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UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

June 04, 2021

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OF:**

APPLICATION NUMBER: 15/471,506

FILING DATE: March 28, 2017

PATENT NUMBER: 10130681

ISSUE DATE: November 20, 2018



Certified by

Andres Ibarra

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

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Application Number: 15471506

Document Date: 03/28/2017

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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:	<i>“Use of a VEGF Antagonist to Treat Angiogenic Eye Disorders”</i>

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

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Telephone: (650) 327-3400
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Electronically Filed

NOTIFICATION OF PRIOR SEQUENCE LISTING Address to: Mail Stop Patent Application Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Attorney Docket	REGN-008CIPCON2
	First Named Inventor	YANCOPOULOS, GEORGE D.
	Application Number	To Be Assigned
	Filing Date	28 March 2017
	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

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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	no	9
			2834e41e9193695ad5d6080d920b4006cedce46c		
Warnings:					
Information:					
2		REGN-008CIPCON2_Specification.pdf	529155	yes	24
			66488c53637f4b7715ffe32f0b6596663f6e02cd		
	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	no	1
			2d582f645d0c5d17d717e589b029a39331991bdb		
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	no	2
			6bda7272374e6af80c8c3d8cf30d012e4657b588		
Warnings:					
The page size in the PDF is too large. The pages should be 8.5 x 11 or A4. If this PDF is submitted, the pages will be resized upon entry into the Image File Wrapper and may affect subsequent processing					
Information:					

5		REGN-008CIPCON2_2017-03-28_pre_amend_asfld.pdf	65192	yes	8
			da1c454ceb9521e936f1b0bea05fe67122482d93		
	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	no	1
			15712f98903ec6052e7e5f716b4a6b7016901474		
Warnings:					
Information:					
7	Sequence Listing (Text File)	REGN-008CIPCON2_SeqList.txt	6076	no	-
Warnings:					
Information:					
8	Fee Worksheet (SB06)	fee-info.pdf	37141	no	2
			66a646fa2e7f56edc76cb7306d608b0aede4f7b0		
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.

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		
<p>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.</p> <p>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.</p>			

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	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 i	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

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.											
<table border="1"> <tr> <td>Please Select One:</td> <td>☒ Customer Number</td> <td>US Patent Practitioner</td> <td>☐ Limited Recognition (37 CFR 11.9)</td> </tr> <tr> <td>Customer Number</td> <td colspan="3">96387</td> </tr> </table>				Please Select One:	☒ Customer Number	US Patent Practitioner	☐ Limited Recognition (37 CFR 11.9)	Customer Number	96387		
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

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.					

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 ^j (if applicable)
Additional Foreign Priority Data may be generated within this form by selecting the Add button.			

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.

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)

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).

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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:

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Assignee	Legal Representative under 35 U.S.C. 117		Joint Inventor
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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		

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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
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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		

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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

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-Fc Δ C1(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 – 179 μ)] on optical coherence tomography (OCT) was reduced from 119 μ to 27 μ as assessed by Fast Macular Scan and from 194 μ to 60 μ 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

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 135 μ , $p < 0.0001$). 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 μ m 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, juxtasceral 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 funduscopy examination, fundus photography and FA. At the Screen Visit (Visit 1) funduscopy 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.

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.

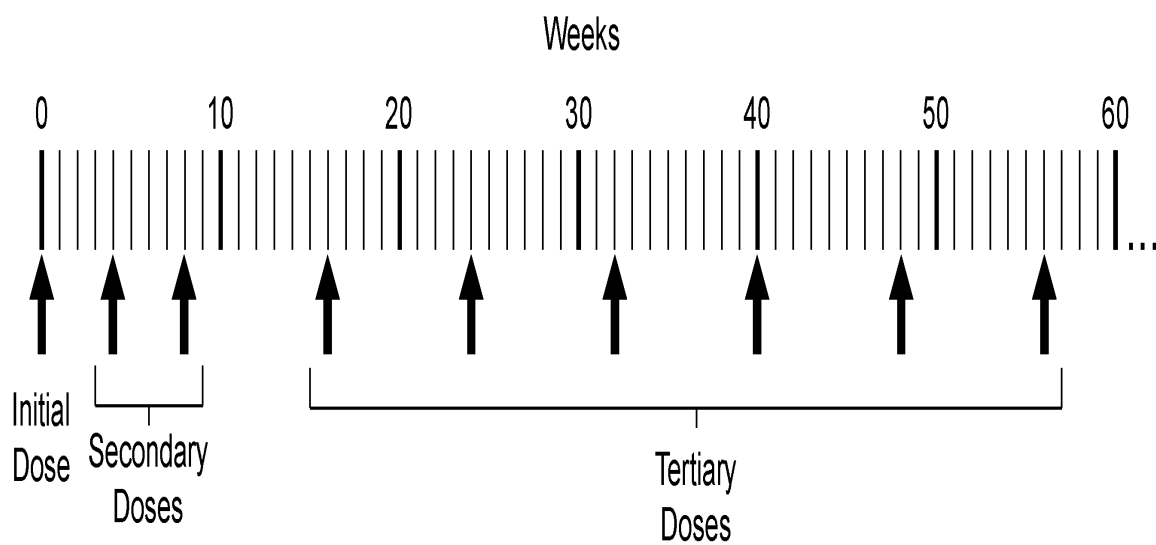
18. The method of claim 17, wherein all doses of the VEGF antagonist comprise from about 0.5 mg to about 2 mg of the VEGF antagonist.

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

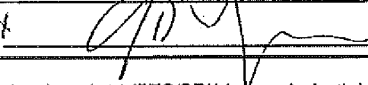
The present invention provides methods for treating angiogenic eye disorders by sequentially administering multiple doses of a VEGF antagonist to a patient. The methods of the present invention include the administration of multiple doses of a VEGF antagonist to a patient at a frequency of once every 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.



1/1

Figure 1

**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
<p>As the below named inventor, I hereby declare that:</p> <p>This declaration ☐ The attached application, or is directed to: ☒ United States application or PCT International application number <u>13/940,370</u> filed on <u>July 12, 2013</u></p> <p>The above-identified application was made or authorized to be made by me.</p> <p>I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.</p> <p>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.</p> <p style="text-align: center;">WARNING:</p> <p>Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.</p> <hr/> <p>LEGAL NAME OF INVENTOR</p> <p>Inventor: <u>YANCOPOULOS, GEORGE D.</u> Date (Optional): <u>10/20/13</u></p> <p>Signature: <u></u></p> <hr/> <p><small>Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form. Use an additional PTO/AIA/01 form for each additional inventor.</small></p>	

This collection of information is required by 35 U.S.C. 115 and 37 CFR 1.63. 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 1 minute 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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7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
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- 10.

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
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Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:	

File Listing:					
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New International Application Filed with the USPTO as a Receiving Office

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Document code: WFEE

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Reviewer: Saleem, Syed (ASRC)

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			325						330					335	
Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly
		340					345						350		

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
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Alexandria, Virginia 22313-1450
www.uspto.gov

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

CONFIRMATION NO. 8014

FILING RECEIPT



0000000090526539

96387

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

Date Mailed: 04/11/2017

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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

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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 35, United States Code, Section 184
Title 37, Code of Federal Regulations, 5.11 & 5.15

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

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

NOT GRANTED

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

SelectUSA

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

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

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
15/471,506	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



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.

/t/c/

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875						Application or Docket Number 15/471,506	
APPLICATION AS FILED - PART I							
(Column 1)		(Column 2)		SMALL ENTITY		OTHER THAN SMALL ENTITY	
FOR	NUMBER FILED	NUMBER EXTRA		RATE(\$)	FEE(\$)		RATE(\$)
BASIC FEE <small>(37 CFR 1.16(a), (b), or (c))</small>	N/A	N/A		N/A			280
SEARCH FEE <small>(37 CFR 1.16(k), (i), or (m))</small>	N/A	N/A		N/A			600
EXAMINATION FEE <small>(37 CFR 1.16(o), (p), or (q))</small>	N/A	N/A		N/A			720
TOTAL CLAIMS <small>(37 CFR 1.16(i))</small>	26	minus 20 =	*			x	80 =
INDEPENDENT CLAIMS <small>(37 CFR 1.16(h))</small>	2	minus 3 =	*			x	420 =
APPLICATION SIZE FEE <small>(37 CFR 1.16(s))</small>	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)		(Column 2)		(Column 3)		SMALL ENTITY	
AMENDMENT A	CLAIMS REMAINING AFTER AMENDMENT	HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE(\$)	ADDITIONAL FEE(\$)		RATE(\$)
	Total <small>(37 CFR 1.16(i))</small>	*	Minus **	=	x	=	x
	Independent <small>(37 CFR 1.16(h))</small>	*	Minus ***	=	x	=	x
	Application Size Fee (37 CFR 1.16(s))						
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
(Column 1)		(Column 2)		(Column 3)		SMALL ENTITY	
AMENDMENT B	CLAIMS REMAINING AFTER AMENDMENT	HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE(\$)	ADDITIONAL FEE(\$)		RATE(\$)
	Total <small>(37 CFR 1.16(i))</small>	*	Minus **	=	x	=	x
	Independent <small>(37 CFR 1.16(h))</small>	*	Minus ***	=	x	=	x
	Application Size Fee (37 CFR 1.16(s))						
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
(Column 1)		(Column 2)		(Column 3)		SMALL ENTITY	
TOTAL ADD'L FEE				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.							

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:	<i>"Use of a VEGF Antagonist to Treat Angiogenic Eye Disorders"</i>

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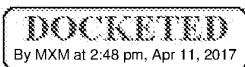
APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY. DOCKET NO	TOT CLAIMS	IND CLAIMS
15/471,506	03/28/2017	1629	2220	REGN-008CIPCON2	26	2

CONFIRMATION NO. 8014

FILING RECEIPT

96387

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



Date Mailed: 04/11/2017



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Inventor(s)

George

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

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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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Title 35, United States Code, Section 184
Title 37, Code of Federal Regulations, 5.11 & 5.15

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NOT GRANTED

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

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.

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

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
	George 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

SUPPLEMENTAL ADS

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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

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

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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

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).

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

SUPPLEMENTAL ADS

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	<u>15/471,506</u>
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

<p>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.</p> <p>☐ 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.</p>	
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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.

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

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	REGN-008CIPCON2
	Application Number	15/371,506
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.

SUPPLEMENTAL ADS

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PTO/AIA/14 (11-15)

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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	REGN-008CIPCON2
	Application Number	15/821,506
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.			
<input type="button" value="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: <input type="text"/>			
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.

SUPPLEMENTAL ADSApproved for use through 04/30/2017. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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Application Data Sheet 37 CFR 1.76		Attorney Docket Number	REGN-008CIPCON2
		Application Number	15/471,506
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	
First Name	Karl	Last Name	Bozicevic	Registration Number	28,807

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

SUPPLEMENTAL ADS

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	<u>15/421,506</u>
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 Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Electronic Acknowledgement Receipt	
EFS ID:	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:					
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Total Files Size (in bytes):			441465		
<p>This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.</p> <p><u>New Applications Under 35 U.S.C. 111</u> If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.</p> <p><u>National Stage of an International Application under 35 U.S.C. 371</u> If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.</p> <p><u>New International Application Filed with the USPTO as a Receiving Office</u> If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.</p>					

Document code: WFEE

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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
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

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

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

NOT GRANTED

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

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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



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/

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.)

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

☒ The address associated with the above-mentioned Customer Number

OR

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OR

Firm or Individual Name					
Address					
City		State		Zip	
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Telephone			Email		

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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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.

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:

1. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached.

2. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached.

[Page 1 of 2]

This collection of information is required by 37 CFR 3.73(b). 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.

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STATEMENT UNDER 37 CFR 3.73(c)

3. From: _____ To: _____

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4. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

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5. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

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6. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached.

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

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

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

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

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

Signature

May 19, 2017

Date

Karl Bozicevic

Printed or Typed Name

28,807

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 amendeded.

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
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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	no	1
			3f7da560f91fb532e67de64443791071352c7d0d		
Warnings:					

Information:					
2	Assignee showing of ownership per 37 CFR 3.73	REGN-008CIPCON2_2017-05-19 _cert_373_c_stmt.pdf	32103 3094385c019a79e356263ad88b9713b262ca1187	no	2
Warnings:					
Information:					
3		REGN-008CIPCON2_2017-05-19 _pre_amend.pdf	61219 0dbe502b0d131584f755e7c3ded399efbe9ae560	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	
Warnings:					
Information:					
Total Files Size (in bytes):			303056		
<p>This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.</p> <p><u>New Applications Under 35 U.S.C. 111</u> If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.</p> <p><u>National Stage of an International Application under 35 U.S.C. 371</u> If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.</p> <p><u>New International Application Filed with the USPTO as a Receiving Office</u> If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.</p>					

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(c), (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))									
						TOTAL			
* If the difference in column 1 is less than zero, enter "0" in column 2.									
APPLICATION AS AMENDED – PART II									
(Column 1)		(Column 2)		(Column 3)					
AMENDMENT	05/19/2017	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 \$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	
(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 \$ =			
	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			
<p>* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.</p> <p>** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".</p> <p>*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".</p> <p>The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.</p>									

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.**

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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

POA ACCEPTANCE LETTER

96387

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



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.

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.

/qtran/

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 Pharmaceuticals, 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 (ranibizumab 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)" <i>ClinicalTrials.gov</i> . 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 neovascular age-related macular degeneration" <i>Expert Opin. Investig. Drugs</i> (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" <i>Br J Ophthalmol.</i> 93(2):144-1449 (February 2009)	

Examiner Signature		Date Considered	
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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

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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" Ophthalmology 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 Ophthalmology, 110(5):979-986 (May 2003)		
	8	HEIER et 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 Ophthalmol., 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" Ophthalmology, 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 Ophthalmology 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		

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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 ophthalmology" 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	
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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.

← 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

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Austria: Federal Office for Safety in Health Care
Belgium: Federal Agency for Medicinal Products and Health Products
Brazil: ANVISA Agencia Nacional de Vigilancia Sanitaria
Colombia: INVIMA Instituto Nacional de Vigilancia de Medicamentos y Alimentos
Czech Republic: State Institute for Drug Control
France: Afssaps - French Health Products Safety Agency
Germany: Federal Institute for Drugs and Medical Devices
Hungary: National Institute of Pharmacy
India: Drugs Controller General of India
Israel: Ministry of Health
Italy: Ethics Committee
Japan: Pharmaceuticals and Medical Devices Agency
South Korea: Korea Food and Drug Administration (KFDA)
Latvia: State Agency of Medicines
Mexico: Federal Commission for Sanitary Risks Protection
Netherlands: The Central Committee on Research Involving Human Subjects (CCMO)
Poland: Office for Registration of Medicinal Products, Medical Devices and Biocidal Products
Portugal: INFARMED National Authority of Medicines and Health Products
Singapore: Health Sciences Authority
Slovakia: State Institute for Drug Control
Spain: Ministry of Health and Consumption
Sweden: Medical Products Agency
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	no	2
			818648a553dc3737ac79e3be0269fac71e0f371d		
Warnings:					

Information:					
2	Information Disclosure Statement (IDS) Form (SB08)	REGN-008CIPCON2_2017-05-26_IDS_SB08A.pdf	46996	no	3
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Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
3	Non Patent Literature	Clin_trials_View_NCT00637377_2010-11-30.pdf	523422	no	4
			2a73b8478aec9323861d628e9e186ac35c5c428a		
Warnings:					
Information:					
Total Files Size (in bytes):			625397		
<p>This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.</p> <p><u>New Applications Under 35 U.S.C. 111</u> If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.</p> <p><u>National Stage of an International Application under 35 U.S.C. 371</u> If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.</p> <p><u>New International Application Filed with the USPTO as a Receiving Office</u> If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.</p>					

Electronically Filed

<p style="text-align: center;">INFORMATION DISCLOSURE STATEMENT</p> <p>Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450</p>	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:	<i>“Use of a VEGF Antagonist to Treat Angiogenic Eye Disorders”</i>

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

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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	Issue Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		Number-Kind Code (if known)			
	1				

U.S. PATENT APPLICATION PUBLICATIONS					
Examiner Initial*	Cite No.	Publication Number	Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		Number-Kind Code (if known)			
	1				

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		Country Code-Number-Kind Code (if known)				
	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	HEIER et al., "Intravitreal Aflibercept (VEGF Trap-Eye) in Wet Age-related macular Degeneration," Ophthalmology, 119:2537-2548 (2012)	

Examiner Signature		Date Considered	
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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.

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 Groetzgach, 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. *Ophthalmology* 2012;119:2537–2548 © 2012 by the American Academy of Ophthalmology.



*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 intravit-

real 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

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 propor-

tion 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.¹⁴ The “alternative treatments to Inhibit VEGF in Age-related chorioidal 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.¹⁵ 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

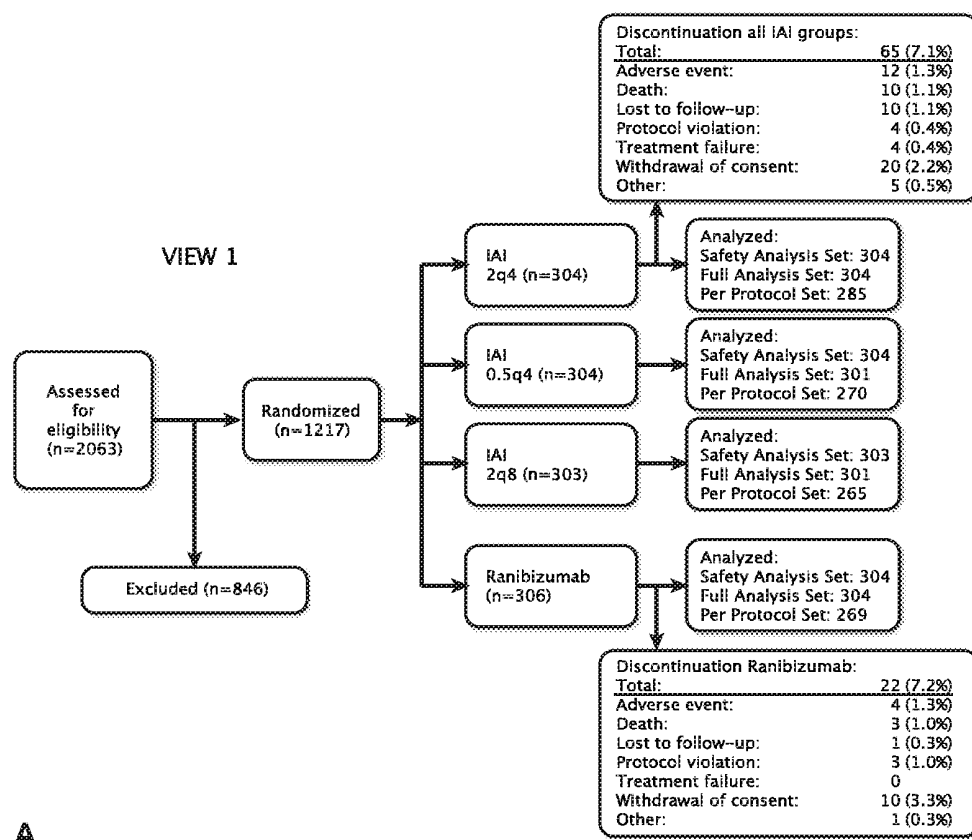


Figure 1. Flowcharts describing treatment allocation and patient disposition in VIEW 1 (A) and VIEW 2 (B). In both VIEW 1 and VIEW 2 studies, the most common reason for patients to be screened but not randomized was ineligibility based on angiographic characteristics as identified by the reading center. 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.

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

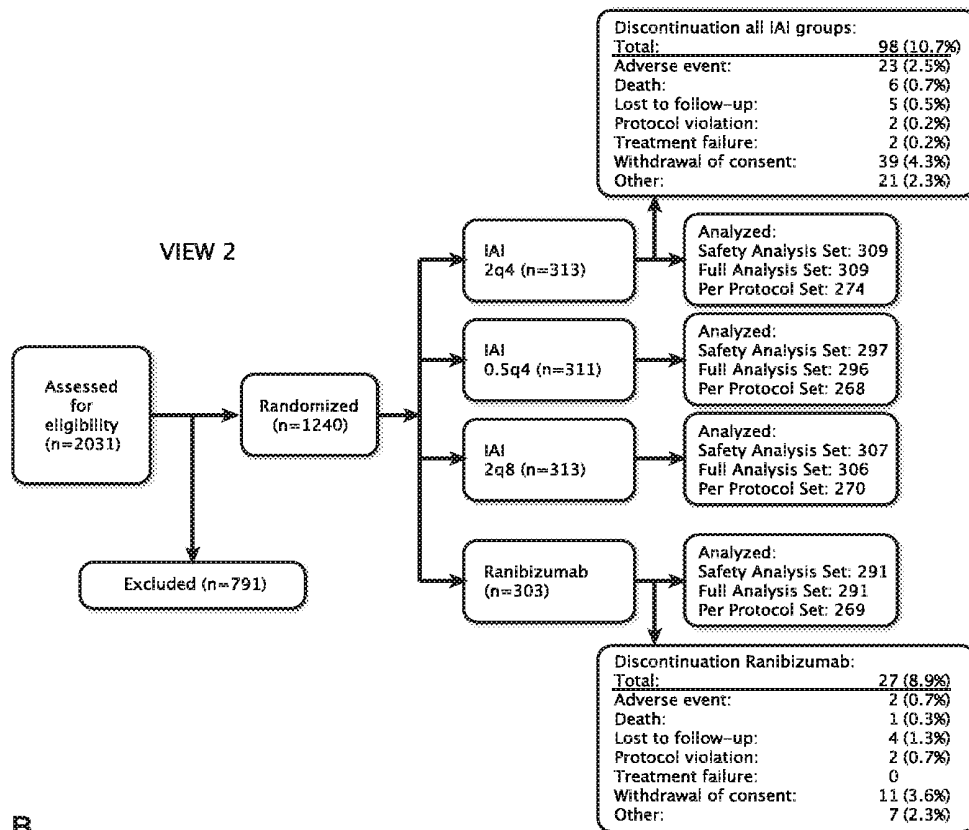


Figure 1. (Continued.)

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

(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 $\pm$ SD)	78.2 $\pm$ 7.6	77.7 $\pm$ 7.9	78.4 $\pm$ 8.1	77.9 $\pm$ 8.4	73.0 $\pm$ 9.0	74.1 $\pm$ 8.5	74.7 $\pm$ 8.6	73.8 $\pm$ 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 $\pm$ SD)	54.0 $\pm$ 13.4	55.2 $\pm$ 13.2	55.6 $\pm$ 13.1	55.7 $\pm$ 12.8	53.8 $\pm$ 13.5	52.8 $\pm$ 13.9	51.6 $\pm$ 14.2	51.6 $\pm$ 13.9
Proportion of patients with $\geq$ 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 $\pm$ SD)	6.53 $\pm$ 5.2	6.59 $\pm$ 5.1	6.49 $\pm$ 4.5	6.57 $\pm$ 5.1	7.59 $\pm$ 5.3	8.25 $\pm$ 5.8	7.70 $\pm$ 5.3	7.75 $\pm$ 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 $\pm$ SD)	6.99 $\pm$ 5.5	6.98 $\pm$ 5.4	6.95 $\pm$ 4.7	6.89 $\pm$ 5.2	8.01 $\pm$ 5.7	8.72 $\pm$ 6.1	8.17 $\pm$ 5.5	8.22 $\pm$ 5.9
Central retinal thickness, μ m (mean $\pm$ SD)	315.3 $\pm$ 108.3	313.6 $\pm$ 103.4	313.2 $\pm$ 106.0	324.4 $\pm$ 111.2	325.9 $\pm$ 110.9	334.6 $\pm$ 119.8	326.5 $\pm$ 116.5	342.6 $\pm$ 124.0
Baseline NEI VFQ-25 scores (mean $\pm$ SD)	71.8 $\pm$ 17.2	70.4 $\pm$ 16.6	71.1 $\pm$ 17.8	69.6 $\pm$ 16.8	72.9 $\pm$ 19.1	70.3 $\pm$ 19.4	74.0 $\pm$ 18.2	71.3 $\pm$ 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.

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 $\pm$ SD)	8.1 $\pm$ 15.3	10.9 $\pm$ 13.8	6.9 $\pm$ 13.4	7.9 $\pm$ 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 $\geq$ 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 $\pm$ SD)	-4.2 $\pm$ 5.6	-4.6 $\pm$ 5.5	-3.5 $\pm$ 5.3	-3.4 $\pm$ 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 $\pm$ SD)	4.9 $\pm$ 14.0	6.7 $\pm$ 13.5	4.5 $\pm$ 11.9	5.1 $\pm$ 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, μ m (mean $\pm$ SD)	-116.8 $\pm$ 109.0	-116.5 $\pm$ 98.4	-115.6 $\pm$ 104.1	-128.5 $\pm$ 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 $\geq$ 15 ETDRS letters from baseline to week 52 was similar in all treatment groups (Table 2), as were other exploratory categorical 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

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 $\pm$ SD)	9.4 $\pm$ 13.5	7.6 $\pm$ 12.6	9.7 $\pm$ 14.1	8.9 $\pm$ 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 $\geq$ 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 $\pm$ SD)	-4.2 $\pm$ 5.9	-6.0 $\pm$ 6.1	-4.2 $\pm$ 6.1	-5.2 $\pm$ 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 $\pm$ SD)	6.3 $\pm$ 14.8	4.5 $\pm$ 15.0	5.1 $\pm$ 13.7	4.9 $\pm$ 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, μ m (mean $\pm$ SD)	-138.5 $\pm$ 122.2	-156.8 $\pm$ 122.8	-129.8 $\pm$ 114.8	-149.2 $\pm$ 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 μ m and decreasing to 8 μ m over the year, with no apparent negative impact on visual acuity outcomes.

Because of the inability of other regimens in the CATT¹³ 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.

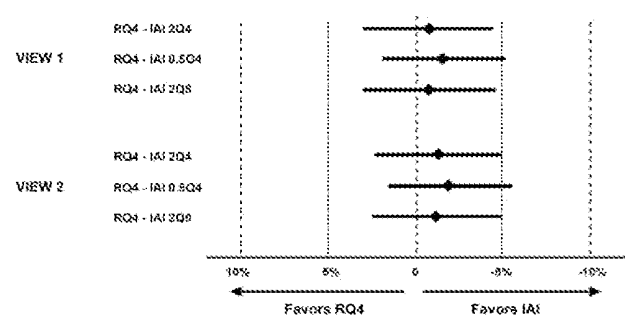


Figure 2. Difference in proportions of patients who maintained vision (losing <15 Early Treatment Diabetic Retinopathy Study [ETDRS] letters) at week 52 in the VIEW studies (per protocol set [PPS]). The diamond symbol denotes the difference between the treatment arms, and the horizontal bars indicate 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.

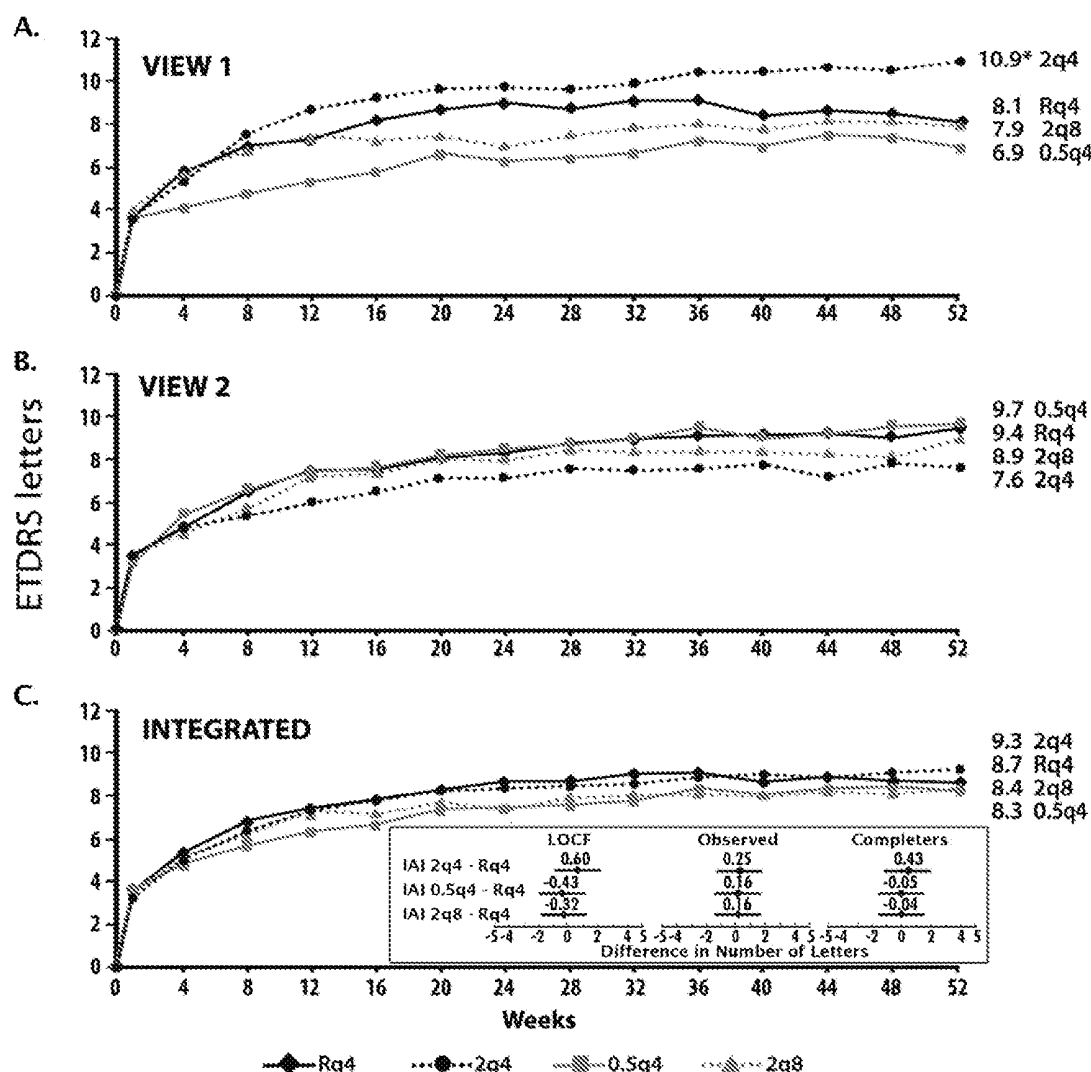


Figure 3. Mean change in best-corrected visual acuity (BCVA) from baseline to week 52 in the individual VIEW studies and in the integrated analysis. Values in the line graphs refer to mean changes in the number of letters from baseline at week 52. Only the intravitreal aflibercept 2q4 arm in VIEW 1 was 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>).

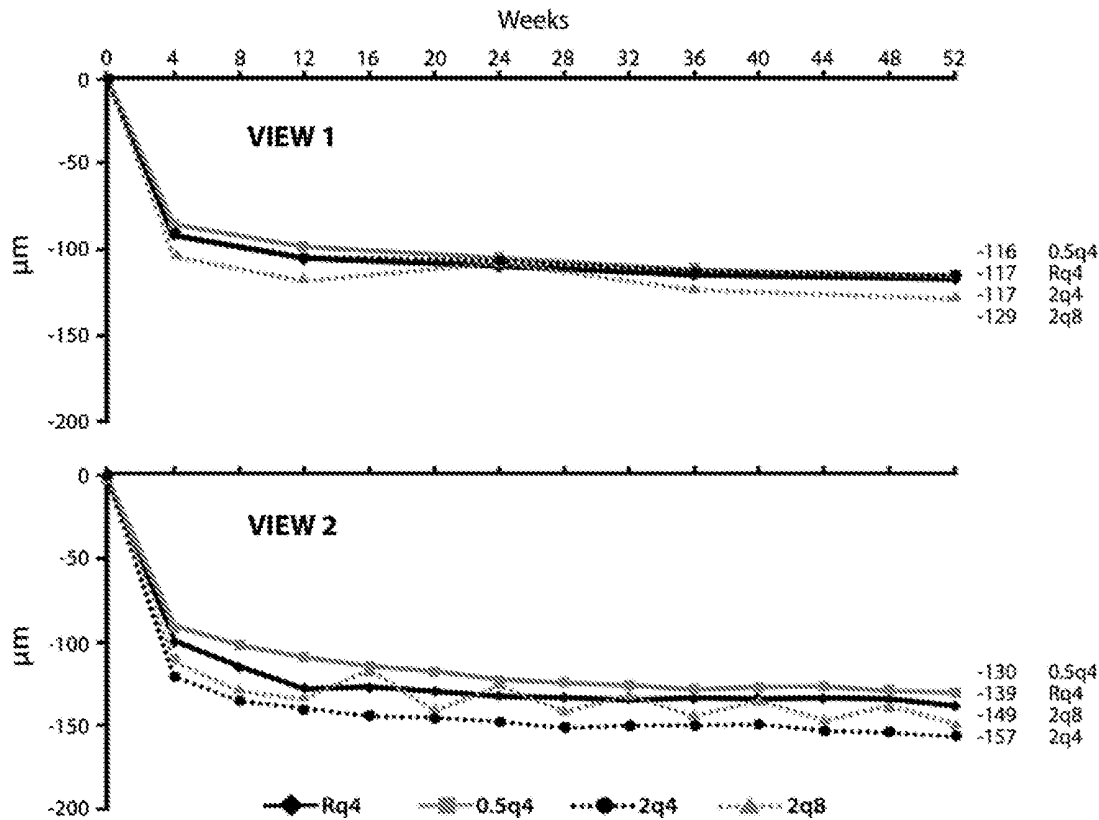


Figure 4. Mean change from baseline in central retinal thickness (full analysis set). As described in the “Materials and Methods” section, in VIEW 1, optical coherence tomography (OCT) was performed at screening, at the treatment initiation visit, and at weeks 4, 12, 24, 36, and 52 (and was optional 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 CATT¹³ highlighted the inability of other regimens, including monthly be-

vacizumab 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 CATT¹³ 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-

Table 3. Serious Ocular Adverse Events in the Study Eye and Other Key Nonocular Events Occurring in $\geq 0.5\%$ * 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 Arteriothrombotic 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

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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	Group Art Unit	1647
	Examiner Name	LOCKARD, JON MCCLELLAND
	Title:	<i>“Use of a VEGF Antagonist to Treat Angiogenic Eye Disorders”</i>

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.

Statements

☐ **No statement**

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- ☒ No fee is believed to be due.
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Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

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U.S. PATENT DOCUMENTS					
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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 Ophthalmology, 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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REVIEWSReview of anti-vascular
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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 dilation 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

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 [2,10].

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 [10–18].

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 [9]. 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 [21].

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 (MacugenTM, 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: results of anti-vascular endothelial growth factor treatment on central retinal vein occlusion macular edema.

Study (year, n)	Dose used	Study design	Follow-up (months) (n)	Results BCVA, MT	n
CRUISE study (2010) (292 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: R3 R5 S = 46.2-47.1-16.9% Mean reduction in MT: R3 R5 S = 94.97-93.23-9%	140
Campochiaro et al. (2010) (20 CRVO, 30 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)	140
ROCC 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)	143
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 B S = 36.39-28%, respectively (p = 0.48) BCVA lost >15 letters: A B S = 9-6-31%, respectively (p = 0.01) Mean reduction in MT: A B S = by 269-210-5 µm, respectively (p < 0.001)	143
Pace et al. (2010) (9 CRVO, 8 BRVO)	Ranibizumab 0.5 mg	Prospective, consecutive, noncomparative case series	12 months; CRVO: n = 3 (range: 2-4) BRVO: n = 3 (range: 3-4)	BCVA gained >15 letters (p < 0.0001); CRVO 90%, BRVO 63% MT reduced by 360 µm in CRVO and by 275 µm in BRVO (p < 0.0001)	144
Figueras et al. (2010) (18 CRVO, 28 BRVO)	Bevacizumab 1.25 mg	Prospective, nonrandomized case series	6 months; CRVO: n = 4 (range: 3-6) BRVO: n = 3 (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	145
Kriechbaum et al. (2008) (8 CRVO, 21 BRVO)	Bovine atezizumab 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)	146
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)	147

A, Pegaptanib 0.3 mg; B, Pegaptanib 1 mg; S, sham; CRVO, central retinal vein occlusion; BRVO, branch retinal vein occlusion; CRVO, central retinal vein occlusion; MT, macular thickness; PRN, as required; R, ranibizumab; S, sham; B, bevacizumab; 0.3 mg; R5, ranibizumab 0.5 mg; S, sham.

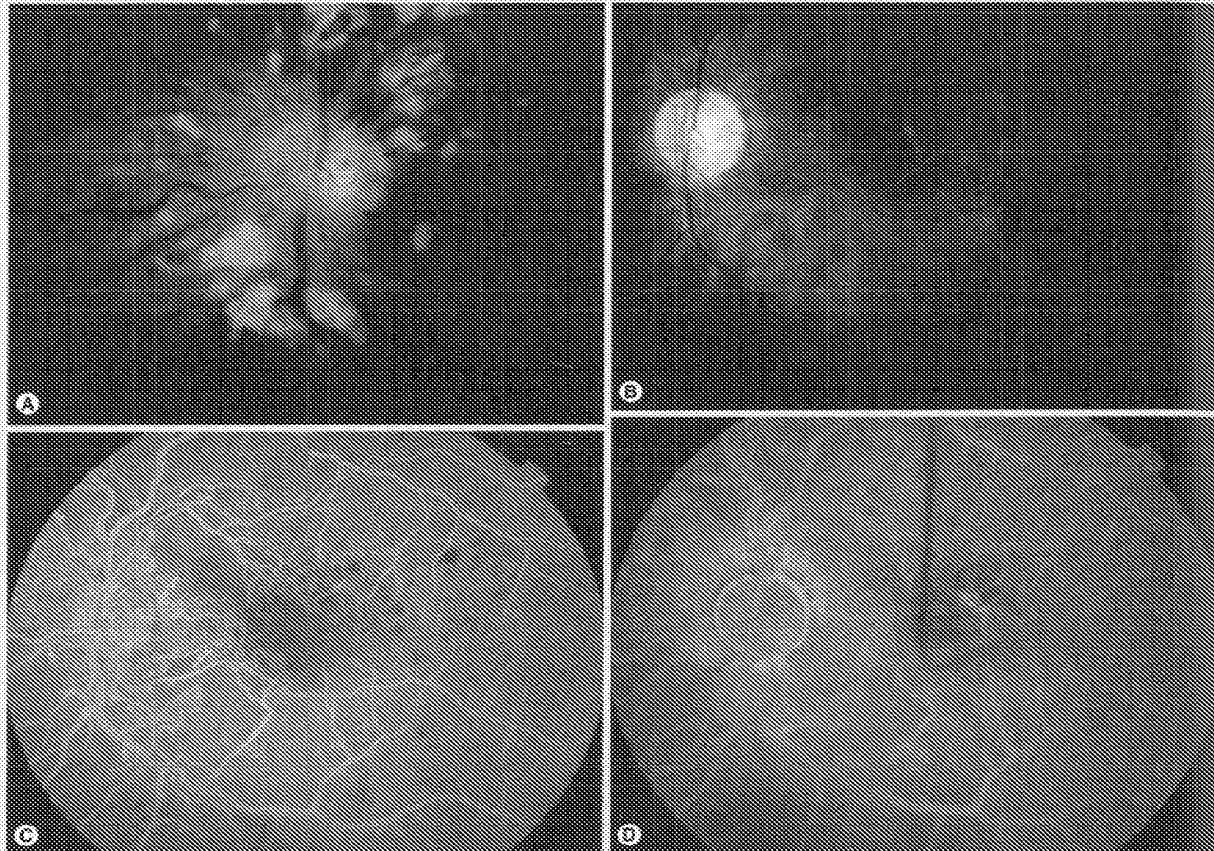


Figure 1. Resolution of ischemic central retinal vein occlusion (without macular edema) after bevacizumab injection. (A) Patient presented with acute reduced vision (counting fingers only) and diagnostic clinical signs of ischemic central retinal vein occlusion. He received an intravitreal bevacizumab 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 VEGFR 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 [40–47]. There were no data on anti-VEGF agents in the subgroup of ischemic CRVO with or without ME. Spaide

et al. studied the effect of ranibizumab in patients who had previous bevacizumab or triamcinolone injections [47]. 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 [48,49]. 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; $p < 0.001$) [49].

Expert commentary

Who will respond?

Intact external limiting membrane

In a recent study, Wolf-Schnurbusch *et al.* attempted to analyze the predictive factors for best-corrected visual acuity (BCVA) after anti-VEGF treatment in patients with treatment-naïve CRVO-ME post. 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 [50]. 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 (figure 1). 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.

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VEGF Trap_{R1R2} suppresses experimental corneal angiogenesis

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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 mm² and 1.53±0.27 mm²) at days 4 and 7, respectively. This was significantly greater than that of mice treated with VEGF Trap (0.24±0.11 mm² and 0.35±0.16 mm² 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

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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 μ l of 12% Hydron in ethanol was added to the suspension, which was then deposited onto a sterilized 15 mm² 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 mm³ 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)

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).

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).

Miquelot 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 = $1.01\text{mm} \pm 0.17\text{mm}$; hFc = $1.21\text{mm} \pm 0.22\text{mm}$; VEGF Trap = $1.10\text{mm} \pm 0.20\text{mm}$; $p=0.30$). Following bFGF pellet implantation, the area of corneal NV in untreated controls was $1.05 \pm 0.12 \text{ mm}^2$ and $1.53 \pm 0.27 \text{ mm}^2$ at days 4 and 7, respectively. This was significantly greater than that of mice treated with VEGF Trap_{R1R2} (Figures 3C and 3F; $0.24 \pm 0.11 \text{ mm}^2$ and $0.35 \pm 0.16 \text{ mm}^2$ 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; $1.21 \pm 0.07 \text{ mm}^2$ and $2.25 \pm 0.30 \text{ mm}^2$ at days 4 and 7, respectively). The results are summarized in Figure 3G.

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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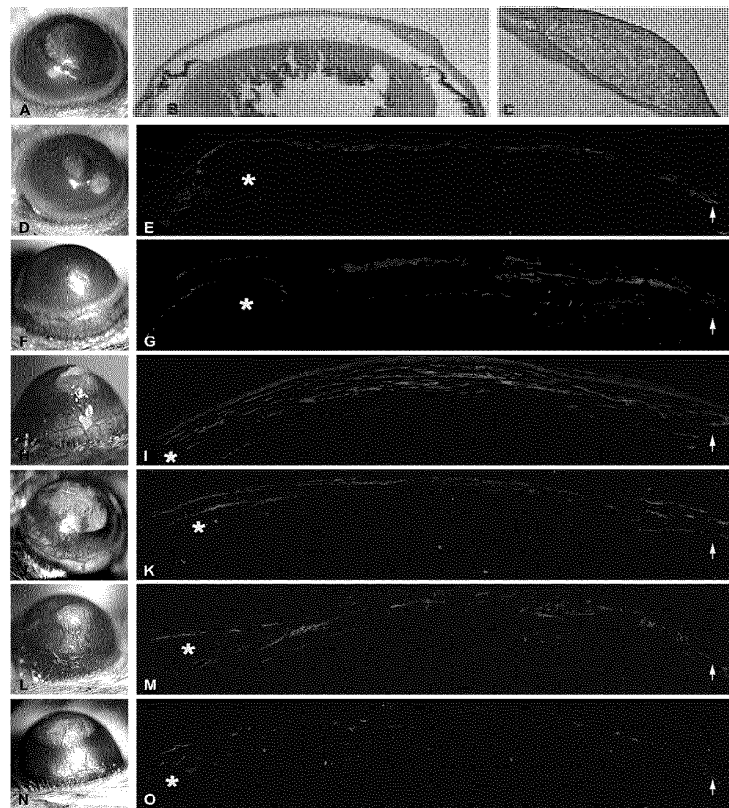


Figure 1.

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.

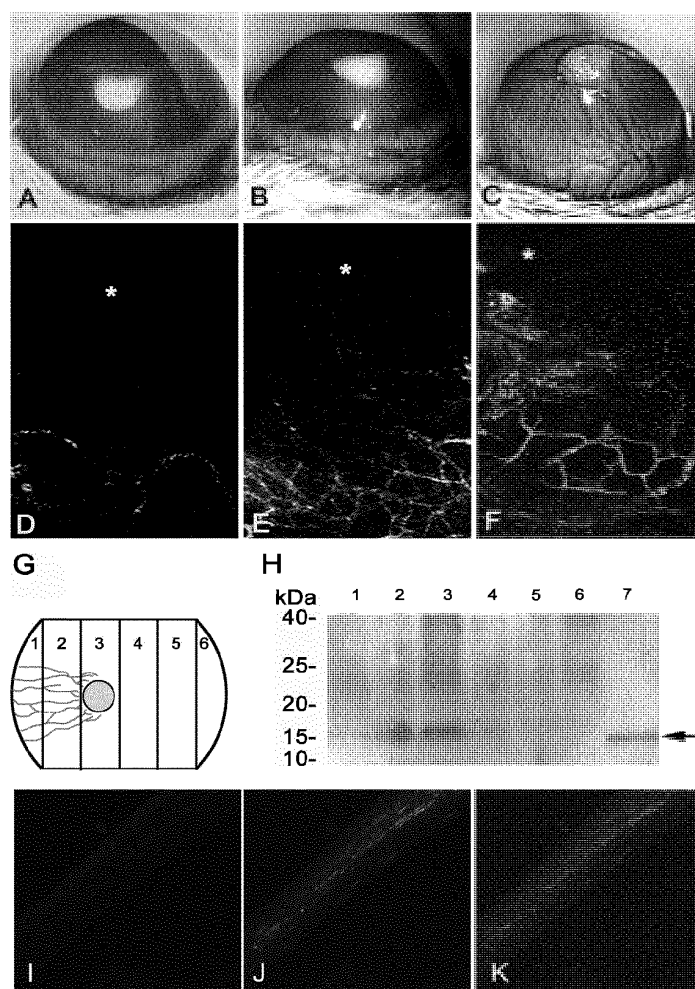


Figure 2.

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)).

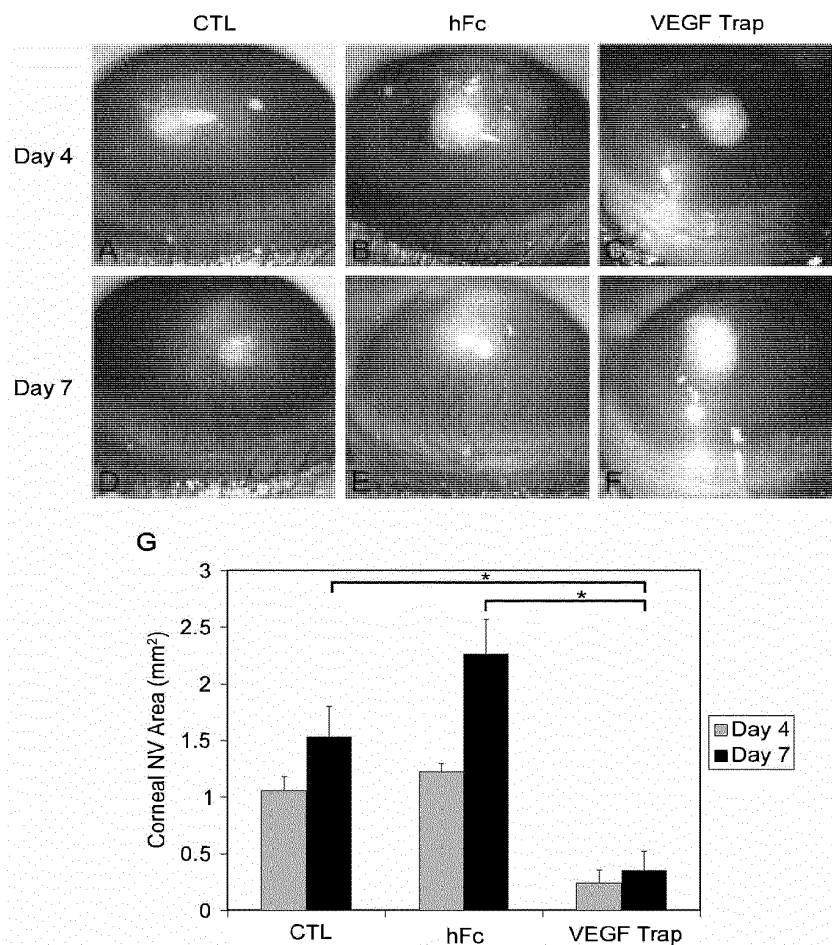


Figure 3.

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).

XP-002770952

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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

<http://www.evaluategroup.com/Universal/View.aspx?type=S...> 09-06-2017

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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HOW WE USE COOKIES

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Electronic Acknowledgement Receipt	
EFS ID:	29958245
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:	02-AUG-2017
Filing Date:	28-MAR-2017
Time Stamp:	12:21:54
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment		no			
File Listing:					
Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
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Warnings:					

Information:					
2	Information Disclosure Statement (IDS) Form (SB08)	REGN-008CIPCON2_2017-08-02_Supp_IDS_SB08A.pdf	24170	no	1
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Total Files Size (in bytes):			5649060		
<p>This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.</p> <p><u>New Applications Under 35 U.S.C. 111</u> If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.</p> <p><u>National Stage of an International Application under 35 U.S.C. 371</u> If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.</p> <p><u>New International Application Filed with the USPTO as a Receiving Office</u> If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.</p>					

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<p style="text-align: center;">INFORMATION DISCLOSURE STATEMENT</p> <p>Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450</p>	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:	<i>“Use of a VEGF Antagonist to Treat Angiogenic Eye Disorders”</i>

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

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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 Geroqe D. Yancopoulos on the ADS, but as George D. Yancopoulos on the signed declaration.

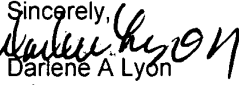
Once an application data sheet or the inventor's oath or declaration is filed in a nonprovisional application, any correction of inventorship must be pursuant to 37 CFR 1.48.

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 the correct spelling of the first Inventors name from George 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:	<i>“Use of a VEGF Antagonist to Treat Angiogenic Eye Disorders”</i>

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

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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.

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

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
	George George	D.	YANCOPOULOS	
Residence Information (Select One) ☒ US Residency ☐ Non US Residency ☐ Active US Military Service				
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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
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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

SUPPLEMENTAL ADS

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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	

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)
15/473,506	Continuation of	14972560	2015-12-17

SUPPLEMENTAL ADS

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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

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	REGN-008CIPCON2
		Application Number	15/472,586
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 ^j (if applicable)
Additional Foreign Priority Data may be generated within this form by selecting the Add button.			

SUPPLEMENTAL ADS

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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

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	REGN-008CIPCON2
	Application Number	<u>15/471,506</u>
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

☐	<p>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.</p> <p>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.</p>
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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.

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

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.

SUPPLEMENTAL ADS

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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

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	REGN-008CIPCON2
	Application Number	15/471,508
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.			
<input type="button" value="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: <input type="text"/>			
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.

SUPPLEMENTAL ADS

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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

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	REGN-008CIPCON2
	Application Number	<u>15/471,595</u>
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)	2017-04-19 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.

SUPPLEMENTAL ADS

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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

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	REGN-008CIPCON2
		Application Number	<u>15/471,506</u>
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 Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Electronic Patent Application Fee Transmittal				
Application Number:		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)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	\$ 140
RAM confirmation Number	090117INTEFSW14381500
Deposit Account	
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:	

File Listing:					
Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Request under Rule 48 correcting inventorship	REGN-008CIPCON2_2017-08-31_Petition.pdf	25453	no	1
			b34c4cc68346e6c207c93bcb2dc516f1ad043d55		
Warnings:					
Information:					
2	Application Data Sheet	REGN-008CIPCON2_2017-08-31_supp_ADS_1.pdf	152722	no	9
			a2751ddc510c502c15b0d78af29289bc33bc2f98		
Warnings:					
Information:					
This is not an USPTO supplied ADS fillable form					
3	Fee Worksheet (SB06)	fee-info.pdf	30896	no	2
			fd48e82f4e1908c87bffe993e56c57e00ee0028d		
Warnings:					
Information:					
Total Files Size (in bytes):			209071		
<p>This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.</p> <p><u>New Applications Under 35 U.S.C. 111</u> If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.</p> <p><u>National Stage of an International Application under 35 U.S.C. 371</u> If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.</p> <p><u>New International Application Filed with the USPTO as a Receiving Office</u> If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.</p>					

Document code: WFEE

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United States Patent and Trademark Office
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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
REPLACEMENT FILING RECEIPT



0000000093850985

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

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.

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NOT GRANTED

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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	Issue Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		Number-Kind Code (if known)			
	1				

U.S. PATENT APPLICATION PUBLICATIONS					
Examiner Initial*	Cite No.	Publication Number	Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		Number-Kind Code (if known)			
	1				

FOREIGN PATENT DOCUMENTS						
Examiner Initial*	Cite No.	Foreign Document Number	Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T
		Country Code-Number-Kind Code (if known)				
	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	
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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.

弓 | 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.*

NDA 21-756 Macugen Final Label

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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/CIEM
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
MEDICAL OFFICER

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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 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

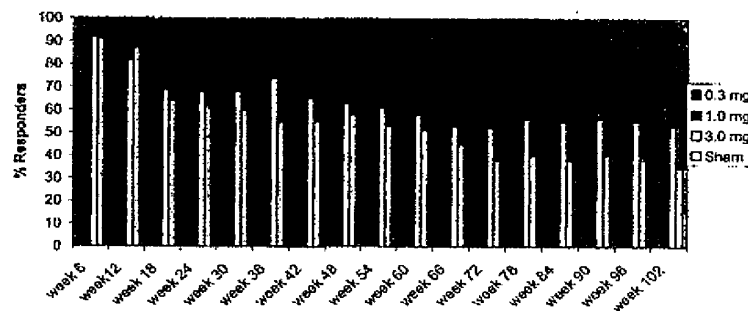
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Efficacy Analysis

Responder Analysis - FTT 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		0.02		

Responder Analysis by Week - Study EOP1004



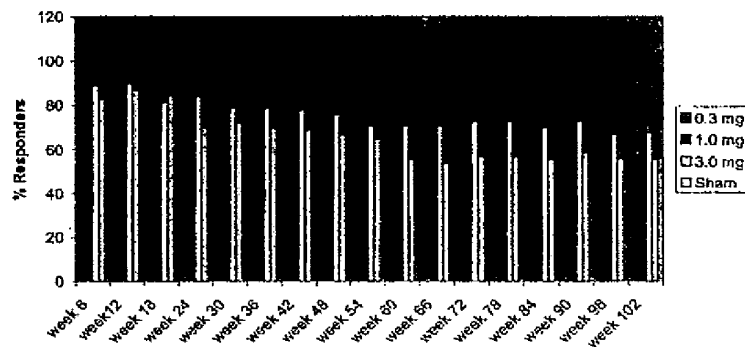
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Responder Analysis – ITT Population– Study 1003

	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



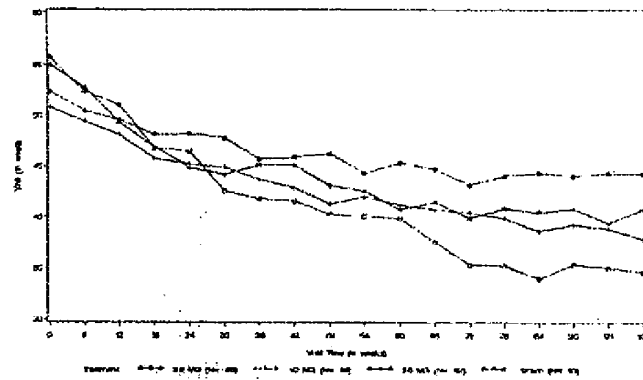
Reviewer's Comments:

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)

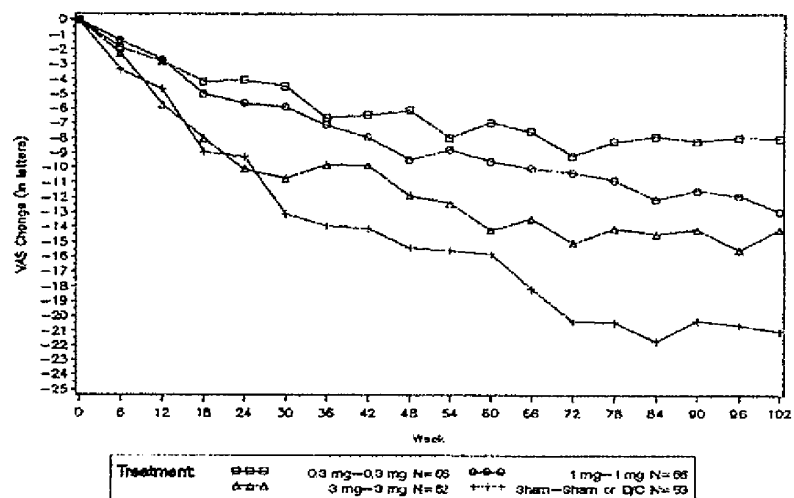


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EOP1004 Mean Changes in Visual Acuity (LOCF), Baseline to Week 102

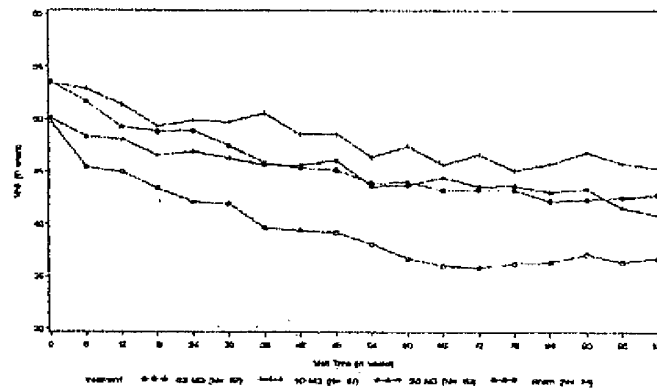


Number of On-Study PDT Treatments Received in the 2nd Year Study EOP1004

	0.3 mg-0.3 mg N=66	1 mg-1 mg N=66	3 mg-3 mg N=62	Sham-sham or d/c N=53
No of PDT treatments	8	14	6	18

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EOP1003: Mean Visual Acuity Over Time ITT (LOCF)

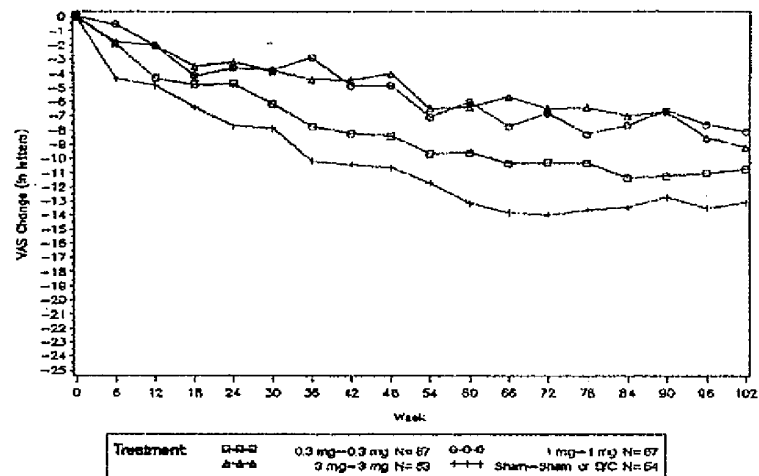


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EOP1003 Mean Changes in Visual Acuity (LOCF), Baseline to Week 102



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=64
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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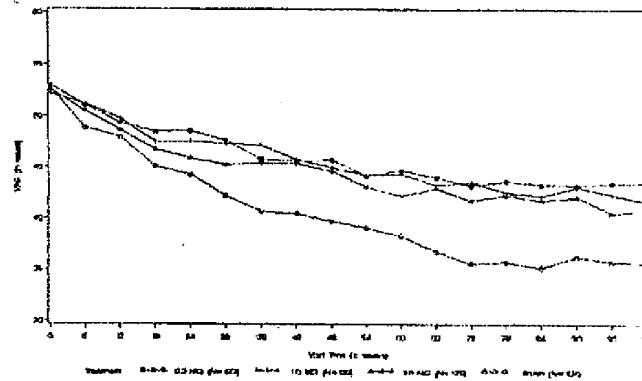
*stabilization is also seen in Study EOP1003 for the 0.3 mg and 1 mg pegaptanib groups
as well as patients in the sham group.*

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Combined Studies: Mean Visual Acuity Over Time - ITT (LOCF)

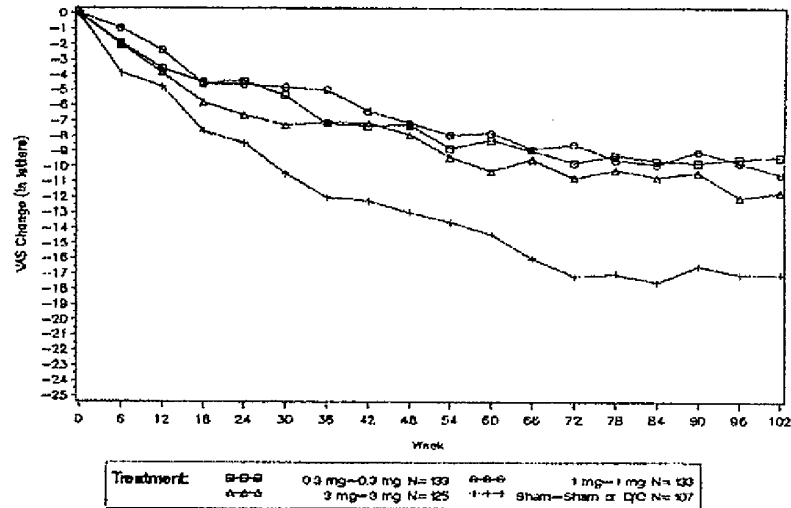


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EOP1004 & EOP1003 Mean Changes in Visual Acuity (LOCF), Baseline to Week 102



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, there 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 question 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.

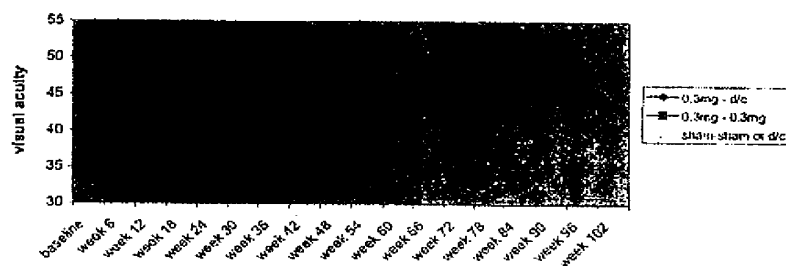
The three patient populations analyzed were:

0.3mg-0.3mg: patients who were on 0.3mg for the 1st and 2nd years

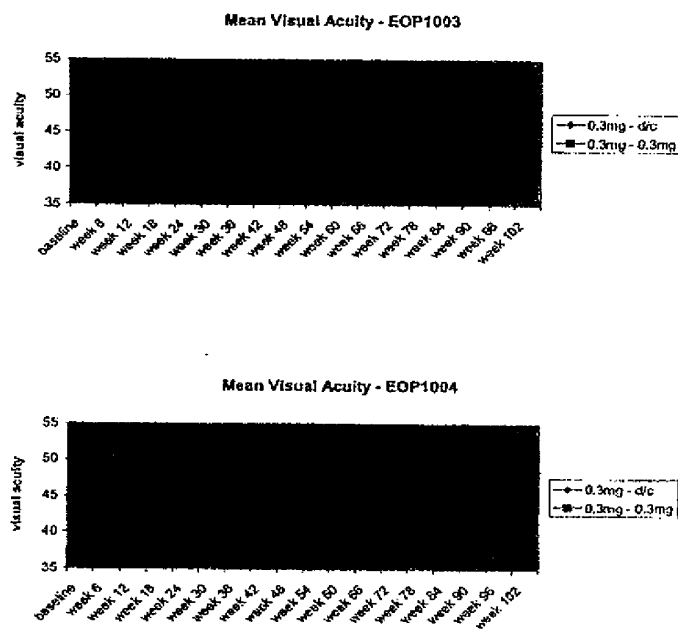
0.3mg-sham: patients who were on 0.3mg during the 1st year and were re-randomized to sham during the 2nd year.

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

Mean Visual Acuity- 1003_1004 Combined Data - ITT



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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%)
Cataract	42 (33%)	46 (37%)	50 (42%)	19 (37%)
Visual acuity reduced	41 (32%)	32 (25%)	34 (28%)	17 (33%)

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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
Retinal exudates	3 (2%)	2 (2%)	0	1 (2%)
Retinal Scar	3 (2%)	2 (2%)	1 (1%)	1 (2%)
Blood and Lymphatic system disorders				
Thrombocythemia	0	2 (2%)	0	2 (1%)
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%)
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%)
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				
Constipation	3 (2%)	6 (5%)	2 (2%)	1 (2%)
Abdominal pain	3 (2%)	4 (3%)	1 (1%)	1 (2%)
General disorders and administration site conditions				
Edema peripheral	4 (3%)	2 (2%)	4 (3%)	2 (4%)
Asthenia	2 (2%)	2 (2%)	2 (2%)	1 (2%)
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
Influenza	12 (9%)	5 (4%)	6 (5%)	5 (10%)
Urinary tract infection				
Sinusitis	3 (2%)	5 (4%)	6 (5%)	3 (6%)
Gastroenteritis viral	2 (2%)	1 (1%)	3 (3%)	2 (4%)
Injury, poisoning and procedural complications				0
Post procedural pain	3 (2%)	4 (3%)	3 (3%)	1 (2%)
Skin laceration	2 (2%)	3 (2%)	3 (3%)	2 (4%)
Abrasion	3 (2%)	0	2 (2%)	3 (6%)
Metabolism and nutrition disorders				0
Musculoskeletal and connective tissue disorders				0
Back pain	7 (5%)	8 (6%)	8 (7%)	5 (10%)
Arthralgia	8 (6%)	4 (3%)	4 (3%)	3 (6%)
Osteoarthritis	2 (2%)	4 (3%)	2 (2%)	1 (2%)
Muscle cramp	2 (2%)	0	3 (3%)	1 (2%)
Neoplasms				0
Basal cell carcinoma	2 (2%)	4 (3%)	2 (2%)	2 (4%)
Prostate cancer	2 (2%)	1 (1%)	2 (2%)	1 (2%)
Nervous system disorders				0
Psychiatric disorders				0

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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%)
Resal and urinary disorders				
Reproductive System				
Respiratory, thoracic and mediastinal disorders				
Nasopharyngitis	15 (12%)	17 (13%)	20 (17%)	7 (14%)
Cough	8 (6%)	5 (4%)	6 (5%)	4 (8%)
Pharyngitis	5 (4%)	3 (2%)	2 (2%)	2 (4%)
Dyspnea	2 (2%)	4 (3%)	7 (6%)	2 (4%)
Euphysona	2 (2%)	1 (1%)	1 (1%)	2 (4%)
Epistaxis	2 (2%)	2 (2%)	2 (2%)	1 (2%)
Pulmonary embolism	2 (2%)	0	0	1 (2%)
Rhinorrhea	3 (2%)	1 (1%)	1 (1%)	1 (2%)
Skin and subcutaneous tissue disorders				
Outis 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				
Hypertension aggravated	4 (4%)	5 (4%)	3 (3%)	3 (6%)
Hypotension	3 (2%)	4 (3%)	2 (2%)	1 (2%)

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%)
Cataract	42 (33%)	46 (37%)	50 (42%)	19 (37%)
Visual acuity reduced	41 (32%)	32 (25%)	34 (28%)	17 (33%)
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%)
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
2 nd 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
1 st 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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IOP (mmHg) at All Study Visits - Study EOP1003 and EOP1004 - ITT Population

IOP (mmHg)	baseline		week 7		week 13		week 19		week 25		week 31		week 37		week 43		week 49		week 55		week 61		week 67		week 73		week 79		week 85		week 91		week 97		week 103	
● 0.3 mg	15.5	14.3	15	14.6	15.2	14.7	15.2	14.9	14.9	15	14.9	14.9	15.3	14.9	15	14.8	14.5	14.8	14.5	14.8	14.5	14.8	14.5	14.8	14.5	14.2	14.5	15.2	14.8	14.5	14.2	14.5	15.2	14.8	14.5	
■ 0.3 mg	16.2	15.2	15.5	15.2	16.1	15	14.9	14.9	15.3	14.9	15	16.4	16.2	15.3	14.8	15.1	14.8	15.1	14.8	15.1	14.8	15.1	14.8	15.1	14.8	15.1	14.8	15.1	14.8	15.1	14.8	15.1	14.8	15.1		
○ 3 mg	15.6	15.9	15.6	15.6	16	16	16.2	16.1	16.2	16.9	16.1	16.3	16.5	16.5	16.3	16.3	16.4	16.2	16.3	16.4	16.2	16.3	16.4	16.2	16.3	16.4	16.2	16.3	16.4	16.2	16.3	16.4	16.2	16.3		
○ Sham	14.8	14.9	15	14.6	15	14.3	15.4	14.4	14.5	14.4	14.5	14.5	13.6	14.2	13.9	14.8	14.6	14.3	14.4	14.6	14.3	14.4	14.6	14.3	14.4	14.6	14.3	14.4	14.6	14.3	14.4	14.6	14.3	14.4		

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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 intravitreal 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 8/iles
HFD-550/CSO/Puglisi
HFD-520/CHEM
HFD-550/PHARM/Z/Chen
HFD-550/MO/Harris
HFD-550/SNO/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, 18 th Floor New York, New York 10018
NDA Drug Classification:	IP
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

Executive Summary Section

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 1 mg 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 intracocular procedures including intravitreal 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 minimize 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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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

Clinical Review Section

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, 18 th Floor New York, New York 10018
NDA Drug Classification:	IP
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 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 minimize 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**

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

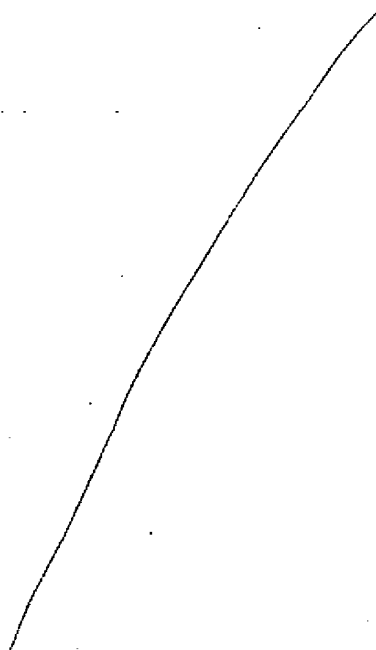
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Analytical Specification for Macugen Injection, 0.3 mg



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Clinical Review Section

III. Human Pharmacokinetics and Pharmacodynamics

A. Pharmacokinetics

PK characteristics:

- Following intravitreal 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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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	Intravitreal 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 with 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	Intravitreal 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 with 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 intravitreal 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
EOP1000	Phase 1/2, multi-center, open label, multiple dose in patients without PDT	Total of 3 consecutive intravitreal 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 intravitreal 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, vitil signs, DLT, PK parameters, immune response, requirement for PDT administration, local ocular events
EOP1006	Phase 2 multi-center, randomized, multiple dose, open label cohort	Intravitreal injections of 3 mg pegaptanib sodium/eye every 6 weeks for 54 weeks	77 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, vitil 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,	Intravitreal 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	Intravitreal 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)				
EOP1007	Phase 1/2, open-label, non-randomized, pilot	Intravitreal 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 completed 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

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 too 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 lost 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 cases 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 Intravitreal 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 intravitreal 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	Sydney	7
64	Jennifer Arnold, MD	Parramatta	34
65	Ian Constable, MD	St. Nedlands	12
66	Paul Mitchell, MD	Westmead	3
73	Robyn Guymer, MD	East Melbourne	16
131	Mark Gillies, MD	Sydney	12
Austria			
67	Michael Stur, MD	Vicenna	11
116	Anton Haas, MD	Graz	4
Belgium			

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Center Number	Principal Investigator	Center Location	Number of Subjects
113	Anita Leys, MD	Leuven	38
Brazil			
70	Michel Furu, MD	Sao Paulo	7
108	Marcos de Avila, MD	Sector Bureno	6
112	Carlos Moreira, MD	Curitiba	3
134	Jaao Lavinsky	Porto Alegre	5
Chile			
71	Jose Manuel Lopez, MD	Santiago	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	Cretail	25
76	Jean-Francois Korobelnik, MD	Bordeaux	5
78	Alain Gaudric, MD	Paris	3
Germany			
79	Stefan Dithmar, MD	Hidelberg	10
80	Daniel Paulckhoff, MD	Munster	1
81	Ulrike Schneider, MD	Tubingen	6
82	Peter Wiedemann, MD	Leipzig	14
83	B Kirchhof, MD	Koln	8
Hungary			
122	Ilidko Suvegcs, MD	Budapest	3
137	Jozsef Gyoty, MD	Veszprem Korbaz	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	Krzyszna Peoold, MD	Poznan	5
128	Jozef Kaluzny, MD	Bydgoszcz	5
Portugal			
93	Jose Cunha-Vaz, MD	Coimbra	25
Spain			
94	Marta Figueras, MD	Madrid	7
136	Jose Ruiz Moreno, MD	Alicante	10
95	Jordi Mones, MD	Barcelona	14
Switzerland			
98	Constantin Pourmaras, 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 Faron, 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 Thomas, MD	Missouri	-
153	Leonard Joffe, MD	Arizona	16
154	Jeffrey Heier, MD	Massachusetts	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 intravitreal injection every 6 weeks for 48 weeks
- Arm B: pegaptanib sodium 1 mg intravitreal injection every 6 weeks for 48 weeks
- Arm C: pegaptanib sodium 3 mg intravitreal injection every 6 weeks for 48 weeks
- Arm D: sham intravitreal 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 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 $>10\text{g/dL}$, platelet count $>130 \times 10^9/\text{L}$ and white blood cell count (WBC) $>3.8 \times 10^9/\text{L}$.
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 $<1.5 \text{ mg/dL}$, 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 tachyarrhythmias 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.*

APPEARS THIS WAY
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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	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																				
Peripartum sodium or sham injection	X	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	S	B	S	S	S	B	S	S	S	B	S	S	S			
Color fundus photographs ¹	B ¹						B				B				B						
Fluorescein angiogram ¹	B ¹						B				B				B						
ICG/OCT ¹	B						B				B										
Safety																					
Physical examination ^a	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Adverse events / serious adverse events	B	B ^a	S ^a	S ^a	S ^a	S ^a	B ^a	S ^a	S ^a	S ^a	B ^a	S ^a	S ^a	S ^a	B ^a	S ^a	S ^a	S ^a			
Intraocular pressure ¹	B	S ¹	S ¹	S ¹	S ¹	S ¹	B ¹	S ¹	S ¹	S ¹	B ¹	S ¹	S ¹	S ¹	B ¹	S ¹	S ¹	S ¹			
Ophthalmic examination	B	S ¹	S ¹	S ¹	S ¹	S ¹	B ¹	S ¹	S ¹	S ¹	B ¹	S ¹	S ¹	S ¹	B ¹	S ¹	S ¹	S ¹			
Vital signs	X	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	X	X	X	X	X	X	X	X			
ECG	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Telephone safety check ¹	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			

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 [Clinical Review Section](#) for efficacy and safety assessments

¹ Received by Eligibility and Classification Quality Assurance Team (ECQAT) for eligibility and randomization stratification

¹ Some selected sites performed optical coherence tomography (OCT) or optical coherence tomography (OCT), but no analyses of data were performed

¹ Physical examination performed post-baseline only if indicated

¹ Application immediately at baseline and for confirmation of IOP-10 mmHg

¹ Before treatment, at least 30 minutes after treatment and 1 week after treatment

¹ Telephone safety check carried out 3 days post-treatment

¹ Trend (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 reticular 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			108 (69.7%)	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			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 p=0.68	1 mg vs. sham p=1.0	3 mg vs. sham 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%)

¹Patients 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%)

¹Patients 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%)

¹Patients 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

¹Patients who lost < 15 letters of vision.

APPEARS THIS WAY
ON ORIGINAL

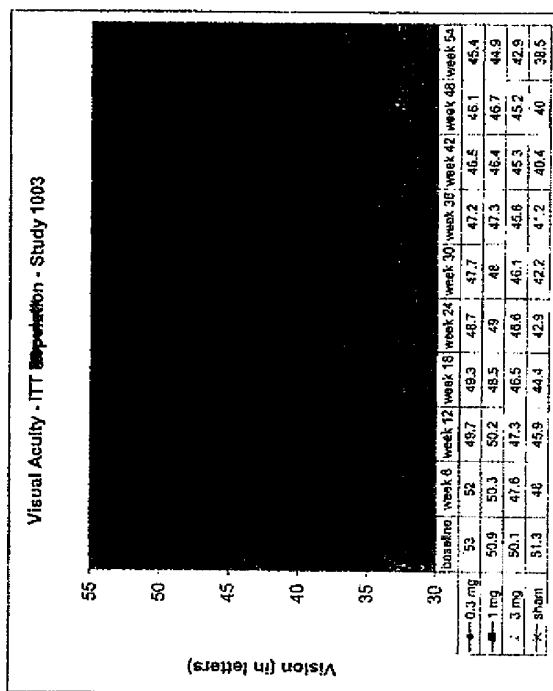
APPEARS THIS WAY
ON ORIGINAL

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CLINICAL REVIEW

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Additional Efficacy Analyses



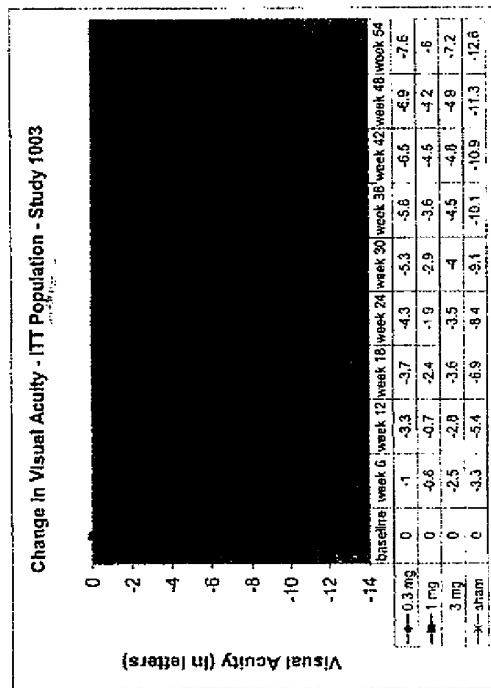
Reviewer's Comments:

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 year data is available.

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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 size¹				
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 Size¹				
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 Size¹				
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 letters¹	Yes	6 (4%)	10 (6%)	7 (5%)	5 (3%)
	p-value	0.93	0.49	- ²	-
Vision gain ≥ 0 letters²	Yes	49 (33%)	59 (38%)	60 (39%)	42 (28%)
	p-value	0.38	0.08	- ²	-

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:

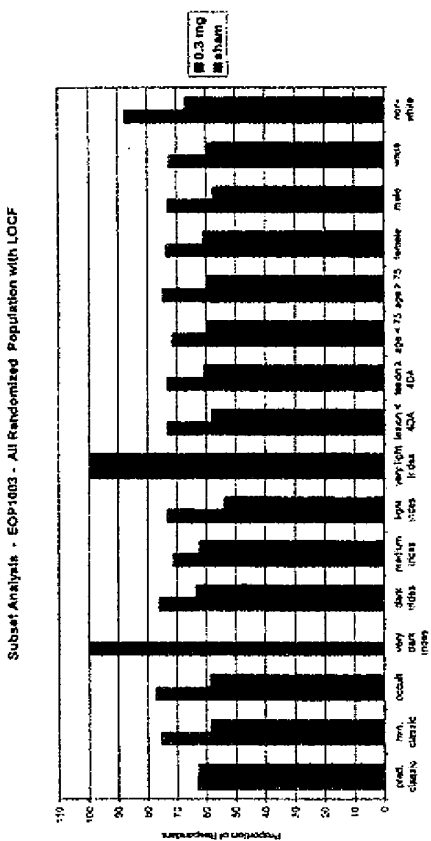
There is only a small percentage of patients in each treatment group that show a clinically meaningful increase in vision and the difference seen between the groups is not statistically significant. This is expected based on the disease process being studied.

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CLINICAL REVIEW

Clinical Review Section

Responder analyses based on baseline characteristics for study EOP003



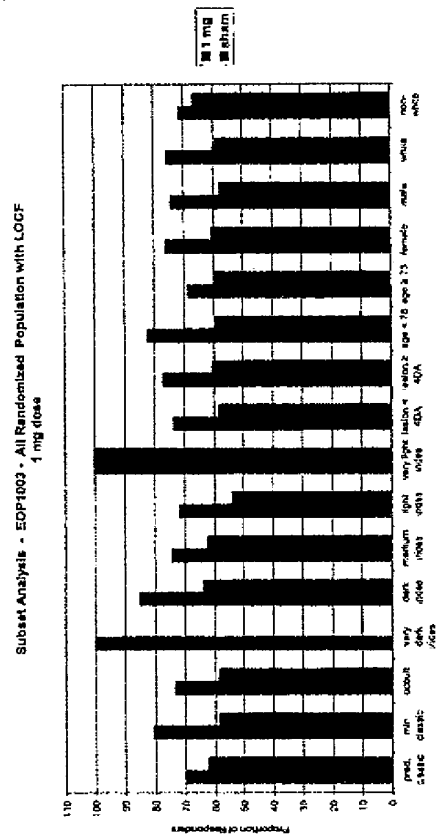
Reviewers Comments:

REVIEWED 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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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 Haller, 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. Ciulla, 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	13
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 Tency, 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	Hilal 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 D'Amico, 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 Varonhorst, 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	13
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 Wrublewski, 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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CLINICAL REVIEW

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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 fragile 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 want 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		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	98 (66.7%)	98 (66.7%)	91 (61.9%)	79 (53.4%)
		p=0.03		p=0.13	

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=133
	Month 6	112 (82.4%) N=136	96 (72.2%) N=133	91 (67.4%) N=135
	Month 9	94 (74.6%) N=126	94 (75.2%) N=125	90 (70.9%) N=127
	Month 12	88 (69.8%) N=126	85 (66.9%) N=127	70 (57.4%) N=122

¹Patients 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	-

¹Patients 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 EOI1004

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 p=0.05	1 mg vs. sham p=0.22	3 mg vs. sham 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
Prodominantly 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.

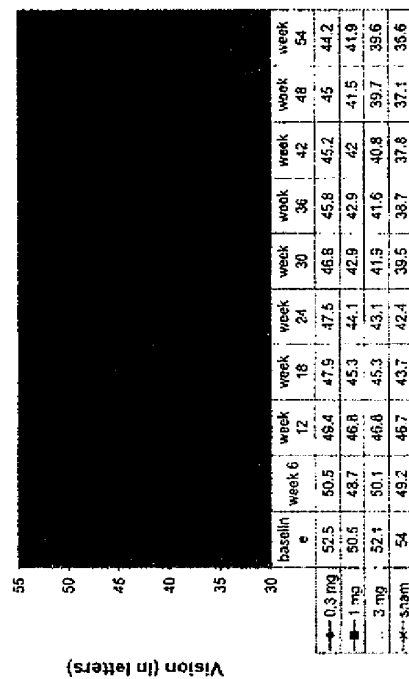
Number of Patients (%) who received PDT before and during the study		0.3 mg N= 13	1 mg N= 12	3 mg N= 14	Sham N= 12
Responders ¹	Month 3	12 (92.3%)	9 (75%)	10 (71.4%)	8 (66.7%)
	Month 6	12 (92.3%)	9 (75%)	11 (78.6%)	6 (50%)
	Month 9	11 (84.6%)	11 (91.7%)	13 (93%)	6 (50%)
	Month 12	10 (76.9%)	9 (75%)	8 (57.1%)	5 (41.7%)

¹ Patients who lost < 15 letters of vision.

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CLINICAL REVIEW
Clinical Review Section

Visual Acuity - ITT Population - Study EOP1004



Reviewer's Comments:

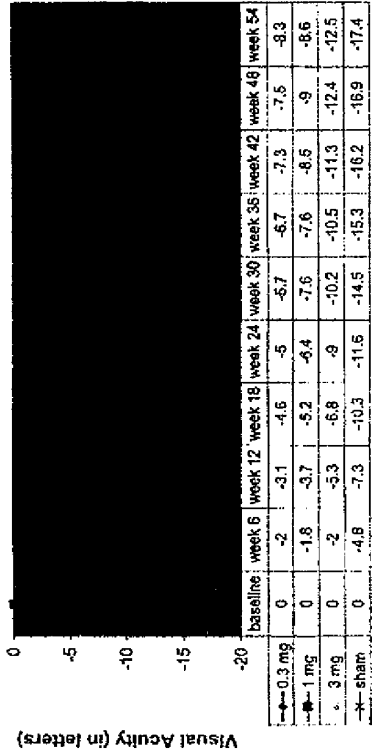
The rate of vision loss in the 0.3 mg is slightly less than in the other treatment groups. This vision loss does not appear to plateau which would suggest that there is there may be continued vision loss despite therapy. This will be analyzed after the results of the 2 years data is available.

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Change in Visual Acuity - ITT Population - Study 1004



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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 size¹				
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 Size¹				
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 Size¹				
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 $\geq$ 15 letters ¹	Yes	12 (8%)	10 (7%)	6 (4%)	1 (1%)
	p-value	0.005	0.01	0.04	-
Vision gain $\geq$ 0 letters ²	Yes	49 (34%)	51 (35%)	33 (23%)	25 (17%)
	p-value	0.0006	0.002	0.17	-

¹ patients who gained $\geq$ 15 letters of vision from baseline to 54 weeks
² patients who gained $\geq$ 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.

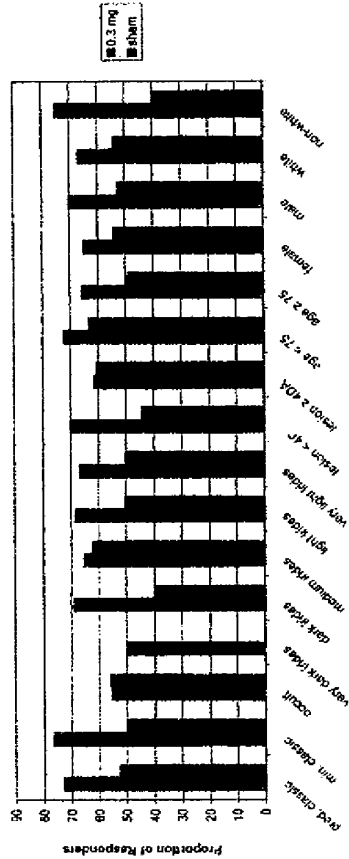
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Responder analyses based on baseline characteristics for study EOP1004

Subset Analysis - EOP1004 - All Randomized Population with LOCF



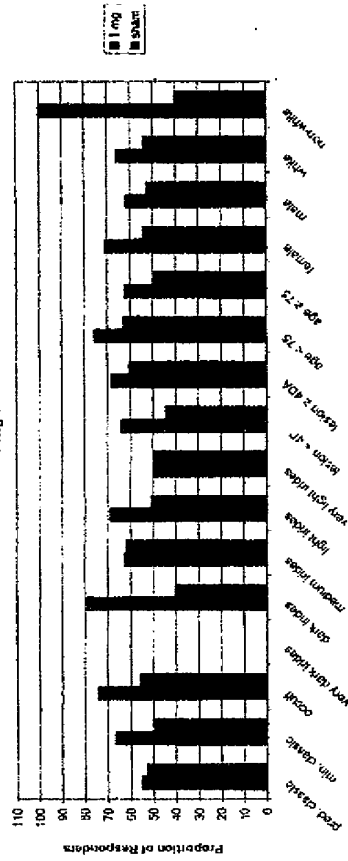
Reviewers Comments:

The white vs non-white treatment groups are grossly imbalanced (N= 283 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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Subset Analysis - EOP1004 - All Randomized Population with LOCF
1 mg dose



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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.

APPEARS THIS WAY
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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 intravitreal 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 intravitreal 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

¹Includes 0.25 mg, 0.5 mg and 2 mg doses from study NX109-01; ²Only the completed cohort from study EOP1006 is included; ³Study 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

¹ Includes 0.25 mg, 0.3 mg and 3 mg doses from study NX109-01. ² Only the completed cohort is included;
³ 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=285	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 intravitreal 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 (3%)	3 (1%)
Coronary artery disease NOS	1 (<1%)	0 (0%)	1 (<1%)	1 (1%)
Ear and labyrinth disorders				
Endocrine disorders				
Acquired hypothyroidism	0 (0%)	2 (1%)	4 (1%)	1 (1%)
Eye disorders				
Visual acuity reduced	82 (28%)	68 (19%)	62 (21%)	82 (28%)
Cataract	64 (22%)	78 (26%)	85 (29%)	68 (23%)
				17 (6%)
				39 (13%)

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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
Abnormal sensation in eye	23 (8%)	21 (7%)	26 (9%)	30 (10%)
Lacrimation increased	25 (8%)	31 (10%)	29 (10%)	30 (10%)
Macular degeneration	25 (8%)	31 (10%)	29 (10%)	36 (12%)
Eye irritation	22 (7%)	24 (8%)	29 (10%)	20 (7%)
Photophobia	22 (7%)	21 (7%)	30 (10%)	23 (8%)
Eye pruritus	22 (7%)	18 (6%)	27 (9%)	23 (8%)
Eye redness	21 (7%)	23 (8%)	19 (6%)	21 (7%)
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%)
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%)
Corneal dystrophy	4 (1%)	6 (2%)	6 (2%)	2 (1%)
Eyelid ptosis	3 (1%)	5 (2%)	8 (3%)	6 (2%)
Keratitis	4 (1%)	7 (2%)	8 (3%)	9 (3%)
Ocular hypertension	4 (1%)	7 (2%)	7 (2%)	5 (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%)
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%)
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	0.3 mg N=295	1 mg N=301	3 mg N=296	Sham N=298
System organ class and preferred term				
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%)	5 (2%)
Constipation	7 (2%)	5 (2%)	9 (3%)	5 (2%)
Gastroesophageal 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%)	1 (1%)	4 (1%)
General disorders and administration site conditions				
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%)
Anaemia	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%)
Influenza	10 (3%)	8 (3%)	7 (2%)	13 (4%)
Sinusitis NOS	6 (2%)	3 (1%)	10 (3%)	7 (2%)
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%)
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	0.3 mg N=295	1 mg N=301	3 mg N=296	Sham N=298
System organ class and preferred terms				
Corneal erosion	1 (0%)	1 (<1%)	3 (1%)	1 (<1%)
Muscle strain	0 (0%)	1 (<1%)	2 (1%)	2 (1%)
Investigations				
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%)
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%)	9 (3%)	14 (5%)
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%)	1 (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				
Dizziness	7 (2%)	7 (2%)	9 (3%)	7 (2%)
Carpal tunnel syndrome	2 (1%)	1 (<1%)	0 (0%)	4 (1%)
Syncope	0 (0%)	3 (1%)	4 (1%)	3 (1%)
Psychiatric disorders				
Depression	11 (4%)	7 (2%)	10 (3%)	11 (4%)
Anxiety	2 (1%)	3 (1%)	3 (1%)	9 (3%)
Confusional state	3 (1%)	2 (1%)	0 (0%)	1 (<1%)
Renal and urinary disorders				
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%)

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CLINICAL REVIEW

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Number of subjects	0.3 mg N=295	1 mg N=301	3 mg N=296	Sham N=298
System organ class and preferred term				
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%)
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				
Cutis laxa	3 (1%)	3 (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%)
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 intracocular 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 S&E	Onset Post Last Injection	Baseline VA	VA Before E-val	VA After E-val	Latent VA WL 54	Outcome	Culture
EOP1003/1004 Week 54 Cohort										
1003-073-015	F/81	3 mg	2	4 days	20/100	20/63	20/125	20/125	de'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	de'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	20/210	20/125	Cont't	Coagulase negative Staph
1003-145-013	M/83	3 mg	6	7 days	20/125	20/400	20/800	20/400	Cont't	Microcococcus sp.
1004-025-001	M/73	0.3 mg	2	3 days	20/40	20/50	20/100	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	Staph epidermidis
1004-042-001	M/77	0.3 mg	1	4 days	20/63	20/63	20/800	20/800	de'd due to AE	Staph hyalourin
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/72	3 mg	5	5 days	20/250	20/320	20/350	20/350	Cont't	Negative
EOP1003/1004 Year 2										
1004-025-005	F/81	masked	10	1 day	20/63	20/160	20/200	20/160 WL 78	Cont't	Negative
1004-035-001	M/74	masked	13	4 days	20/160	20/80	20/100	20/160 WL 103	de'd due to AE	Coagulase negative Staph
1004-048-017	F/72	masked	9	5 days	20/80	20/250	20/320	20/320 WL 84	de'd due to AE	Negative
EOP1005 Ongoing										
1005-017-001	F/59	masked	1	3 days	20/80	20/63	20/125	20/160 WL 30	de'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 intravitreal 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 intravitreal 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	183	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	33	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	22	Massive Gastric Bleeding
EOP1003-083-001	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	88/F	3 mg	116	30	Cardiac Arrest
EOP1003-064-012	82/M	Sham	142	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
EOP1004-016-017	81/M	1 mg	431	93	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	353	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.

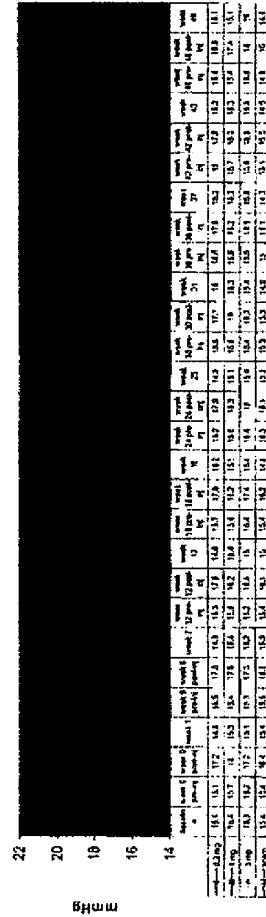
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CLINICAL REVIEW

Clinical Review Section

Study Eye IOP - Safety population - Study EOP1003

Study Eye IOP - Safety population - Study EOP1003



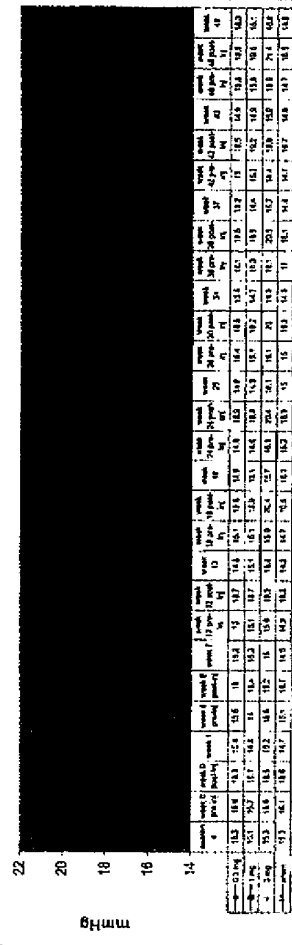
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CLINICAL REVIEW

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Study Eye IOP - Safety population - Study EOP1004

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 or 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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CLINICAL REVIEW

Clinical Review Section

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 1 st 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		23 (41%)	22 (37%)	67 (40%)	75 (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 (26%)	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 (8%)
	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 REVIEW

Clinical Review Section

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 and 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	U/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	μMOL/L	>1.3xULN	10(3)	11(4)	12(4)	33(4)	7(2)
Creatinine	μMOL/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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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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Clinical Review Section

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 intravitreal 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 minimize 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 adequacy 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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CLINICAL REVIEW

Clinical Review Section

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 Harrie
9/16/04 10:02:05 AM
MEDICAL OFFICER

Wiley Chambers
9/17/04 07:40:06 AM
MEDICAL OFFICER

引用非特許文南大

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	Rhca 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, " ☐ — ☐ " 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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 § 552(b)(4) Trade Secret / Confidential

✓ § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process

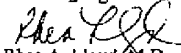
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Recommendations

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 C - 3 neovascular C - 3 age related macular degeneration.


Rhea A. Lloyd, M.D.
Medical Officer, Ophthalmology

cc: William Boyd, MD *W.B. 6/2/08*
Wiley Chambers, MD *W.C. 6/2/08*
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 $\text{C} - \text{D}$ neovascular $\text{C} - \text{D}$ age related macular degeneration

Intended Population

Adults with neovascular (wet) age-related macular degeneration

Formulation

Ingredients	Active ingredient	Reference to Standard or Specification
Ranibizumab	Active ingredient	
α, α -trehalose dehydrate		
histidine HCl		Ph. Eur.
$\text{C} - \text{D}$		USP and Ph. Eur.
$\text{C} - \text{D}$		NF and Ph. Eur.
Polysorbate 20		
Water for Injection		USP and Ph. Eur.

^a Target fill volume of $\text{C} - \text{D}$ 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 ☐ neovascular ☐ 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

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	Amount	Reference to Standard or Specification
Ranibizumab	Active ingredient	
α , α -trehalose dehydrate		
histidine HCl		Ph. Eur.
E - 3		USP and Ph. Eur.
E - 3		NF and Ph. Eur.
Polysorbate 20		USP and Ph. Eur.
Water for Injection		

^a Target fill volume 0.5 mL 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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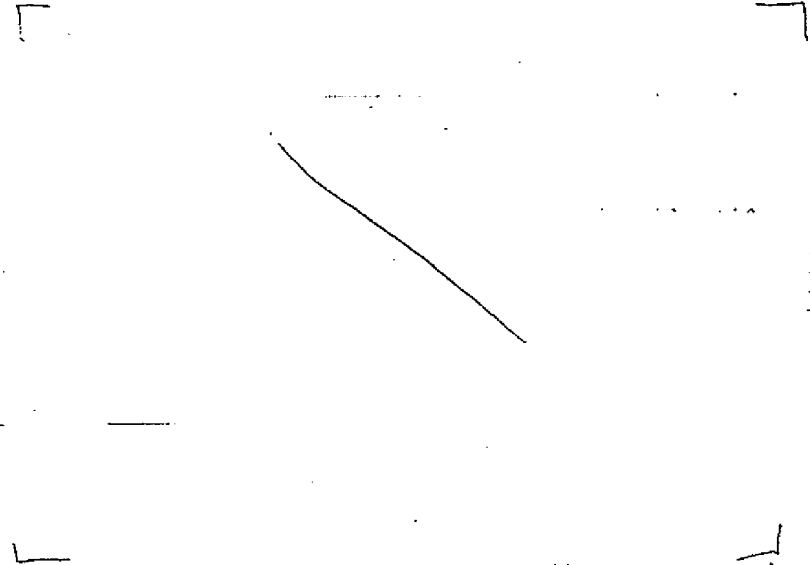
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interim acceptance criteria after three commercial post-approval campaigns (consisting of a minimum of — additional lots). The re-evaluation is expected to take place within two years after approval but will ultimately depend on the currently unknown manufacturing schedule for ranibizumab Drug Substance.

Lucentis Drug Product Release and Shelf-Life Specifications.

Test Code	Test Name	Acceptance Criteria	Release	Shelf-life
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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	Intervention 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	79	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	Number of Subjects	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 ^a	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 (n=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 q3 mos, 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)
CRFB002H 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.

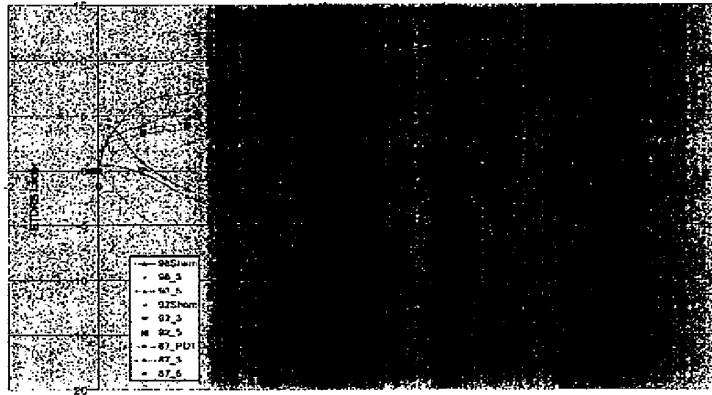
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INTEGRATED REVIEW OF EFFICACY

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.

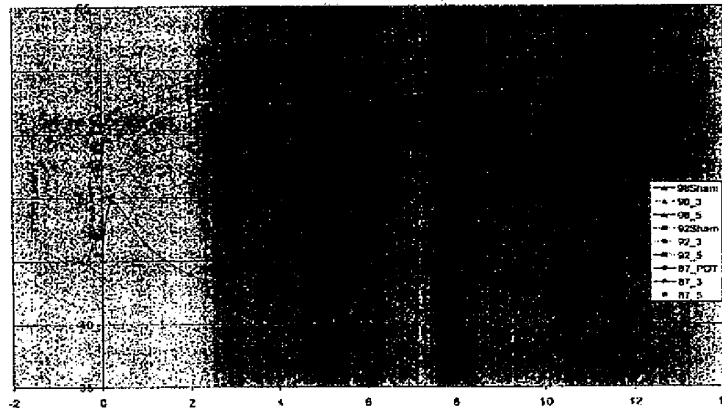


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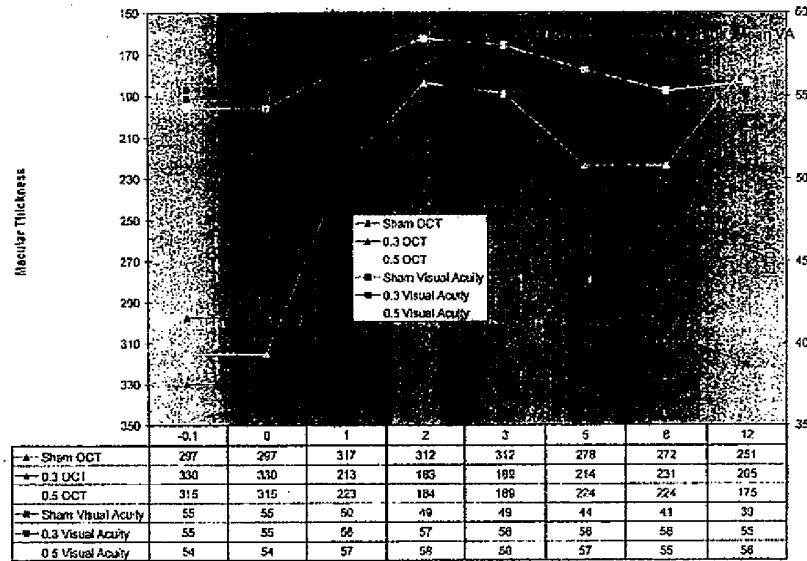
The 0.5 dose was consistently more effective than the 0.3 dose and each were more effective than the control group. The slope of the best fit line between month 3 and month 12 demonstrated a two thirds reduced effect of ranibizumab when the product was administered every three months compared to monthly 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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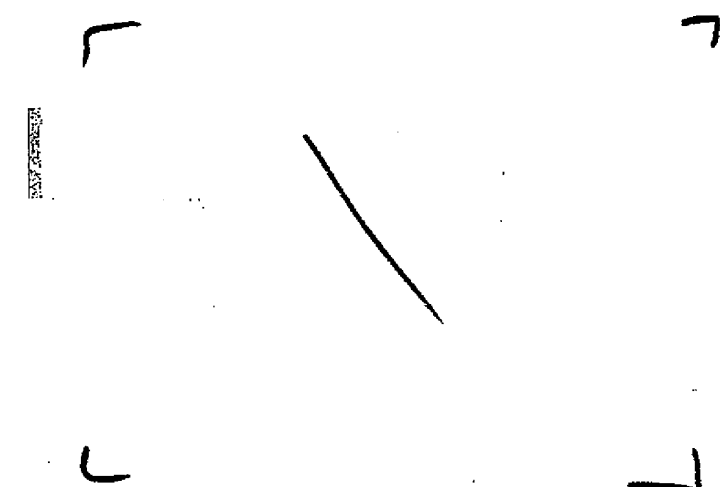
Noted above, there is no correlation between OCT and visual acuity. Treatment with ranibizumab results in a thinner macula even when the visual acuity decreases. The month 12 values illustrate this point. At month 12 for the ranibizumab 0.3 group, the mean macular thickness has its lowest value; however the visual acuity is at its worst.

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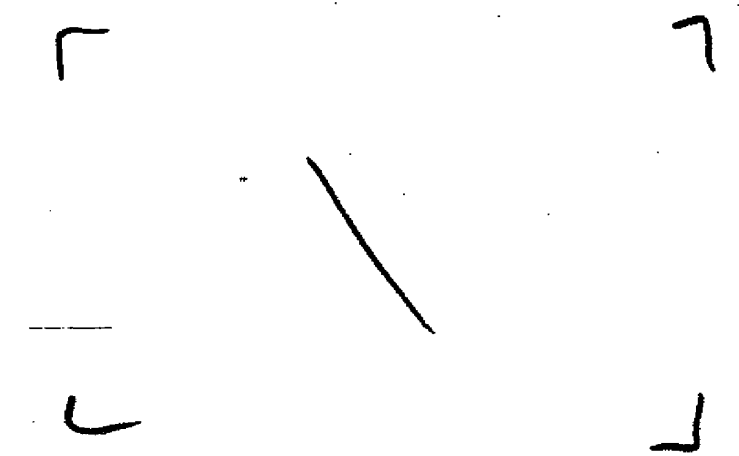
This graph illustrates that a substantially larger proportion of patients treated with ranibizumab injection develop thinner maculae and have improved visual acuity. While there is not a direct correlation between visual acuity and macular thickness over the course of this study, there is a general tendency 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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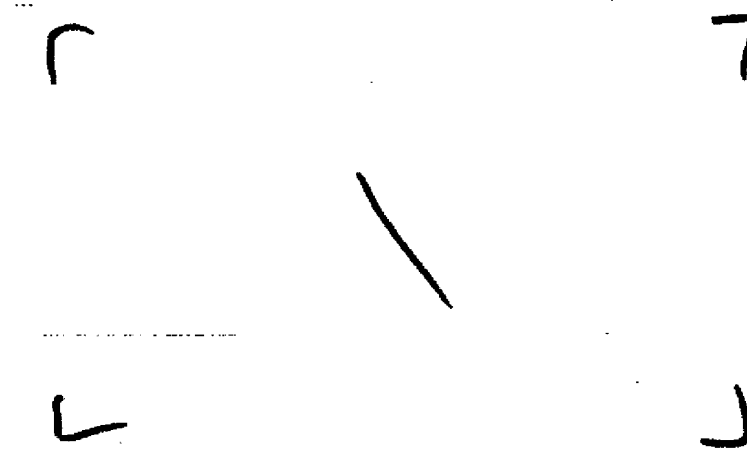
This graph presents a comparison between a change in OCT and the visual acuity at the next visit. Although not shown, data looks very similar for predictions of visual acuity at visits after the next visit. The graph illustrates that macular thickness is not predictive of visual acuity at later visits.

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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 ~~0.5-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.

Macular thickness is not predictive of current or future visual acuity, although macular thickness above 200 μ m and particularly greater than 400 μ m 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	FV2557g Ranibizumab					
	0.1 mg N=137	0.3 mg N=137	0.5 mg N=137	0.7 mg N=137	0.9 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	26/206 (12.6%)	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. ITR=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 FV2598g.

In Study FV2587g, 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	Subject ID	Visit	CRF	Intraocular Inflammation Diagnosis
FVF2428g	Verteporfin PDT + sham	91103	34 / Month 1	1.200	No CRF found
		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 0.3mg	321003	-7 / Screening	0.945	Yes - Vitritis
		334003	176 / Month 6	2.300	Yes - Iritis
		337012	-26 / Screening	0.938	Yes - Iritis
		351004	344 / Month 12	2.190	No
		352006	-10 / Screening	2.070	No
			180 / Month 6	1.890	No
	Ranibizumab 0.5mg		162 / Month 12	1.860	No
		403003	-1 / Screening	0.910	No
		306020	174 / Month 6	1.530	Yes - Vitritis
			362 / Month 12	1.850	No
		337009	364 / Month 12	1.270	Yes - Iritis, Vitritis
		342007	174 / Month 6	2.450	
			360 / Month 12	3.060	
		346001	182 / Month 6	1.260	No
			361 / Month 12	1.770	
		389001	-28 / Screening	1.240	Yes - Vitritis
			182 / Month 6	0.993	
FVF2598g	Sham		365 / Month 12	0.952	
		102003	183 / Month 6	1.230	No
			358 / Month 12	2.090	

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Study	Treatment Group	Subject ID	Visit	Log ₁₀ CFU/mL	Adverse Event	Intraocular Inflammation Diagnosis
		463 / Early 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 ^a
		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		
	Ranibizumab 0.5 mg	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		
		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	Subject ID	Visit	Titers	Diagnosis	Day of 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	
					No CRF found	
		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.
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	Sham (n=140)	Ranibizumab 0.5 mg (n=140)
TOTAL *	2 (0.8%)	8 (3.4%)
Hypertension events	0	1 (0.4%)
Arterial thromboembolic events	2 (0.8%)	5 (2.1%)
Non-ocular hemorrhages	0	1 (0.4%)
Other potentially associated events	0	1 (0.4%)

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	Study 1 (n=1000)	Study 2 (n=1000)	Study 3 (n=1000)	Study 4 (n=1000)	Study 5 (n=1000)	Study 6 (n=1000)	Pooled Ranibiz- umab 0.5 mg N=379
TOTAL *	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)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Medical- 244

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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 C

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

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)(4) Draft Labeling

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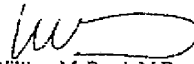
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Recommendations

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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125156
Lucentis (ranibizumab injection)

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

[

Intended Population

Adults with neovascular (wet) age-related macular degeneration

Formulation

Ingredients		Reference to Standard or Specification
Ranibizumab	Active ingredient	
α , α -trehalose dehydrate		
histidine HCl		Ph. Eur.
[		
[		USP and Ph. Eur.
Polysorbate 20		NF and Ph. Eur.
Water for Injection		USP and Ph. Eur.

* Target fill volume of —, per vial.

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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 28, 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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Lucentis (ranibizumab injection)

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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Lucentis (ranibizumab injection)

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	Reference to Standard or Specification
Ranibizumab	Active ingredient	
α , α -trehalose dehydrate		Ph. Eur.
histidine HCl		USP and Ph. Eur.
Polysorbate 20		NF and Ph. Eur.
Water for Injection		USP and Ph. Eur.

* Target fill volume of — 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.

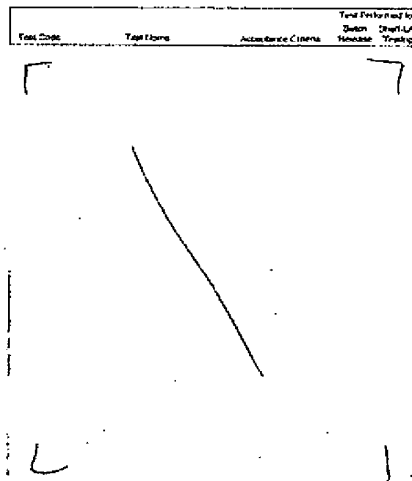
Genentech intends to use a life-cycle approach for setting ranibizumab specifications. This life-cycle approach will use interim acceptance criteria based upon the limited data available at the time of submission. Since campaign-to-campaign variation can be larger than the variation within a campaign, Genentech proposes a post-approval commitment for re-evaluating the interim acceptance criteria after three commercial post-approval campaigns (consisting of a minimum of —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.

Test Code	Test Name	Acceptance Criteria	Test Performed for	
			Stability	Shelf-Life
			Temperature	Time



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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 multiple 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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PTOTAL PHASE 3 TRIALS						
Study	Phase	Design (Study)	Study Population	Intervention	Control	Outcome
FV15878	3	Randomized, double-masked, double-sham, active treatment-controlled (US, Europe, Australia)	Subjects with predominantly classic subfoveal neovascular AMD	Intravitreal injection q month, max. 24 injections over 2 yrs, or verteporfin PDT q mos as needed	Sham injection (n=143)	Ongoing
FV15982	3	Randomized, double-masked, sham-controlled (US)	Subjects with minimally classic or occult subfoveal neovascular AMD	Intravitreal injection q mo., max. 24 injections over 2 years	Sham injection (n=238)	Ongoing
ADDITIONAL PHASE 3 TRIALS						
FV13192g	3b	Randomized, double-masked, sham-controlled (US)	Subjects with recurrent subfoveal CNV with or without classic CNV secondary to AMD	Intravitreal injection q month for 3 doses (Day 0, Month 1, Month 2) followed by doses q 3 months (Mths. 5, 8, 11, 14)	Sham injection (Target: 61-62 subjects per group)	Ongoing

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Study	Phase	Design (Site)	Population	Control	No. of Enrolled Subjects	Treatment Frequency and Duration	Ranibizumab Dose(s)	Status
FVF2508g	Extension	Extension (US)	Subjects with neovascular AMD who completed a Genentech Phase 1/2 ranibizumab study	None	70	Intravitreal injections every 28 days ($\pm$ 5 days) through October 2006 or until 30 days after product launch	0.5 mg (n=66)	Ongoing
FVF2426g	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 FVF2426g 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								
FV2425g	I	Randomized, open-label, multiple-dose escalating regimens (US)	Subjects with classic neovascular AMD	None	29 ^a	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 injections (n=9); 0.3 mg to 2.0 mg escalating regimen with 9 total injections (n=10); 0.3 mg to 2.0 mg escalating regimen with 5 total injections (n=10)	Completed
FV2128g	I/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
FV2170g	I	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 (Site)	Population	Control	No. of Enrolled Subjects	Treatment Frequency and Duration	Ranibizumab Dose(s)	Status
FVF2428g C - S	1/2	Randomized, single-masked, sham-controlled, combination treatment (US)	Subjects with predominantly classic neovascular AMD	Verteporfin PDT (+sham injection)	162	Intravitreal injection qmonth, max. 24 injections over 2 years, in combination with verteporfin PDT q3mos, as needed	0.5 mg (n=106), sham injection (n=56)	Ongoing
NOVARTIS SPONSORED TRIALS								
CRF002A1201*	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
CRF002B2201*	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% (IC₅₀); 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 umbilical 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 fluorescein angiography.

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 **Lucentis** 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 $\geq$ 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 $\geq 10\%$ 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

- 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.
- Total area of CNV (including both classic and occult components) encompassed within the lesion $\geq 50\%$ of the total lesion area.
- Total lesion area ≤ 12 disc areas (DA) in size
- 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

- Prior treatment with verteporfin, external-beam radiation therapy, or transpupillary thermotherapy (TTT) in the study eye
- Treatment with verteporfin in the non-study (fellow) eye less than 7 days preceding Day 0
- 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 $\geq 50\%$ 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 rhegmalogenous 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 been validated against actual activities of daily living.

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Lucentis (ranibizumab injection)

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	
Intraocular inflammation	Dose was held if intraocular inflammation was $\geq 2+$ 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 $\geq 2+$ 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 held if there was a subretinal hemorrhage involving the center of the fovea in the study eye, if the size of the hemorrhage was either $\geq 50\%$ 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 χ^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 χ^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 $\alpha=0.0001$.

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Study Period	Screen	Treatment Phase											
		Day						Month					
		28 to 31	1	2	3	4	5	6	7	8	9	10	11
Assessment (NINDS) (Days)													
perception													
Vital Signs													
Concomitant Medications													
Concomitant ocular procedures													
Adverse Events													
Follow-up contact													

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.

- For amblyopia who withdrew from the study early: Performed 30 days (±7 days) following the last injection or study visit.
- Significant medical/surgical history, including chronic and ongoing conditions (e.g., trauma, cancer history, and ophthalmic history).
- 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.
- For women of childbearing potential.
- Performed pre-injection.
- Performed prior to dilating eyes.
- Also assessed at a starting distance of 4 meters after assessment at a starting distance of 2 meters.
- Laboratory evaluations included hematology, blood chemistry, and urinalysis.
- Obtained pre-injection for both eyes and 60 minutes (±10 minutes) post injection for study eye only.
- The measurement method used for a subject was to remain consistent throughout the study.
- Injecting physician was to perform within 15 minutes post-injection for study eye only.
- Performed post-injection.
- 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.
- Adverse events were collected from Day 0 through the last study visit. Adverse events assessed by the evaluating physician as (a) 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.
- 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

				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

	0.5 mg (N=140)	0.5 mg (N=140)	0.5 mg (N=140)
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 FVF2594g

Subject ID	Reason	Count
S07438	Subject's Decision	332
S08127	AE - Worsening AMD	127
S08536	AE - Pneumonia, COPD Exacerbation x 2	265
S08255	AE - Worsening AMD	148
S08215	Subject's Decision - no improvement in VA	284
S08165	Physician's Decision - Intra Vit Kenalog given	236
S07439	Randomized in error	93
S08082	Lost to follow-up	36
S08239	Subject's Decision / AE - Mild iritis	158
S08235	Subject's Decision - Never received treatment	1
S08130	AE - 30 letter loss of vision - Worsened AMD	50
S08246	Subject's Decision	239
S08111	Subject's Condition Mandated Other Treatment	154
S08248	AE - Lung lesion, elevated liver enzymes	259
S08586	Randomized in error	1
S08088	Subject's Decision	127
S08212	AE - Worsening AMD	127
S08212	Lost to follow-up	331
S08187	Subject's Decision	36
S08187	AE - Worsening AMD	359
S08187	Subject's Decision	127
S00399	Subject's Decision	8
S08133	Subject's Decision	120
S08231	AE - Worsening AMD	295
S00266	Subject's Condition Mandated Other Treatment	309
S08146	AE - Lung cancer treatment	176
S08194	Subject's Decision	317
S02507	Subject's Condition Mandated Other Treatment	162
S07387	AE - Acute Gout	359
S08252	AE - Worsening AMD	133
S08882	AE - Death due to Asthma / COPD	333
AE Group		
S07438	AE - Death - Myocardial infarction	12
S08127	AE - Lymphoma	372
S08536	Subject's Decision	258
S08144	Subject's Decision	324
S08092	AE - Severe aortic stenosis	96
S08190	AE - Worsening AMD	66
S08246	AE - Vulvar adenocarcinoma	210
S08189	AE - Iritis	121
S00399	AE - Loss of vision	100
S08084	Lost to follow-up	218
AE Group		
S08092	AE - Cardiac arrhythmia	100
S08082	Subject's Decision	1
S07442	Subject's Decision - Did not receive treatment	28

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Study Site ID	Subject ID	Adverse Event	Number of Subjects
S08081	130013	AE - Swollen 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	Sham (n = 238)	Ranibizumab (n = 238)	0.5 mg (n = 119)
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**

		Ranibizumab	
		0.3 mg (n=238)	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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**Table 6.1.3.1-10 Fluorescein Angiography and Fundus Photography
 Characteristics of the Study Eye at Baseline
 Intent-to-Treat, Randomized Subjects**

Characteristics	Sham (n=220)	Ranibizumab 0.5 mg (n=218)
CNV classification		
Predominantly classic	0	1 (0.4%) ^a
Minimally classic	87 (36.6%)	86 (36.1%)
Occult without classic	151 (63.4%)	151 (63.4%)
Total area of lesion (DA)		
Mean (SD)	4.41 (2.48)	4.26 (2.54)
Range	0.20-11.75	0.10-11.80
≤ 4 DA	124 (52.1%)	134 (56.3%)
> 4 DA	114 (47.9%)	115 (47.9%)
Total area of CNV (DA)		
Mean (SD)	4.28 (2.41)	4.13 (2.47)
Range	0.20-11.75	0.02-11.80
Area of classic CNV (DA)		
Mean (SD)	0.17 (0.36)	0.16 (0.35)
Range	0.00-2.50	0.00-2.50
Total area of leakage from CNV plus intense progressive RPE staining (DA)^c		
Mean (SD)	3.54 (2.47)	3.59 (2.50)
Range	0.00-12.85	0.00-11.95
Area of serous sensory retinal detachment or subretinal fluid (DA)		
Mean (SD)	4.45 (3.44)	4.52 (3.54)
Range	0.00-16.00	0.00-17.00
Occult CNV present	238 (100%)	235 (98.7%)

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 I

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

Procedures	Ranibizumab		
	0.3 mg (n = 238)	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%)	76 (31.6%)	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%)
Anxiolytic 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 Verteporfin 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 ≥ 3% 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 $\geq 30\%$ 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**

	Sham (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 (55.3%)	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**

	Ranibizumab 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 0.3 mg N=140	All Subjects N=423
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4 Page(s) Withheld

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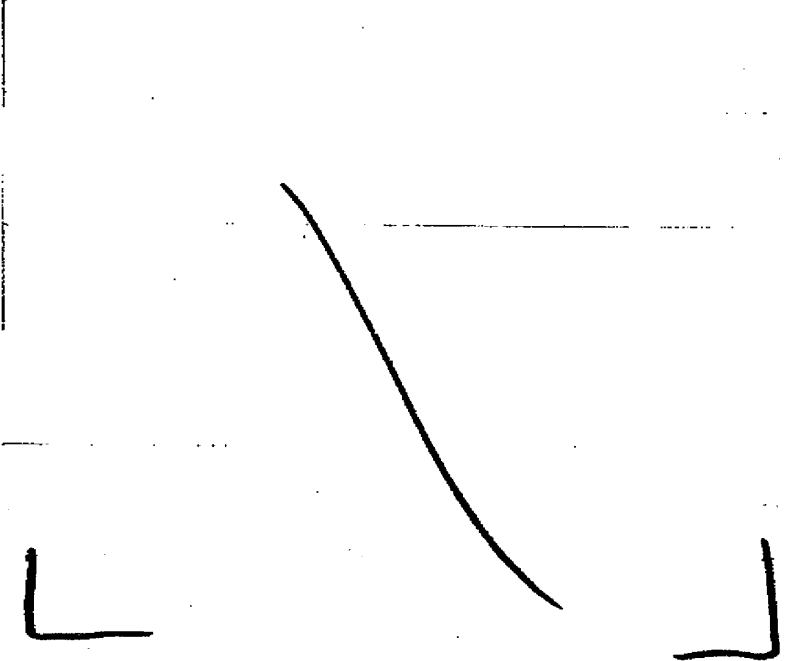
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Overall Study Design

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 infection. 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, 15, 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 $\geq 2+$ 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 $\geq 2+$ 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 $\geq 50\%$ 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 placebo from 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 subjects and 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 χ^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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Table 6.1.3.2-4
 Study Flowchart: Screening, Treatment Phase Day 0 through Month 12, and Early Termination

Study Period	Screening	Treatment Phase Day 0 through Month 12	Early Termination
Informed Consent	X		
Inclusion/Exclusion Criteria	X		
Demographic data	X		
Height and Weight	X		
Medical and surgical history ^a	X		
VFQ-25 ^c	X		
SP-36 Health Survey ^b	X		
HUI (if selected sites only) ^c	X		
VAS ^d	X		
Review of Body Systems	X		
Serum pregnancy test ^e	X		
Contrast Sensitivity test ^{e,f}	X		
Best corrected visual acuity ^{e,f}	X		
(2 meter starting distance) ^{e,f}	X		

- a. For subjects who withdrew 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 (where local languages were available), SP-36 Health Survey (where local languages are available), HUI questionnaire (selected sites only), and VAS were to be administered to the subject prior to the subject's completing any other study procedures.
 d. For women of childbearing potential.
 e. Performed pre-treatment.
 f. Performed prior to dilating eyes.
 g. Also assessed at a starting test distance of 4 meters after assessing at a starting test distance of 2 meters.

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Study Arm	Day	Treatment Phase												Early Term*	
		Month													
		0	1	2	3	4	5	6	7	8	9	10	11		12
Baseline	0														
Slit Lamp Examination	0	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Dilated binocular indirect fundus examination	0	x	x	x	x	x	x	x	x	x	x	x	x	x	x
high-magnification fundus photography	0	x	x	x	x	x	x	x	x	x	x	x	x	x	x
ophthalmoscopy	0	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Lens status assessment	0	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Fundus Photography	0	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Fluorescein Angiography	0	x	x	x	x	x	x	x	x	x	x	x	x	x	x
OCT (at selected sites)	0	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Laboratory Samples	0	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Serum samples for antibodies to ranibizumab and pharmacokinetic sample	0	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Intraocular pressure	0	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Active (verteporfin) or sham (saline) photodynamic therapy (study eye only)	0	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Ranibizumab administration or sham injection (study eye only)	0	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Finger count, hand motion, light perception n	0	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Vital Signs	0	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												Early Termination		
		Day		Month												
		-28 to -1	0	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	±7
Concomitant Medications ^p	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 ^{q,r}		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Follow-up contact ^r		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

^p Recorded any prescription drugs or over-the-counter preparations other than protocol-specified procedural medications (e.g., dilating drops, fluorescein dyes, etc.) and pre- and post-injection medications used by a subject within 7 days preceding Day0.

^q Adverse events were to be collected from Day 0 through the last study visit. Adverse events assessed by the evaluating physician as related to ranibizumab were to be followed, even after the subject's study participation was over, until the event resolved or the event was assessed as irreversible, chronic or stable.

^r Subjects were contacted 2 days (±1 day) following treatment to elicit reports of any decreased 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 6.1.3.2-4
 Study Flowchart: Screening, Treatment Phase Day 0 through Month 12, and Early Termination

Study Period	Treatment Phase												Early Term
	Month												
	1	2	3	4	5	6	7	8	9	10	11	12	
VFQ-25 ^a	X	X						X			X		X
SF-36 Health Survey ^b								X					X
HUI (for selected sites only) ^c									X			X	X
VAS ^d									X			X	X
Review of Body Systems													X
Best corrected visual acuity (2 meter starting distance) ^{e,f}													X ^g
Slit Lamp Examination ^e													X
Dilated binocular indirect and high-magnification ophthalmoscopy ^e													X
Lens status assessment													X
Fundus Photography												X ^h	X
Fluorescein Angiography												X ^h	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), SP-36 Health Survey (where local languages are available), HUI questionnaire (selected sites 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															
	Month															
	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
Assessment Window (days)	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7
Contrast Sensitivity ^d																
Laboratory Samples ^e																
Serum antibodies to ranibizumab and serum pharmacokinetic sample ^f																
Intraocular pressure ^g																
Active (verteporfin) or sham (saline) photodynamic therapy (study eye only) ^h																
Ranibizumab administration or sham injection (study eye only) ⁱ																
Finger count, hand motion, light perception																

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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Study Visit	Post-treatment Phase										Study Term
	1	2	3	4	5	6	7	8	9	10	
Vital Signs ^m	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications ^r	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
Adverse Events ^{e,m}	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

! Injecting physician was to be performed within 15 minutes post-injection for study eye only.

m Performed post-treatment

n Adverse events were collected from Day 0 through the last study visit. Adverse events assessed by the evaluating physician as related to ranibizumab should be followed, even after the subject's study participation is over, until the event resolves or the event is assessed as irreversible, chronic, or stable.

o Subjects were contacted 2 days ($\pm$ 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 6.1.3.2-5 Subject Disposition
Randomized Subjects

	0.3 mg group	0.5 mg group	0.7 mg group
Completed Month 12 ^a	127 (88.3%)	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

	0.3 mg (N=140)	0.5 mg (N=140)
Any deviation	21 (14.7%)	26 (18.6%)
Treatment error: incorrect treatment	2 (1.4%)	7 (5.0%)
Treatment error: received verteporfin PDT + ranibizumab at the same visit	0	2 (1.4%)
Treatment error: incorrect administration	1 (0.7%)	3 (2.1%)
Treatment error: received study drug kit from Study FVF2598G	0	3 (2.1%)
Treatment: off-schedule verteporfin/sham PDT	0	1 (0.7%)
Treatment assignment unmasked	2 (1.4%)	1 (0.7%)
Pre- and post-treatment procedure not followed	4 (2.8%)	9 (6.4%)
Treatment holding criteria not followed	2 (1.4%)	1 (0.7%)
Open-label verteporfin PDT in fellow eye <21 days after last ranibizumab/sham injection	5 (3.5%)	7 (5.0%)
Open-label verteporfin PDT in fellow eye <5 days after last ranibizumab/sham injection	1 (0.7%)	2 (1.4%)
Received excluded concomitant treatment in study eye	1 (0.7%)	0
Cataract surgery in the study eye within <28 days of a ranibizumab/sham injection	0	4 (2.9%)
Visual acuity (4m) not assessed at Day 0 (study eye)	2 (1.4%)	7 (5.0%)
Visual acuity (2 m) not assessed at Day 0 (study eye)	0	1 (0.7%)
Visual acuity (2m) assessment incomplete; unknown if vision was better than 20/20 (study eye)	0	1 (0.7%)
Inconsistent method for measuring IOP	2 (1.4%)	2 (1.4%)
Vital signs assessed pre-dose	5 (3.5%)	3 (2.1%)

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 FVF2-37g

Study Site ID	Subject ID	Reason for Discontinuation	Number of Subjects
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 blepharconjunctivitis	3
S09325	381008	AE - Retinal detachment	211
S09311	384007	AE - Death, Cardiac arrest	121
S09339	403002	Lost to follow-up (after Month 8)	368
Verteporfin 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
Verteporfin 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	IVT (n = 140)	IVT (n = 140)	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 13% 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	0.3 mg (n = 140)	0.5 mg (n = 140)
Years since first diagnosis of neovascular AMD		
N	142	140
Mean (SD)	0.4 (0.9)	0.3 (0.6)
Range	0.0 - 5.4	0.0 - 5.4
Visual acuity at a starting test distance of 4 meters		
N	141	133
Number of letters (0-100)		
Mean (SD)	45.1 (15.2)	47.4 (13.7)
Range	3-73	1-74
≤ 44	62 (44.0%)	52 (39.1%)
≥ 45	79 (56.0%)	81 (60.9%)
Approximate Snellen equivalent		
Median	20/125	20/100
20/200 or worse	39 (27.7%)	37 (27.8%)
Better than 20/200 but worse than 20/40	100 (70.9%)	92 (69.2%)
20/40 or better	2 (1.4%)	4 (3.0%)
Intraocular pressure (mmHg)		
N	143	140
Mean (SD)	15.2 (3.2)	15.2 (3.7)
Range	3-24	9-26
0-21	136 (95.1%)	133 (95.0%)
22-29	7 (4.9%)	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	Ranibizumab	
	0.3 mg (n=140)	0.5 mg (n=140)
CNV classification		
Predominantly classic	141 (98.6%)	134 (95.7%)
Minimally classic	2 (1.4%)	5 (3.6%)
Occult without classic	0	1 (0.7%)
Total area of lesion (DA)		
Mean (SD)	1.88 (1.40)	1.89 (1.44)
Range	0.07-5.75	0.12-7.20
≤ 2 DA	93 (65.0%)	98 (70.0%)
>2 to 4 DA	34 (23.8%)	32 (22.9%)
> 4 DA	16 (11.2%)	10 (7.1%)
Total area of CNV (DA)		
Mean (SD)	1.48 (1.25)	1.48 (1.33)
Range	0.07-5.55	0.11-6.80
Area of classic CNV (DA)		
Mean (SD)	1.36 (1.13)	1.28 (1.05)
Range	0.07-5.55	0.00-6.40
Total area of leakage from CNV plus intense progressive RPE staining (DA)		
Mean (SD)	3.06 (1.81)	3.00 (1.92)
Range	0.20-8.20	0.20-11.00
Area of subretinal fluid (DA)^a		
Mean (SD)	4.34 (2.15)	4.17 (2.43)
Range	0.00-9.00	0.00-14.00
Presence of occult CNV		
Absent	114 (79.7%)	107 (76.4%)
Questionable	13 (9.1%)	12 (8.6%)
Present	16 (11.2%)	21 (15.0%)

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:

Ranibizumab			
0.3 mg			
0.5 mg			
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%)
Per Protocol			
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 ($p < 0.0001$).

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.I-2
Sensitivity Analysis of Visual Acuity for the Study Eye at 12 Months
(Worst Outcome Imputation) at a Starting Distance of 4 Meters

	0.5 mg (N=230)
N	229
Responders	118 (51.5%)
95% CI of the % ^a	(45.1%, 58.0%)
Difference in % (vs. sham) ^b	36.2%
95% CI of the difference ^c	(28.5%, 44.0%)
p-value (vs. sham) ^c	<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.

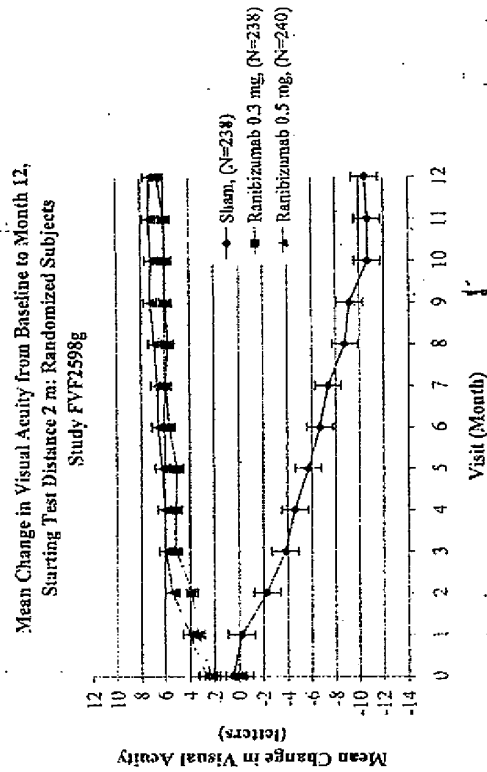
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SECONDARY EFFICACY ENDPOINT RESULTS

Chart 6.i.4.1-1



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 ($p < 0.001$) at each monthly assessment.

The Agency prefers that visual acuity testing be performed with at target distance 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		Sham (N=240)	0.3 mg (N=240)	0.5 mg (N=240)
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		Sham (N=240)	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 $\leq 20/200$		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 Baseline	Sham	Lucentis	Lucentis
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 ($p < 0.0001$). ^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 Baseline	Sham	Ranibizumab
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 central retinal subfield (encompassing the foveal region), which in turn is one of 9 subfields outlined 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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Chart 6.J.4.1-2

Mean Change from Baseline in Foveal Retinal Thickness (μm) in the Study Eye:
Randomized Subjects in the OCT Subset



Note: The LOCF method was used to impute missing data.

Reviewer's Comment:

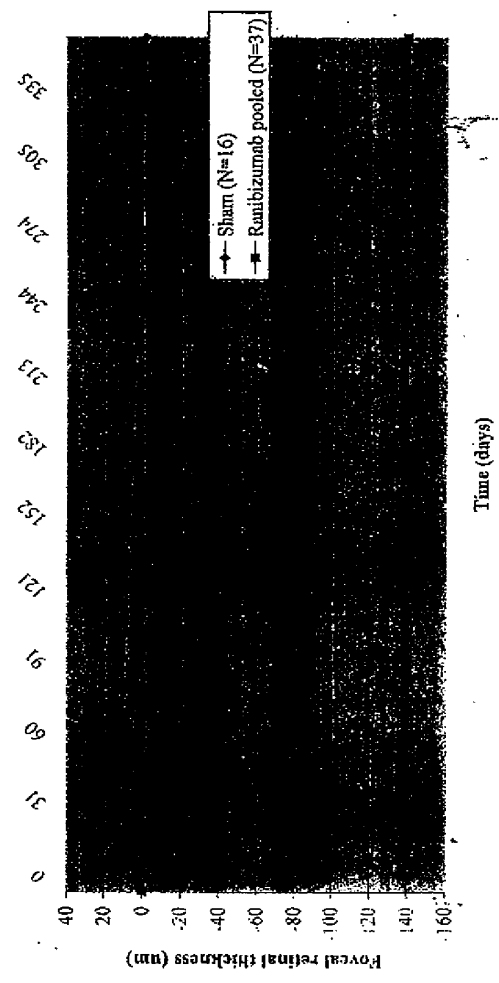
There is a statistically significant difference in foveal retinal thickness (μm) between the sham-injection group and pooled ranibizumab group at Month 1 ($p < 0.0122$) and at Month 12 ($p < 0.0143$).

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Chart 6.1.4.1.3

Mean Change from Baseline in Central Retinal Thickness (µm) 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 Starting Test Distance of 4 Meters: Randomized Subjects

	Age < 75 Years				Age ≥ 75 Years			
	73	75	78	75	75	78	81	82
N								
n (%)	47 (64.4%)	70 (93.3%)	70 (93.3%)	70 (93.3%)	91 (58.3%)	143 (92.9%)	139 (89.7%)	139 (89.7%)
95% CI of the %	(53.4%, 75.4%)	(87.7%, 99.0%)	(87.7%, 99.0%)	(87.7%, 99.0%)	(50.6%, 66.1%)	(88.8%, 96.9%)	(84.9%, 94.5%)	(84.9%, 94.5%)
Difference in % (vs. Sham)		28.9%	28.9%	28.9%		34.3%	31.3%	31.3%
p-value (vs. sham)		<0.0001	<0.0001	<0.0001		<0.0001	<0.0001	<0.0001
N	152	148	148	148	79	81	82	82
n (%)	90 (59.2%)	139 (93.9%)	135 (91.2%)	135 (91.2%)	48 (62.3%)	74 (91.4%)	74 (90.2%)	74 (90.2%)
95% CI of the %	(51.4%, 67.0%)	(90.1%, 97.8%)	(86.7%, 95.8%)	(86.7%, 95.8%)	(51.5%, 73.2%)	(85.2%, 97.5%)	(83.8%, 96.7%)	(83.8%, 96.7%)
Difference in % (vs. Sham)		34.7 %	32.0%	32.0%		29.0%	27.9%	27.9%
p-value (vs. sham)		<0.0001	<0.0001	<0.0001		<0.0001	<0.0001	<0.0001
N	103	110	110	114	126	119	116	116
n (%)	74 (71.8%)	104 (94.5%)	104 (94.5%)	108 (94.7%)	64 (50.8%)	74 (91.4%)	74 (90.2%)	74 (90.2%)
95% CI of the %	(63.2%, 80.5%)	(90.3%, 98.8%)	(90.3%, 98.8%)	(90.6%, 98.8%)	(42.1%, 59.5%)	(86.6%, 96.6%)	(81.0%, 93.2%)	(81.0%, 93.2%)
Difference in % (vs. Sham)		22.7 %	22.7 %	22.9%		40.8%	36.3%	36.3%
p-value (vs. sham)		<0.0001	<0.0001	<0.0001		<0.0001	<0.0001	<0.0001

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Loss of < 15 Letters from Baseline at Month 12 in the Study Eye	Sham		Ranibizumab		Sham	Ranibizumab	
	Minimally Classic CNV at Baseline		0.5 mg			0.3 mg	
	0.3 mg	0.5 mg	0.3 mg	0.5 mg		0.3 mg	0.5 mg
	Occult with No Classic CNV at Baseline						
N	80	85	88		149	143	
n (%)	51 (63.8%)	79 (92.9%)	81 (92.0%)		87 (58.4%)	133 (93.0%)	
95% CI of the %	(53.2%, 74.3%)	(87.5%, 98.4%)	(86.4%, 97.7%)		(50.5%, 66.3%)	(88.8%, 97.2%)	
Difference in % (vs. Sham)		29.2 %	28.3 %			31.7 %	
p-value (vs. sham)		<0.0001	<0.0001			<0.0001	
	Baseline Lesion Size ≤ 4 DA						
N	119	130	119		110	99	
n (%)	72 (60.5%)	121 (93.1%)	81 (92.0%)		66 (60.0%)	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%)	
Difference in % (vs. Sham)		32.6 %	32.8 %			28.3 %	
p-value (vs. sham)		<0.0001	<0.0001			<0.0001	
	Baseline Lesion Size > 4 DA						
N	20	12	14		209	217	
n (%)	10 (50.0%)	12 (100.0%)	13 (92.9%)		128 (61.2%)	201 (92.6%)	
95% CI of the %	(28.1%, 71.9%)	(100%, 100%)	(79.4%, 100%)		(54.6%, 67.8%)	(89.1%, 96.1%)	
Difference in % (vs. Sham)		50.0 %	42.9 %			29.5 %	
p-value (vs. sham)		0.0040	0.0068			<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 ≤ 54 Letters, the treatment effect was approximately 27%.

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 unaccommodation 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

Study FVF2587g - Primary Efficacy Results			
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 $\alpha=0.0246$; ^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

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 $\alpha=0.0246$ 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 $\alpha=0.0246$) 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 Population	Lucentis	Verteporfin
N	141	133
Responders	79 (56.0%)	113 (85.0%)
95% CI of the % ^a	(47.8%, 64.2%)	(78.9%, 91.0%)
Difference in % (vs. Verteporfin PDT) ^b		28.9%
95% CI of the difference ^b		(18.7%, 39.1%)
Non-inferiority test		
One-sided (1 - α) 100% CI of the difference (vs. verteporfin PDT) ^{b,c}		(19.1%, -)
p-value (vs. Verteporfin PDT) ^{d,e}		<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 $\alpha=0.0246$ 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.

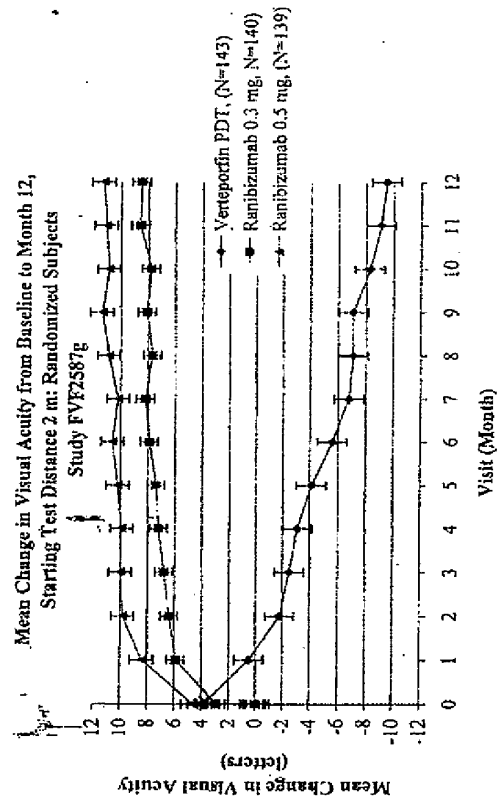
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SECONDARY EFFICACY ENDPOINT RESULTS

Chart 6.1.4.2-1



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

		0.3 mg (N=141)	0.5 mg (N=133)	0.7 mg (N=139)
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 comparisons 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

Visual Acuity at Month 12				
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

	(N=140)		
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 95-99% 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:

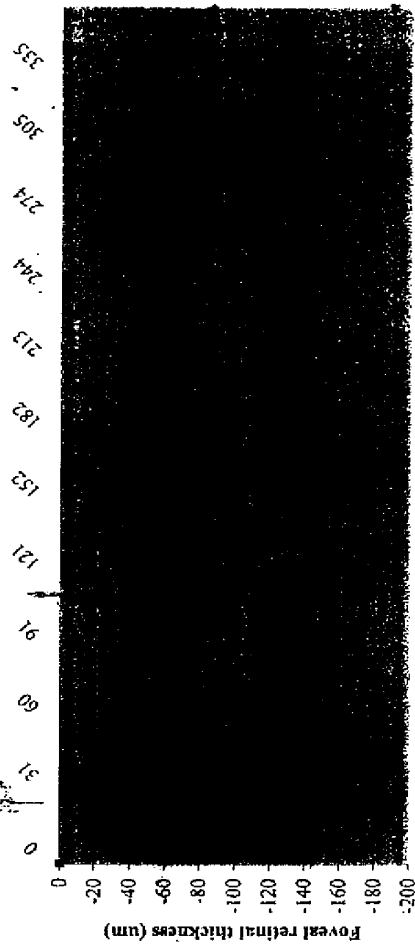
Ranibizumab groups showed highly statistically significant differences with the verteporfin PDT group ($p < 0.0001$) in the mean change from baseline at 12 months in the total lesion area, total area of CNV, area of subretinal fluid and in the growth of CNV.

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Q1 BLA
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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



Time (days)

--- Verteporfin PDT (N=17) --- Ranibizumab pooled (N=44)

Note: The LOCF method was used to impute missing data

Reviewer's Comment:

There is a statistically significant difference in foveal retinal thickness (um) between the verteporfin PDT group and pooled ranibizumab group at Month 1 ($p < 0.0045$) and at Month 12 ($p < 0.0004$).

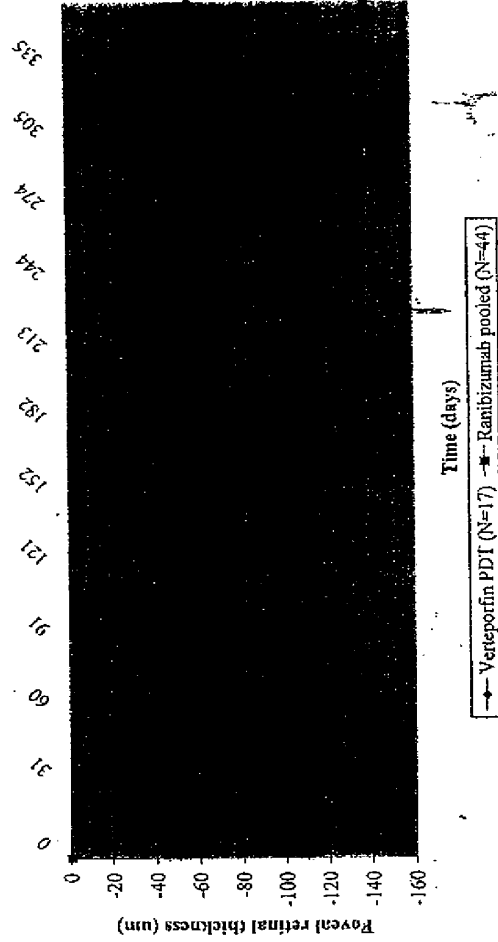
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Chart 6.1.4.2-3

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 ($p < 0.0377$).