related Macular Degeneration" Opthamology, J.B. Lippincott Co., Philadelphia, PA, US, 116(11):2141-2148 (November 1, 2009)	
	17	NGUYEN et al., "A phase I trial of an IV-administered vascular endothelial growth factor trap for treatment in patients with choroidal neovascularization due to age-related macular degeneration" Ophthalmology (Sept 2006) 113(9):1522e1-1522e14 (epub July 28,2006)	
	18	NICHOLS, EARL R., "AAO: Ranibizumab (rhuRab) May Improve Vision in Age-Related Macular Degeneration" Doctor's Guide Global Edition, www.pslgroup.com/dg/23f2aa.htm, pp. 1-2 (November 24, 20013)	
	19	PAI et al., "Current concepts in intravitreal drug therapy for diabetic retinopathy" Saudi Journal of Opthamology 24(4):143-149 (June 30, 2010)	
	20	Regeneron Pharmaceuticals, Inc. FORM 10-Q, published on 7 November 2007 for the period ending 30 September 2007	

Examiner Signature		Date Considered	

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Receipt date: 05/26/2017

INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	15/471,506
				Filing Date	March 28, 2017
				First Named Inventor	YANCOPOULOS, GEORGE D.
				Art Unit	N/A
				Examiner Name	N/A
Sheet	3	of	3	Attorney Docket Number	REGN-008CIPCON2

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	21	Regeneron, Press release "Regeneron Reports First Quarter 2008 Financial and Operating Results", May 1, 2008.	
	22	Regeneron Press Release "Bayer and Regeneron Report Positive Top-Line Results of Two Phase 3 Studies with VEGF Trap-Eye in Wet Age-related Macular Degeneration" November 22, 2010	
	23	Regeneron Press Release "Regeneron and Bayer Report Positive Results for VEGF Trap-Eye in Phase 3 Study in Central Retinal Vein Occlusion (CRVO) and in Phase 2 Study in Diabetic Macular Edema (DME)" December 20, 2010	
	24	Simo and Hernandez, "Advances in Medical Treatment of Diabetic Retinopathy" Diabetes Care, Volume 32, Number 8, August 2009	
	25	Slides for the 2008 Retina Society Meeting "VEGF Trap-Eye in Wet AMD CLEAR-IT 2: Summary of One-Year Key Results", September 28, 2008.	
	26	STEWART, "THe expanding role of vascular endothelial growth factor inhibitors in opthamology" Mayo Clin Proc. 87(1):77-88 (January 2012)	
	27	THOMAS REUTERS INTEGRITY "VEGF Trap-Eye final phase II results in age-related macular degeneration presented at 2008 Retina Society Meeting" (September 28, 2008)	
	28	WHO Drug Information, "International Nonproprietary Names for Pharmaceutical Substances (INN)" Vol. 20, No. 2, 2006, pages 115-119.	

Examiner Signature	/JON M LOCKARD/	Date Considered	03/29/2018

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Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15471506	YANCOPOULOS, GEORGE D.
	Examiner	Art Unit
	JON M LOCKARD	1647

CPC- SEARCHED		
Symbol	Date	Examiner

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner
NONE		3/29/2018	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
STIC Search of SEQ ID NO:2. See search results in SCORE.	3/29/2018	JML
EAST (USPAT, US-PGPUB, EPO, DERWENT): See attached search history.	3/29/2018	JML
STN (MEDLINE, SCISEARCH, EMBASE, BIOSIS): See attached search history.	3/29/2018	JML
PALM: Inventor search.	3/29/2018	JML

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner

EAST Search History

EAST Search History (Prior Art) /J.L./

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	6537	(flt1 or vegfr1 or (vegf adj r1)) same ((flk1 or kdr or vegfr2 or (vegf adj r2)) or (Flt4 vegfr3 or (vegf adj r3)))	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2018/03/29 18:42
L2	1645	L1 and ((chimer$ or fusion) same vegf)	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2018/03/29 18:42
L3	637	L1 same ((chimer$ or fusion) same vegf)	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2018/03/29 18:42
L4	6386	(flt1 or vegfr1 or (vegf adj r1)) with ((flk1 or kdr or vegfr2 or (vegf adj r2)) or (Flt4 vegfr3 or (vegf adj r3)))	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2018/03/29 18:42
L5	329	L4 with ((chimer$ or fusion) with vegf)	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2018/03/29 18:42
L6	2004	(L4 or L5) and ((eye or ocular or retina$ or macular) with disorder)	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2018/03/29 18:42
L7	274	(L3 or L5) and ((eye or ocular or retina$ or macular) with disorder)	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2018/03/29 18:42
L8	14	(L3 or L5) same ((eye or ocular or retina$ or macular) with disorder)	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2018/03/29 18:42
L9	422	yancopoulos-g$.in.	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2018/03/29 18:42
L10	44	L7 and L9	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2018/03/29 18:42
L11	13	L10 and (eye ocular macular).clm.	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2018/03/29 18:42

3/29/2018 6:43:13 PM
C:\Users\jlockard\Documents\EAST\Workspaces\15471506.wsp

Receipt date: 08/02/2017

INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	15/471,506
				Filing Date	March 28, 2017
				First Named Inventor	YANCOPOULOS, GEORGE D.
				Art Unit	1647
				Examiner Name	LOCKARD, JON MCCLELLAND
Sheet	1	of	1	Attorney Docket Number	REGN-008CIPCON2

U.S. PATENT DOCUMENTS

Examiner Initial*	Cite No.	Patent Number Number-Kind Code (*if known*)	Issue Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1				

U.S. PATENT APPLICATION PUBLICATIONS

Examiner Initial*	Cite No.	Publication Number **Number-Kind Code** (*if known*)	Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1				

FOREIGN PATENT DOCUMENTS

Examiner Initial*	Cite No.	Foreign Document Number Country Code-Number-Kind Code (*if known*)	Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T
	1					

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T
/J.L/	1	MITRA et al., "Review of anti-vascular endothelial growth factor therapy in macular edema secondary to central retinal vein occlusions" Expert Review in Ophthalmo, Taylor & Francis, GB (January 1, 2011) 6(6):623-629	
/J.L/	2	OLIVERA et al., "VEGF Trap R1R2 suppresses experimental corneal angiogenesis" European Journal of Ophthalmology (January 1, 2010) 20(1):48-54	
/J.L/	3	Regeneron Pharmaceuticals Inc., "VEGF Trap-Eye Final Phase 2 Results in Age-related Macular Degeneration Presented at 2008 Retina Society Meeting" (September 28, 2008) (XP-002770952)	

Examiner Signature	/JON M LOCKARD/	Date Considered	03/29/2018

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

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Apr 03, 2018 04:27:35 AM

Dear PAIR Customer:

Regeneron - Bozicevic, Field & Francis
201 REDWOOD SHORES PARKWAY
SUITE 200
REDWOOD CITY, CA 94065
UNITED STATES

The following USPTO patent application(s) associated with your Customer Number, 96387 , have new outgoing correspondence. This correspondence is now available for viewing in Private PAIR.

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

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Application	Document	Mailroom Date	Attorney Docket No.
15471506	CTNF	04/03/2018	REGN-008CIPCON2
	1449	04/03/2018	REGN-008CIPCON2
	1449	04/03/2018	REGN-008CIPCON2
	1449	04/03/2018	REGN-008CIPCON2
	1449	04/03/2018	REGN-008CIPCON2

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PATENT APPLICATION INFORMATION RETRIEVAL SYSTEM

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AMENDMENT UNDER 37 C.F.R. §1.111 Address to: Mail Stop Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450		
	Attorney Docket No.	REGN-008CIPCON2
	Confirmation No.	8014
	First Named Inventor	YANCOPOULOS, GEORGE D.
	Application Number	15/471,506
	Filing Date	March 28, 2017
	Group Art Unit	1647
	Examiner Name	LOCKARD, JON MCCLELLAND
	Title: "*Use of a VEGF Antagonist to Treat Angiogenic Eye Disorders*"	

Sir:

This amendment is responsive to the Office Action dated April 3, 2017 for which a three-month period for response was given making this response timely filed on or before July 3, 2018.

Amendments to the Specification begin on page 2 of this document

Amendments to the Claims begin on page 3 of this document.

Remarks/Arguments begin on page 7 of this document.

AMENDMENTS TO THE SPECIFICATION

Please amend paragraph [0001] on page1 of the specification to read as follows:

[0001] This application is a continuation of U.S. Patent Application Serial No. 14/972,560, filed December 17, 2015~~ (now allowed)~~**, now U.S. Patent No. 9,669,069 issued June 6, 2017** which is a continuation of U.S. Patent Application Serial No. 13/940,370 filed July 12, 2013, now U.S. Patent No. 9,254,338 issued February 9, 2016 which is a continuation-in-part of International Patent Application No. PCT/US2012/020855, filed on January 11, 2012, which claims the benefit of US Provisional Application Nos. 61/432,245, filed on January 13, 2011, 61/434,836, filed on January 21, 2011, and 61/561,957, filed on November 21, 2011, the contents of which are hereby incorporated by reference in their entireties.

AMENDMENTS TO THE CLAIMS:

1. - 20. (**Canceled**)

21. (Previously Presented) A method for treating an angiogenic eye disorder in a patient, said method comprising sequentially administering to the patient a single initial dose of a VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonist;

wherein each secondary dose is administered 2 to 4 weeks after the immediately preceding dose; and

wherein each tertiary dose is administered at least 8 weeks after the immediately preceding dose;

wherein the VEGF antagonist is a VEGF receptor-based chimeric molecule comprising (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;

wherein exclusion criteria for the patient include all of:

(1) active intraocular inflammation;

(2) active ocular or periocular infection;

(3) any ocular or periocular infection within the last 2 weeks prior to treatment.

22. (Previously Presented) The method of claim 21, wherein only a single secondary dose is administered to the patient, and wherein the single secondary dose is administered 4 weeks after the initial dose of the VEGF antagonist.

23. (Previously Presented) The method of claim 21, wherein only two secondary doses are administered to the patient, and wherein each secondary dose is administered 4 weeks after the immediately preceding dose.

24. (Previously Presented) The method of claim 23, wherein each tertiary dose is administered 8 weeks after the immediately preceding dose.

25. (Previously Presented) The method of claim 21, wherein at least 5 tertiary doses of the VEGF antagonist are administered to the patient, and wherein the first four tertiary doses are administered 8 weeks after the immediately preceding dose, and wherein each subsequent tertiary dose is administered 8 or 12 weeks after the immediately preceding dose.

26. (Previously Presented) The method of claim 21, wherein the angiogenic eye disorder is selected from the group consisting of: age related macular degeneration, diabetic retinopathy, diabetic macular edema, central retinal vein occlusion, branch retinal vein occlusion, and corneal neovascularization.

27. (Previously Presented) The method of claim 26, wherein the angiogenic eye disorder is age related macular degeneration.

28. (Previously Presented) The method of claim 21, wherein all doses of the VEGF antagonist are administered to the patient by topical administration or by intraocular administration.

29. (Previously Presented) The method of claim 28, wherein all doses of the VEGF antagonist are administered to the patient by intraocular administration.

30. (Previously Presented) The method of claim 29, wherein the intraocular administration is intravitreal administration.

31. (Previously Presented) The method of claim 30, wherein all doses of the VEGF antagonist comprise from about 0.5 mg to about 2 mg of the VEGF antagonist.

32. (Previously Presented) The method of claim 31, wherein all doses of the VEGF antagonist comprise 0.5 mg of the VEGF antagonist.

33. (Previously Presented) The method of claim 31, wherein all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist.

34. (Previously Presented) A method for treating an angiogenic eye disorder in a patient, said method comprising sequentially administering to the patient a single initial dose of a VEGF antagonist,

followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonist;

wherein each secondary dose is administered 2 to 4 weeks after the immediately preceding dose; and

wherein each tertiary dose is administered at least 8 weeks after the immediately preceding dose;

wherein the VEGF antagonist is a VEGF receptor-based chimeric molecule comprising VEGFR1R2-FcΔC1(a) encoded by the nucleic acid sequence of SEQ ID NO:1;

wherein exclusion criteria for the patient include all of:

(1) active intraocular inflammation;

(2) active ocular or periocular infection;

(3) any ocular or periocular infection within the last 2 weeks prior to treatment.

35. (Previously Presented) The method of claim 34, wherein only a single secondary dose is administered to the patient, and wherein the single secondary dose is administered 4 weeks after the initial dose of the VEGF antagonist.

36. (Previously Presented) The method of claim 34, wherein only two secondary doses are administered to the patient, and wherein each secondary dose is administered 4 weeks after the immediately preceding dose.

37. (Previously Presented) The method of claim 36, wherein each tertiary dose is administered 8 weeks after the immediately preceding dose.

38. (Previously Presented) The method of claim 37, wherein the angiogenic eye disorder is age related macular degeneration.

39. (Previously Presented) The method of claim 34, wherein at least 5 tertiary doses of the VEGF antagonist are administered to the patient, and wherein the first four tertiary doses are administered 8 weeks after the immediately preceding dose, and wherein each subsequent tertiary dose is administered 8 or 12 weeks after the immediately preceding dose.

40. (Previously Presented) The method of claim 34, wherein the angiogenic eye disorder is selected from the group consisting of: age related macular degeneration, diabetic retinopathy, diabetic macular edema, central retinal vein occlusion, branch retinal vein occlusion, and corneal neovascularization.

41. (Previously Presented) The method of claim 34, wherein all doses of the VEGF antagonist are administered to the patient by topical administration or by intraocular administration.

42. (Previously Presented) The method of claim 41, wherein all doses of the VEGF antagonist are administered to the patient by intraocular administration.

43. (Previously Presented) The method of claim 41, wherein the intraocular administration is intravitreal administration.

44. (Previously Presented) The method of claim 43, wherein all doses of the VEGF antagonist comprise from about 0.5 mg to about 2 mg of the VEGF antagonist.

45. (Previously Presented) The method of claim 44, wherein all doses of the VEGF antagonist comprise 0.5 mg of the VEGF antagonist.

46. (Previously Presented) The method of claim 44, wherein all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist.

REMARKS

FORMAL MATTERS:

Claims 21-46 are now pending in this application.

Claims 1-20 were previously canceled without prejudice.

No claims are amended or added.

No new matter is added.

DOUBLE PATENTING REJECTIONS – '338 PATENT

Claims 21-46 were rejected on the grounds of non-statutory obviousness-type double patenting over claims 1-26 of issued U.S. Patent 9,254,338 and claims 1-12 of U.S. Patent 9,669,069.

Without acquiescing to the validity of the rejection, applicants have attached a terminal disclaimer which is specific to U.S Patent 9,254,338 and 9,669,069 thereby rendering the rejection moot.

DOUBLE PATENTING REJECTIONS – '746; '747; '799; AND '049 PATENTS

There are four additional obviousness type double patenting rejections.

In section 8 of the Office Action, claims 21-46 are rejected on the grounds of non-statutory obviousness-type double patenting over claims 1-5 of issued U.S. Patent 7,303,746.

In section 9 of the Office Action, claims 21-46 were rejected on the grounds of non-statutory obviousness-type double patenting over claims 1-6 of issued U.S. Patent 7,303,747.

In section 10 of the Office Action, claims 21-46 were rejected on the grounds of non-statutory obviousness-type double patenting over claims 1-11 of issued U.S. Patent 7,306,799.

In section 11 of the Office Action, claims 21-46 were rejected on the grounds of non-statutory obviousness-type double patenting as being unpatentable over claims 1-15 of issued U.S. Patent 7,521,049.

The rejections in sections 8, 9, 10 and 11 are traversed for the reasons indicated below and as further supported by the attached publication.

NON-OBVIOUSNESS RESPONSE

None of the '746, '747, '799 or '049 patents disclose the treatment protocol of the pending claims. Thus, based on the working examples set forth in the present application, along with the

endorsement of the present invention as set out in the attached (Heier et al.) peer reviewed publication, as well as the facts and reasoning provided below, the rejection should be reconsidered and withdrawn.

At the time of the invention the well accepted standard of care for the treatment of the neovascular (or wet) form of age-related macular degeneration (AMD) was to administer an antibody formulation (ranibizumab) by injection to the eye once per month (see the attached Heier et al. paper).

This treatment protocol is (1) expensive; (2) painful to the patient; (3) inconvenient for the patient as well as the patient's family; (4) psychologically and physically traumatic to the patient; and (5) subjects the patient to potential adverse effects such as infection with each treatment event.

Due to all the above factors (1-5) there was a need in the art for alternative treatment protocols whereby the treatment would be carried out with less inconvenience and reduced safety risks to the patient. However, until the present invention once a month treatment remained the standard of care.

There are virtually an infinite number of different treatment protocols that could be tested. A drug could be administered more frequently, or less frequently, relative to the accepted standard of care. Further, different variations in timing between dosing events are possible. Due to the virtually infinite number of combinations, applicants do not believe that the claimed treatment protocol is *prima facie* obvious in view of the prior art standard of care which is administration of the drug once per month. However, notwithstanding that position, any *prima facie* case of obviousness is overcome by the showing of improved unexpected results. Thus, while the rejection is citing case law (In re Aller) which supports the position that where the general conditions of a claim are disclosed within the prior art, it is not inventive to discover optimal ranges, the Examiner is aware that this case law is not applicable to situations where improved unexpected results are shown (MPEP 2145). Such results have been obtained and are described in the working examples of the present application and in the attached (Heier et al.) publication, portions of which are referred to below.

Applicants do not acquiesce to the *prima facie* obviousness of the claimed invention over the invention claimed within the cited patents. This is because there are virtually an infinite number of different possible treatment protocols. However, notwithstanding any *prima facie* case of obviousness, applicants have demonstrated improved and unexpected results, and based on such, the rejections should be reconsidered and withdrawn.

The attached Heier et al. paper published in December of 2012, and as such is not prior art with respect to the present application filed on January 11, 2012 and claiming priority to November 21, 2011.

The Heier et al. paper shows results of a treatment protocol of the type claimed on over 2,400 patients. The studies summarized in the Heier *et al.* paper correspond to the clinical trials disclosed in Example 4 of the present application which involve the use of the VEGF receptor-based chimeric molecule known as aflibercept or "VEGF Trap."[1] The results clearly show that by administering the specifically claimed VEGF antagonist in accordance with a dosage regimen as claimed in independent claim 1, it is possible to treat angiogenic eye disorders such as AMD while administering doses on a less frequent basis than previously thought possible. This (1) provides enormous benefits to patients, (2) reduces health care cost, (3) reduces the pain and (4) suffering of the patient, as well as (5) the inconvenience to the patient and their family, and as such provides a major step forward in the treatment of patients suffering from angiogenic eye disorders, which is worthy of patent protection.

The attached Heier et al. article is a peer reviewed article published in "Ophthalmology" which describes the aforementioned clinical trial as follows:

> "Patients were randomized in a 1:1:1:1 ratio to the following regimens: 0.5 mg aflibercept every 4 weeks (0.5q4); 2 mg aflibercept every 4 weeks (2q4); 2mg aflibercept every 8 weeks (2q8) after 3 injections at week 0, 4 and 8 (to maintain masking, sham injections were given at the interim 4-week visits after week 8); or 0.5mg ranibizumab every 4 weeks (Rq4). Consecutively enrolled patients were assigned to treatment groups on the basis of predetermined central randomization scheme with balanced allocation, managed by an interactive voice response system. "

In the "primary end point analysis" section of the paper, it is indicated that the proportion of patients maintaining vision was similar among all treatment groups and this is dramatically shown within Table 2 of Heier et al. Thus, the results show that the treatment groups which were compared with the monthly treatment groups surprisingly did not obtain an inferior result. As such, the PRN treatment protocol as encompassed by the presently pending independent claim 21 and 34 achieves results which are as good or better than the results obtained with monthly treatment.

Within the "Discussion" section of the Heier et al. paper, it is noted that the treatment group treated every two months achieved a visual acuity score within 0.3 letters of the group treated on a

[1] Aflibercept is a VEGF receptor-based chimeric molecule as defined in the claims and specifically in claims 21 and 34.

monthly basis. See also the results summarized in Table 1, page 15, of the present application. Thus, it is indicated that the treatment group which received the drug far less frequently than the monthly dosing arm achieved remarkably similar improvements without requiring the monthly monitoring and visits to the health care provider.

Similar remarkable results are shown in Example 5 of the present application, which illustrates an administration regimen encompassed by claims 21 and 34 (*i.e.*, 3 initial doses of VEGF Trap administered once every four weeks, followed by additional doses administered as needed (PRN)) for the effective treatment of diabetic macular edema (DME). As noted at paragraph [0065] of the present specification: "the administration of VEGFT to patients suffering from angiogenic eye disorders (*e.g.*, AMD and DME) at a frequency of once every 8 weeks, following a single initial dose and two secondary doses administered four weeks apart, resulted in significant prevention of moderate or severe vision loss or improvements in visual acuity."

An acknowledgement of the unexpected results of the administration regimen of the present invention is echoed in the Heier et al. paper, which points out that less frequent injections should also provide an ocular safety benefit, and that using fewer injections may substantially decrease the cumulative population risk of certain adverse events which can have a considerable impact considering the millions of injections given each year. For example, Heier et al. states on page 2546, middle left column that:

> "The demonstration that monthly aflibercept provides similar efficacy and safety as the current approved standard of monthly ranibizumab is important, but the finding that remarkably similar improvement in vision and anatomic measures can be achieved with less than monthly intravitreal aflibercept injections and without requiring monthly monitoring visits provides an important advance for both patients and their treating physicians."

Moreover, the final paragraph of the Heier et al. paper reads as follows:

> "In conclusion, intravitreal aflibercept dosed monthly or every 2 months after 3 initial monthly doses resulted in similar visual and anatomic outcomes as ranibizumab dosed monthly, as well as similar safety and tolerability. Intravitreal aflibercept dosed every 2 months has the potential to provide patients, their families and clinicians the

opportunity for the optimal vision gains and anatomic disease control they have come to expect from monthly ranibizumab, with a substantially decreased treatment and compliance burden, and a lower cumulative risk of injection-related adverse events."

Based on the above, it is clear that the claimed treatment protocol provides enormous advantages to patients. Further, in view of the disadvantages of carrying out the treatment on a once per month basis, there was a need in the art for alternative treatment protocols. However, this did not occur until the present invention and as such, the claimed treatment protocol is inventive above and beyond the inventions claimed within the patents cited in the obviousness type double patenting rejection. In view of such, those rejections should be reconsidered and withdrawn.

STATEMENT UNDER 37 C.F.R. §§1.56 AND 1.2

Applicants hereby advise the Examiner of the status of a co-pending application in compliance with the Applicant's duty to disclose under 37 C.F.R. §§1.56 and 1.2 (see also MPEP §2001.06(b)) as discussed in *McKesson Info. Soln. Inc., v. Bridge Medical Inc.*, 487 F.3d 897; 82 USPQ2d 1865 (Fed. Cir. 2007).

The Applicants wish to bring to the Examiner's attention that U.S. Patent Application 14/972,560, filed December 16, 2015 which issued on June 6, 2017 as U.S. Patent No. 9,669,069.

The Applicants wish to bring to the Examiner's attention that U.S. Patent Application 13/940,370, filed July 12, 2013 which issued on February 9, 2016 as U.S. Patent No. 9,254,338.

The Applicants wish to bring to the Examiner's attention that U.S. Patent Application 10/988,243, filed November 12, 2004 which issued on December 4, 2007 as U.S. Patent No. 7,303,746.

The Applicants wish to bring to the Examiner's attention that U.S. Patent Application 11/218,234, filed September 1, 2005 which issued on December 4, 2007 as U.S. Patent No. 7,303,747.

The Applicants wish to bring to the Examiner's attention that U.S. Patent Application 11/089,803, filed March 25, 2005 which issued on December 11, 2007 as U.S. Patent No. 7,306,799.

The Applicants wish to bring to the Examiner's attention that U.S. Patent Application 11/998,709, filed November 30, 2007 which issued on April 21, 2009 as U.S. Patent No. 7,521,049.

These documents are available on PAIR, and thus are not provided with this communication. Please inform the undersigned if there is any difficulty in obtaining the documents from PAIR.

CONCLUSION

Applicants do not acquiesce to the *prima facie* obviousness of the claimed invention over the invention claimed within the cited patents. This is because there are virtually an infinite number of different possible treatment protocols. However, notwithstanding any *prima facie* case of obviousness, applicants have demonstrated improved and unexpected results, and based on such, the rejections should be reconsidered and withdrawn.

Applicant submits that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees up to a strict limit of $3,000.00 beyond that authorized on the credit card, but not more than $3,000.00 in additional fees due with any communication for the above referenced patent application, including but not limited to any necessary fees for extensions of time, or credit any overpayment of any amount to Deposit Account No. 50-0815, order number REGN-008CIPCON2.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: June 25, 2018

By: /Karl Bozicevic, Reg. No. 28,807/
Karl Bozicevic, Reg. No. 28,807

Enclosures: (1) Heier et al.
(2) Terminal Disclaimer regarding U.S. Patent Nos. 9,254,338 and 9,669,069

BOZICEVIC, FIELD & FRANCIS LLP
201 Redwood Shores Parkway, Suite 200
Redwood City, California 94065
Telephone: (650) 327-3400
Direct: (650) 833-7735
Facsimile: (650) 327-3231

Electronic Patent Application Fee Transmittal					
Application Number:	15471506				
Filing Date:	28-Mar-2017				
Title of Invention:	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS				
First Named Inventor/Applicant Name:	George D. YANCOPOULOS				
Filer:	Karl Bozicevic/Savanna Fuentes				
Attorney Docket Number:	REGN-008CIPCON2				
Filed as Large Entity					
Filing Fees for **Utility under 35 USC 111(a)**					
Description		**Fee Code**	**Quantity**	**Amount**	**Sub-Total in USD($)**
Basic Filing:					
Pages:					
Claims:					
Miscellaneous-Filing:					
Petition:					
Patent-Appeals-and-Interference:					
Post-Allowance-and-Post-Issuance:					
Extension-of-Time:					

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
STATUTORY OR TERMINAL DISCLAIMER	1814	1	160	160
		Total in USD ($)		**160**

Electronic Acknowledgement Receipt	
EFS ID:	32990996
Application Number:	15471506
International Application Number:	
Confirmation Number:	8014
Title of Invention:	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS
First Named Inventor/Applicant Name:	George D. YANCOPOULOS
Customer Number:	96387
Filer:	Karl Bozicevic/Savanna Fuentes
Filer Authorized By:	Karl Bozicevic
Attorney Docket Number:	REGN-008CIPCON2
Receipt Date:	25-JUN-2018
Filing Date:	28-MAR-2017
Time Stamp:	15:48:58
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$160
RAM confirmation Number	062618INTEFSW15493700
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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Non Patent Literature	Heier_2012.pdf	714624 e4142a2e2bb06b1ad89fce84878c9b42f4c69a0d	no	12
Warnings:					
Information:					
2	Terminal Disclaimer Filed	REGN-008CIPCON2_2018-06-25_terminal_disclaimer.pdf	25749 059a288c91f5413711c0e43c3899b9afa9825371	no	2
Warnings:					
Information:					
3		REGN-008CIPCON2_2018-06-25_amend.pdf	98613 c8d66e3ce0e9ac79df839c52a1ef708ee433a6a9	yes	12

Multipart Description/PDF files in .zip description

Document Description	Start	End
Amendment/Req. Reconsideration-After Non-Final Reject	1	1
Specification	2	2
Claims	3	6
Applicant Arguments/Remarks Made in an Amendment	7	12

Warnings:					
Information:					
4	Fee Worksheet (SB06)	fee-info.pdf	30325 3da1bf3908f62060984bfaa5c0f15c3a88b023b5	no	2
Warnings:					
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		Total Files Size (in bytes):	869311		

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New Applications Under 35 U.S.C. 111

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

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

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

New International Application Filed with the USPTO as a Receiving Office

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

Intravitreal Aflibercept (VEGF Trap-Eye) in Wet Age-related Macular Degeneration

*Jeffrey S. Heier, MD,[1] David M. Brown, MD,[2] Victor Chong, MD,[3] Jean-Francois Korobelnik, MD,[4] Peter K. Kaiser, MD,[5] Quan Dong Nguyen, MD,[6] Bernd Kirchhof, MD,[7] Allen Ho, MD,[8] Yuichiro Ogura, MD,[9] George D. Yancopoulos, MD, PhD,[10] Neil Stahl, MD,[10] Robert Vitti, MD,[10] Alyson J. Berliner, MD, PhD,[10] Yuhwen Soo, PhD,[10] Majid Anderesi, MD,[11] Georg Groetzbach, MD,[11] Bernd Sommerauer, PhD,[11] Rupert Sandbrink, MD, PhD,[11,12] Christian Simader, MD,[13] Ursula Schmidt-Erfurth, MD,[13] for the VIEW 1 and VIEW 2 Study Groups**

Objective: Two similarly designed, phase-3 studies (VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD [VIEW 1, VIEW 2]) of neovascular age-related macular degeneration (AMD) compared monthly and every-2-month dosing of intravitreal aflibercept injection (VEGF Trap-Eye; Regeneron, Tarrytown, NY, and Bayer HealthCare, Berlin, Germany) with monthly ranibizumab.

Design: Double-masked, multicenter, parallel-group, active-controlled, randomized trials.

Participants: Patients (n = 2419) with active, subfoveal, choroidal neovascularization (CNV) lesions (or juxtafoveal lesions with leakage affecting the fovea) secondary to AMD.

Intervention: Patients were randomized to intravitreal aflibercept 0.5 mg monthly (0.5q4), 2 mg monthly (2q4), 2 mg every 2 months after 3 initial monthly doses (2q8), or ranibizumab 0.5 mg monthly (Rq4).

Main Outcome Measures: The primary end point was noninferiority (margin of 10%) of the aflibercept regimens to ranibizumab in the proportion of patients maintaining vision at week 52 (losing <15 letters on Early Treatment Diabetic Retinopathy Study [ETDRS] chart). Other key end points included change in best-corrected visual acuity (BCVA) and anatomic measures.

Results: All aflibercept groups were noninferior and clinically equivalent to monthly ranibizumab for the primary end point (the 2q4, 0.5q4, and 2q8 regimens were 95.1%, 95.9%, and 95.1%, respectively, for VIEW 1, and 95.6%, 96.3%, and 95.6%, respectively, for VIEW 2, whereas monthly ranibizumab was 94.4% in both studies). In a prespecified integrated analysis of the 2 studies, all aflibercept regimens were within 0.5 letters of the reference ranibizumab for mean change in BCVA; all aflibercept regimens also produced similar improvements in anatomic measures. Ocular and systemic adverse events were similar across treatment groups.

Conclusions: Intravitreal aflibercept dosed monthly or every 2 months after 3 initial monthly doses produced similar efficacy and safety outcomes as monthly ranibizumab. These studies demonstrate that aflibercept is an effective treatment for AMD, with the every-2-month regimen offering the potential to reduce the risk from monthly intravitreal injections and the burden of monthly monitoring.

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**Group members listed online in Appendix 1 (http://aaojournal.org).*

Age-related macular degeneration (AMD) is a leading cause of vision loss and blindness in industrialized countries.[1] The most severe vision loss occurs in the neovascular (or wet) form of AMD, involving choroidal neovascularization (CNV) and associated retinal edema. Early treatments for CNV (laser ablation, photodynamic therapy with verteporfin), although clearly better than no treatment at all, decreased severe vision loss rather than truly stabilizing vision or resulting in clinically significant improvements in visual acuity.[2–4] The suggestion that vascular endothelial growth factor (VEGF) might be driving the CNV and associated edema seen in AMD led to a paradigm shift with the success of the first anti-VEGF therapy, pegaptanib sodium.[5,6] Monthly intravitreal injections of 0.5 mg ranibizumab, a humanized monoclonal antibody fragment that blocks VEGF, not only prevent vision loss in most patients but also lead to significant visual gain in approximately one-third.[7,8] The risk of rare but serious adverse events resulting from the intravitreal procedure, together with the significant burden of making monthly visits to their retinal specialist, have led to extensive efforts to decrease injection and monitoring frequency. However, fixed quarterly[9,10] or "as needed" (pro re nata [PRN]) dosing regimens,[11,12] without requiring monthly monitoring visits, were not effective at maintaining vision.

The Comparison of AMD Treatments Trials (CATT)[13] recently compared monthly ranibizumab with monthly

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bevacizumab, as well as with PRN regimens that required monthly monitoring visits during which treatment decisions primarily were made on the basis of anatomic criteria. Monthly bevacizumab resulted in mean best-corrected visual acuity (BCVA) gains (8.0 letters) similar to those for monthly ranibizumab (8.5 letters), whereas PRN ranibizumab yielded a mean BCVA gain of 1.7 letters less than that of the monthly standard (with a confidence interval [CI] extending to 4.7 letters below) that achieved noninferiority, and PRN bevacizumab yielded a mean BCVA gain 2.6 letters below the monthly standard (with a CI extending to 5.9 letters below) that did not achieve noninferiority. In the CATT, monthly bevacizumab and both PRN regimens were significantly worse than monthly ranibizumab in terms of the proportion of patients who had fluid-free retinas on optical coherence tomography (OCT). Although CIs were not provided for monthly and PRN regimens, switching from monthly to PRN regimens in the second year of the CATT resulted in a significant worsening of BCVA and retinal thickness, as well as a significant decrease in the proportion of patients without retinal fluid.[34] The "alternative treatments to Inhibit VEGF in Age-related choroidal Neovascularization" (IVAN) study also found that the mean foveal retinal thickness and the percentage of patients with fluorescein leakage were significantly higher with the PRN regimen compared with the monthly regimen.[35] In the HARBOR study (Invest Ophthalmol Vis Sci 2012;53:E-Abstract 3677), PRN regimens of both the approved 0.5 mg dose and the higher 2 mg dose of

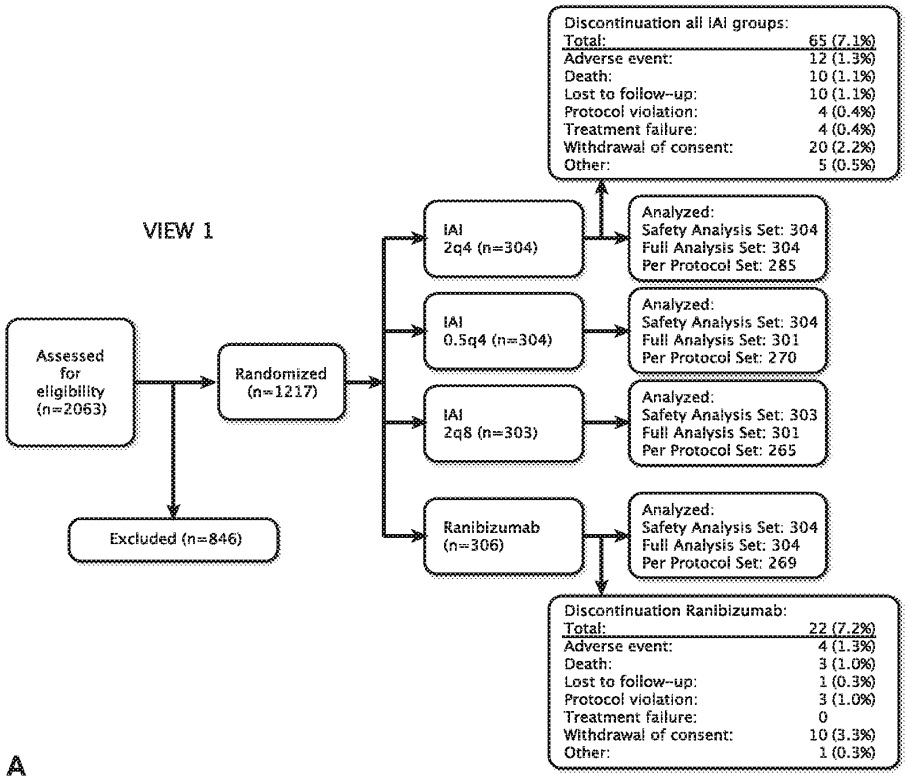

Figure 1. Flowcharts describing treatment allocation and patient disposition in VIEW 1 (**A**) and VIEW 2 (**B**). In both VIEW 1 and VIEW 2 studies, the most common reason for patients to be screened but not randomized was ineligibility based on angiographic characteristics as identified by the reading center. The second most common reason was visual acuity out of range. Discontinuations are those that occurred from the study. Two milligrams intravitreal aflibercept every 2 months (2q8) dosing was performed after 3 initial monthly doses. The numbers of patients who prematurely discontinued study medication in the 2q4, 0.5q4, 2q8, and Rq4 groups were 16 (5.3%), 30 (9.9%), 30 (9.9%), and 27 (8.8%), respectively, in VIEW 1; and 37 (11.8%), 45 (14.5%), 33 (10.5%), and 33 (10.9%), respectively, in VIEW 2. In VIEW 1, 1089 patients were included in the per protocol set (PPS), with 92.6% to 96.1% completing week-52 visual acuity assessment. A total of 128 patients were not included in the PPS for the following reasons (in order of occurrence): missed 2 consecutive injections before ninth injection, major protocol deviation, received <9 injections, had <9 assessments, no baseline assessments, no post-baseline assessments. In VIEW 2, 1081 patients were included in the PPS with 95.9% to 97.8% completing week-52 visual acuity assessment. A total of 159 patients were not included in the PPS for the following main reasons: missed 2 consecutive injections before ninth injection, major protocol deviation, received <9 injections, had <9 assessments, no baseline assessments, no post-baseline assessments, unmasking by investigator or Global Pharmacovigilance. 0.5q4 = 0.5 mg IAI monthly; 2q4 = 2 mg IAI monthly; 2q8 = 2 mg IAI every 2 months after 3 initial monthly doses; IAI = intravitreal aflibercept injection.

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ranibizumab did not achieve noninferiority compared with monthly ranibizumab, with the 0.5 mg PRN regimen yielding a mean BCVA gain 2.0 letters below the monthly standard (with a CI extending to 4.5 letters below). Of note, just like the CATT PRN regimens, the HARBOR PRN regimens still depended on monthly monitoring visits. Thus, there remains a need for new therapies that will provide equivalent efficacy and anatomic disease control to monthly ranibizumab, while reducing the risk of monthly injections and the burden of mandatory monthly monitoring visits.

Intravitreal aflibercept injection (IAI) (previously known in the scientific literature as VEGF Trap-Eye, Regeneron, Tarrytown, NY, and Bayer HealthCare, Berlin, Germany) is a soluble decoy receptor fusion protein[16,17] that is specifically purified and formulated for intraocular injection. Intravitreal aflibercept at doses of 0.5 mg and 2 mg provided the most robust outcomes in the Clinical Evaluation of Antiangiogenesis in the Retina Intravitreal Trial Phase 2 (CLEAR-IT 2) study after 4 monthly administrations followed by PRN dosing to week 52.[18] The binding affinity of intravitreal aflibercept to VEGF is substantially greater than that of bevacizumab or ranibizumab.[17] The greater affinity could translate into a higher efficacy or, as predicted by a mathematic model, into a substantially longer duration of action in the eye,[19] allowing for less frequent dosing, as supported by early clinical trials.[18,20] In this article, we report the first-year results of 2 phase 3 studies comparing intravitreal aflibercept, monthly or every 2 months, with monthly ranibizumab.

Materials and Methods

Study Design

The "VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD" studies (VIEW 1 and VIEW 2) were similarly designed, prospective, double-masked, multinational, parallel-group, active-controlled, randomized clinical trials. The investigators from the VIEW 1 and VIEW 2 studies are listed in Appendix 1, available at http://aaojournal.org. Patients in VIEW 1 (registered at www.clinicaltrials.gov on July 31, 2007; NCT00509795. Accessed August 8, 2012) were randomized at 154 sites in the United States and Canada. Patients in VIEW 2 (registered at www.clinicaltrials.gov on March 12, 2008; NCT00637377. Accessed August 8, 2012) were randomized at 172 sites in Europe, the Middle East, Asia-Pacific, and Latin America; the last patient in both studies completed 52 weeks in September 2010. The study protocols were approved by institutional review boards or ethics committees for each clinical site; all participants provided written informed consent. All the US study sites complied with the Health Insurance

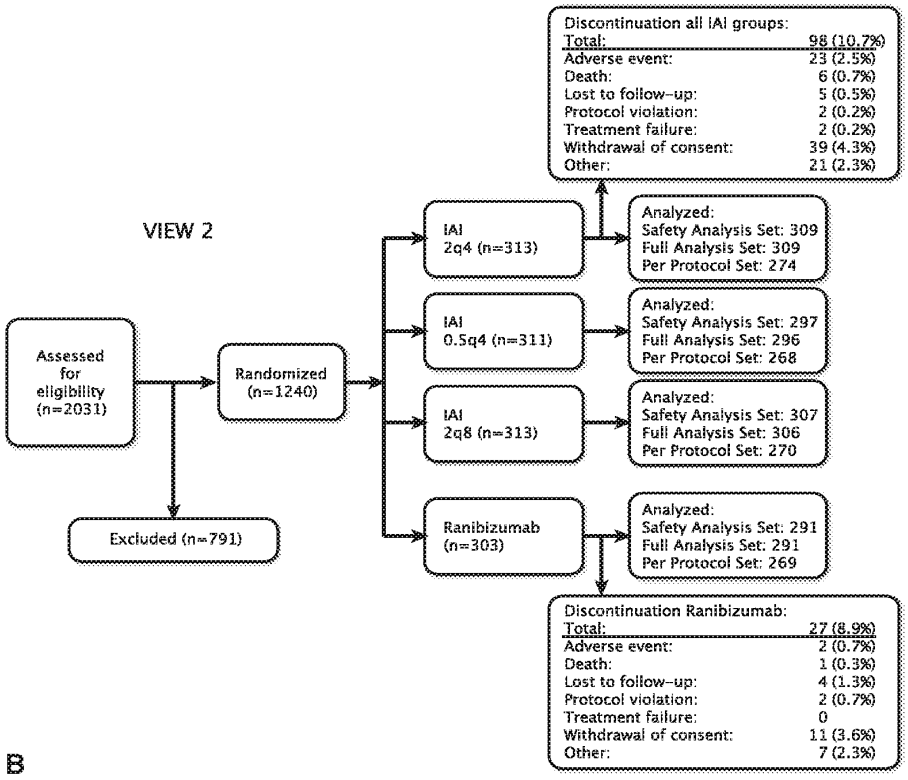

Figure 1. (Continued.)

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Portability and Accountability Act. The 52-week outcomes are reported.

Participants

Inclusion and exclusion criteria were designed to maintain constancy with the pivotal trials for the reference drug ranibizumab, consistent with regulatory guidelines for noninferiority studies, and included (1) age ≥50 years with active subfoveal CNV lesions (any subtype) secondary to AMD; juxtafoveal lesions with leakage affecting the fovea also were allowed; (2) CNV comprising at least 50% of total lesion size; and (3) BCVA between 73 and 25 Early Treatment Diabetic Retinopathy Study chart (ETDRS) letters (20/40–20/320 Snellen equivalent). Patients with prior treatment for AMD (including an investigational agent or anti-VEGF therapy) in the study eye were excluded. Eligibility was determined using fluorescein angiography at the reading center. Complete eligibility criteria are shown in Appendix 2 (available at http://aaojournal.org).

Treatment Groups and Randomization

Patients were randomized in a 1:1:1:1 ratio to the following regimens: 0.5 mg aflibercept every 4 weeks (0.5q4); 2 mg aflibercept every 4 weeks (2q4); 2 mg aflibercept every 8 weeks (2q8) after 3 injections at week 0, 4, and 8 (to maintain masking, sham injections were given at the interim 4-week visits after week 8); or 0.5 mg ranibizumab every 4 weeks (Rq4). Consecutively enrolled patients were assigned to treatment groups on the basis of a predetermined central randomization scheme with balanced allocation, managed by an interactive voice response system.

End Points and Statistical Analyses

The primary end point analysis, noninferiority margins, and definition of "clinical equivalence" were established in discussion with the Food and Drug Administration (FDA) (as part of a Special Protocol Assessment), European Medicines Agency, Pharmaceutical and Medical Device Agency and other regulatory authorities, with the intent of maintaining constancy with the previous ranibizumab pivotal trials[7,8] and preserving the majority of the treatment effect demonstrated in these trials. The primary end point analysis was noninferiority of the intravitreal aflibercept regimens to ranibizumab in the proportion of patients maintaining vision at week 52 (losing <15 ETDRS letters; per protocol data set) in each study. A noninferiority margin of 10% in the individual studies was chosen to preserve approximately two-thirds of the ranibizumab effect for prevention of moderate vision loss (loss of <15 letters) demonstrated in pivotal ranibizumab studies,[7,8] using the 2 CI approach. The FDA suggested that a margin of 5% could determine clinical equivalence. Thus, the margin of 10% was used for assessing noninferiority, and the margin of 5% was used for assessing clinical equivalence. The prespecified analysis plan also included a prospectively planned integrated analysis combining the 2 VIEW studies; in this integrated analysis, the European Medicines Agency/Committee for Medicinal Products for Human Use requested a noninferiority margin of 7%. In the individual studies, the primary end point was assessed by a prespecified hierarchical testing sequence of noninferiority to ranibizumab with the sequence of aflibercept 2q4, 0.5q4, and then 2q8 to control the 5% (4.9% for VIEW 1) overall type I error while maintaining a 5% significance level (4.9% for VIEW 1) for each individual comparison (see Appendices 3 and 4 for details of the statistical analysis, available at http://aaojournal.org). If all aflibercept groups demonstrated noninferiority to ranibizumab for the primary end point, additional comparisons with ranibizumab were prespecified regarding the secondary end points, also using a hierarchical testing sequence in which each secondary end point was tested for superiority of aflibercept over ranibizumab. Prespecified secondary efficacy variables compared baseline and 52-week data regarding mean change in BCVA; gaining ≥15 letters; change in total National Eye Institute 25-Item Visual Function Questionnaire (NEI VFQ-25) score; and change in CNV area on fluorescein angiography. Anatomic measures included retinal thickness and persistent fluid as assessed by OCT. Change in BCVA also was assessed as part of the prospectively planned prespecified integrated analysis combining the 2 studies.

The full analysis set included all randomized patients who received any study medication and had a baseline and at least 1 post-baseline BCVA assessment. The per protocol set (PPS) included all patients in the full analysis set who (1) received at least 9 doses of study drug and attended at least 9 scheduled visits during the first year, (2) had not missed 2 consecutive injections before administration of the ninth injection (per patient), and (3) did not have major protocol violations. Sham injections were counted as doses administered for the purpose of defining the PPS. The PPS included patients who discontinued the study because of treatment failure, without a major protocol deviation, at any time during the first 52 weeks (even if they met points 1 and 2 above). These patients were considered nonresponders for the primary end-point analysis. The last observation carried forward (LOCF) approach was used to impute missing values. When indicated, the robustness of analysis results was assessed by using the observed case or completers' data. A completer was defined as a patient who received treatment for at least 9 months and had efficacy data for at least 9 months during the 52 weeks of study. The missing values for completers also were imputed using the LOCF approach.

Schedule of Visits and Assessments

Patients were examined on the day of treatment initiation and every 4 weeks thereafter through 52 weeks, as well as 1 week after first treatment for safety assessment (subsequent safety assessments occurred by telephone). Each 4-week visit included BCVA assessment and anterior/posterior segment examination (with intraocular pressure determination) before injection (active or sham) and posterior segment examination with intraocular pressure determination 30 to 60 minutes after injection. For the 2q8 treatment group, no treatment decisions were made at the interim monthly visits. The NEI VFQ-25 assessment occurred at screening and weeks 12, 24, 36, and 52. Adverse events were recorded at every visit.

Imaging Assessments

Fundus photography and fluorescein angiography were performed at screening and weeks 24 and 52, and evaluated by an independent center (Digital Angiography Reading Center, New York). Optical coherence tomography was performed using time domain Stratus machines (Carl Zeiss Meditec, Jena, Germany) and evaluated by an independent center (VIEW 1: OCT Reading Center at Duke, Durham, NC; VIEW 2: Vienna Reading Center, Austria). Visual acuity examiners were certified to ensure consistent measurement of BCVA. In VIEW 1, OCT was performed at screening, at the treatment initiation visit, and at weeks 4, 12, 24, 36, and 52

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(and was optional at the investigators' discretion at other study visits). In VIEW 2, OCT was performed at every study visit. Areas of visible CNV (classic or occult) were identified when angiographic analyses showed evidence of late leakage or pooling of dye.

Masking

Patients were masked as to treatments. An unmasked investigator performed the study drug or sham injection. An unmasked investigator also was responsible for the receipt, tracking, preparation, destruction, and administration of study drug, as well as safety assessments both pre- and post-dose. A separate masked physician assessed adverse events and supervised the masked assessment of efficacy. All other study site personnel were masked to treatment assignment by separating study records or masked packaging. Optical coherence tomography technicians and visual acuity examiners remained masked relative to treatment assignment. Intravitreal aflibercept and sham kits were packaged identically. Lucentis (Genentech Inc, South San Francisco, CA) was obtained commercially but only prepared and delivered by unmasked personnel at the sites.

Results

Patient Disposition, Baseline Characteristics, and Exposure

The disposition of patients is shown in Figure 1A-B. In VIEW 1, 1217 patients were randomized, with 91.1% to 96.4% of patients completing 52 weeks. In VIEW 2, 1240 patients were randomized, with 88.1% to 91.1% completing 52 weeks. Baseline demographics and disease characteristics were evenly balanced among all treatment groups (Table 1). The mean number of active injections received by patients in all monthly treatment arms, which were scheduled to receive 13 monthly injections, was 12.1 to 12.5 in VIEW 1 and 12.2 to 12.4 in VIEW 2. The aflibercept every-2-month groups, scheduled to receive 3 initial monthly injections followed by 5 active injections over the next 10 months, received an average of 7.5 active injections in VIEW 1 and in VIEW 2.

Primary End Point Analysis

In both studies, the proportion of patients maintaining vision was similar among all treatment groups in the prespecified per-protocol analysis and the full analysis set (Table 2). All aflibercept groups achieved statistical noninferiority compared with monthly ranibizumab, with the CIs of the difference between ranibizumab and

Table 1. Patient Demographics and Baseline Characteristics

	VIEW 1				VIEW 2			
	Ranibizumab	*Intravitreal Aflibercept*			*Ranibizumab*	*Intravitreal Aflibercept*		
	0.5q4	*2q4*	*0.5q4*	*2q8*	*0.5q4*	*2q4*	*0.5q4*	*2q8*
N (full analysis set)	304	304	301	301	291	309	296	306
Age, yrs (mean ± SD)	78.2±7.6	77.7±7.9	78.4±8.1	77.9±8.4	73.0±9.0	74.1±8.5	74.7±8.6	73.8±8.6
Race								
White	296 (97.4)	295 (97.0)	291 (96.7)	287 (95.3)	213 (73.2)	226 (73.1)	219 (74.0)	217 (70.9)
Black	1 (0.3)	1 (0.3)	0	1 (0.3)	1 (0.3)	0	1 (0.3)	2 (0.7)
Asian	0	3 (1.0)	5 (1.7)	4 (1.3)	60 (20.6)	67 (21.7)	61 (20.6)	69 (22.5)
Other	7 (2.3)	5 (1.6)	5 (1.7)	9 (3.0)	17 (5.8)	16 (5.2)	15 (5.1)	18 (5.9)
Sex								
Men, n (%)	132 (43.4)	110 (36.2)	134 (44.5)	123 (40.9)	122 (41.9)	133 (43.0)	149 (50.3)	131 (42.8)
Women, n (%)	172 (56.6)	194 (63.8)	167 (55.5)	178 (59.1)	169 (58.1)	176 (57.0)	147 (49.7)	175 (57.2)
Baseline ETDRS BCVA (mean ± SD)	54.0±13.4	55.2±13.2	55.6±13.1	55.7±12.8	53.8±13.5	52.8±13.9	51.6±14.2	51.6±13.9
Proportion of patients with ≥20/40 BCVA, % (n)	4.3% (13)	4.9% (15)	6.3% (19)	6.6% (20)	2.7% (8)	2.6% (8)	5.4% (16)	3.3% (10)
CNV area, mm^2 (mean ± SD)	6.53±5.2	6.59±5.1	6.49±4.5	6.57±5.1	7.59±5.3	8.25±5.8	7.70±5.3	7.75±5.5
Lesion type								
Predominantly classic, n (%)	82 (27.0)	87 (28.6)	81 (26.9)	71 (23.6)	70 (24.1)	72 (23.3)	80 (27.0)	88 (28.8)
Minimally classic, n (%)	101 (33.2)	105 (34.5)	97 (32.2)	110 (36.5)	104 (35.7)	112 (36.2)	103 (34.8)	106 (34.6)
Occult, n (%)	115 (37.8)	110 (36.2)	121 (40.2)	118 (39.2)	116 (39.9)	123 (39.8)	113 (38.2)	110 (35.9)
Patients with juxtafoveal lesions, n (%)	15 (4.9)	13 (4.3)	17 (5.6)	17 (5.6)	20 (6.9)	15 (4.9)	11 (3.7)	14 (4.6)
Lesion size, mm^2 (mean ± SD)	6.99±5.5	6.98±5.4	6.95±4.7	6.89±5.2	8.01±5.7	8.72±6.1	8.17±5.5	8.22±5.9
Central retinal thickness, μm (mean ± SD)	315.3±108.3	313.6±103.4	313.2±106.0	324.4±111.2	325.9±110.9	334.6±119.8	326.5±116.5	342.6±124.0
Baseline NEI VFQ-25 scores (mean ± SD)	71.8±17.2	70.4±16.6	71.1±17.8	69.6±16.8	72.9±19.1	70.3±19.4	74.0±18.2	71.3±19.1

0.5q4 = 0.5 mg monthly; 2q4 = 2 mg monthly; 2q8 = 2 mg every 2 months after 3 initial monthly doses; BCVA = best-corrected visual acuity; CNV = choroidal neovascularization; ETDRS = Early Treatment Diabetic Retinopathy Study; NEI VFQ-25 = National Eye Institute 25-Item Visual Functioning Questionnaire; SD = standard deviation.

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Table 2. Prespecified Efficacy

	VIEW 1			
	Ranibizumab	*Intravitreal Aflibercept*		
	0.5q4	*2q4*	*0.5q4*	*2q8*
Primary end point				
N (PPS)	269	285	270	265
Proportion maintaining vision (losing <15 ETDRS letters), % (n)	94.4% (254)	95.1% (271)	95.9% (259)	95.1% (252)
N (full analysis set)	304	304	301	301
Proportion maintaining vision (losing <15 ETDRS letters, LOCF), % (n)	93.8% (285)	95.1% (289)	95.0% (286)	94.4% (284)
Secondary end points				
N (full analysis set)	304	304	301	301
Change in ETDRS BCVA (mean ± SD)	8.1±15.3	10.9±13.8	6.9±13.4	7.9±15.0
LS mean difference between IAI and ranibizumab (95% CI)*		3.15 (0.92 to 5.37)	−0.80 (−3.03 to 1.43)	0.26 (−1.97 to 2.49)
Proportion gaining ≥15 ETDRS letters, % (n)	30.9% (94)	37.5% (114)	24.9% (75)	30.6% (92)
LS mean difference between IAI and ranibizumab (95% CI)*		6.58 (−0.98 to 14.14)	−6.00 (−13.17 to 1.16)	−0.36 (−7.74 to 7.03)
Change in CNV area, mm^2 (mean ± SD)	−4.2±5.6	−4.6±5.5	−3.5±5.3	−3.4±6.0
LS mean difference between IAI and ranibizumab (95% CI)*		−0.33 (−1.04 to 0.38)	0.71 (−0.01 to 1.42)	0.86 (0.15–1.58)
Change in total NEI VFQ-25 score (mean ± SD)	4.9±14.0	6.7±13.5	4.5±11.9	5.1±14.7
LS mean difference between IAI and ranibizumab (95% CI)*		1.28 (−0.73 to 3.28)	−0.67 (−2.69 to 1.35)	−0.60 (−2.61 to 1.42)
Exploratory end point				
Change in central retinal thickness, μm (mean ± SD)	−116.8±109.0	−116.5±98.4	−115.6±104.1	−128.5±108.5
Post hoc end point†				
Proportion with dry retina (absence of cystic intraretinal edema and subretinal fluid on OCT), % (n)	63.6% (171)	64.8% (184)	56.7% (148)	63.4% (168)

0.5q4 = 0.5 mg monthly; 2q4 = 2 mg monthly; 2q8 = 2 mg every 2 months after 3 initial monthly doses; BCVA = best-corrected visual acuity; aflibercept injection; LOCF = last observation carried forward; LS = least-squares; NEI VFQ-25 = National Eye Institute 25-Item Visual
*95.1% CI for VIEW 1.
†Observed case.

each aflibercept group within the prespecified 10% margin (Fig 2), and the point estimates of the differences in means favoring the aflibercept groups in all cases. All the aflibercept regimens also met the prespecified 7% noninferiority margin in the prespecified integrated analysis combining the 2 VIEW studies, as well as the prespecified 5% margin for clinical equivalence compared with ranibizumab in the individual VIEW studies. Moreover, the results of multiple imputation analyses were consistent with those using the LOCF.

Mean Changes in Best-Corrected Visual Acuity and Other Visual Acuity End Points

The mean change in BCVA was a clinically important secondary end point in both studies. On the basis of the hierarchical testing sequence, only the aflibercept 2q4 group was statistically superior to ranibizumab, and only in VIEW 1, with a gain of +10.9 versus +8.1 letters (Table 2). Small numeric differences between treatment groups in one study at any given timepoint were not reproduced in the other study, suggesting that they reflected random variability even in groups of this size (Fig 3A, B); this interpretation was supported by a prespecified integrated analysis that combined the 2 studies (Fig 3C), showing similar visual acuity scores across the entire 52-week study for all treatment groups. All groups behaved similarly in this integrated analysis (Fig 3C), with rapid increases in mean visual acuity after the first injection followed by incremental gains that were durable and maintained through week 52. Regardless of whether the analysis was by LOCF, by multiple imputations, by assessing completers, or by using actual observed data, intravitreal aflibercept dosed every 2 months achieved a mean visual acuity score within 0.3 letters of monthly ranibizumab in the integrated analysis, with a CI of less than 2 letters (Fig 3C, inset).

In both studies, the secondary end point of proportions of patients gaining ≥15 ETDRS letters from baseline to week 52 was similar in all treatment groups (Table 2), as were other exploratory categoric measures of visual outcome (Appendix 5, available at http://aaojournal.org). Likewise, vision-related quality of life, assessed by the change of total score of the NEI VFQ-25, improved in all groups in both studies (Table 2).

Key Anatomic Measures

In both studies, all groups demonstrated a comparable decrease in the secondary end point of change in area of active CNV

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Outcomes at Week 52

	VIEW 2			
	Ranibizumab	*Intravitreal Aflibercept*		
	0.5q4	*2q4*	*0.5q4*	*2q8*
Primary end point				
N (PPS)	269	274	268	270
Proportion maintaining vision (losing <15 ETDRS letters), % (n)	94.4% (254)	95.6% (262)	96.3% (258)	95.6% (258)
N (full analysis set)	291	309	296	306
Proportion maintaining vision (losing <15 ETDRS letters, LOCF), % (n)	94.8% (276)	94.5% (292)	95.3% (282)	95.4% (292)
Secondary end points				
N (full analysis set)	291	309	296	306
Change in ETDRS BCVA (mean ± SD)	9.4±13.5	7.6±12.6	9.7±14.1	8.9±14.4
LS mean difference between IAI and ranibizumab (95% CI)*		−1.95 (−4.10 to 0.20)	−0.06 (−2.24 to 2.12)	−0.90 (−3.06 to 1.26)
Proportion gaining ≥15 ETDRS letters, % (n)	34.0% (99)	29.4% (91)	34.8% (103)	31.4% (96)
LS mean difference between IAI and ranibizumab (95% CI)*		−4.57 (−12.02 to 2.88)	0.78 (−6.91 to 8.46)	−2.65 (−10.18 to 4.88)
Change in CNV area, mm^2 (mean ± SD)	−4.2±5.9	−6.0±6.1	−4.2±6.1	−5.2±5.9
LS mean difference between IAI and ranibizumab (95% CI)*		−1.18 (−1.98 to −0.38)	0.17 (−0.63 to 0.97)	−0.73 (−1.53 to 0.07)
Change in total NEI VFQ-25 score (mean ± SD)	6.3±14.8	4.5±15.0	5.1±13.7	4.9±14.7
LS mean difference between IAI and ranibizumab (95% CI)*		−2.79 (−4.90 to −0.68)	−0.93 (−3.07 to 1.20)	−1.95 (−4.07 to 0.17)
Exploratory end point				
Change in central retinal thickness, μm (mean ± SD)	−138.5±122.2	−156.8±122.8	−129.8±114.8	−149.2±119.7
Post hoc end point†				
Proportion with dry retina (absence of cystic intraretinal edema and subretinal fluid on OCT), % (n)	60.4% (162)	80.3% (220)	63.9% (170)	71.9% (197)

CNV = choroidal neovascularization; CI = confidence interval; ETDRS = Early Treatment Diabetic Retinopathy Study; IAI = intravitreal Functioning Questionnaire; OCT = optical coherence tomography; PPS = per protocol set; SD = standard deviation.

(Table 2). Likewise, all aflibercept groups in both studies had reductions in central retinal thickness similar to those for monthly ranibizumab as assessed by OCT, with a large and rapid reduction evident by week 4 (with retinal thickness approaching normal levels) that was maintained to week 52 (Table 2, Fig 4). Minor fluctuations in central retinal thickness were seen in the 2q8 group after sham injections in the VIEW 2 study; these fluctuations attenuated over time, starting at 17 μm and decreasing to 8 μm over the year, with no apparent negative impact on visual acuity outcomes.

Because of the inability of other regimens in the CATT[13] to match the retinal thickness and retinal fluid improvements seen with monthly ranibizumab, a post hoc analysis was performed to determine the percentage of patients who had fluid-free retinas, which were defined, on OCT, by the absence of both cystic intraretinal edema and subretinal fluid. All intravitreal aflibercept groups were similar to the monthly ranibizumab group in terms of this end point, with numerically higher percentages of dry retinas seen in the 2q4 and 2q8 regimens largely driven by VIEW 2 (Table 2; Appendix 6, available at http://aaojournal.org). Integrated analysis combining both studies for proportions of patients with dry retinas for ranibizumab and the aflibercept regimens of 2q4, 0.5q4, and 2q8 showed percentages of 62.0%, 72.4%, 60.3%, and 67.7%, respectively.

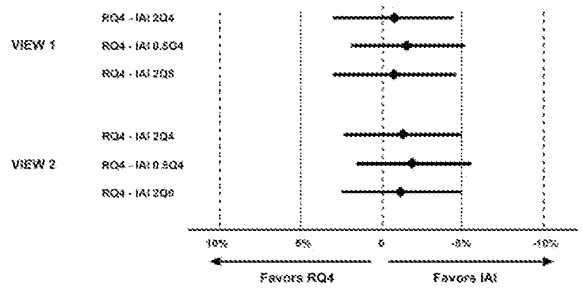

Figure 2. Difference in proportions of patients who maintained vision (losing <15 Early Treatment Diabetic Retinopathy Study [ETDRS] letters) at week 52 in the VIEW studies (per protocol set [PPS]). The *diamond symbol* denotes the difference between the treatment arms, and the *horizontal bars* indicate 95% confidence interval (CI) range. The CI within the left 10% (*dashed vertical lines*) indicates that all intravitreal aflibercept arms were noninferior to ranibizumab. The CI within the left 5% (*dotted vertical line*) indicates clinical equivalence to ranibizumab. The last observation carried forward (LOCF) was used for imputing the missing values. RQ4 = 0.5 mg ranibizumab monthly; 0.5Q4 = 0.5 mg IAI monthly; 2Q4 = 2 mg IAI monthly; 2Q8 = 2 mg IAI every 2 months after 3 initial monthly doses; IAI = intravitreal aflibercept injection.

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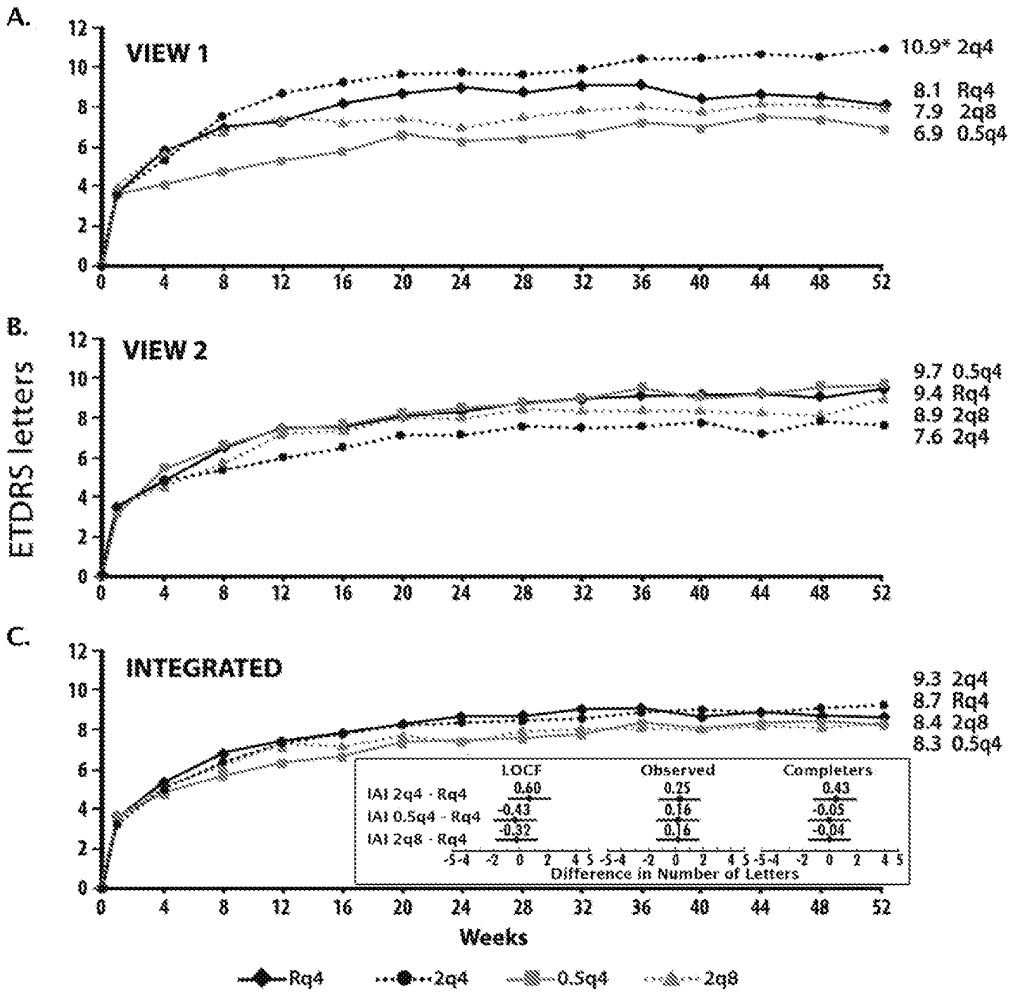

Figure 3. Mean change in best-corrected visual acuity (BCVA) from baseline to week 52 in the individual VIEW studies and in the integrated analysis. Values in the line graphs refer to mean changes in the number of letters from baseline at week 52. Only the intravitreal aflibercept 2q4 arm in VIEW 1 was significantly different from ranibizumab (*P = 0.005 for the difference). The panel inset (integrated analysis) shows the difference in visual acuity between each intravitreal aflibercept arm and ranibizumab (least-square mean with 95% confidence interval [CI]) at week 52, using 3 different analyses: by last observation carried forward (LOCF), using observed case data, and by assessing completers. Rq4 = 0.5 mg ranibizumab monthly; 0.5q4 = 0.5 mg IAI monthly; 2q4 = 2 mg IAI monthly; 2q8 = 2 mg IAI every 2 months after 3 initial monthly doses; ETDRS = Early Treatment Diabetic Retinopathy Study; IAI = intravitreal aflibercept injection.

Safety

Intravitreal aflibercept was generally well tolerated and had a profile of ocular treatment-emergent adverse experiences, including serious ocular adverse events, similar to those for monthly ranibizumab (Table 3; Appendix 7, available at http://aaojournal.org). Differences were noted in the prespecified analyses of intraocular pressure: Fewer patients treated with aflibercept had increases in intraocular pressure over the 52 weeks of the VIEW 1 and VIEW 2 studies (Appendix 7, available at http://aaojournal.org). There were few ocular injection–related treatment-emergent serious adverse events in the study eye. The combined data for both studies showed a rate of events/1000 injections of 1.1, 0.8, 0.1, and 0.2 for the ranibizumab 0.5q4 and intravitreal aflibercept 2q4, 0.5q4, and 2q8 groups, respectively. These events included eye disorders, endophthalmitis, procedural complications, and increased intraocular pressure.

There was a similar overall incidence of systemic (nonocular) adverse events (Appendix 7, available at http://aaojournal.org), serious systemic adverse events, specific arterial thromboembolic end points as set forth by the Anti-Platelet Trialists' Collaboration, and deaths between intravitreal aflibercept and ranibizumab (Table 3). Among the aflibercept treatment groups, there was no evidence of a dose-response for adverse events: The group with the highest exposure, the aflibercept 2q4 group, generally had the lowest rates of adverse events. There was little to no immunogenicity associated with intravitreal aflibercept (Appendix 8, available at http://aaojournal.org).

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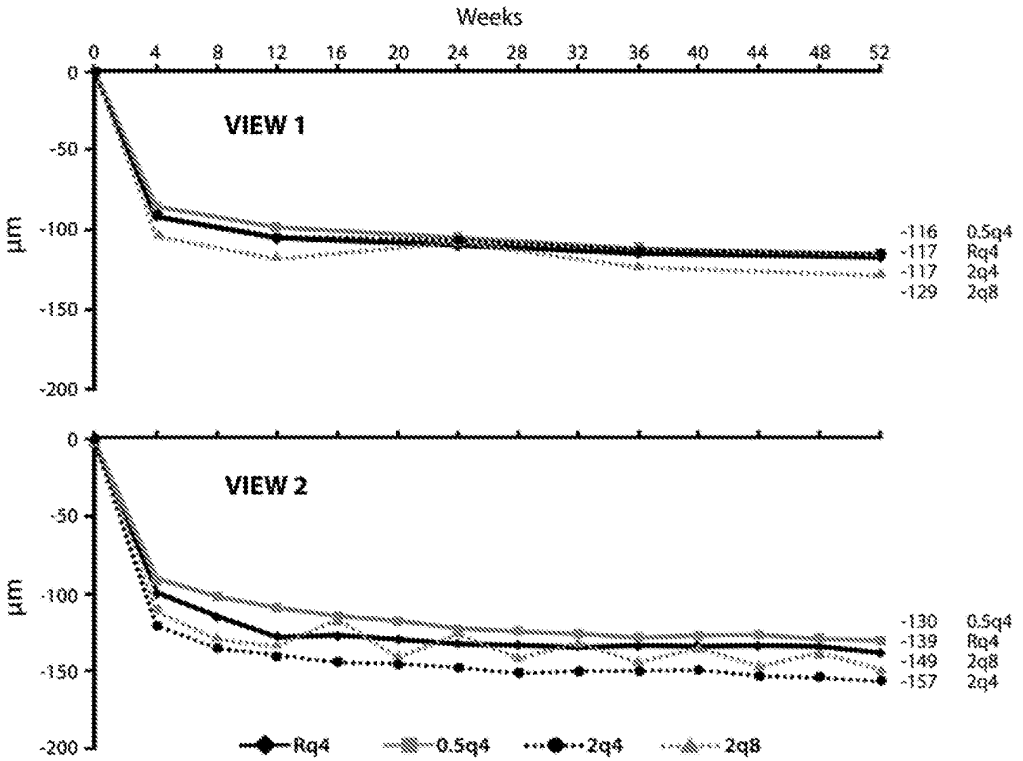

Figure 4. Mean change from baseline in central retinal thickness (full analysis set). As described in the "Materials and Methods" section, in VIEW 1, optical coherence tomography (OCT) was performed at screening, at the treatment initiation visit, and at weeks 4, 12, 24, 36, and 52 (and was optional at the investigators' discretion at other study visits). In VIEW 2, OCT was performed at every study visit. The last observation carried forward (LOCF) was used for imputing the missing values. Rq4 = 0.5 mg ranibizumab monthly; 0.5q4 = 0.5 mg intravitreal aflibercept injection (IAI) monthly; 2q4 = 2 mg IAI monthly; 2q8 = 2 mg IAI every 2 months after 3 initial monthly doses.

Discussion

We have described 2 large and similarly designed clinical trials involving more than 2400 patients with neovascular AMD. In both trials, all 3 aflibercept treatment regimens (including the every-2-month regimen after 3 initial monthly loading doses) were statistically noninferior to monthly ranibizumab in preventing moderate visual acuity loss at 1 year, meeting the primary outcome of the trials; all the aflibercept regimens also met the stricter margin of 5% for clinical equivalence compared with monthly ranibizumab. In terms of mean change in BCVA over time, all aflibercept regimens behaved similarly to monthly ranibizumab, with rapid increases after the first treatment followed by incremental gains that were durable and maintained through week 52. Mean visual acuity scores were within 1 letter of each other at week 52 in the prespecified integrated analysis combining the 2 studies; of note, aflibercept dosed every 2 months achieved a visual acuity score within 0.3 letters of monthly ranibizumab, with a CI of less than 2 letters, regardless of the analysis set used. Because the CATT[13] highlighted the inability of other regimens, including monthly bevacizumab and PRN ranibizumab or bevacizumab, to match the retinal thickness and retinal fluid improvements seen with monthly ranibizumab, it is notable that all 3 aflibercept regimens behaved similarly to monthly ranibizumab in terms of these anatomic measures.

Because of the large treatment burden, extensive efforts have been devoted toward developing an optimized treatment paradigm that avoids the need for monthly injections or monitoring visits. The CATT and HARBOR studies used noninferiority margins of change from baseline BCVA of 5 letters and 4 letters, respectively, to evaluate the efficacy of PRN regimens (Invest Ophthalmol Vis Sci 2012;53:E-Abstract 3677).[13] The CATT[13] generated much interest, in part because it showed that PRN ranibizumab and bevacizumab regimens approached the visual acuity outcomes achieved with monthly ranibizumab; however, these PRN regimens produced numerically smaller gains in BCVA at 52 weeks (by 1.7–2.6 letters) with poorer anatomic outcomes. Switching from a monthly to a PRN regimen during the second year of the CATT significantly worsened visual and anatomic out-

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Table 3. Serious Ocular Adverse Events in the Study Eye and Other Key Nonocular Events Occurring in ≥0.5%* of Patients in Any Study Arm

	VIEW 1				VIEW 2			
	Ranibizumab	*Intravitreal Aflibercept*			*Ranibizumab*	*Intravitreal Aflibercept*		
	0.5q4	*2q4*	*0.5q4*	*2q8*	*0.5q4*	*2q4*	*0.5q4*	*2q8*
N (safety analysis set)	304	304	304	303	291	309	297	307
Patients with at least 1 ocular SAE, n (%)	10 (3.3)	7 (2.3)	6 (2.0)	3 (1.0)	9 (3.1)	6 (1.9)	5 (1.7)	9 (2.9)
Serious ocular adverse event, n (%)								
Endophthalmitis	3 (1.0)	3 (1.0)	0	0	0	0	0	0
Visual acuity reduced	2 (0.7)	1 (0.3)	2 (0.7)	0	1 (0.3)	1 (0.3)	1 (0.3)	5 (1.6)
Retinal hemorrhage	2 (0.7)	0	0	2 (0.7)	1 (0.3)	2 (0.6)	1 (0.3)	1 (0.3)
Posterior capsule opacification	—	—	—	—	2 (0.7)	0	0	0
Serious systemic (or nonocular) adverse event	57 (18.8)	40 (13.2)	50 (16.4)	51 (16.8)	26 (8.9)	36 (11.7)	37 (12.5)	38 (12.4)
APTC ATE events								
Any APTC ATE event	5 (1.6)	2 (0.7)	7 (2.3)	6 (2.0)	5 (1.7)	4 (1.3)	5 (1.7)	8 (2.6)
Vascular death	1 (0.3)	0	1 (0.3)	4 (1.3)	1 (0.3)	1 (0.3)	2 (0.7)	1 (0.3)
Nonfatal myocardial infarction	4 (1.3)	1 (0.3)	4 (1.3)	1 (0.3)	2 (0.7)	2 (0.6)	2 (0.7)	5 (1.6)
Nonfatal stroke	0	1 (0.3)	2 (0.7)	1 (0.3)	2 (0.7)	1 (0.3)	1 (0.3)	2 (0.7)
Any AE of hypertension	29 (9.5)	25 (8.2)	26 (8.6)	31 (10.2)	29 (10.0)	31 (10.0)	22 (7.4)	28 (9.1)
SAEs of interest occurring in any patient								
Venous thromboembolic event	1 (0.3%)	0	1 (0.3%)	0	0	0	0	0
Congestive heart failure event	2 (0.7%)	1 (0.3%)	2 (0.7%)	3 (1.0%)	1 (0.3%)	0	0	1 (0.3%)
GI perforation or fistula event	0	0	0	0	0	0	1 (0.3%)	1 (0.3%)
Nonocular hemorrhagic event	1 (0.3%)	1 (0.3%)	3 (1.0%)	3 (1.0%)	0	2 (0.6%)	0	1 (0.3%)
Delayed wound healing	0	0	0	0	0	0	0	0

0.5q4 = 0.5 mg monthly; 2q4 = 2 mg monthly; 2q8 = 2 mg every 2 months after 3 initial monthly doses; AE = adverse event; APTC ATE = Anti-platelet Trialists' Collaboration Arteriothrombolic Event; GI = gastrointestinal; SAE = serious adverse event.
*For SAEs of interest, occurrence in any patient is reported.

comes and resulted in a decrease in the proportion of patients without retinal fluid.[14] The results from the HARBOR study showed that PRN regimens of ranibizumab (including a higher 2 mg dose) did not achieve noninferiority compared with monthly ranibizumab (Invest Ophthalmol Vis Sci 2012;53:E-Abstract 3677). Moreover, the PRN regimens in both CATT and HARBOR still required mandatory monthly visits, during which treatment decisions had to be made largely on the basis of anatomic measures. The demonstration that monthly aflibercept provides similar efficacy and safety as the current approved standard of monthly ranibizumab is important, but the finding that remarkably similar improvement in vision and anatomic measures can be achieved with less than monthly intravitreal aflibercept injections and without requiring monthly monitoring visits provides an important advance for both patients and their treating physicians. The FDA has approved intravitreal aflibercept injection for AMD and recommended the regimen of 2 mg once every 2 months after 3 initial monthly doses (Eylea [package insert]. Tarrytown, NY: Regeneron Pharmaceuticals, Inc; 2011. Available at: http://www.regeneron.com/Eylea/eylea-fpi.pdf. Accessed August 8, 2012). This approval was based on the evaluation that this regimen provided the best benefit/risk; the approved label notes that aflibercept can be dosed as often as every 4 weeks, although additional efficacy was not reported with such frequent dosing. By halving the need for monthly visits, the every-2-month regimen of aflibercept may markedly decrease the treatment burden experienced by patients and their families. Less frequent injections also should provide an ocular safety benefit. Although the VIEW studies were not powered to see differences in rare but serious intraocular complications (e.g., endophthalmitis and retinal detachment), it is likely that fewer injections may substantially decrease the cumulative population risk of such events, considering that millions of injections are given each year.

After the 1-year primary end point of VIEW 1/VIEW 2 presented in this article, all treatment groups' dosing intervals were changed to a common protocol of modified quarterly dosing with their originally randomized dose and drug (all patients were monitored monthly and received a minimum of dosing every 12 weeks with interim as-needed monthly intravitreal injections). The results of this second year were recently presented (Invest Ophthalmol Vis Sci 2012;53:E-Abstract 6962) and reveal 81.6% to 85.7% patient retention in all groups with comparable visual acuity maintenance (91%–92%) in each group at the 96-week time point. The total number of active injections (baseline to week 96) was 16.0 to 16.2 in the monthly intravitreal aflibercept groups, 16.5 in the monthly ranibizumab group, and 11.2 in the original 2q8 group. The finding that visual acuity maintenance can be achieved for up to 96 weeks in the 2q8 group with similar gains in BCVA compared with ranibizumab despite more than 5 fewer doses is encouraging and implies that the treatment burden of neovascular AMD may be meaningfully reduced with this 2q8 intravitreal aflibercept regimen.

The sustained durability of intravitreal aflibercept as demonstrated by the every-2-month regimen is consistent

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with the rationale that a higher binding affinity could lead to increased durability.[17] It is encouraging that the increased affinity of intravitreal aflibercept did not result in an observed increase in ocular or systemic adverse events. In the VIEW 1 and VIEW 2 trials, no differences in systemic or ocular safety were noted between any of the doses or dosing regimens of intravitreal aflibercept. Systemic exposure of aflibercept injected intravitreally is extremely low (Eylea [package insert]. Tarrytown, NY: Regeneron Pharmaceuticals, Inc; 2011. Available at: http://www.regeneron.com/Eylea/eylea-fpi.pdf. Accessed August 8, 2012). After intravitreal administration of 2 mg per eye of aflibercept to patients with wet AMD, the mean maximum concentration of free aflibercept in the plasma was 0.02 μg/ml (range, 0–0.054 μg/ml) and was attained in 1 to 3 days. The free aflibercept plasma concentrations were undetectable 2 weeks post-dosing in all patients. Aflibercept did not accumulate in plasma when administered as repeated doses intravitreally every 4 weeks. It is estimated that after intravitreal administration of 2 mg to patients, the mean maximum plasma concentration of free aflibercept is more than 100-fold lower than the concentration of aflibercept required to half-maximally bind systemic VEGF.

In conclusion, intravitreal aflibercept dosed monthly or every 2 months after 3 initial monthly doses resulted in similar visual and anatomic outcomes as ranibizumab dosed monthly, as well as similar safety and tolerability. Intravitreal aflibercept dosed every 2 months has the potential to provide patients, their families, and clinicians the opportunity for the optimal vision gains and anatomic disease control they have come to expect from monthly ranibizumab, with a substantially decreased treatment and compliance burden, and a lower cumulative risk of injection-related adverse events.

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References

1. Congdon NG, Friedman DS, Lietman T. Important causes of visual impairment in the world today. JAMA 2003;290: 2057–60.
2. Macular Photocoagulation Study Group. Laser photocoagulation of subfoveal neovascular lesions in age-related macular degeneration. Results of a randomized clinical trial. Arch Ophthalmol 1991;109:1220–31.
3. Treatment of Age-related Macular Degeneration with Photodynamic Therapy (TAP) Study Group. Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin: one-year results of 2 randomized clinical trials–TAP report 1. Arch Ophthalmol 1999; 117:1329–45.
4. Verteporfin in Photodynamic Therapy Study Group. Verteporfin therapy of subfoveal choroidal neovascularization in age-related macular degeneration: two-year results of a randomized clinical trial including lesions with occult with no classic choroidal neovascularization–Verteporfin in Photodynamic Therapy report 2. Am J Ophthalmol 2001;131:541–60.
5. Yancopoulos GD. Clinical application of therapies targeting VEGF. Cell 2010;143:13–6.
6. Ferrara N. VEGF-A: a critical regulator of blood vessel growth. Eur Cytokine Netw 2009;20:158–63.
7. Rosenfeld PJ, Brown DM, Heier JS, et al, MARINA Study Group. Ranibizumab for neovascular age-related macular degeneration. N Engl J Med 2006;355:1419–31.
8. Brown DM, Kaiser PK, Michels M, et al, ANCHOR Study Group. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. N Engl J Med 2006;355: 1432–44.
9. Schmidt-Erfurth U, Eldem B, Guymer R, et al, EXCITE Study Group. Efficacy and safety of monthly versus quarterly ranibizumab treatment in neovascular age-related macular degeneration: the EXCITE study. Ophthalmology 2011;118: 831–9.
10. Regillo CD, Brown DM, Abraham P, et al, PIER Study Group. Randomized, double-masked, sham-controlled trial of ranibizumab for neovascular age-related macular degeneration: PIER Study year 1. Am J Ophthalmol 2008;145:239–48.
11. Boyer DS, Heier JS, Brown DM, et al. A Phase IIIb study to evaluate the safety of ranibizumab in subjects with neovascular age-related macular degeneration. Ophthalmology 2009; 116:1731–9.
12. Singer MA, Awh CC, Sadda S, et al. HORIZON: an open-label extension trial of ranibizumab for choroidal neovascularization secondary to age-related macular degeneration. Ophthalmology 2012;119:1175–83.
13. CATT Research Group, Martin DF, Maguire MG, Ying GS, et al. Ranibizumab and bevacizumab for neovascular age-related macular degeneration. N Engl J Med 2011;364: 1897–908.
14. Comparison of Age-related Macular Degeneration Treatments Trials (CATT) Research Group, Martin DF, Maguire MG, Fine SL, et al. Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: two-year results. Ophthalmology 2012;119:1388–98.
15. IVAN Study Investigators, Chakravarthy U, Harding SP, Rogers CA, et al. Ranibizumab versus bevacizumab to treat neovascular age-related macular degeneration: one-year findings from the IVAN randomized trial. Ophthalmology 2012;119: 1399–411.
16. Economides AN, Carpenter LR, Rudge JS, et al. Cytokine traps: multi-component, high-affinity blockers of cytokine action. Nat Med 2003;9:47–52.
17. Holash J, Davis S, Papadopoulos N, et al. VEGF-Trap: a VEGF blocker with potent antitumor effects. Proc Natl Acad Sci U S A 2002;99:11393–8.
18. Heier JS, Boyer D, Nguyen QD, et al, CLEAR-IT 2 Investigators. The 1-year results of CLEAR-IT 2, a phase 2 study of vascular endothelial growth factor Trap-Eye dosed as-needed after 12-week fixed dosing. Ophthalmology 2011;118:1098–106.
19. Stewart MW, Rosenfeld PJ. Predicted biological activity of intravitreal VEGF Trap. Br J Ophthalmol 2008;92:667–8.
20. Brown DM, Heier JS, Ciulla T, et al, CLEAR-IT 2 Investigators. Primary endpoint results of a phase II study of vascular endothelial growth factor Trap-Eye in wet age-related macular degeneration. Ophthalmology 2011;118: 1089–97.

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Footnotes and Financial Disclosures

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[1] Ophthalmic Consultants of Boston and Tufts University School of Medicine, Boston, Massachusetts.

[2] Retina Consultants of Houston, Houston, Texas.

[3] Oxford Eye Hospital, University of Oxford, Oxford, United Kingdom.

[4] CHU de Bordeaux – Université Bordeaux 2, Bordeaux, France.

[5] Cole Eye Institute, Cleveland, Ohio.

[6] Wilmer Eye Institute, Johns Hopkins University, Baltimore, Maryland.

[7] University of Cologne, Cologne, Germany.

[8] Wills Eye Hospital, Philadelphia, Pennsylvania.

[9] Nagoya City University, Nagoya, Japan.

[10] Regeneron Pharmaceuticals Inc., Tarrytown, New York.

[11] Bayer HealthCare, Berlin, Germany.

[12] Department of Neurology, Heinrich-Heine-Universität Düsseldorf, Germany.

[13] Medical University of Vienna, Vienna, Austria.

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Correspondence:
Ursula Schmidt-Erfurth, MD, Department of Ophthalmology, Medical University of Vienna, Waehringer Guertel 18-20, A-1090 Vienna, Austria. E-mail: ursula.schmidt-erfurth@meduniwien.ac.at.

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In re Application of: **YANCOPOULOS, GEORGE D.**

Application No.: **15/471,506**

Filed: **March 28, 2017**

For: **Use of a VEGF Antagonist to Treat Angiogenic Eye Disorders**

The owner*, **REGENERON PHARMACEUTICALS, INC.** , of **100** percent interest in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of **prior patent** No. **9,669,069 and 9,254,338** 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.

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/Karl Bozicevic, Reg. No. 28,807/ — Signature

June 25, 2018 — Date

Karl Bozicevic — Typed or printed name

650-833-7735 — Telephone Number

☒ Terminal disclaimer fee under 37 CFR 1.20(d) included.

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

*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.

This collection of information is required by 37 CFR 1.321. 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 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS

ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Application Number	Application/Control No.	Applicant(s)/Patent under Reexamination	
	15/471,506	YANCOPOULOS, GEORGE D.	

Document Code - DISQ	Internal Document – DO NOT MAIL

TERMINAL DISCLAIMER	☒ APPROVED	☐ DISAPPROVED
Date Filed : 6/25/18	This patent is subject to a Terminal Disclaimer	

Approved/Disapproved by:
Lawana Hixon

U.S. Patent and Trademark Office

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 15/471,506	Filing Date 03/28/2017	☐ To be Mailed

ENTITY: ☑ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED - PART I

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

APPLICATION AS AMENDED - PART II

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT	06/25/2018	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 26	Minus	** 26	= 0		x $100 =	0
	Independent (37 CFR 1.16(h))	* 2	Minus	*** 3	= 0		x $460 =	0
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	0

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=		x $ 0 =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=		x $ 0 =	
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.	LIE
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".	Moliki I May
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".	
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.	

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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

96387 7590 07/26/2018

Regeneron - Bozicevic, Field & Francis
201 REDWOOD SHORES PARKWAY
SUITE 200
REDWOOD CITY, CALIFORNIA 94065
UNITED STATES OF AMERICA

EXAMINER
LOCKARD, JON MCCLELLAND

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 07/26/2018

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/471,506	03/28/2017	George D. YANCOPOULOS	REGN-008CIPCON2	8014

TITLE OF INVENTION: USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1000	$0.00	$0.00	$1000	10/26/2018

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

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

96387 7590 07/26/2018
Regeneron - Bozicevic, Field & Francis
201 REDWOOD SHORES PARKWAY
SUITE 200
REDWOOD CITY, CALIFORNIA 94065
UNITED STATES OF AMERICA

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission
I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/471,506	03/28/2017	George D. YANCOPOULOS	REGN-008CIPCON2	8014

TITLE OF INVENTION: USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1000	$0.00	$0.00	$1000	10/26/2018

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/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. The following fee(s) are submitted:

❑ Issue Fee

❑ Publication Fee (No small entity discount permitted)

❑ Advance Order - # of Copies _____

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

❑ A check is enclosed.

❑ Payment by credit card. Form PTO-2038 is attached.

❑ The director is hereby authorized to charge the required fee(s), any deficiency, or credits any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

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

❑ Applicant certifying micro entity status. See 37 CFR 1.29

❑ 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.
15/471,506	03/28/2017	George D. YANCOPOULOS	REGN-008CIPCON2	8014

96387 7590 07/26/2018

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201 REDWOOD SHORES PARKWAY
SUITE 200
REDWOOD CITY, CALIFORNIA 94065
UNITED STATES OF AMERICA

EXAMINER	
LOCKARD, JON MCCLELLAND	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 07/26/2018

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

PTOL-85 (Rev. 02/11)

Notice Requiring Inventor's Oath or Declaration	Application No. 15/471,506	Applicant(s) George D. YANCOPOULOS	
	Examiner LOCKARD, JON MCCLELLAND	Art Unit 1647	

This notice is an attachment to the Notice of Allowability (PTOL-37), or the Notice of Allowability For A Design Application (PTOL-37D).

An inventor's oath or declaration in compliance with 37 CFR 1.63 or 1.64 executed by or with respect to each inventor has not yet been submitted.

An oath or declaration in compliance with 37 CFR 1.63, or a substitute statement in compliance with 37 CFR 1.64, executed by or with respect to each inventor (for any inventor for which a compliant oath, declaration, or substitute statement has not yet been submitted) MUST be filed no later than the date on which the issue fee is paid. See 35 U.S.C. 115(f). Failure to timely comply will result in ABANDONMENT of this application.

A properly executed inventor's oath to declaration has not been received for the following inventor(s):

If applicant previously filed one or more oaths, declarations, or substitute statements, applicant may have received an informational notice regarding deficiencies therein.

The following deficiencies are noted:

INFORMAL ACTION PROBLEMS

- A properly executed inventor's oath or declaration has not been received for the following inventor(s): **George D. YANCOPOULOS**.
  Applicant may submit the inventor's oath or declaration at any time before the Notice of Allowance and Fee(s) Due, PTOL-85, is mailed.

Questions relating to this Notice should be directed to the Application Assistance Unit at 571-272-4200.

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

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

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

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Notice of Allowability	Application No. 15/471,506	Applicant(s) YANCOPOULOS, George D.	
	Examiner JON M LOCKARD	Art Unit 1647	AIA Status No

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

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☑ This communication is responsive to the Amendment filed 25 June 2018.
   ☐ 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 21-46 (renumbered as claims 1-26, respectively) . 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 areply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____ .

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____.
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____.
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date. _____.
5. ☐ Examiner's Amendment/Comment
6. ☐ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

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

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15/471,506	YANCOPOULOS, George D.
	Examiner	**Art Unit**
	JON M LOCKARD	1647

CPC						
Symbol					**Type**	**Version**
A61K	/	38	/	179	F	2013-01-01
C07K	/	16	/	22	I	2013-01-01
C07K	/	14	/	71	I	2013-01-01
A61K	/	9	/	0048	I	2013-01-01
A61K	/	2039	/	505	A	2013-01-01
C07K	/	2319	/	30	A	2013-01-01
C07K	/	2319	/	32	A	2013-01-01

CPC Combination Sets							
Symbol					**Type**	**Set**	**Ranking**	**Version**
	/		/					

/JON M LOCKARD/ Examiner, Art Unit 1647	19 July 2018	**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	26	
/CHRISTINE J SAOUD/ Primary Examiner, Art Unit 1647	22 July 2018	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	NONE

U.S. Patent and Trademark Office — Part of Paper No.: 20180718A

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15/471,506	YANCOPOULOS, George D.
	Examiner	**Art Unit**
	JON M LOCKARD	1647

INTERNATIONAL CLASSIFICATION				
CLAIMED				
A61K	/	39	/	395
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	19 July 2018	**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	26	
/CHRISTINE J SAOUD/ Primary Examiner, Art Unit 1647	22 July 2018	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	NONE

U.S. Patent and Trademark Office — Part of Paper No.: 20180718A

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15/471,506	YANCOPOULOS, George D.
	Examiner	**Art Unit**
	JON M LOCKARD	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

/JON M LOCKARD/ Examiner, Art Unit 1647	19 July 2018	**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	26	
/CHRISTINE J SAOUD/ Primary Examiner, Art Unit 1647	22 July 2018	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	NONE

U.S. Patent and Trademark Office — Part of Paper No.: 20180718A

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15/471,506	YANCOPOULOS, George D.
	Examiner	Art Unit
	JON M LOCKARD	1647

CPC - Searched*		
Symbol	Date	Examiner

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner
NONE		3/29/2018	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
STIC Search of SEQ ID NO:2. See search results in SCORE.	3/29/2018	JML
EAST (USPAT, US-PGPUB, EPO, DERWENT): See attached search history.	3/29/2018	JML
STN (MEDLINE, SCISEARCH, EMBASE, BIOSIS): See attached search history.	3/29/2018	JML
PALM: Inventor search.	3/29/2018	JML

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner
	STIC Search of SEQ ID NO:2. See search results in SCORE.	07/19/2018	JML
	EAST (USPAT): See attached search history.	07/19/2018	JML
	PALM: Inventor search.	07/19/2018	JML

/J.L/ Examiner, Art Unit 1647	

Inventor Information for 15/471506

/J.L./

Inventor Name	City	State/Country
YANCOPOULOS, GEORGE D.	YORKTOWN HEIGHTS	NEW YORK

Appln Info | Contents | Petition Info | Atty/Agent Info | Continuity Data | Foreign Data | **Inventors** | Applicants | Address | Fees | Post Info | Pre Gr

Search Another: Application # Search **or Patent #** Search **or International Registration #** Search

PCT / / Search **or PG PUBS #** Search

Attorney Docket # Search

Bar Code # Search

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EAST Search History

EAST Search History (Interference) /J.L./

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	2149	(flt1 or vegfr1 or (vegf adj r1)) same ((flk1 or kdr or vegfr2 or (vegf adj r2)) or (Flt4 vegfr3 or (vegf adj r3)))	USPAT	OR	ON	2018/07/19 16:45
L2	547	l1 and ((chimer$ or fusion) same vegf)	USPAT	OR	ON	2018/07/19 16:45
L3	185	l1 same ((chimer$ or fusion) same vegf)	USPAT	OR	ON	2018/07/19 16:46
L4	2108	(flt1 or vegfr1 or (vegf adj r1)) with ((flk1 or kdr or vegfr2 or (vegf adj r2)) or (Flt4 vegfr3 or (vegf adj r3)))	USPAT	OR	ON	2018/07/19 16:46
L5	98	l4 with ((chimer$ or fusion) with vegf)	USPAT	OR	ON	2018/07/19 16:46
L6	691	(l4 or l5) and ((eye or ocular or retina$ or macular) with disorder)	USPAT	OR	ON	2018/07/19 16:46
L7	84	(l3 or l5) and ((eye or ocular or retina$ or macular) with disorder)	USPAT	OR	ON	2018/07/19 16:46
L8	6	(l3 or l5) same ((eye or ocular or retina$ or macular) with disorder)	USPAT	OR	ON	2018/07/19 16:47
L9	2	l7 and "l9"	USPAT	OR	ON	2018/07/19 16:47
L10	133	yancopoulos-g$.in.	USPAT	OR	ON	2018/07/19 16:47
L11	20	l7 and l10	USPAT	OR	ON	2018/07/19 16:47
L12	5	l11 and (eye ocular macular).clm.	USPAT	OR	ON	2018/07/19 16:47

7/ 19/ 2018 4:48:12 PM
C:\ Users\ jlockard\ Documents\ EAST\ Workspaces\ 15471506.wsp

To: docket@bozpat.com,,
From: PAIR_eOfficeAction@uspto.gov
Cc: PAIR_eOfficeAction@uspto.gov
Subject: Private PAIR Correspondence Notification for Customer Number 96387

Jul 26, 2018 04:09:32 AM

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201 REDWOOD SHORES PARKWAY
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Application	Document	Mailroom Date	Attorney Docket No.
15471506	NOA	07/26/2018	REGN-008CIPCON2

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PATENT APPLICATION INFORMATION RETRIEVAL SYSTEM

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

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/471,506	03/28/2017	George D. YANCOPOULOS	REGN-008CIPCON2	8014

7590 08/03/2018

Regeneron - Bozicevic, Field & Francis
201 REDWOOD SHORES PARKWAY
SUITE 200
REDWOOD CITY, CA 94065

EXAMINER	
LOCKARD, JON MCCLELLAND	

ART UNIT	PAPER NUMBER
1647	

NOTIFICATION DATE	DELIVERY MODE
08/03/2018	ELECTRONIC

Letter Withdrawing a Notice Requiring Inventor's Oath or Declaration

The Notice Requiring Inventor's Oath or Declaration mailed on 7/26/18 was sent in error, and is hereby withdrawn. The time period set forth in the Notice of Allowance and Fee(s) Due to file a reply and pay the required fees continues to run from the mailing date of the Notice of Allowance and Fee(s) Due. Any time period set forth in the Notice of Allowability continues to run from the mailing date of the Notice of Allowability.

Questions relating to this Notice should be directed to the Application Assistance Unit at 571-272-4200.

M. Adams

(571)-272-4200 or 1(888)-786-0101
Patent Publication Branch
Office of Data Management

To: docket@bozpat.com,,
From: PAIR_eOfficeAction@uspto.gov
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Subject: Private PAIR Correspondence Notification for Customer Number 96387

Aug 08, 2018 03:52:09 AM

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Application	Document	Mailroom Date	Attorney Docket No.
15471506	M327	08/03/2018	REGN-008CIPCON2

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

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PATENT APPLICATION INFORMATION RETRIEVAL SYSTEM

Doc Code: IFEE PTOL/85B-EFS

Document Description: Issue Fee Payment (PTO-85B)

Issue Fee Transmittal Form

Application Number	Filing Date	First Named Inventor	Atty. Docket No.	Confirmation No.
15471506	28-Mar-2017	George YANCOPOULOS	REGN-008CIPCON2	8014

TITLE OF INVENTION :

USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS

Entity Status	Application Type	Art Unit	Class - Subclass	EXAMINER
Regular Undiscounted	Utility under 35 USC 111(a)	1647	134100	JON LOCKARD

Issue Fee Due	Publication Due	Total Fee(s) Due	Date Due	Prev. Paid Fee
$1000	$0	$1000	26-Oct-2018	$0

1.Change of Correspondence Address and/or Indication Of Fee Address (37 CFR 1.33 & 1.363)

Current Correspondence Address:	Current Indicated Fee Address :
96387 Regeneron - Bozicevic, Field & Francis 201 REDWOOD SHORES PARKWAY SUITE 200 REDWOOD CITY CA 94065 UNITED STATES 650 327 3400 docket@bozpat.com	
☐ Change of correspondence address requested, system generated AIA/122-EFS form attached	☐ Fee Address indication requested, system generated SB/47-EFS form attached

2.Entity Status

Change in Entity Status

○ Applicant certifying micro entity status; system generated Micro Entity certification form attached. See 37 CFR 1.29.
Note: Absent a valid certification of micro entity status, issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment. If this box is checked, you will be prompted to choose a micro entity status on the gross income basis (37 CFR 1.29(a)) or the institution of higher education basis (37 CFR 1.29(d)), and make the applicable certification online.

○ Applicant asserting small entity status. See 37 CFR 1.27.
Note: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

◉ Applicant changing to regular undiscounted fee status.
Note: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

WEB IFEE 1.0

Doc Code: IFEE PTOL/85B-EFS

Document Description: Issue Fee Payment (PTO-85B)

3.The Following Fee(s) Are Submitted:

☒ Issue Fee	☐ I authorize USPTO to apply my previously paid issue fee to the current fees due
☐ Publication Fee	☐ The Director is hereby authorized to apply my previously paid issue fee to the current fee due and to charge deficient fees to Deposit Account Number _____
☐ Advance Order - # of copies _____	☒ If **in addition to** the payment of the issue fee amount submitted with this form, there are any discrepancies in any amount(s) due, the Director is authorized to charge any deficiency or credit any overpayment, to Deposit Account Number 50-0815 . The **issue fee must be submitted** with this form. **If payment of the issue fee does not accompany this form, checking this box and providing a deposit account number will NOT be effective to satisfy full payment of the fee(s) due.**

4.Firm and/or Attorney Names To Be Printed

NOTE: If no name is listed, no name will be printed
For printing on the patent front page, list to be displayed as entered

1. Karl Bozicevic
2. Bozicevic, Field & Francis LLP
3.

5.Assignee Name(s) and Residence Data To Be Printed

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

Name	City	State	Country	Category
REGENERON PHARMACEUTICALS, INC.	Tarrytown	NEW YORK	united states	corporation

6.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 filed and has been granted power of attorney in this application. I also certify that this Fee(s) Transmittal form is being transmitted to the USPTO via EFS-WEB on the date indicated below.

Signature	/Karl Bozicevic, 28,807/	**Date**	10-17-2018
Name	Karl Bozicevic	**Registration Number**	28807

WEB IFEE 1.0

Electronic Patent Application Fee Transmittal	
Application Number:	15471506
Filing Date:	28-Mar-2017
Title of Invention:	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS
First Named Inventor/Applicant Name:	George D. YANCOPOULOS
Filer:	Karl Bozicevic/Savanna Fuentes
Attorney Docket Number:	REGN-008CIPCON2
Filed as Large Entity	
Filing Fees for Utility under 35 USC 111(a)	

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
UTILITY APPL ISSUE FEE	1501	1	1000	1000
PUBL. FEE- EARLY, VOLUNTARY, OR NORMAL	1504	1	0	0
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**1000**

Electronic Acknowledgement Receipt	
EFS ID:	34033707
Application Number:	15471506
International Application Number:	
Confirmation Number:	8014
Title of Invention:	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS
First Named Inventor/Applicant Name:	George D. YANCOPOULOS
Customer Number:	96387
Filer:	Karl Bozicevic/Savanna Fuentes
Filer Authorized By:	Karl Bozicevic
Attorney Docket Number:	REGN-008CIPCON2
Receipt Date:	17-OCT-2018
Filing Date:	28-MAR-2017
Time Stamp:	12:36:26
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$1000
RAM confirmation Number	101718INTEFSW12362401
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)	Web85b.pdf	46406 959c136ca5e68b9bd6e1c2d574dbd685d8e2440e	no	2
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	31733 57ecf70bfdbb182d88137b0655c4d86cd6fd16c8	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	78139		

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 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.
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If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.
New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

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APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/471,506	11/20/2018	10130681	REGN-008CIPCON2	8014

96387 7590 10/31/2018

Regeneron - Bozicevic, Field & Francis
201 REDWOOD SHORES PARKWAY
SUITE 200
REDWOOD CITY, CA 94065

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment is 0 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Data Management (ODM) at (571)-272-4200.

APPLICANT(s) (Please see PAIR WEB site http://pair.uspto.gov for additional applicants):

George D. YANCOPOULOS, Yorktown Heights, NY;
REGENERON PHARMACEUTICALS, INC., Tarrytown, NY

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To: docket@bozpat.com,,
From: PAIR_eOfficeAction@uspto.gov
Cc: PAIR_eOfficeAction@uspto.gov
Subject: Private PAIR Correspondence Notification for Customer Number 96387

Nov 01, 2018 04:45:46 AM

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Application	Document	Mailroom Date	Attorney Docket No.
15471506	ISSUE.NTF	10/31/2018	REGN-008CIPCON2

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PATENT APPLICATION INFORMATION RETRIEVAL SYSTEM

The United States Patent and Trademark Office
PATENT TRIAL AND APPEAL BOARD

A petition has been filed in Patent Number 10,130,681, Application Number 15/471,506 on 7/1/2022 (Date).

The Case Number is IPR2022-01225.
(IPR, CBM, PGR, DER #)

To view the documents filed in this petition, go to https://ptab.uspto.gov.

Use the Search PTAB tab and enter the Patent Number or the Trial or Case Number and select the Search button.

Questions regarding this notice should be directed to the Patent Trial and Appeal Board at 571-272-7822.

AO 120 (Rev. 08/10)

TO:	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK
Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court Northern District of West Virginia on the following

☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
1:22-cv-61	8/2/2022	Northern District of West Virginia

PLAINTIFF	DEFENDANT
REGENERON PHARMACEUTICALS, INC.	MYLAN PHARMACEUTICALS, INC.

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	See attached		
2			
3			
4			
5			

In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1		
2		
3		
4		
5		

In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE
CHERYL DEAN RILEY	/s/ D. Kinsey	8/3/2022

Copy 1—Upon initiation of action, mail this copy to Director Copy 3—Upon termination of action, mail this copy to Director
Copy 2—Upon filing document adding patent(s), mail this copy to Director Copy 4—Case file copy

PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
7,070,959	July 4, 2006	Regeneron Pharmaceuticals, Inc.
9,222,106	December 29, 2015	Regeneron Pharmaceuticals, Inc.
9,254,338	February 9, 2016	Regeneron Pharmaceuticals, Inc.
9,669,069	June 6, 2017	Regeneron Pharmaceuticals, Inc.
9,816,110	November 14, 2017	Regeneron Pharmaceuticals, Inc.
10,130,681	November 20, 2018	Regeneron Pharmaceuticals, Inc.
10,406,226	September 10, 2019	Regeneron Pharmaceuticals, Inc.
10,415,055	September 17, 2019	Regeneron Pharmaceuticals, Inc.
10,464,992	November 5, 2019	Regeneron Pharmaceuticals, Inc.
10,669,594	June 2, 2020	Regeneron Pharmaceuticals, Inc.
10,857,205	December 8, 2020	Regeneron Pharmaceuticals, Inc.
10,888,601	January 12, 2021	Regeneron Pharmaceuticals, Inc.
10,927,342	February 23, 2021	Regeneron Pharmaceuticals, Inc.
10,973,879	April 13, 2021	Regeneron Pharmaceuticals, Inc.
11,053,280	July 6, 2021	Regeneron Pharmaceuticals, Inc.
11,066,458	July 20, 2021	Regeneron Pharmaceuticals, Inc.
11,084,865	August 10, 2021	Regeneron Pharmaceuticals, Inc.
11,104,715	August 31, 2021	Regeneron Pharmaceuticals, Inc.
11,174,283	November 16, 2021	Regeneron Pharmaceuticals, Inc.
11,186,625	November 30, 2021	Regeneron Pharmaceuticals, Inc.
11,253,572	February 22, 2022	Regeneron Pharmaceuticals, Inc.
11,299,532	April 12, 2022	Regeneron Pharmaceuticals, Inc.
11,306,135	April 19, 2022	Regeneron Pharmaceuticals, Inc.
11,332,771	May 17, 2022	Regeneron Pharmaceuticals, Inc.