8319732

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

November 29, 2022

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

APPLICATION NUMBER: *16/397,267*
FILING DATE: *April 29, 2019*
PATENT NUMBER: *10888601*
ISSUE DATE: *January 12, 2021*

Certified by

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

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-008CIPCON5
	Confirmation No.	To Be Assigned
	First Named Inventor	YANCOPOULOS, GEORGE D.
	Application Number	To Be Assigned
	Filing Date	April 29, 2019
	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.

Electronically Filed

NOTIFICATION OF PRIOR SEQUENCE LISTING		
	Attorney Docket	REGN-008CIPCON4
	First Named Inventor	YANCOPOULOS, GEORGE D.
	Application Number	To Be Assigned
	Filing Date	April 29, 2019
Address to: Mail Stop Patent Application Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Confirmation Number	To Be Assigned
	Group Art Unit	To Be Assigned
	Examiner Name	To Be Assigned
	Title: "USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS"	

Sir:

The above-identified patent application contains sequences of nucleic acid and polypeptides. A sequence listing was prepared for parent application, **16/159,282,** filed **October 12, 2018**, 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-008CIPCON5.

Respectfully submitted,

BOZICEVIC, FIELD & FRANCIS LLP

Dated: 29 April 2019

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

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

SEQUENCE LISTING

<110> George D. Yancopoulos

<120> Use of a VEGF Antagonist to Treat Angiogenic Eye Disorders

<130> 725A1

<140> To be assigned
<141> Filed herewith

<150> PCT/US2012/020855
<151> 2012-01-11

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Samsung Bioepis Exhibit 1012 - Page 4
Biocon Exhibit 1012 - Page 4

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Samsung Bioepis Exhibit 1012 - Page 5
Biocon Exhibit 1012 - Page 5

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Samsung Bioepis Exhibit 1012 - Page 6
Biocon Exhibit 1012 - Page 6

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-008CIPCON5
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	300	300
UTILITY SEARCH FEE	1111	1	660	660
UTILITY EXAMINATION FEE	1311	1	760	760
Pages:				
Claims:				
CLAIMS IN EXCESS OF 20	1202	9	100	900
INDEPENDENT CLAIMS IN EXCESS OF 3	1201	1	460	460
Miscellaneous-Filing:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
PUBL. FEE- EARLY, VOLUNTARY, OR NORMAL	1504	1	0	0
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**3080**

Electronic Acknowledgement Receipt	
EFS ID:	35858839
Application Number:	16397267
International Application Number:	
Confirmation Number:	8135
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-008CIPCON5
Receipt Date:	29-APR-2019
Filing Date:	
Time Stamp:	14:51:44
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$3080
RAM confirmation Number	043019INTEFSW14522800
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-008CIPCON5_2019-04-29_ADS.pdf	1256704 0e88f782022f8326bee7e55bd6957f75e862209c	no	9
Warnings:					
Information:					
2		REGN-008CIPCON5_2019-04-29_Appln_as_fld.pdf	155991 85273a495296621a979ffed2ccdec6502c799c0c	yes	24

Multipart Description/PDF files in .zip description

Document Description	Start	End
Abstract	24	24
Claims	22	23
Specification	1	21

Warnings:					
Information:					
3	Drawings-only black and white line drawings	REGN-008CIPCON5_Figure.pdf	105393 2d582f645d0c5d17d717e589b029a39331991bdb	no	1
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The page size in the PDF is too large. The pages should be 8.5 x 11 or A4. If this PDF is submitted, the pages will be resized upon entry into the Image File Wrapper and may affect subsequent processing					
Information:					
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The page size in the PDF is too large. The pages should be 8.5 x 11 or A4. If this PDF is submitted, the pages will be resized upon entry into the Image File Wrapper and may affect subsequent processing					
Information:					

5		REGN-008CIPCON5_2019-04-29_pre_amend_asfld.pdf	46449 ddb00b729b9b88f23f25609bea2b88928efdfd95	yes	7
	Multipart Description/PDF files in .zip description				
	Document Description		**Start**	**End**	
	Applicant Arguments/Remarks Made in an Amendment		6	7	
	Claims		2	5	
	Preliminary Amendment		1	1	
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Information:					
6	Sequence Listing	REGN-008CIPCON5_2019-04-29_seq_list_trans.pdf	27214 a9c529b4a455314e4c569d3545204027bacf5d68	no	1
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		Total Files Size (in bytes):	1828026		

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

New Applications Under 35 U.S.C. 111

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

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

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

New International Application Filed with the USPTO as a Receiving Office

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

PTO/AIA/14 (02-18)
Approved for use through 11/30/2020. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	REGN-008CIPCON5
	Application Number	
Title of Invention	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS	

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

Secrecy Order 37 CFR 5.2:

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

Inventor Information:

Inventor 1 — Remove

Legal Name

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

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

City	State/Province	Country of Residence
Yorktown Heights	NY	US

Mailing Address of Inventor:

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

City	State/Province	Postal Code	Country
Tarrytown	NY	10591	US

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

Correspondence Information:

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

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

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

Application Information:

Title of the Invention	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS		
Attorney Docket Number	REGN-008CIPCON5	**Small Entity Status Claimed**	☐
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	1	**Suggested Figure for Publication (if any)**	1

PTO/AIA/14 (02-18)
Approved for use through 11/30/2020. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	REGN-008CIPCON5
	Application Number	
Title of Invention	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS	

Filing By Reference:

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

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

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

Publication Information:

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

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

Representative Information:

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

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

Domestic Benefit/National Stage Information:

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

Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
	Continuation of	16159282	2018-10-12

PTO/AIA/14 (02-18)
Approved for use through 11/30/2020. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	REGN-008CIPCON5
	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)
16159282	Continuation of	15471506	2017-03-28	10130691	2018-11-20
Prior Application Status	Patented				Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
15471506	Continuation of	14972560	2015-12-17	9669069	2017-06-06
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14972560	Continuation of	13940370	2013-07-12	9254338	2016-02-09
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13940370	Continuation in part of	PCT/US2012/020855	2012-01-11		
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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		
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Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)		
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Prior Application Status	Expired				Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)		
PCT/US2012/020855	Claims benefit of provisional	61561957	2011-11-21		
Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add** button.					Add

Foreign Priority Information:

PTO/AIA/14 (02-18)
Approved for use through 11/30/2020. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	REGN-008CIPCON5
	Application Number	
Title of Invention	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS	

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

Remove

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

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

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

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

PTO/AIA/14 (02-18)
Approved for use through 11/30/2020. OMB 0651-0032
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-008CIPCON5
	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).

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.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	REGN-008CIPCON5
	Application Number	
Title of Invention	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS	

Applicant Information:

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Clear

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

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

Name of the Deceased or Legally Incapacitated Inventor:

If the Applicant is an Organization check here. ☒

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Email Address			

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Organization Name	REGENERON PHARMACEUTICALS, INC.

Mailing Address Information For Assignee including Non-Applicant Assignee:

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City	Tarrytown	**State/Province**	NY
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Phone Number		Fax Number	
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Signature	/Karl Bozicevic, Reg. No. 28,807/			Date (YYYY-MM-DD)	2019-04-29
First Name	Karl	Last Name	Bozicevic	Registration Number	28807

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	REGN-008CIPCON5
	Application Number	
Title of Invention	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS	

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

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

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

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ABSTRACT

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

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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.

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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.

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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 of 16/159,282 filed October 12, 2018, which is a continuation of 15/471,506 filed March 28, 2017, now U.S. Patent No. 10,130,691 issued November 20, 2018, which is a continuation of 14/972,560 filed December 17, 2015, now U.S. Patent No. 9,669,069 issued June 6, 2017, which is a continuation of 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.

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.

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[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."

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[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

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[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

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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

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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

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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

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patient exhibits a loss of 15 or fewer letters on the Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity chart. In certain embodiments, "efficacy" means a gain of one or more (*e.g.*, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or more) letters on the ETDRS chart from the time of initiation of treatment.

EXAMPLES

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

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

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

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

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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 135μ, $p < 0.0001$). Mean change from baseline in visual acuity, a key secondary endpoint of the study, also demonstrated statistically significant improvement (all groups combined, increase of 5.9 letters, $p < 0.0001$). Moreover, patients in the dose groups that received only a single dose, on average, demonstrated a decrease in excess retinal thickness ($p < 0.0001$) and an increase in visual acuity ($p = 0.012$) at 12 weeks. There were no drug-related serious adverse events, and treatment with the VEGF antagonists was generally well-tolerated. The most common adverse events were those typically associated with intravitreal injections.

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

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

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

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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

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as every 4 weeks, but no less frequently than every 12 weeks, according to the following criteria: (i) increase in central retinal thickness of ≥100 μm compared to the lowest previous value as measured by optical coherence tomography (OCT); or (ii) a loss from the best previous letter score of at least 5 ETDRS letters in conjunction with recurrent fluid as indicated by OCT; or (iii) new or persistent fluid as indicated by OCT; or (iv) new onset classic neovascularization, or new or persistent leak on fluorescein angiography (FA); or (v) new macular hemorrhage; or (vi) 12 weeks have elapsed since the previous injection. According to the present protocol, subjects must receive an injection at least every 12 weeks.

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

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

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

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

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

[0051] Exclusion criteria for both studies were as follows: 1. Any prior ocular (in the study eye) or systemic treatment or surgery for neovascular AMD except dietary supplements or vitamins. 2. Any prior or concomitant therapy with another investigational agent to treat neovascular AMD in the study eye, except dietary supplements or vitamins. 3. Prior treatment with anti-VEGF agents as

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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

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the subject beyond what is to be expected from standard procedures of intraocular injection, or which otherwise may interfere with the injection procedure or with evaluation of efficacy or safety. 30. History of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that might affect interpretation of the results of the study or render the subject at high risk for treatment complications. 31. Participation as a subject in any clinical study within the 12 weeks prior to Day 1. 32. Any systemic or ocular treatment with an investigational agent in the past 3 months prior to Day 1. 33. The use of long acting steroids, either systemically or intraocularly, in the 6 months prior to day 1. 34. Any history of allergy to povidone iodine. 35. Known serious allergy to the fluorescein sodium for injection in angiography. 36. Presence of any contraindications indicated in the FDA Approved label for ranibizumab (Lucentis®). 37. Females who were pregnant, breastfeeding, or of childbearing potential, unwilling to practice adequate contraception throughout the study. Adequate contraceptive measures include oral contraceptives (stable use for 2 or more cycles prior to screening); IUD; Depo-Provera®; Norplant® System implants; bilateral tubal ligation; vasectomy; condom or diaphragm plus either contraceptive sponge, foam or jelly.

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

[0053] The study procedures are summarized as follows:

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

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

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[0056] Fundus Photography and Fluorescein Angiography (FA): The anatomical state of the retinal vasculature of the study eye was evaluated by funduscopic examination, fundus photography and FA. At the Screen Visit (Visit 1) funduscopic examination, fundus photography and FA were captured and transmitted for both eyes. Fundus and angiographic images were sent to an independent reading center where images were read by masked readers. The reading center confirmed subject eligibility based on angiographic criteria prior to randomization. All FAs and fundus photographs were archived at the site as part of the source documentation. Photographers were required to be certified by the reading center to ensure consistency and quality in image acquisition. Adequate efforts were made to ensure that all photographers at the site remain masked to treatment assignment.

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

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

[0059]

C. Results Summary (52 Week Data)

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

Table 1

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

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[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	Mean change in visual acuity at week 52 versus baseline

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		(letters)	(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 weeks[a] (2Q8)	42	8.5**	9.7**
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

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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).

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[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).

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[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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ELSVGEKLVLNCTARTELNVGIDFNWEYPSSKHQHKKLVNRDLKTQSGSEMKKFLSTLTIDGVTRS
DQGLYTCAASSGLMTKKNSTFVRVHEKDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV
TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV
SNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPEN
NYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

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

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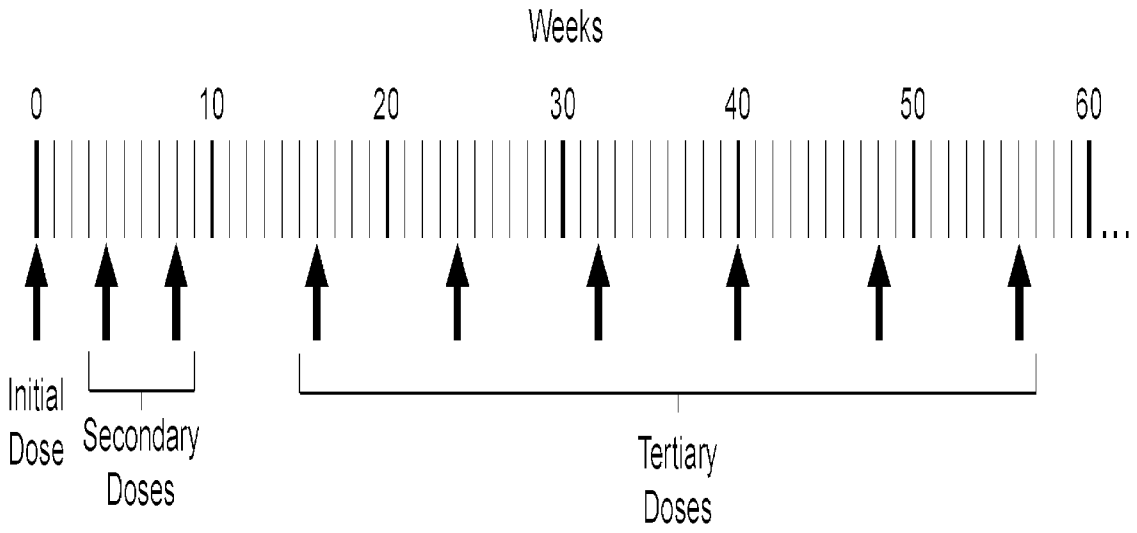

Weeks
0
10
20
30
40
50
60
...
Initial Dose
Secondary Doses
Tertiary Doses

Figure 1

PTO/AIA/01 (06-12)
Approved for use through 01/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

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

As the below named inventor, I hereby declare that:

This declaration is directed to:

☐ The attached application, or

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

filed on July 12, 2013.

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

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

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

WARNING:

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

LEGAL NAME OF INVENTOR

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

Signature: [signature]

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.

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.**

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

Privacy Act Statement

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

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

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.
10.

REMARKS UNDER 37 CFR § 1.115

Formal Matters

Claims 21-49 are pending after entry of the amendments set forth herein.

Claims 1-20 are canceled without prejudice.

Claims 21-49 are added.

Support for new claims 21-49 can be found in originally pending now canceled claims 1-20, and throughout the specification.

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

No new matter has been added.

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 U.S. Patent Application No. 14/972,560, filed December 17, 2015 which issued on June 6, 2018 as U.S. Patent No. 9,669,069.

The Applicants wish to bring to the Examiner's attention U.S. Patent Application No. 15/471,506, filed March 28, 2017 which issued on November 20, 2018 as U.S. Patent No. 10,130,691..

The Applicants wish to bring to the Examiner's attention co-pending U.S. Patent Application No. 16/055,847, filed August 6, 2018 for which no actions have been mailed.

The Applicants wish to bring to the Examiner's attention co-pending U.S. Patent Application No. 16/159,282, filed October 12, 2018 for which a non-final Office Action was mailed April 3, 2019.

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-008CIPCON5.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: 29 April 2019

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

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AMENDMENTS TO THE CLAIMS

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

21. (**New**) A method for treating age related macular degeneration in a patient, comprising administering, to said patient, by intravitreal injection, 2 mg aflibercept approximately every 4 weeks for the first 3 months, followed by 2 mg aflibercept approximately once every 8 weeks or once every 2 months.

22. (**New**) The method of claim 21, wherein the age-related macular degeneration is neovascular (wet).

23. (**New**) The method of claim 21, wherein approximately every 4 weeks comprises approximately every 28 days or approximately monthly.

24. (**New**) The method of claim 23, wherein the age-related macular degeneration is neovascular (wet).

25. (**New**) The method of claim 22 wherein the patient loses less than 15 letters of Best Corrected Visual Acuity (BCVA) score.

26. (**New**) The method of claim 25 wherein Best Corrected Visual Acuity (BCVA) is measured by Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

27. (**New**) The method of claim 22 wherein the patient gains at least 15 letters of Best Corrected Visual Acuity (BCVA) score.

28. (**New**) The method of claim 27 wherein Best Corrected Visual Acuity (BCVA) is measured by Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

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29. (**New**) A method for treating diabetic macular edema in a patient, comprising administering, to said patient, by intravitreal injection, 2 mg aflibercept approximately every 4 weeks for the first 5 injections followed by 2 mg aflibercept approximately once every 8 weeks or once every 2 months.

30. (**New**) The method of claim 29, wherein approximately every 4 weeks comprises approximately every 28 days or approximately monthly.

31. (**New**) The method of claim 29, further comprising, after 20 weeks, administering, via intravitreal injection, 2 mg of aflibercept once every 4 weeks.

32. (**New**) The method of claim 29 wherein the patient loses less than 15 letters of Best Corrected Visual Acuity (BCVA) score.

33. (**New**) The method of claim 32 wherein Best Corrected Visual Acuity (BCVA) is measured by Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

34. (**New**) The method of claim 29 wherein the patient gains at least 15 letters of Best Corrected Visual Acuity (BCVA) score.

35. (**New**) The method of claim 34 wherein Best Corrected Visual Acuity (BCVA) is measured by Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

36. (**New**) A method for treating diabetic retinopathy in a patient, comprising administering, to said patient, by intravitreal injection, 2 mg aflibercept approximately every 4 weeks for the first 5 injections followed by 2 mg aflibercept approximately once every 8 weeks or 2 months.

37. (**New**) The method of claim 36, wherein approximately every 4 weeks comprises approximately every 28 days or approximately monthly.

38. (**New**) The method of claim 36, further comprising after 20 weeks, administering via intravitreal injection 2 mg of aflibercept once every 4 weeks

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39. (**New**) The method of claim 36 wherein the patient loses less than 15 letters of Best Corrected Visual Acuity (BCVA) score.

40. (**New**) The method of claim 37 wherein Best Corrected Visual Acuity (BCVA) is measured by Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

41. (**New**) The method of claim 36 wherein the patient gains at least 15 letters of Best Corrected Visual Acuity (BCVA) score.

42. (**New**) The method of claim 41 wherein Best Corrected Visual Acuity (BCVA) is measured by Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

43. (**New**) A method for treating diabetic retinopathy in a patient with diabetic macular edema, comprising administering, to said patient, by intravitreal injection, 2 mg aflibercept approximately every 4 weeks for the first 5 injections followed by 2 mg aflibercept approximately once every 8 weeks or 2 months.

44. (**New**) The method of claim 43, wherein approximately every 4 weeks comprises approximately every 28 days or approximately monthly.

45. (**New**) The method of claim 43, further comprising after 20 weeks, administering via intravitreal injection 2 mg of aflibercept once every 4 weeks

46. (**New**) The method of claim 43 wherein the patient loses less than 15 letters of Best Corrected Visual Acuity (BCVA) score.

47. (**New**) The method of claim 46 wherein Best Corrected Visual Acuity (BCVA) is measured by Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

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48. (**New**) The method of claim 43 wherein the patient gains at least 15 letters of Best Corrected Visual Acuity (BCVA) score.

49. (**New**) The method of claim 48 wherein Best Corrected Visual Acuity (BCVA) is measured by Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

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DocCode – SEQ.TXT

SCORE Placeholder Sheet for IFW Content

Application Number: 16397267 Document Date: 04/29/2019

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PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 16/397,267

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY FEE($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	300
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	660
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	760
TOTAL CLAIMS (37 CFR 1.16(i))	29 minus 20 =	* 9			OR	x 100 =	900
INDEPENDENT CLAIMS (37 CFR 1.16(h))	4 minus 3 =	* 1				x 460 =	460
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						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	3080

APPLICATION AS AMENDED - PART II

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

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

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

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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
16/397,267	04/29/2019	1629	3080	REGN-008CIPCON5	29	4

CONFIRMATION NO. 8135

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

FILING RECEIPT

OC000000108021427

Date Mailed: 05/09/2019

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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: None

Domestic Priority data as claimed by applicant

This application is a CON of 16/159,282 10/12/2018
which is a CON of 15/471,506 03/28/2017 PAT 10130681
which 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.

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The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 16/397,267**

Projected Publication Date: 08/15/2019

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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Application	Document	Mailroom Date	Attorney Docket No.
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PATENT APPLICATION INFORMATION RETRIEVAL SYSTEM

INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	16/397,267
				Filing Date	April 29, 2019
				First Named Inventor	YANCOPOULOS, GEORGE D.
				Art Unit	N/A
				Examiner Name	Jon McClelland Lockard
Sheet	1	of	5	Attorney Docket Number	REGN-008CIPCON5

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	7303746	2007-12-04	Wiegand	
	2	7303748	2007-12-04	Wiegand	
	3	7306799	2007-12-11	Wiegand	
	4	7396664	2008-07-08	Daly et al.	
	5	9254338	2016-02-09	Yancopoulos	
	6	9669069	2017-06-06	Yancopoulos	
	7	10130681	2018-11-20	Yancopoulos	

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 2006/047325	2006-03-04	Genentech, Inc.		
	2	WO 2000/75319	2000-12-14	Regeneron Pharmaceuitcals, Inc.		
	3	WO 2007/022101 A2	2007-02-22	Regeneron Pharmaceuticals, Inc.		
	4	WO 2008/063932	2008-05-29	Genentech, Inc.		
	5	JP 2010-509369	2010-03-25	Genentech, Inc.	See WO 2008/063932 for English Equivalent	
	6	WO 2012/097019	2012-07-19	Regeneron Pharmaceuticals, Inc.		

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T
	1	ANONYMOUS "Lucentis (rangibizymab injection) Intravitreal Injection" pp. 103 (June 2006)	
	2	BROWNING et al. "Aflibercept for age-related macular degeneration: a game-changer or quiet addition?" American Journal of Ophthalmology, Vol. 154(2):222-226 (08/01/2012)	

Examiner Signature		Date Considered	

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	16/397,267
				Filing Date	April 29, 2019
				First Named Inventor	YANCOPOULOS, GEORGE D.
				Art Unit	N/A
				Examiner Name	Jon McClelland Lockard
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	3	CAMPOCHIARO et al. "Ranibizumab for Macular Edema Due to Retinal Vein Occlusions Implication of VEGF as a Critical Stimulator" Molecular Therapy, 16(4):791-799 (2008)	
	4	Information from ClinicalTrials.gov archive View of NCT00637377 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Wet Age-Related Macular Degeneration (AMD) (VIEW 2)" *ClinicalTrials.gov*. Web. 2010-11-30.	
	5	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>	
	6	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>	
	7	CAO, "A Subretinal Matrigel Rat Choroidal Neovascularization (CNV) Model and Inhibition of CNV and Associated Inflammation and Fibrosis by VEGF Trap" Investigative Ophthalmology & Visual Science, 51(11):6009- 6017 (11/2010)	
	8	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	
	9	DIXON et al., "VEGF Trap-Eye for the treatment of neobascular age-related macular degeneration" Expert Opin. Investig. Drugs (2009) 18 (10): 1-8.	
	10	DO et al., "An exploratory study of the safety, tolerability and bioactivity of a single intravitreal injection of vascular endothelial growth factor Trap-Eye in patients with diabetic macular oedema" Br J Opthamol. 93(2):144-1449 (February 2009)	
	11	DO et al., "The DA VINCI Study: phase 2 primary results of VEGF Trap-Eye in patients with diabetic macular edema" Opthamology 118(9):1819-1826 (September 2011)	
	12	EICHTEN, "Rapid decrease in tumor perfusion following VEGF blockade predicts long-term tumor growth inhibition in preclinical tumor models" Angiogenesis, 16:429-441 (2013)	
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	14	HEIERet al., " rhuFab V2 (anti-VEGF Antibody) for Treatment of Exudative AMD" Symposium 8:Experimental and Emerging Treatments for Choroidal Neovascularization, 10 pp (2002)	
	15	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)	
	16	HEIER et al., "Intravitreal Aflibercept (VEGF Trap-Eye) in Wet Age-related macular Degeneration," Ophthalmology, 119:2537-2548 (2012)	
	17	HO, "VEGF Trap-Eye in Wet AMD - CLEAR-IT 2: One-Year OCT and FA Outcomes" CLEAR-IT 2 Study Group, pp 1-24 (09/28/2008)	
	18	HOLASH, "VEGF-Trap: A VEGF blocker with potent antitumor effects" PNAS 99(17)11393-11398 (8/20/2002)	
	19	HOLASH, "Inhibitors of growth factor receptors, signaling pathways and angiogenesis as therapeutic molecular agents." Cancer Metastasis 25:243-252 (2006)	

Examiner Signature		Date Considered	

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

INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	16/397,267
				Filing Date	April 29, 2019
				First Named Inventor	YANCOPOULOS, GEORGE D.
				Art Unit	N/A
				Examiner Name	Jon McClelland Lockard
Sheet	3	of	5	Attorney Docket Number	REGN-008CIPCON5

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
	20	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.	
	21	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)	
	22	Information from ClinicalTrials.gov archive on the view of NCT00789477 "DME and VEGF Trap-Eye: Investigation of Clinical Impact" (11-18-2010)	
	23	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)	
	24	KARIA, Niral, "Retinal vein occlusion: pathophysiology and treatment options" Clinical Ophthalmology, 4:809-816 (2010)	
	25	KUO, "Comparative evaluation of the antitumor activity of antiangiogenic proteins delivered by gene transfer" PNAS 98(8):4605-4610 (04/10/2001)	
	26	KRZYSTOLIK et al., "Prevention of Experimental Choroidal NEovascularization With Intravitreal Anti-Vascular Endothelial Growth Factor Antibody Fragment" Arch Ophthamol., 120:338-346 (Mar. 2002)	
	27	Lucentis Label Title, 7 pages, 30/06/2010 **[Cited in Third Party Observations filed in parent application USSN 16/055,847 for which a copy is unavailable on PAIR]**	
	28	MITRA et al., "Review of anti-vascular endothelial growth factor therapy in macular edema secondary to central retinal vein occlusions" Expert Review in Ophthalmo, Taylor & Francis, GB (January 1, 2011) 6(6):623-629	
	29	MOUSA AND MOUSA, "Current Status of Vascular Endothelial Growth Factor Inhibition in Age-Related Macular Degeneration" Biodrugs 2010; 24(3); 183-194.	
	30	NGUYEN et al., "A Phase I Study of Intravitreal Vascular Endothelial Growth Factor Trap-Eye in Patients with Neovascular Age-Related Macular Degeneration" Opthamology, J.B. Lippincott Co., Philadelphia, PA, US, 116(11):2141-2148 (November 1, 2009) 116(11):2141-2148 (November 1, 2009)	
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Examiner Signature		Date Considered	

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

INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	16/397,267
				Filing Date	April 29, 2019
				First Named Inventor	YANCOPOULOS, GEORGE D.
				Art Unit	N/A
				Examiner Name	Jon McClelland Lockard
Sheet	4	of	5	Attorney Docket Number	REGN-008CIPCON5

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
	37	PAPADPPOULOS, "Binding and neutralization of vascular endothelial growth factor (VEGF) and related ligands by VEGF Trap, ranibizumab and bevacizumab" Angiogenesis, 15:171-185 (2012)	
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	39	Regeneron, Press release "Regeneron Reports First Quarter 2008 Financial and Operating Results", May 1, 2008.	
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	42	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	
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Examiner Signature		Date Considered	

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

INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	16/397,267
				Filing Date	April 29, 2019
				First Named Inventor	YANCOPOULOS, GEORGE D.
				Art Unit	N/A
				Examiner Name	Jon McClelland Lockard
Sheet	5	of	5	Attorney Docket Number	REGN-008CIPCON5

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
	54	WACHSBERGER, "VEGF trap in combination with radiotherapy improves tumor control in u87 glioblastoma." Int. J. Radiation Oncology Biol Phys. 67(5):1526-1537 (2007)	
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	59	Vascular Endothelial Growth Factor Trap‐ Eye Investigation of Efficacy and Safety in Central Retinal Vein Occlusion title, 8 pages, 11/12/2009, US **[Cited in Third Party Observations filed in parent application USSN 16/055,847 for which a copy is unavailable on PAIR]**	

Examiner Signature		Date Considered	

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

Electronic Acknowledgement Receipt

EFS ID:	36351485
Application Number:	16397267
International Application Number:	
Confirmation Number:	8135
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-008CIPCON5
Receipt Date:	19-JUN-2019
Filing Date:	29-APR-2019
Time Stamp:	17:50:43
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-008CIPCON5_2019-06-19_IDS_trans.pdf	52048 ea0b2da55b1503c70404a22bd20ee1ac4584afb0	no	2

Warnings:

Information:					
2	Information Disclosure Statement (IDS) Form (SB08)	REGN-008CIPCON5_2019-06-19_IDS_SB08A.pdf	69369 1ed84d7d4d1bb583a8b744bf7e12778f135b446e	no	5
Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
			Total Files Size (in bytes):	121417	

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New Applications Under 35 U.S.C. 111

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

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

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

New International Application Filed with the USPTO as a Receiving Office

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

Electronically Filed 6/19/2019

INFORMATION DISCLOSURE STATEMENT	Attorney Docket No.	REGN-008CIPCON5
	Confirmation No.	8135
	First Named Inventor	George D. Yancopoulos
	Application Number	16/397,267
	Filing Date	April 29, 2019
	Group Art Unit	
Address to: Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Examiner Name	Jon McClelland Lockard
	Title: "*Use of a VEGF Antagonist to Treat Angiogenic Eye Disorders*"	

Sir:

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

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 16/159,282, and as such, copies thereof 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-008CIPCON5.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: June 19, 2019

By: /Karl Bozicevic, Reg. No. 28,807/
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Facsimile: (650) 327-3231

Electronically Filed

SECOND 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-008CIPCON5
	Confirmation No.	8135
	First Named Inventor	YANCOPOULOS, GEORGE D.
	Application Number	16/397,267
	Filing Date	April 29, 2019
	Group Art Unit	1647
	Examiner Name	LOCKARD, Jon McClelland
	Title: *"Use of a VEGF Antagonist to Treat Angiogenic Eye Disorders"*	

Sir:

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

AMENDMENTS TO THE CLAIMS

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

21. (Previously Presented) A method for treating age related macular degeneration in a patient, comprising administering, to said patient, by intravitreal injection, 2 mg aflibercept approximately every 4 weeks for the first 3 months, followed by 2 mg aflibercept approximately once every 8 weeks or once every 2 months.

22. (Previously Presented) The method of claim 21, wherein the age-related macular degeneration is neovascular (wet).

23. (Previously Presented) The method of claim 21, wherein approximately every 4 weeks comprises approximately every 28 days or approximately monthly.

24. (Previously Presented) The method of claim 23, wherein the age-related macular degeneration is neovascular (wet).

25. (Previously Presented) The method of claim 22 wherein the patient loses less than 15 letters of Best Corrected Visual Acuity (BCVA) score.

26. (Previously Presented) The method of claim 25 wherein Best Corrected Visual Acuity (BCVA) is measured by Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

27. (Previously Presented) The method of claim 22 wherein the patient gains at least 15 letters of Best Corrected Visual Acuity (BCVA) score.

28. (Previously Presented) The method of claim 27 wherein Best Corrected Visual Acuity (BCVA) is measured by Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

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29. (Previously Presented) A method for treating diabetic macular edema in a patient, comprising administering, to said patient, by intravitreal injection, 2 mg aflibercept approximately every 4 weeks for the first 5 injections followed by 2 mg aflibercept approximately once every 8 weeks or once every 2 months.

30. (Previously Presented) The method of claim 29, wherein approximately every 4 weeks comprises approximately every 28 days or approximately monthly.

31. (Previously Presented) The method of claim 29, further comprising, after 20 weeks, administering, via intravitreal injection, 2 mg of aflibercept once every 4 weeks.

32. (Previously Presented) The method of claim 29 wherein the patient loses less than 15 letters of Best Corrected Visual Acuity (BCVA) score.

33. (Previously Presented) The method of claim 32 wherein Best Corrected Visual Acuity (BCVA) is measured by Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

34. (Previously Presented) The method of claim 29 wherein the patient gains at least 15 letters of Best Corrected Visual Acuity (BCVA) score.

35. (Previously Presented) The method of claim 34 wherein Best Corrected Visual Acuity (BCVA) is measured by Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

36. (Previously Presented) A method for treating diabetic retinopathy in a patient, comprising administering, to said patient, by intravitreal injection, 2 mg aflibercept approximately every 4 weeks for the first 5 injections followed by 2 mg aflibercept approximately once every 8 weeks or 2 months.

37. (Previously Presented) The method of claim 36, wherein approximately every 4 weeks comprises approximately every 28 days or approximately monthly.

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38. (Previously Presented) The method of claim 36, further comprising after 20 weeks, administering via intravitreal injection 2 mg of aflibercept once every 4 weeks

39. (Previously Presented) The method of claim 36 wherein the patient loses less than 15 letters of Best Corrected Visual Acuity (BCVA) score.

40. (Previously Presented) The method of claim 37 wherein Best Corrected Visual Acuity (BCVA) is measured by Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

41. (Previously Presented) The method of claim 36 wherein the patient gains at least 15 letters of Best Corrected Visual Acuity (BCVA) score.

42. (Previously Presented) The method of claim 41 wherein Best Corrected Visual Acuity (BCVA) is measured by Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

43. (Previously Presented) A method for treating diabetic retinopathy in a patient with diabetic macular edema, comprising administering, to said patient, by intravitreal injection, 2 mg aflibercept approximately every 4 weeks for the first 5 injections followed by 2 mg aflibercept approximately once every 8 weeks or 2 months.

44. (Previously Presented) The method of claim 43, wherein approximately every 4 weeks comprises approximately every 28 days or approximately monthly.

45. (Previously Presented) The method of claim 43, further comprising after 20 weeks, administering via intravitreal injection 2 mg of aflibercept once every 4 weeks

46. (Previously Presented) The method of claim 43 wherein the patient loses less than 15 letters of Best Corrected Visual Acuity (BCVA) score.

47. (Previously Presented) The method of claim 46 wherein Best Corrected Visual Acuity (BCVA) is measured by Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

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48. (Previously Presented) The method of claim 43 wherein the patient gains at least 15 letters of Best Corrected Visual Acuity (BCVA) score.

49. (Previously Presented) The method of claim 48 wherein Best Corrected Visual Acuity (BCVA) is measured by Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

50. (**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 4 weeks after the immediately preceding dose; and

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

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

an immunoglobin-like (Ig) domain 2 of a first VEGF receptor and Ig domain 3 of a second VEGF receptor, and a multimerizing component.

51. (**New**) The method of claim 50 wherein the first VEGF receptor is Flt1 and the second VEGF receptor is Flk1.

52. (**New**) The method of claim 50 wherein the VEGF antagonist is aflibercept.

53. (**New**) The method of claim 51, wherein all doses of the VEGF antagonist are administered to the patient by intraocular administration.

54. (**New**) The method of claim 53, wherein the intraocular administration is intravitreal administration.

55. (**New**) The method of claim 54, wherein all doses of the VEGF antagonist comprise from about 0.5 mg to about 2 mg of the VEGF antagonist.

56. (**New**) The method of claim 55, wherein all doses of the VEGF antagonist comprise 0.5 mg of the VEGF antagonist.

57. (**New**) The method of claim 55, wherein all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist.

58. (**New**) The method of claim 51, 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.

59. (**New**) The method of claim 51 wherein the angiogenic eye disorder is age related macular degeneration.

60. (**New**) The method of claim 51 wherein the angiogenic eye disorder is diabetic retinopathy.

61. (**New**) The method of claim 51, wherein the angiogenic eye disorder is diabetic macular edema.

62. (**New**) The method of claim 59 wherein all doses of VEGF antagonist comprise 0.5 mg of the VEGF antagonist.

63. (**New**) The method of claim 59 wherein all doses of VEGF antagonist comprise 2.0 mg of the VEGF antagonist.

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REMARKS UNDER 37 CFR § 1.115

Formal Matters

Claims 21-63 are pending after entry of the amendments set forth herein.

Original claims 1-20 were previously canceled without prejudice.

Claims 21-49 were previously added in the Preliminary Amendment filed April 29, 2019.

Claims 50-63 are added here.

Support for new claims 50-63 as well as previously added claims 21-49 can be found in originally pending now canceled claims 1-20, and throughout the specification.

No new matter has been added.

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 U.S. Patent Application No. 14/972,560, filed December 17, 2015 which issued on June 6, 2018 as U.S. Patent No. 9,669,069.

The Applicants wish to bring to the Examiner's attention U.S. Patent Application No. 15/471,506, filed March 28, 2017 which issued on November 20, 2018 as U.S. Patent No. 10,130,691..

The Applicants wish to bring to the Examiner's attention co-pending U.S. Patent Application No. 16/055,847, filed August 6, 2018 for which no actions have been mailed.

The Applicants wish to bring to the Examiner's attention co-pending U.S. Patent Application No. 16/159,282, filed October 12, 2018 for which a non-final Office Action was mailed April 3, 2019.

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.

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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-008CIPCON5.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: 14 August 2019

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

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Samsung Bioepis Exhibit 1012 - Page 83
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Electronic Patent Application Fee Transmittal

Application Number:	16397267
Filing Date:	29-Apr-2019
Title of Invention:	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS
First Named Inventor/Applicant Name:	George D. YANCOPOULOS
Filer:	Karl Bozicevic/Savanna Fuentes
Attorney Docket Number:	REGN-008CIPCON5

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
CLAIMS IN EXCESS OF 20	1202	4	100	400
INDEPENDENT CLAIMS IN EXCESS OF 3	1201	1	460	460
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**860**

Electronic Acknowledgement Receipt	
EFS ID:	36873462
Application Number:	16397267
International Application Number:	
Confirmation Number:	8135
Title of Invention:	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS
First Named Inventor/Applicant Name:	George D. YANCOPOULOS
Customer Number:	96387
Filer:	Karl Bozicevic/Savanna Fuentes
Filer Authorized By:	Karl Bozicevic
Attorney Docket Number:	REGN-008CIPCON5
Receipt Date:	14-AUG-2019
Filing Date:	29-APR-2019
Time Stamp:	16:57:54
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$860
RAM confirmation Number	E20198DG58088162
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		REGN-008CIPCON5_2019-08-14_supp_pre_amend.pdf	50102 92cd1b790a43367a7c992bfc6946afcc520b8ed1	yes	8

Multipart Description/PDF files in .zip description

Document Description	Start	End
Preliminary Amendment	1	1
Claims	2	6
Applicant Arguments/Remarks Made in an Amendment	7	8

Warnings:

Information:

2	Fee Worksheet (SB06)	fee-info.pdf	32341 284bd4278c910f6b381685ce97aca740c847a3d9	no	2

Warnings:

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Total Files Size (in bytes):	82443

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New Applications Under 35 U.S.C. 111

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New International Application Filed with the USPTO as a Receiving Office

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Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
16/397,267	04/29/2019	George D. YANCOPOULOS	REGN-008CIPCON5

CONFIRMATION NO. 8135

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

PUBLICATION NOTICE

OC000000110424420

Title:USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS

Publication No.US-2019-0247463-A1
Publication Date:08/15/2019

NOTICE OF PUBLICATION OF APPLICATION

The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

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Office of Data Managment, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

Samsung Bioepis Exhibit 1012 - Page 89
Biocon Exhibit 1012 - Page 89

PTO/SB/06 (09-11)
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 16/397,267	Filing Date 04/29/2019	☐ To be Mailed

ENTITY: ☑ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A		N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A		N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*		x $100 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*		x $460 =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).				
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))					
* If the difference in column 1 is less than zero, enter "0" in column 2.				TOTAL	

APPLICATION AS AMENDED - PART II

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT	08/14/2019	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 33	Minus	** 29	= 4		x $100 =	400
	Independent (37 CFR 1.16(h))	* 5	Minus	*** 4	= 1		x $460 =	460
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	860

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

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.	LIE
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".	/TAMMY D MCBETH BROWN/
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Aug 16, 2019 03:27:05 AM

Dear PAIR Customer:

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

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Application	Document	Mailroom Date	Attorney Docket No.
16397267	NTC.PUB	08/15/2019	REGN-008CIPCON5

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UNITED STATES PATENT AND TRADEMARK OFFICE

PATENT APPLICATION INFORMATION RETRIEVAL SYSTEM

INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	16/397,267
				Filing Date	April 29, 2019
				First Named Inventor	Yancopoulos, George D.
				Art Unit	1647
				Examiner Name	Jon McClelland Lockard
Sheet	1	of	3	Attorney Docket Number	REGN-008CIPCON5

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				
	2				

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	**2008/0220004**	2008-09-11	Wiegand et al.	
	2				

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					
	2					

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	BARBAZETTO, "DOSING REGIMEN AND THE FREQUENCY OF MACULAR HEMORRHAGES IN NEOVASCULAR AGE-RELATED MACULAR DEGENERATION TREATED WITH RANIBIZUMAB." Retina, 30:9, 1376-85, 2010	
	2	Bayer Investor News, "Bayer and Regeneron Start additional Phase 3 Study for VEGF Trap=Eye in Wet Age-related Macular Degeneration." May 8, 2008	
	3	BOYER, "A Phase IIIb Study to Evaluate the Safety of Ranibizumab in Subjects with Neovascular Age-related Macular Degeneration." Opthalmology, 116:9, 1731-39, September 2009.	
	4	BROWN, "Ranibizumab versus Verteporfin for Neovascular Age-Related Macular Degeneration." N Engl J Med 355:14, 1432-44, October 5, 2006	
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	7	CAMPOCHIARO, "Ranibizumab for Macular Edema following Branch Retinal Vein Occlusion." Ophthalmology, 2010.	
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	9	CSAKY, "Safety Implications of Vascular Endothelial Growh Factor Blockade for Subjects Receiving Intravitreal Anti-Vascular Endothelial Growth Factor Therapies." Am. J. Ophthalmology, 148:5, 647-56, November 2009.	

Examiner Signature		Date Considered	

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

INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	16/397,267
				Filing Date	April 29, 2019
				First Named Inventor	Yancopoulos, George D.
				Art Unit	1647
				Examiner Name	Jon McClelland Lockard
Sheet	2	of	3	Attorney Docket Number	REGN-008CIPCON5

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
	10	DO, "One-Year Outcomes of the DA VINCI Study of VEGF Trap-Eye in Eyes with Diabetic Macular Edema." Ophthalmology, 2012.	
	11	ENGELBERT, "The 'Treat and Extend' Dosing Regimen of Intravitreal Anti-Vascular Endothelial Growth Factor Therapy for Neovascular Age-Related Macular Degeneration." Ophthalmology Management, June 2010, available at http://www.visioncareprofessional.com/emails/amdupdate/index.asp?issue=42	
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	19	GRAGOUDAS, "Pegaptanib for Neovascular Age-Related Macular Degeneration." N Engl J Med 351:27, 2805-16, December 30, 2004	
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	26	LEVINE, "MACULAR HEMORRHAGE IN NEOVASCULAR AGE-RELATED MACULAR DEGENERATION AFTER STABILIZATION WITH ANTIANGIOGENIC THERAPY." Retina, 29:8, 1074-79, 2009.	

Examiner Signature		Date Considered	

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

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				First Named Inventor	Yancopoulos, George D.
				Art Unit	1647
				Examiner Name	Jon McClelland Lockard
Sheet	3	of	3	Attorney Docket Number	REGN-008CIPCON5

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
	27	MARGOLIS, "HEMORRHAGIC RECURRENCE OF NEOVASCULAR AGE-RELATED MACULAR DEGENERATION NOT PREDICTED BY SPECTRAL DOMAIN OPTICAL COHERENCE TOMOGRAPHY." Retinal Cases & Brief Reports, 4:1, 2010	
	28	MASSIN, "Safety and Efficacy of Ranibizumab in Diabetic Macular Edema (RESOLVE Study*)." Diabetes Care, 33:11, 2399-405, November 2010.	
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	35	SCHMIDT-ERFURTH, "Efficacy and Safety of Monthly versus Quarterly Ranibizumab Treatment in Neovascular Age-related Macular Degeneration." Ophthalmology, 2010.	
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	39	YANCOPOULOS, "Vascular-specific growth factors and blood vessel formation." Nature 407:242-48, September 14, 2000.	
	40	YANCOPOULOS, "Clinical Application of Therapies Targeting VEGF." Cell 143, October 1, 2010.	
	41	YUNG, "moving Toward the Next Steps in Angiogenesis Therapy?" Society for Neuro-Oncology, 10:939, 2008	

Examiner Signature		Date Considered	

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

Electronic Acknowledgement Receipt

EFS ID:	37202823
Application Number:	16397267
International Application Number:	
Confirmation Number:	8135
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-008CIPCON5
Receipt Date:	18-SEP-2019
Filing Date:	29-APR-2019
Time Stamp:	15:32:26
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	Transmittal Letter	REGN-008CIPCON5_2019-09-18_IDS_trans.pdf	52094 a69133c25dca9be2f48b37b6b9eb6aacb2fd2b76	no	2

Warnings:

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2	Information Disclosure Statement (IDS) Form (SB08)	REGN-008CIPCON5_2019-09-18_IDS_SB08A.pdf	49068 bbbe2ea0a56368f82ff36d9a1f1689ece59d960e	no	3
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New Applications Under 35 U.S.C. 111

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

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

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

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Electronically Filed 9/18/2019

INFORMATION DISCLOSURE STATEMENT	Attorney Docket No.	REGN-008CIPCON5
	Confirmation No.	8135
	First Named Inventor	George D. Yancopoulos
	Application Number	16/397,267
	Filing Date	April 29, 2019
	Group Art Unit	1647
Address to: Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Examiner Name	Jon McClelland Lockard
	Title: "*Use of a VEGF Antagonist to Treat Angiogenic Eye Disorders*"	

Sir:

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

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 16/159,282, and as such, copies thereof are not included pursuant to the provisions of 37 CFR § 1.98(d).

Statements

☒ **No statement**

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(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

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☐ **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

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Fees

☒ No fee is believed to be due.

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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-008CIPCON5.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: September 18, 2019

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

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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
16/397,267	April 29, 2019

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

OR

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

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☐ Firm or Individual Name					
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I am the Applicant (if the Applicant is a juristic entity, list the Applicant name in the box):

Regeneron Pharmaceuticals, Inc.

☐ Inventor or Joint Inventor (title not required below)

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

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

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

SIGNATURE of Applicant for Patent

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

Signature	/Frank R. Cottingham/	Date (Optional)	September 6, 2019
Name	Frank R. Cottingham		
Title	Executive Director, Assistant General Counsel, Patents, Regeneron Pharmaceuticals, Inc.		

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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PTO/AIA/96 (08-12)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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STATEMENT UNDER 37 CFR 3.73(c)

Applicant/Patent Owner: Regeneron Pharmaceuticals, Inc.

Application No./Patent No.: 16/397,267 Filed/Issue Date: April 29, 2019

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 (choose **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), of an undivided interest in the entirety (a complete transfer of ownership interest was made). The certified document(s) showing the transfer is attached.

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

A. ☑ An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel 050278, Frame 0613, 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

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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.

PTO/AIA/96 (08-12)
Approved for use through 01/31/2013. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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STATEMENT UNDER 37 CFR 3.73(c)

3. From: _____ To: _____

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

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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/	2019/09/27
Signature	Date
Karl Bozicevic	28,807
Printed or Typed Name	Title or Registration Number

Privacy Act Statement

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

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

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Electronic Acknowledgement Receipt

EFS ID:	37284164
Application Number:	16397267
International Application Number:	
Confirmation Number:	8135
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/Halle Jarman
Filer Authorized By:	Karl Bozicevic
Attorney Docket Number:	REGN-008CIPCON5
Receipt Date:	27-SEP-2019
Filing Date:	29-APR-2019
Time Stamp:	18:37:04
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	0725US06_POA.pdf	169021 4f8368c019dbee50cae97a4f05b90c9acf7fd883	no	1

Warnings:

Information:					
2	Power of Attorney	REGN-008CIPCON5_aia0096.pdf	118186 685a2d201bf52f3aa05d8a008e168775302 9dae0	no	3
Warnings:					
Information:					
			Total Files Size (in bytes):	287207	

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New Applications Under 35 U.S.C. 111

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

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

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

New International Application Filed with the USPTO as a Receiving Office

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

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
16/397,267	04/29/2019	George D. YANCOPOULOS	REGN-008CIPCON5

CONFIRMATION NO. 8135

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

POA ACCEPTANCE LETTER

OC000000111575443

Date Mailed: 10/02/2019

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 09/27/2019.

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**.

/ltaba/

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

Oct 02, 2019 03:33:27 AM

Dear PAIR Customer:

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

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

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

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

Application	Document	Mailroom Date	Attorney Docket No.
16397267	N570	10/02/2019	REGN-008CIPCON5

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

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

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

Thank you for prompt attention to this notice,

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PATENT APPLICATION INFORMATION RETRIEVAL SYSTEM

Electronically Filed

SECOND 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-008CIPCON5
	Confirmation No.	8135
	First Named Inventor	YANCOPOULOS, GEORGE D.
	Application Number	16/397,267
	Filing Date	April 29, 2019
	Group Art Unit	1647
	Examiner Name	LOCKARD, Jon McClelland
	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.

Electronic Acknowledgement Receipt	
EFS ID:	38221376
Application Number:	16397267
International Application Number:	
Confirmation Number:	8135
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-008CIPCON5
Receipt Date:	07-JAN-2020
Filing Date:	29-APR-2019
Time Stamp:	12:27:41
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		0725-US06_REGN-008CIPCON5_2020-01-07_third_supp_prelim_amend.pdf	52805 131002db171e4170e2a8116e4bfce7cf64bb5876	yes	8

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Applicant Arguments/Remarks Made in an Amendment	7	8
	Claims	2	6
	Preliminary Amendment	1	1
Warnings:			
Information:			
	Total Files Size (in bytes):	52805	

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New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.
National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.
New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

REMARKS UNDER 37 CFR § 1.115

Formal Matters

Claims 21-63 are pending after entry of the amendments set forth herein.

Original claims 1-20 were previously canceled without prejudice.

Claims 21, 29, 36, 38, 43, 45 and 50 have been amended to more particularly point out and distinctly claim the invention. Support for these amendments can be found throughout the specification.

No new matter has been added.

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 U.S. Patent Application No. 14/972,560, filed December 17, 2015 which issued on June 6, 2018 as U.S. Patent No. 9,669,069.

The Applicants wish to bring to the Examiner's attention U.S. Patent Application No. 15/471,506, filed March 28, 2017 which issued on November 20, 2018 as U.S. Patent No. 10,130,691.

The Applicants wish to bring to the Examiner's attention co-pending U.S. Patent Application No. 16/055,847, filed August 6, 2018 for which a non-final Office Action was mailed on December 10, 2019.

The Applicants wish to bring to the Examiner's attention co-pending U.S. Patent Application No. 16/159,282, filed October 12, 2018 for which a non-final Office Action was mailed October 1, 2019.

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.

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Biocon Exhibit 1012 - Page 110

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-008CIPCON5.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: 7 January 2020

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, California 94065
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Facsimile: (650) 327-3231

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AMENDMENTS TO THE CLAIMS

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

21. (**Currently amended**) A method for treating age related macular degeneration in a patient, comprising **intravitreally** administering, to said patient, ~~**by intravitreal injection,**~~ **an effective amount of aflibercept which is** 2 mg ~~**aflibercept**~~ approximately every 4 weeks for the first 3 months, followed by 2 mg ~~**aflibercept**~~ approximately once every 8 weeks or once every 2 months.

22. (Previously Presented) The method of claim 21, wherein the age-related macular degeneration is neovascular (wet).

23. (Previously Presented) The method of claim 21, wherein approximately every 4 weeks comprises approximately every 28 days or approximately monthly.

24. (Previously Presented) The method of claim 23, wherein the age-related macular degeneration is neovascular (wet).

25. (Previously Presented) The method of claim 22 wherein the patient loses less than 15 letters of Best Corrected Visual Acuity (BCVA) score.

26. (Previously Presented) The method of claim 25 wherein Best Corrected Visual Acuity (BCVA) is measured by Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

27. (Previously Presented) The method of claim 22 wherein the patient gains at least 15 letters of Best Corrected Visual Acuity (BCVA) score.

28. (Previously Presented) The method of claim 27 wherein Best Corrected Visual Acuity (BCVA) is measured by Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

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29. (**Currently amended**) A method for treating diabetic macular edema in a patient, comprising **intravitreally** administering, to said patient**~~, by intravitreal injection~~**, **an effective amount of aflibercept which is** 2 mg **~~aflibercept~~** approximately every 4 weeks for the first 5 injections followed by 2 mg **~~aflibercept~~** approximately once every 8 weeks or once every 2 months.

30. (Previously Presented) The method of claim 29, wherein approximately every 4 weeks comprises approximately every 28 days or approximately monthly.

31. (Previously Presented) The method of claim 29, further comprising, after 20 weeks, administering, via intravitreal injection, 2 mg of aflibercept once every 4 weeks.

32. (Previously Presented) The method of claim 29 wherein the patient loses less than 15 letters of Best Corrected Visual Acuity (BCVA) score.

33. (Previously Presented) The method of claim 32 wherein Best Corrected Visual Acuity (BCVA) is measured by Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

34. (Previously Presented) The method of claim 29 wherein the patient gains at least 15 letters of Best Corrected Visual Acuity (BCVA) score.

35. (Previously Presented) The method of claim 34 wherein Best Corrected Visual Acuity (BCVA) is measured by Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

36. (**Currently amended**) A method for treating diabetic retinopathy in a patient, comprising **intravitreally** administering, to said patient, **~~by intravitreal injection,~~** **an effective amount of aflibercept which is** 2 mg **~~aflibercept~~** approximately every 4 weeks for the first 5 injections followed by 2 mg **~~aflibercept~~** approximately once every 8 weeks or 2 months.

37. (Previously Presented) The method of claim 36, wherein approximately every 4 weeks comprises approximately every 28 days or approximately monthly.

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38. (**Currently amended**) The method of claim 36, further comprising, after 20 weeks, administering, via intravitreal injection, 2 mg of aflibercept once every 4 weeks.

39. (Previously Presented) The method of claim 36 wherein the patient loses less than 15 letters of Best Corrected Visual Acuity (BCVA) score.

40. (Previously Presented) The method of claim 37 wherein Best Corrected Visual Acuity (BCVA) is measured by Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

41. (Previously Presented) The method of claim 36 wherein the patient gains at least 15 letters of Best Corrected Visual Acuity (BCVA) score.

42. (Previously Presented) The method of claim 41 wherein Best Corrected Visual Acuity (BCVA) is measured by Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

43. (**Currently amended**) A method for treating diabetic retinopathy in a patient with diabetic macular edema, comprising **intravitreally** administering, to said patient, ~~**by intravitreal injection,**~~ **an effective amount of aflibercept which is** 2 mg ~~**aflibercept**~~ approximately every 4 weeks for the first 5 injections followed by 2 mg ~~**aflibercept**~~ approximately once every 8 weeks or 2 months.

44. (Previously Presented) The method of claim 43, wherein approximately every 4 weeks comprises approximately every 28 days or approximately monthly.

45. (**Currently amended**) The method of claim 43, further comprising, after 20 weeks, administering, via intravitreal injection, 2 mg of aflibercept once every 4 weeks.

46. (Previously Presented) The method of claim 43 wherein the patient loses less than 15 letters of Best Corrected Visual Acuity (BCVA) score.

47. (Previously Presented) The method of claim 46 wherein Best Corrected Visual Acuity (BCVA) is measured by Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

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48. (Previously Presented) The method of claim 43 wherein the patient gains at least 15 letters of Best Corrected Visual Acuity (BCVA) score.

49. (Previously Presented) The method of claim 48 wherein Best Corrected Visual Acuity (BCVA) is measured by Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

50. (**Currently Amended**) A method for treating an angiogenic eye disorder in a patient, said method comprising ~~**sequentially**~~ administering to the patient **an effective sequential dosing regimen of** 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 4 weeks after the immediately preceding dose; and

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

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

an immunoglobin-like (Ig) domain 2 of a first VEGF receptor and Ig domain 3 of a second VEGF receptor, and a multimerizing component.

51. (Previously Presented) The method of claim 50 wherein the first VEGF receptor is Flt1 and the second VEGF receptor is Flk1.

52. (Previously Presented) The method of claim 50 wherein the VEGF antagonist is aflibercept.

53. (Previously Presented) The method of claim 51, wherein all doses of the VEGF antagonist are administered to the patient by intraocular administration.

54. (Previously Presented) The method of claim 53, wherein the intraocular administration is intravitreal administration.

55. (Previously Presented) The method of claim 54, wherein all doses of the VEGF antagonist comprise from about 0.5 mg to about 2 mg of the VEGF antagonist.

56. (Previously Presented) The method of claim 55, wherein all doses of the VEGF antagonist comprise 0.5 mg of the VEGF antagonist.

57. (Previously Presented) The method of claim 55, wherein all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist.

58. (Previously Presented) The method of claim 51, 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.

59. (Previously Presented) The method of claim 51 wherein the angiogenic eye disorder is age related macular degeneration.

60. (Previously Presented) The method of claim 51 wherein the angiogenic eye disorder is diabetic retinopathy.

61. (Previously Presented) The method of claim 51, wherein the angiogenic eye disorder is diabetic macular edema.

62. (Previously Presented) The method of claim 59 wherein all doses of VEGF antagonist comprise 0.5 mg of the VEGF antagonist.

63. (Previously Presented) The method of claim 59 wherein all doses of VEGF antagonist comprise 2.0 mg of the VEGF antagonist.

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United States Patent and Trademark Office

Office of the Chief Financial Officer

Document Code:WFEE

User :65444

Sale Accounting Date:01/14/2020

Sale Item Reference Number	Effective Date
16397267	08/14/2019

Document Number	Fee Code	Fee Code Description	Amount Paid	Payment Method
I20201DK35179217	1202	CLAIMS IN EXCESS OF 20	$1,000.00	Deposit Account

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 16/397,267	Filing Date 04/29/2019	☐ To be Mailed

ENTITY: ☑ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A		N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A		N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*		x $100 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*		x $460 =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).				
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))					
* If the difference in column 1 is less than zero, enter "0" in column 2.				TOTAL	

APPLICATION AS AMENDED - PART II

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT	08/14/2019	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 43	Minus	** 29	= 14		x $100 =	1400
	Independent (37 CFR 1.16(h))	* 5	Minus	*** 4	= 1		x $460 =	460
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	1860

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT	01/07/2020	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 43	Minus	** 43	= 0		x $100 =	0
	Independent (37 CFR 1.16(h))	* 5	Minus	*** 5	= 0		x $460 =	0
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	0

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

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

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

INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	16/397,267
				Filing Date	April 29, 2019
				First Named Inventor	George D. Yancopoulos
				Art Unit	
				Examiner Name	
Sheet	1	of	2	Attorney Docket Number	REGN-008CIPCON5

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				
	2				

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				
	2				

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					
	2					

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	16/055,847 – Third Party Submissions dated May 1, 2019	
	2	16/159,282 – Third Party Submissions dated May 31, 2019	
	3	BROWN, "Long-term Outcomes of Ranibizumab Therapy for Diabetic Macular Edema: The 36-Month Results from Two phase III Trials." Ophthalmology, 120(10):2013-22 (October 2013)	
	4	CAMPOCHIARO, "Ranibizumab for Macular Edema following Branch Retinal Vein Occlusion: six-month primary end point results of a phase III study." Ophthalmology, 117(6):1102-1112 (June 2010)	
	5	DIXON et al., "VEGF Trap-Eye for the treatment of neovascular age-related macular degeneration" Expert Opin. Investig. Drugs, 18(10):1573-1580 (2009)	
	6	DO, "One-Year Outcomes of the DA VINCI Study of VEGF Trap-Eye in Eyes with Diabetic Macular Edema." Ophthalmology, 119(8):1658-65 (2012)	
	7	ENGELBERT, "The 'Treat and Extend' Dosing Regimen of Intravitreal Anti-Vascular Endothelial Growth Factor Therapy for Neovascular Age-Related Macular Degeneration." Ophthalmology Management, Issue 42, (June 2010) available at http://www.visioncareprofessional.com/emails/amdupdate/index.asp?issue=42	
	8	GOMEZ-MANZANO, "VEGF Trap induces antiglioma effect at different stages of disease." Neuro-Oncology, 10:940-945 (December 2008)	
	9	GUTIERREZ et al., "Intravitreal bevacizumab (Avastin) in the treatment of macular edema secondary to retinal vein occlusion" Clin. Ophthalmol., 2(4):787,791 (2008)	
	10	HEIER, "Intravitreal Aflibercept for Diabetic Macular Edema: 148-Week Results from the VISTA and VIVID Studies." Ophthalmology, 123(11):2376-2385 (November 2016)	

Examiner Signature		Date Considered	

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

INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	16/397,267
				Filing Date	April 29, 2019
				First Named Inventor	George D. Yancopoulos
				Art Unit	
				Examiner Name	
Sheet	2	of	2	Attorney Docket Number	REGN-008CIPCON5

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
	11	Information from ClinicalTrials.gov archive on the view of NCT01012973 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)(GALILEO) 7 pages, first posted 11/13/2009; results first posted 11/22/2012; last update posted 11/3/14; printed 12/4/19 (https://clinicaltrials.gov/ct2/show/study/NCT01012973) (NOTE: May correspond to "Vascular Endothelial Growth Factor Trap‐ Eye Investigation of Efficacy and Safety in Central Retinal Vein Occlusion title, 8 pages, 11/12/2009, US **[Cited in Third Party Observations filed in parent application USSN 16/055,847 for which a copy is unavailable on PAIR]"** which was cited in the Third Party Observations dated 05/01/19)	
	12	KAISER, "Vascular endothelial growth factor Trap-Eye for diabetic macular oedema." Br. J. Ophthalmol, 93(2):135-36 (February 2009)	
	13	MARGOLIS, "Hemorrhagic Recurrence Of Neovascular Age-Related Macular Degeneration Not Predicted By Spectral Domain Optical Coherence Tomography." Retinal Cases & Brief Reports, 4:1-4 (2010)	
	14	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, 2003)	
	15	SCHMIDT-ERFURTH, "Efficacy and Safety of Monthly versus Quarterly Ranibizumab Treatment in Neovascular Age-related Macular Degeneration: The EXCIE Study" Ophthalmology, 118(5)831-839 (2010)	
	16	SCHNICHELS, "Comparative toxicity and proliferation testing of aflibercept, bevacizumab and ranibizumab on different ocular cells." Br. J. Ophthalmol., 97:917-923 (2013)	
	17	SIMO AND HERNANDEZ, "Advances in Medical Treatment of Diabetic Retinopathy" Diabetes Care, 32(8):1556-1562 (August 2009)	
	18	SPAIDE, "Ranibizumab According to Need: A Treatment for Age-related Macular Degeneration." Am J Ophthalmology, 143(4):679-680 (April 2007)	
	19	Vascular Endothelial Growth Factor Trap‐ Eye Investigation of Efficacy and Safety in Central Retinal Vein Occlusion title, 8 pages, 11/12/2009, US **[Cited in Third Party Observations filed in parent application USSN 16/055,847 for which a copy is unavailable on PAIR] NOTE:** May correspond to **"**Information from ClinicalTrials.gov archive on the view of NCT01012973 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)(GALILEO) 7 pages, first posted 11/13/2009; results first posted 11/22/2012; last update posted 11/3/14; printed 12/4/19 (https://clinicaltrials.gov/ct2/show/study/NCT01012973)" cited by the Examiner in the Office Action dated 12/10/19 in USSN 16/055,847	
	20	YANCOPOULOS, "Clinical Application of Therapies Targeting VEGF." Cell 143:13-16 (October 1, 2010)	

Examiner Signature		Date Considered	

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

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/055,847	08/06/2018	George D. Yancopoulos	REGN-008CIPCON3	3451

96387 7590 05/01/2019

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

EXAMINER
LOCKARD, JON MCCLELLAND

ART UNIT	PAPER NUMBER
1647	

NOTIFICATION DATE	DELIVERY MODE
05/01/2019	ELECTRONIC

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

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

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

docket@bozpat.com

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APPLICATION NO./ CONTROL NO.	FILING DATE	FIRST NAMED INVENTOR/ PATENT IN REEXAMINATION	ATTORNEY DOCKET NO.
16/055,847	08/06/2018	Yancopoulos, George D.	REGN-008CIPCON3

		EXAMINER	
Regeneron - Bozicevic, Field & Francis 201 REDWOOD SHORES PARKWAY SUITE 200 REDWOOD CITY, CA 94065		MARIANNE C SEIDEL	
		ART UNIT	PAPER
		1600	20190429

DATE MAILED: _____

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

Commissioner for Patents

The third-party submission under 37 CFR 1.290 filed on 4/21/19 and 4/27/19 for the instant application has been determined to be compliant with 35 U.S.C. 122(e) and 37 CFR 1.290 and is being entered in the application. Please allow a few days for the submission to be visible in the Patent Application Information Retrieval (PAIR) system.

/MARIANNE C SEIDEL/
Quality Assurance Specialist, Art Unit 1600

PTO-90C (Rev.04-03)

Doc Code: 3P.RELEVANCE
Document Description: Concise Description of Relevance

U.S. Patent and Trademark Office
Department of Commerce

THIRD-PARTY SUBMISSION UNDER 37 CFR 1.290
CONCISE DESCRIPTION OF RELEVANCE

Application Number	16055847

U.S. PATENTS

Cite No	Patent Number	Concise Description of Relevance

U.S. PATENT APPLICATION PUBLICATION

Cite No	Publication Number	Concise Description of Relevance

FOREIGN PATENT DOCUMENTS		
CiteNo	**Foreign Document Number**	**Concise Description of Relevance**

NON-PATENT PUBLICATIONS		
Cite No	**Reference**	**Concise Description of Relevance**
1	Vascular Endothelial Growth Factor Trap‐Eye Investigation of Efficacy and Safety in Central Retinal Vein Occlusion title, 8 pages, 11/12/2009, US	See Attached

2	Niral Karia Author, Retinal vein occlusion: pathophysiology and treatment options title, 8 pages, 07/31/2010, Clinical Ophthalmology publisher	See Attached

3	RAFAEL Author, Advances in the Medical Treatment of Diabetic Retinopathy, 7 pages, 08/31/2009, DIABETES CARE publisher	See Attached

PTO/SB/429(08-12)
Approved for use through 07/31/2015. OMB 0651-0031
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THIRD-PARTY SUBMISSION UNDER 37 CFR 1.290	Application Number	16055847

U.S. PATENTS				
Cite No	Patent Number	Kind Code[1]	Issue Date (YYYY-MM-DD)	First Named Inventor

U.S. PATENT APPLICATION PUBLICATIONS				
Cite No	Publication Number	Kind Code[1]	Publication Date (YYYY-MM-DD)	First Named Inventor

FOREIGN PATENTS AND PUBLISHED FOREIGN PATENT APPLICATIONS						
Cite No	Foreign Document Number[3]	Country Code[2]	Kind Code[1]	Publication Date (YYYY-MM-DD)	Applicant, Patentee or First Named Inventor	T[5]
						☐

NON-PATENT PUBLICATIONS (e.g., journal article, Office action)			
Cite No	Author (if any), title of the publication, page(s) being submitted, publication date, publisher (where available), place of publication (where available).	T[5]	E[6]

THIRD-PARTY SUBMISSION UNDER 37 CFR 1.290	Application Number	16055847

1	RAFAEL Author, Advances in the Medical Treatment of Diabetic Retinopathy, 7 pages, 08/31/2009, DIABETES CARE publisher	☐	☒
2	Niral Karia Author, Retinal vein occlusion: pathophysiology and treatment options title, 8 pages, 07/31/2010, Clinical Ophthalmology publisher	☐	☒
3	Vascular Endothelial Growth Factor Trap‐Eye Investigation of Efficacy and Safety in Central Retinal Vein Occlusion title, 8 pages, 11/12/2009, US	☐	☒

STATEMENTS

The party making the submission is not an individual who has a duty to disclose information with respect to the above-identified application under 37 CFR 1.56.

This submission complies with the requirements of 35 U.S.C. 122(e) and 37 CFR 1.290.

EFS Web 2.1.17

THIRD-PARTY SUBMISSION UNDER 37 CFR 1.290	Application Number	16055847

☐ The fee set forth in 37 CFR 1.290(f) has been submitted herewith.			
☒ The fee set forth in 37 CFR 1.290(f) is not required because this submission lists three or fewer total items and, to the knowledge of the person signing the statement after making reasonable inquiry, this submission is the first and the only submission under 35 U.S.C 122(e) filed in the above-identified application by the party making the submission or by a party in privity with the party.			
☐ This resubmission is being made responsive to a notification of non-compliance issued for an earlier filed third-party submission. The corrections in this resubmission are limited to addressing the non-compliance. As such, the party making this resubmission: (1) requests that the Office apply the previously-paid fee set forth in 37 CFR 1.290(f), or (2) states that no fee is required to accompany this resubmission as the undersigned is again making the fee exemption statement set forth in 37 CFR 1.290(g).			
Signature	/Joe Reynolds/		
Name/Print	Joe	Registration Number (if applicable)	

Examiner Signature		Date Considered	

*EXAMINER: Signature indicates all documents listed above have been considered,except for citations through which a line is drawn. Draw line through citation if not considered. Include a copy of this form with next communication to applicant. 1. If known, enter kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16. See MPEP 901.04(a). 2. Enter the country or patent office that issued the document, by two-letter code under WIPO standard ST.3. See MPEP 1851. 3. For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. 4. If known, enter the kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 . See MPEP 901.04(a). 5. Check mark indicates translation attached. 6. Check mark indicates evidence of publication attached.

Concise Description of Relevance

The following references are being submitted:

P1: Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO); web site: https://clinicaltrials.gov/ct2/history/NCT01012973?V_1=View#StudyPageTop; Published on Nov 12, 2009;

P2: Niral Karia, Retinal vein occlusion: pathophysiology and treatment options. Clinical Ophthalmology 2010:4 809–816, Published on Jul, 2010;

P3: RAFAEL SIM ´O and CRISTINA HERN´ANDEZ, Advances in the Medical Treatment of Diabetic Retinopathy. DIABETES CARE, VOLUME 32, NUMBER 8, AUGUST 2009, page 1559, Published on Aug, 2009.

As the claim chart shows below, **P1** discloses study description of clinical trial NCT01012973, which aims to determine the efficacy of vascular endothelial growth factor (VEGF) Trap-Eye injected into the eye on vision function in subjects with macular edema as a consequence of central retinal vein occlusion. The only difference is that Claim 21 uses "2 mg aflibercept" instead of "VEGF Trap-Eye" used in P1;

P2 discloses that Retinal vein occlusion (RVO) is the most common retinal vascular disease after diabetic retinopathy. Depending on the area of retinal venous drainage effectively occluded it is broadly classified as either central retinal vein occlusion (CRVO), hemispheric retinal vein occlusion (HRVO), or branch retinal vein occlusion (BRVO). (*see* page 809 introduction section first two sentences);

P3 discloses that aflibercept also known as a VEGF Trap-Eye because its ability to block VEGF proteins, is a fusion protein comprised of segments of the extracellular domains of human VEGF receptor 1 and 2 fused to the constant region of human IgG. (*see* page 1559 right column third paragraph);

Besides, as it is mentioned in the present invention, 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." (*see* paragraph [0008]);

	U.S. Application No. 16/055,847	Concise Description of Relevance
Claim #	Claim Elements	Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)
21	A method for treating macular edema following retinal vein occlusion in a human subject comprising administering 2 mg aflibercept to the subject	To determine the efficacy of vascular endothelial growth factor (VEGF) Trap-Eye injected into the eye on vision function in subjects with macular edema as a consequence of central retinal vein occlusion. [Study Description]
	by intravitreal injection	Intravitreal injection. [Assigned Interventions]
	once every 4 weeks.	Weeks 0 to 20 injection of VEGF Trap-Eye every 4 weeks [Assigned Interventions]

Electronic Acknowledgement Receipt	
EFS ID:	35851526
Application Number:	16055847
International Application Number:	
Confirmation Number:	3451
Title of Invention:	
First Named Inventor/Applicant Name:	
Correspondence Address:	- - - - - - - - - - -
Filer:	Joe Reynolds
Filer Authorized By:	
Attorney Docket Number:	
Receipt Date:	27-APR-2019
Filing Date:	
Time Stamp:	21:09:41
Application Type:	

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	Concise Description of Relevance	Concise-description-generated.pdf	32661 846d65f66190992370cec1261748f68cf4cc673f	no	4
Warnings:					
Information:					
2	Third-Party Submission Under 37 CFR 1.290	Third-party-preissuance-submission.pdf	44466 e6a9d076030d0aca379d98a73373d704e9b2afc6	no	3
Warnings:					
Information:					
3	Request for Notification of Non-compliant Third-Party Submission	Third-party-notification-request.pdf	20027 458cf58b9516e443d102fb4934eaadf17bbf64ec	no	1
Warnings:					
Information:					
4	Concise Description of Relevance	Concise-description.pdf	116758 f737b13f87e153c3f9661833e3265158eedb8133	no	2
Warnings:					
Information:					
5	Evidence of Publication	Evidence-pub-3.pdf	86747 a92ecf8c1f3e7d8e4825700b9d68497d1d6be612	no	7
Warnings:					
Information:					
6	Evidence of Publication	Evidence-pub-2.pdf	162155 73c3a794cd2d69eeb692c5a0add3e4473a05a979	no	8
Warnings:					
Information:					
		Total Files Size (in bytes):	462814		

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New Applications Under 35 U.S.C. 111

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

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

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

New International Application Filed with the USPTO as a Receiving Office

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

Doc Code: 3P.RELEVANCE
Document Description: Concise Description of Relevance

U.S. Patent and Trademark Office
Department of Commerce

THIRD-PARTY SUBMISSION UNDER 37 CFR 1.290
CONCISE DESCRIPTION OF RELEVANCE

Application Number	16055847

U.S. PATENTS

Cite No	Patent Number	Concise Description of Relevance

U.S. PATENT APPLICATION PUBLICATION

Cite No	Publication Number	Concise Description of Relevance

FOREIGN PATENT DOCUMENTS		
CiteNo	**Foreign Document Number**	**Concise Description of Relevance**

NON-PATENT PUBLICATIONS		
Cite No	**Reference**	**Concise Description of Relevance**
1	Peter AUTHER, Ranibizumab for Macular Edema Due to Retinal Vein Occlusions Implication of VEGF as a Critical Stimulator title, 9 pages , 30/08/2008	See Attached

2	Lucentis Label title ,7 pages, 30/06/2010	See Attached

PTO/SB/429(08-12)
Approved for use through 07/31/2015. OMB 0651-0031
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THIRD-PARTY SUBMISSION UNDER 37 CFR 1.290	Application Number	16055847

U.S. PATENTS				
Cite No	Patent Number	Kind Code[1]	Issue Date (YYYY-MM-DD)	First Named Inventor

U.S. PATENT APPLICATION PUBLICATIONS				
Cite No	Publication Number	Kind Code[1]	Publication Date (YYYY-MM-DD)	First Named Inventor

FOREIGN PATENTS AND PUBLISHED FOREIGN PATENT APPLICATIONS						
Cite No	Foreign Document Number[3]	Country Code[2]	Kind Code[1]	Publication Date (YYYY-MM-DD)	Applicant, Patentee or First Named Inventor	T[5]
						☐

NON-PATENT PUBLICATIONS (e.g., journal article, Office action)			
Cite No	Author (if any), title of the publication, page(s) being submitted, publication date, publisher (where available), place of publication (where available).	T[5]	E[6]

THIRD-PARTY SUBMISSION UNDER 37 CFR 1.290	Application Number	16055847

1	Lucentis Label title ,7 pages, 30/06/2010	☐	☒
2	Peter AUTHER, Ranibizumab for Macular Edema Due to Retinal Vein Occlusions Implication of VEGF as a Critical Stimulator title, 9 pages , 30/08/2008	☐	☒

STATEMENTS

The party making the submission is not an individual who has a duty to disclose information with respect to the above-identified application under 37 CFR 1.56.

This submission complies with the requirements of 35 U.S.C. 122(e) and 37 CFR 1.290.

☐ The fee set forth in 37 CFR 1.290(f) has been submitted herewith.

☒ The fee set forth in 37 CFR 1.290(f) is not required because this submission lists three or fewer total items and, to the knowledge of the person signing the statement after making reasonable inquiry, this submission is the first and the only submission under 35 U.S.C 122(e) filed in the above-identified application by the party making the submission or by a party in privity with the party.

☐ This resubmission is being made responsive to a notification of non-compliance issued for an earlier filed third-party submission. The corrections in this resubmission are limited to addressing the non-compliance. As such, the party making this resubmission: (1) requests that the Office apply the previously-paid fee set forth in 37 CFR 1.290(f), or (2) states that no fee is required to accompany this resubmission as the undersigned is again making the fee exemption statement set forth in 37 CFR 1.290(g).

THIRD-PARTY SUBMISSION UNDER 37 CFR 1.290	Application Number	16055847

Signature	/Elizabeth Thompson/		
Name/Print	Elizabeth	Registration Number (if applicable)	
Examiner Signature		Date Considered	

*EXAMINER: Signature indicates all documents listed above have been considered,except for citations through which a line is drawn. Draw line through citation if not considered. Include a copy of this form with next communication to applicant. 1. If known, enter kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16. See MPEP 901.04(a). 2. Enter the country or patent office that issued the document, by two-letter code under WIPO standard ST.3. See MPEP 1851. 3. For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. 4. If known, enter the kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 . See MPEP 901.04(a). 5. Check mark indicates translation attached. 6. Check mark indicates evidence of publication attached.

Electronic Acknowledgement Receipt	
EFS ID:	35783629
Application Number:	16055847
International Application Number:	
Confirmation Number:	3451
Title of Invention:	
First Named Inventor/Applicant Name:	
Correspondence Address:	- - - - - - - - - - -
Filer:	Elizabeth Thompson
Filer Authorized By:	
Attorney Docket Number:	
Receipt Date:	21-APR-2019
Filing Date:	
Time Stamp:	21:29:30
Application Type:	

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	Concise Description of Relevance	Concise-description-generated.pdf	30185 1fd17ba5e73b9f30386d2803b71e9bc73fd08cb4	no	3
Warnings:					
Information:					
2	Third-Party Submission Under 37 CFR 1.290	Third-party-preissuance-submission.pdf	43151 79d1d8f0f8ebf66c58ca2108d13dcc72cab805d0	no	3
Warnings:					
Information:					
3	Request for Notification of Non-compliant Third-Party Submission	Third-party-notification-request.pdf	20074 40d5d061fee7b35a11a9fd0caf93f69559afcb7d	no	1
Warnings:					
Information:					
		Total Files Size (in bytes):	93410		

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New Applications Under 35 U.S.C. 111

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

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

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

New International Application Filed with the USPTO as a Receiving Office

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

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/159,282	10/12/2018	George D. Yancopoulos	REGN-008CIPCON4	8618

96387 7590 05/31/2019

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

EXAMINER
LOCKARD, JON MCCLELLAND

ART UNIT	PAPER NUMBER
1647	

NOTIFICATION DATE	DELIVERY MODE
05/31/2019	ELECTRONIC

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

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

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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APPLICATION NO./ CONTROL NO.	FILING DATE	FIRST NAMED INVENTOR/ PATENT IN REEXAMINATION	ATTORNEY DOCKET NO.
16/159,282	10/12/2018	Yancopoulos, George D.	REGN-008CIPCON4

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201 REDWOOD SHORES PARKWAY SUITE 200
REDWOOD CITY, CA 94065

EXAMINER	
MARIANNE C SEIDEL	
ART UNIT	PAPER
1600	20190529

DATE MAILED: _____

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

Commissioner for Patents

The third-party submission under 37 CFR 1.290 filed on 5/28/19 for the instant application has been determined to be compliant with 35 U.S.C. 122(e) and 37 CFR 1.290 and is being entered in the application. Please allow a few days for the submission to be visible in the Patent Application Information Retrieval (PAIR) system.

/MARIANNE C SEIDEL/
Quality Assurance Specialist, Art Unit 1600

PTO-90C (Rev.04-03)

Concise Description of Relevance

VEGF Trap-Eye for the Treatment of Neovascular Age-Related Macular Degeneration

James A. Dixon et al. *Expert Opin. Investig. Drugs* (**2009**) 18(10):1573-1580 (hereafter "Dixon")

Dixon is prior art under pre-AIA §102(b) because it published more than one year before the earliest effective filing date (January 13, 2011) of U.S. Application No. 16/159,282 (hereafter "the '282 application).

U.S. Application No. 16/159,282	Relevant disclosure in Dixon
21. A method for treating an angiogenic eye disorder in a patient, said method comprising	**Dixon** is related to clinical trial results of treating neovascular age-related macular degeneration (wet AMD) with VEGF Trap-eye. Wet AMD is an angiogenic eye disorder. *See e.g.*, ***Background/p. 1573***, disclosing that aflibercept (VEGF Trap-eye) is a promising therapy for AMD by interrupting angiogenesis. *See also* the definition of "angiogenic eye disorder" in the '282 application (para. [0004]).
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;	Phase II trial ***(§2.6.2, p. 1576***) teaches that patients with CNV (subfoveal choroidal neovascularization), a subtype of AMD, received monthly dose of 0.5mg or 2mg for 12 weeks (0, 4, 8, 12) followed by treatment of the same dose on a PRN basis. Thus, DIXON teaches AMD patients being treated by (1) a **single initial dose** of 0.5mg or 2mg at **week 0**, followed by **3 secondary doses** in 4-week intervals (*i.e.*, on **week 4, 8 and 12 after the initial dose**); followed by **tertiary doses** on **PRN basis**. **Dixon** further teaches criteria for re-dosing, including basis on visual (ETDRS letters) or anatomical (retinal thickness by OCT).
wherein each secondary dose is administered **4 weeks after the immediately preceding dose**; and	
wherein each **tertiary dose is administered on an as-needed/pro re nata (PRN) basis, based on visual and/or anatomical outcomes as assessed by a physician or other qualified medical professional**;	
wherein the **VEGF antagonist** is a receptor-based chimeric molecule comprising an immunoglobin-like (Ig) domain 2 of a first VEGF receptor and Ig domain 3 of a second VEGF	VEGF Trap-eye is a VEGF antagonist having key binding domains of human VEGFR-1 and -2 combined with a human

receptor, and a multimerizing component.	IgG Fc fragment. (***§2.2, p 1575***)
22. The method of claim 21, wherein the VEGF antagonist is **aflibercept**.	VEGF Trap-eye is chemically identical to aflibercept. (***§2.3, p 1575***)
23. The method of claim 22, wherein all doses of the VEGF antagonist are administered to the patient by **intraocular** administration.	Phase II trial ***(§2.6.2, p. 1576***) teaches AMD patients received VEGF Trap-eye in one eye (*i.e.*, intraocular administration). **Dixon** teaches intravitreal injection throughout.
24. The method of claim 23, wherein the intraocular administration is **intravitreal** administration.	Phase II trial ***(§2.6.2, p. 1576***) teaches AMD patients received VEGF Trap-eye in one eye (*i.e.*, intraocular administration). **Dixon** teaches intravitreal injection throughout.
25. The method of claim 24, wherein all doses of the VEGF antagonist comprise from about **0.5 mg** to about **2 mg** of the VEGF antagonist.	Phase II trial ***(§2.6.2, p. 1576***) teaches AMD patients received VEGF Trap-eye in 0.5mg or 2mg per dose.
28. The method of claim 27, 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.	AMD is an angiogenic eye disorder.
29. The method of claim 28 wherein the angiogenic eye disorder is age related macular degeneration.	AMD is an angiogenic eye disorder.
30. The method of claim 28 wherein the angiogenic eye disorder is diabetic retinopathy.	VEGF Trap-Eye was used to treat diabetic retinopathy (***§2.6.1, p1575, the third paragraph***).
31. The method of claim 28, wherein the angiogenic eye disorder is diabetic macular edema.	VEGF Trap-Eye was used to treat diabetic macular edema ***(§2.6.1, p1575, the fourth paragraph***).

Concise Description of Relevance

Enrollment Completed in Regeneron and Bayer HealthCare Two Phase 3 Studies of VEGF Trap-Eye in Neovascular Age-Related Macular Degeneration (Wet AMD)

Regeneron Press Release dated **September 14, 2009** (hereafter "**Regeneron**")

https://newsroom.regeneron.com/static-files/661111b9-3da3-459b-b0da-c74f00ab4b32

Regeneron is prior art under pre-AIA §102(b) because it published more than one year before the earliest effective filing date (January 13, 2011) of U.S. Application No. 16/159,282 (hereafter "the '282 application."

U.S. Application No. 16/159,282	Relevant disclosure in Regeneron (with evidentiary support from Dixon)
32. A method for treating an angiogenic eye disorder in a patient, said method comprising	**Regeneron** discloses the VIEW Program, which included Phase 3 studies for treating neovascular age-related macular degeneration (wet AMD). Wet AMD is a known angiogenic eye disorder. *See also* definition of "angiogenic eye disorder" in the '282 application (para. [0004]).
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;	The VIEW Program teaches patients with wet AMD are to receive regular doses of 0.5mg or 2mg VEGF Trap-eye at 4-week intervals in the first year, followed by continued treatment for another year on a flexible, criteria-based extended PRN regimen with a dose administered ***at least every 12 weeks***, but not more often than every four weeks. Thus, **Regeneron** teaches AMD patients being treated by (1) a ***single initial dose*** of 0.5mg or 2mg, followed by (2) ***secondary doses at 4-week intervals*** for a year, followed by (3) treatment for another year based on a flexible schedule, which would include ***at least one tertiary dose at 12-week*** from the immediately preceding dose. *See also*, Example 4 of the '282 application, which tracks closely to the VIEW program. Example 4 provides the written support for the dosing regimen recited in claim 32.
wherein each secondary dose is administered **4 weeks** after the immediately preceding dose; and	
wherein each tertiary dose is administered **12 weeks** after the immediately preceding dose;	
wherein the VEGF antagonist is a receptor-	VEGF Trap-eye is an anti-VEGF agent, a soluble

based chimeric molecule comprising an immunoglobin-like (Ig) domain 2 of a first VEGF receptor and Ig domain 3 of a second VEGF receptor, and a multimerizing component.	VEGF receptor fusion protein that binds all forms of VEGF-A along with the related placental growth factor (PIGF). *See* "About VEGF Trap-Eye; *see also* evidentiary support in **Dixon**.
33. The method of claim 22*, wherein the VEGF antagonist is **aflibercept**. * *It appears that claim 32 was intended.*	VEGF Trap-eye is chemically identical to aflibercept. *See also* evidentiary support in **Dixon (*§2.3, p 1575*)**.
34. The method of claim 23*, wherein all doses of the VEGF antagonist are administered to the patient by **intraocular** administration. * *It appears that claim 33 was intended.*	The VIEW program evaluates the effect of VEGF Trap-eye "on maintaining and improving vision when dosed as an ***intravitreal*** injection…" *See* the first paragraph. Intravitreal injection is a type of intraocular administration.
35. The method of claim 23*, wherein the intraocular administration is **intravitreal** administration. * *It appears that claim 33 was intended.*	The VIEW program evaluates the effect of VEGF Trap-eye "on maintaining and improving vision when dosed as an ***intravitreal*** injection…" *See* the first paragraph of page 1.
36. The method of claim 25*, wherein all doses of the VEGF antagonist comprise from about **0.5 mg** to about **2 mg** of the VEGF antagonist. * *It appears that claim 35 was intended.*	The VIEW program evaluates the effect of VEGF Trap-eye of two dosing strengths (0.5mg and 2mg) administered on regular schedules. *See* paragraph 1 and paragraph 4 on page 1.
37. The method of claim 36, wherein all doses of the VEGF antagonist comprise **0.5 mg** of the VEGF antagonist.	
38. The method of claim 36, wherein all doses of the VEGF antagonist comprise **2 mg** of the VEGF antagonist.	
39. The method of claim 36, 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	**Regeneron** teaches that VEGF Trap-eye is used for treating eye diseases, including wet AMD, diabetic macular edema (DME), and Central Retinal Vein Occlusion (CRVO). *See* the second paragraph on page 1.

corneal neovascularization.	
40. The method of claim 39 wherein the angiogenic eye disorder is age related macular degeneration.	**Regeneron** teaches treating AMD throughout.
41. The method of claim 39 wherein the angiogenic eye disorder is diabetic retinopathy.	**Regeneron** teaches that the primary endpoint is evaluated using the standard Early Treatment Diabetic Retinopathy Study (ETDRS) chart for visual acuity, suggesting that an effective therapy for treating AMD could also be used to treat diabetic retinopathy.
42. The method of claim 39, wherein the angiogenic eye disorder is diabetic macular edema.	**Regeneron** teaches VEGF Trap-eye is also for treatment of diabetic macular edema. *See* the second paragraph on page 2.

Doc Code: 3P.RELEVANCE
Document Description: Concise Description of Relevance

U.S. Patent and Trademark Office
Department of Commerce

THIRD-PARTY SUBMISSION UNDER 37 CFR 1.290
CONCISE DESCRIPTION OF RELEVANCE

Application Number	16159282

U.S. PATENTS

Cite No	Patent Number	Concise Description of Relevance

U.S. PATENT APPLICATION PUBLICATION

Cite No	Publication Number	Concise Description of Relevance

FOREIGN PATENT DOCUMENTS		
CiteNo	**Foreign Document Number**	**Concise Description of Relevance**

NON-PATENT PUBLICATIONS		
Cite No	**Reference**	**Concise Description of Relevance**
1	Regeneron Press Release dated September 14, 2009	See Attached

2	James A. Dixon et al., Expert Opin. Investig. Drugs (2009) 18(10):1573-1580	See Attached

PTO/SB/429(08-12)
Approved for use through 07/31/2015. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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THIRD-PARTY SUBMISSION UNDER 37 CFR 1.290	Application Number	16159282

U.S. PATENTS				
Cite No	Patent Number	Kind Code[1]	Issue Date (YYYY-MM-DD)	First Named Inventor

U.S. PATENT APPLICATION PUBLICATIONS				
Cite No	Publication Number	Kind Code[1]	Publication Date (YYYY-MM-DD)	First Named Inventor

FOREIGN PATENTS AND PUBLISHED FOREIGN PATENT APPLICATIONS						
Cite No	Foreign Document Number[3]	Country Code[2]	Kind Code[1]	Publication Date (YYYY-MM-DD)	Applicant, Patentee or First Named Inventor	T[5]
						☐

NON-PATENT PUBLICATIONS (e.g., journal article, Office action)			
Cite No	Author (if any), title of the publication, page(s) being submitted, publication date, publisher (where available), place of publication (where available).	T[5]	E[6]

THIRD-PARTY SUBMISSION UNDER 37 CFR 1.290	Application Number	16159282

1	James A. Dixon et al., Expert Opin. Investig. Drugs (2009) 18(10):1573-1580	☐	☐
2	Regeneron Press Release dated September 14, 2009	☐	☐

STATEMENTS

The party making the submission is not an individual who has a duty to disclose information with respect to the above-identified application under 37 CFR 1.56.

This submission complies with the requirements of 35 U.S.C. 122(e) and 37 CFR 1.290.

☐ The fee set forth in 37 CFR 1.290(f) has been submitted herewith.

☒ The fee set forth in 37 CFR 1.290(f) is not required because this submission lists three or fewer total items and, to the knowledge of the person signing the statement after making reasonable inquiry, this submission is the first and the only submission under 35 U.S.C 122(e) filed in the above-identified application by the party making the submission or by a party in privity with the party.

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THIRD-PARTY SUBMISSION UNDER 37 CFR 1.290	Application Number	16159282

Signature	/Michael Berry/		
Name/Print	Michael Berry	Registration Number (if applicable)	
Examiner Signature		Date Considered	

*EXAMINER: Signature indicates all documents listed above have been considered,except for citations through which a line is drawn. Draw line through citation if not considered. Include a copy of this form with next communication to applicant. 1. If known, enter kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16. See MPEP 901.04(a). 2. Enter the country or patent office that issued the document, by two-letter code under WIPO standard ST.3. See MPEP 1851. 3. For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. 4. If known, enter the kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 . See MPEP 901.04(a). 5. Check mark indicates translation attached. 6. Check mark indicates evidence of publication attached.

Electronic Acknowledgement Receipt	
EFS ID:	36133892
Application Number:	16159282
International Application Number:	
Confirmation Number:	8618
Title of Invention:	
First Named Inventor/Applicant Name:	
Correspondence Address:	- - - - - - - - - - -
Filer:	Michael Berry
Filer Authorized By:	
Attorney Docket Number:	
Receipt Date:	28-MAY-2019
Filing Date:	
Time Stamp:	18:48:57
Application Type:	

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Non Patent Literature	Expert_Opinion_2009_Dixon.PDF	309524 2c3c83ba00e8ab387c5811f4e8a8cd525b78e5c8	no	8
Warnings:					
Information:					
2	Non Patent Literature	REGN_News_2009_9_14_General_Releases.PDF	19451 e3bd0705cfeb86d02dd060253ce18d308faa9985	no	2
Warnings:					
Information:					
3	Concise Description of Relevance	Concise_Description_of_Relevance_Dixon.pdf	126013 799231529e1c7dc8e3ca6157997f40484631c099	no	2
Warnings:					
Information:					
4	Concise Description of Relevance	Concise_Description_of_Relevance_Regeneron.pdf	129770 e0e1d202349cb183cbcc9d2d4a02388680c27991	no	3
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Information:					
5	Concise Description of Relevance	Concise-description-generated.pdf	29880 ae58db77ab1df26a286651d7edc3d47bd40693a5	no	3
Warnings:					
Information:					
6	Third-Party Submission Under 37 CFR 1.290	Third-party-preissuance-submission.pdf	42846 a9a51a283af49cfe20e69f4f802c10f06a583271	no	3
Warnings:					
Information:					
7	Request for Notification of Non-compliant Third-Party Submission	Third-party-notification-request.pdf	19739 7952fd2c976baa92be77b598e0026bbcd475d8a4	no	1
Warnings:					
Information:					

Total Files Size (in bytes):	677223

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New Applications Under 35 U.S.C. 111

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

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Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO) (GALILEO)

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Read our disclaimer for details.

ClinicalTrials.gov Identifier: NCT01012973

Recruitment Status : Completed
First Posted : November 13, 2009
Results First Posted : November 22, 2012
Last Update Posted : November 3, 2014

Sponsor:
Bayer

Collaborator:
Regeneron Pharmaceuticals

Information provided by (Responsible Party):
Bayer

Study Details | Tabular View | Study Results | Disclaimer | How to Read a Study Record

Samsung Bioepis Exhibit 1012 - Page 159
Biocon Exhibit 1012 - Page 159

Study Description

Go to

Brief Summary:

To determine the efficacy of vascular endothelial growth factor (VEGF) Trap-Eye injected into the eye on vision function in subjects with macular edema as a consequence of central retinal vein occlusion

Condition or disease	Intervention/treatment	Phase
Retinal Vein Occlusion	Biological: Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321) Other: Sham treatment	Phase 3

Study Design

Go to

Study Type	:	Interventional (Clinical Trial)
Actual Enrollment	:	177 participants
Allocation:		Randomized
Intervention Model:		Parallel Assignment
Masking:		Triple (Participant, Investigator, Outcomes Assessor)
Primary Purpose:		Treatment
Official Title:		A Randomized, Double-masked, Sham-controlled Phase 3 Study of the Efficacy, Safety and Tolerability of Repeated Intravitreal Administration of VEGF Trap-Eye in Subjects With Macular Edema Secondary to Central Retinal Vein Occlusion (CRVO)
Study Start Date	:	October 2009
Actual Primary Completion Date	:	February 2011
Actual Study Completion Date	:	February 2012

Resource links provided by the National Library of Medicine

NIH NLM

MedlinePlus related topics: Edema

Drug Information available for: Aflibercept Ziv-aflibercept

U.S. FDA Resources

Samsung Bioepis Exhibit 1012 - Page 160
Biocon Exhibit 1012 - Page 160

Arms and Interventions

Go to

Arm	Intervention/treatment
Experimental: Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321) Participants received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered every 4 weeks from Day 1 through Week 20, later as often as every 4 weeks depending on the study retreatment criteria from Week 24 through Week 48. Follow-up phase: Participants on IAI, who continued the study, received 2 mg dose of IAI depending on the study retreatment criteria at Week 60 and 68.	Biological: Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321) Intravitreal injection. Weeks 0 to 20 of Aflibercept Injection every 4 weeks; Weeks 24 to 52 every 4 weeks PRN (pro re nata, on demand); plus additional on Week 60 and 68. Other: Sham treatment Sham treatment. Weeks 0 to 52 sham treatment every 4 weeks; plus additional on Week 60 and 68.
Sham Comparator: Sham treatment Participants received sham treatment administered every 4 weeks from Day 1 through Week 52. Follow-up phase: Participants on sham treatment, who switched to Intravitreal Aflibercept Injection (IAI), received a 2 mg dose of IAI at week 52 and depending on the study retreatment criteria at Week 60 and 68.	Other: Sham treatment Sham treatment. Weeks 0 to 52 sham treatment every 4 weeks; plus additional on Week 60 and 68.

Outcome Measures

Go to

Primary Outcome Measures :

1. Percentage of Participants Who Gained at Least 15 Letters in BCVA as Measured by ETDRS Letter Score Compared With Baseline at Week 24 With Discontinued Participants Before Week 24 Evaluated as Failures [Time Frame: Baseline and Week 24]

Samsung Bioepis Exhibit 1012 - Page 161
Biocon Exhibit 1012 - Page 161

Defined study baseline range of Early Treatment Diabetic Retinopathy Study (ETDRS) Best Corrected Visual Acuity (BCVA) letter score of 73 to 24 (= Acuity of 20/40 to 20/320) in the study eye; a higher score represents better functioning. Nominator = (Number of participants who maintained vision * 100); Denominator = Number of participants analyzed.

Secondary Outcome Measures :

1. Change From Baseline in BCVA as Measured by Early Treatment Diabetic Retinopathy Study (ETDRS) Letter Score at Week 24 - Last Observation Carried Forward (LOCF) [Time Frame: Baseline and Week 24]

   Defined study baseline range of ETDRS Best Corrected Visual Acuity letter score of 73 to 24 (= Acuity of 20/40 to 20/320) in the study eye; a higher score represents better functioning. However, because this was assessed at the screening visit, subjects may have had a higher BCVA recorded at the baseline visit and would not have been excluded from the study.

2. Change From Baseline in Central Retinal Thickness (CRT) at Week 24 - LOCF [Time Frame: Baseline and Week 24]
3. Percentage of Participants Who Developed Neovascularization During the First 24 Weeks [Time Frame: From baseline until Week 24]

   Formation of blood vessels in the anterior segment, optic disc, or elsewhere in the fundus up to Week 24

4. Change From Baseline in National Eye Institute 25-item Visual Function Questionnaire (NEI VFQ-25) Total Score at Week 24 - LOCF [Time Frame: Baseline and Week 24]

   The NEI VFQ-25 total score ranges from 0-100 with a score of 0 being the worst outcome and 100 being the best outcome. The NEI VFQ questionnaire is organized as a collection of subscales which are all scored from 0-100. To reach the overall composite score, each sub-scale score is averaged in order to give each sub-scale equal weight

5. Change From Baseline in European Five-dimensional Health Scale (EQ-5D) Score at Week 24 - LOCF [Time Frame: Baseline and Week 24]

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EQ-5D is a quality of life questionnaire based on a scale from -0.594 (worst) to 1.00 (best).

Eligibility Criteria

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Ages Eligible for Study:	18 Years and older (Adult, Older Adult)
Sexes Eligible for Study:	All
Accepts Healthy Volunteers:	No

Criteria

Inclusion Criteria:

- Center-involved macular edema secondary to central retinal vein occlusion (CRVO) for no longer than 9 months with mean central subfield thickness ≥ 250 µm on optical coherence tomography (OCT)
- Adults ≥ 18 years
- Early treatment diabetic retinopathy study (ETDRS) best corrected visual acuity (BCVA) of 20/40 to 20/320 (73 to 24 letters) in the study eye

Exclusion Criteria:

- Any prior treatment with anti-VEGF agents in the study eye (Pegaptanib sodium, anecortave acetate, bevacizumab, ranibizumab, etc.) or previous administration of systemic anti-angiogenic medications
- Prior panretinal laser photocoagulation or macular laser photocoagulation in the study eye
- CRVO disease duration > 9 months from date of diagnosis

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- Previous use of intraocular corticosteroids in the study eye or use of periocular corticosteroids in the study eye within the 3 months prior to Day 1
- Iris neovascularization, vitreous hemorrhage, traction retinal detachment, or preretinal fibrosis involving the macula in either the study eye or fellow eye

Contacts and Locations

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Publications of Results:

Holz FG, Roider J, Ogura Y, Korobelnik JF, Simader C, Groetzbach G, Vitti R, Berliner AJ, Hiemeyer F, Beckmann K, Zeitz O, Sandbrink R. VEGF Trap-Eye for macular oedema

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secondary to central retinal vein occlusion: 6-month results of the phase III GALILEO study. Br J Ophthalmol. 2013 Mar;97(3):278-84. doi: 10.1136/bjophthalmol-2012-301504. Epub 2013 Jan 7. Erratum in: Br J Ophthalmol. 2015 Dec;99(12):1746.

Korobelnik JF, Holz FG, Roider J, Ogura Y, Simader C, Schmidt-Erfurth U, Lorenz K, Honda M, Vitti R, Berliner AJ, Hiemeyer F, Stemper B, Zeitz O, Sandbrink R; GALILEO Study Group. Intravitreal Aflibercept Injection for Macular Edema Resulting from Central Retinal Vein Occlusion: One-Year Results of the Phase 3 GALILEO Study. Ophthalmology. 2014 Jan;121(1):202-208. doi: 10.1016/j.ophtha.2013.08.012. Epub 2013 Sep 29.

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Other Study ID Numbers:	14130
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- Macular Edema
- Central Retinal Vein Occlusion
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- VEGF Trap-Eye
- best-corrected visual acuity

Additional relevant MeSH terms:

Retinal Vein Occlusion	Thrombosis
Retinal Diseases	Embolism and Thrombosis
Eye Diseases	Vascular Diseases
Venous Thrombosis	Cardiovascular Diseases

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Intravitreal bevacizumab (Avastin) in the treatment of macular edema secondary to retinal vein occlusion

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Objective: To evaluate efficacy and safety of intravitreal injections of bevacizumab in the treatment of macular edema secondary to retinal vein occlusion (RVO).

Methods: Prospective study, noncomparative, interventional case series. Twelve consecutive patients (12 eyes) with macular edema associated with nonischemic retinal vein occlusion were treated with intravitreal bevacizumab (1.25 mg). All subjects underwent standardized ophthalmic evaluation at baseline and at weeks 1, 4, 12, and 24, consisting of visual acuity (VA) measurement using ETDRS charts, and imaging with ocular coherence tomography evaluating changes in foveal thickness (FT) and macular volume (MV).

Results: The median age was 66 years (± 4.16), and the median duration of symptoms was 4 months (± 1.81). There were six cases of inferior branch vein occlusion and six cases of superior branch retinal vein occlusion. Mean VA improved from 1.32 ± 0.24 (logMAR values) at baseline to 0.8 ± 0.15 ($p = 0.0003$) at the 6-month follow-up. The macular edema responded promptly, and a trend to restoration of normal macular anatomy was observed at by the seventh day. Mean FT improved from 615.50 ± 116.29 microns to 420 ± 72.53 microns ($p = 0.001$), and the mean MV improved from 19.81 ± 2.31mm3 to 9.23 ± 1.38 ($p = 0.0001$) at the 6-month follow-up.

Keywords: Bevacizumab, retinal vein occlusion, intravitreal injection, vascular endothelial growth factor

Introduction

Retinal vein occlusion (RVO) is the second most common retinal vascular disease, after diabetic retinopathy. Visual loss may result from ischemic damage and/or macular edema. Early treatment may be required to improve vision because longstanding macular edema results in irreversible photoreceptor damage (CRVO 1995). Intravitreal triamcinolone is a treatment option that has demonstrated promising short-term results for the management of macular edema associated with RVO (Mohammed et al 2007). A multicenter, randomized and controlled clinical trial (Standard Care Versus Corticosteroid for Retina Vein Occlusion Study) is currently underway.

Retinal vein occlusion is associated with varying amounts of retinal ischaemia and, consequently, increased concentrations of vascular endothelial growth factor (VEGF) (Hayreh 1983). Early case reports on bevacizumab showed an increase in visual acuity (VA) and a decrease in macular edema secondary to exudative age-related macular degeneration (AMD) and central retinal vein occlusion (CRVO) (Rosenfeld et al 2005a). A nonrandomized study of intravitreal bevacizumab in patients with CRVO resulted in reduced macular swelling and increased VA (Iturralde et al 2006). However, because a physiological level of vascular endothelial growth factor may be necessary to maintain the homeostasis of the retina, care might be required to avoid the possible negative consequences of a complete blockade of VEGF.

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These reports, along with results from preclinical and human studies that suggest a possible role of VEGF in RVO and the absence of a proven therapy, prompted us to investigate the effects of intravitreal bevacizumab injection in patients with macular edema associated with RVO.

Methods

Study design

This was a prospective, consecutive, noncomparative study that adhered to the Declaration of Helsinki and which was approved by our institutional review board. An intravitreal off-label bevacizumab injection was recommended. The Spanish Ministry of Health and Consumer Affairs approved compassionate use. Patients were fully informed verbally about the experimental nature of the treatment and they signed an informed consent form.

Cases were recruited from the Hospital Universitari de Bellvitge (Barcelona, Spain) from January–March 2007. Inclusion criteria were: 1) patients aged 50 or older 2) macular edema secondary to nonischemic RVO and 3) VA between 20/400 and 20/50 (Snellen equivalent). Exclusion criteria were: 1) history of retinal surgery or photocoagulation; 2) any history of a thromboembolic event; 3) bleeding disorders; and 4) use of anticoagulative medication other than aspirin. No patient refused treatment.

A comprehensive ophthalmic evaluation was performed; it included a medical history review, best corrected visual acuity testing (using ETDRS charts), slit-lamp biomicroscopy, dilated funduscopic examination using a 78-diopters lens and time domain ocular computed tomography (OCT) (Carl Zeiss Meditec, Dublin, CA, USA) that consisted of an acquisition protocol "Radial lines" (6 linear, 6 mm scans oriented at intervals of 30° and centered on the foveal region). Macular maps were obtained using the "retinal thickness/volume" analysis protocol, and values for central foveal thickness (FT) and total macular volume (MV) were recorded. Follow-up examinations were scheduled at weeks 1, 4, 12, and 24 post-injection, or on demand, if a decrease in VA was noted by the patient. These follow-up examinations used exactly the same procedures as those used in the baseline visit. The incidence of adverse events were monitored throughout the study. The effects of treatment, both on VA and on anatomical changes in the macula shown by OCT, were evaluated. There was no loss of follow-up.

Treatment procedure

Patients received an intravitreal dosage of bevacizumab of 1.25 mg (0.05 mL) at baseline and once every four weeks if OCT indicated macular swelling (quantitatively characterized by a macular thickness larger than 250 microns in any of the six radial scans). All treatments were performed in the office using topical anaesthesia (tetracaine+oxibuprocaine) under sterile conditions. Bevacizumab was injected (using a 30-G needle) through the inferotemporal pars plana, 3.5 mm (pseudophakic) or 4 mm (phakic) posterior to the limbus. A drop of ofloxacine was applied to the affected eye immediately after the procedure and again every 6 hours for 4 days.

Statistical data analysis

All data were collected in an Microsoft Excel 2000 spreadsheet (Microsoft Corporation, Spain). For statistical analysis, the Wilcoxon test was performed. VA measurements were converted to logMAR equivalents to perform analysis. $p < 0.05$ was considered significant.

Results

Twelve patients (seven women and five men) were included. The median age was 66 years and the median duration of symptoms prior to treatment was 4 months. Vein occlusion was located at the inferior branch in six patients and at the superior branch in the remaining six patients. There was a history of hypertension in four patients. All patients completed the 24-week follow-up examination; their baseline characteristics are summarized in Table 1.

Best corrected visual acuity (BCVA) data obtained over the course of the study are summarized in Table 2. Evaluation of BCVA revealed significant improvement at all times compared with baseline. Mean VA improved from 1.32 ± 0.24 (logMAR values) at baseline, to 0.8 ± 0.15 ($p = 0.0003$) at the 6-month follow-up. The macular edema responded promptly, and a reduction in the submacular fluid was observed at the seventh day. At baseline, the mean FT was 615.50 ± 116.29 microns; it declined to 420 ± 72.53 microns ($p = 0.001$). The mean MV improved from 19.81 ± 2.31 mm^3 to 9.23 ± 1.38 mm^3 ($p = 0.0001$) at the 6-month follow-up. Mean changes in parameters recorded by OCT on weeks 1, 4, 12, and 24 post-injection are summarized in Table 3. Overall, four patients were retreated: 2 patients received two consecutive injections of intravitreal bevacizumab, and two patients received three injections. No ocular or systemic adverse events were observed.

Discussion

This study demonstrates the early and clinically relevant benefits of bevacizumab injection for macular edema due to RVO. In this prospective case series, we found that intravitreal

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Table 1 Baseline characteristics

Case, age, sex	Affected ye, localization	Duration (months)	logMAR BCVA	OCT FT (microns)	OCT MV (mm^3)
1, 64, F	OD, inferior	2.5	0.63	664	12.91
2, 63, F	OD, inferior	5	1.7	545	22.17
3, 75, M	OD, superior	6	1.05	410	16.65
4, 57, M	OD, superior	3	1.63	667	21.23
5, 67, F	OD, superior	2.5	1.96	601	20.82
6, 66, F	OS, inferior	2	0.62	763	11.9
7, 61 F	OD, superior	3	1.6	495	21.16
8, 75, F	OD, superior	4	1.04	630	15.64
9, 77, M	OS, superior	4	1.62	239	20.22
10, 66, M	OS, inferior	7	1.34	885	12.97
11, 59, M	OS, inferior	6	1.3	498	11.2
12, 79, F	OS, inferior	7	0.96	998	19.81
Median: 66 SD: 7,26 Confidence intervals (CI): 4.16		Median: 4 SD: 1.81 CI: 1.02	Median: 1.32 SD: 0.43 CI: 0.24	Median: 615.50 SD: 205.547 CI: 116.29	Median: 19.81 SD: 4.10 CI: 2.31

Abbreviations: F, female; M, male; SD, standard deviation; OD, right eye; OS, left eye; BCVA, best corrected visual activity; FT, foveal thickness; MV, macular volume.

injections of bevacizumab led both to a significant reduction of FT, as well as to an improvement of visual acuity in patients with RVO. A beneficial effect of intravitreal bevacizumab was observerd as early as the first week and over a 6-month follow-up period.

Our study supports the preliminary results of several recently published papers. The most detailed data on the natural history of CRVO were provided by the Central Vein Occlusion Study Group (CRVO 1995). Clinical outcomes of every new treatment option for CRVO must match with these data. In the natural course of CRVO, only 19% of patients with initial visual acuity of less than 20/200 had a chance of visual acuity of better than 20/200. Patients presenting with initial visual acuity between 20/200 and 20/50 had improvement to better than 20/50 in 19% of cases; in 44% of cases acuity stayed between 20/200 and 20/50. The visual acuity of only 37% of patients became worse than 20/200. Compared with these data, patients treated with intravitreal injections of bevacizumab showed much greater improvement. Priglinger and colleagues (2007) reported improvement in visual acuity from 20/250 at baseline to 20/80 at the 6-month follow-up ($p < 0.001$) in a group of 46 CRVO patients. Mean central retinal thickness decreased from 535 ± 48 microns at baseline to 323 ± 116 microns at the 6-month follow-up (Priglinger et al 2007). In a series of 30 CRVO patients followed for 6 months, Jason and colleagues (2007) reported improvement in VA from 20/394 at baseline to 20/313 at the 3-month follow-up, ($p < 0.05$) and no significant changes after the fourth month. This indicates that bevacizumab represents an effective treatment option for CRVO and that the drug may improve the long-term prognosis of CRVO.

The intravitreal use of bevacizumab may provide anatomical and functional amelioration of the macula in patients with macular edema due to RVO. The electrical responses in the fovea and parafovea of the multifocal electroretinography recording depict a significant improvement at 1 and 3 months after the injection (Moschos and Moschos 2008).

Table 2 logMAR BCVA (baseline and 1, 4 12, and 24 weeks post-injection)

logMAR BCVA baseline	logMAR BCVA, week 1	logMAR BCVA week 4	logMAR BCVA week 12	logMAR BCVA week 24
0.63	0.35	0.17	0.23	0.43
1.7	1.3	0.75	0.77	0.77
1.05	1.01	1.03	1	0.89
1.63	1.47	1.2	1.35	1.17
1.96	0.4	0.43	0.61	0.53
0.62	0.36	0.17	0.23	0.42
1.6	1.2	0.75	0.78	0.76
1.04	1.02	1.02	1	0.86
1.62	1.48	1.3	1.36	1.19
1.34	1	0.78	0.86	0.83
1.3	1.28	1.24	1.28	1.25
0.96	0.5	0.42	0.62	0.56

Note: p (baseline-week 24) = 0.0003
Abbreviation: BCVA, best corrected visual acuity.

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Table 3 FT (microns) and MV (mm3) (baseline and 1, 4, 12, and 24 week post-injection)

Case 1	Baseline	Week 1	Week 4	Week 12	Week 24
FT	664	220	166	167	189
MV	12.91	8.48	7.87	8.38	8.34
Case 2					
FT	545	440	165	481	654
MV	22.17	6.96	6.64	9.33	8.35
Case 3					
FT	410	166	496	509	578
MV	16.65	12.17	13.2	13.95	12.95
Case 4					
FT	667	565	459	500	475
MV	21.23	17.32	15.16	15.69	14.63
Case 5					
FT	601	436	175	501	420
MV	20.82	6.66	6.83	9.2	9.5
Case 6					
FT	763	400	170	456	432
MV	11.9	7.47	6.86	7.37	10.56
Case 7					
FT	495	175	195	225	235
MV	21.16	5.95	5.63	8.32	7.35
Case 8					
FT	630	220	460	335	342
MV	15.64	11.16	12.1	12.94	10.55
Case 9					
FT	239	442	336	402	389
MV	20.22	16.31	12.1	14.68	12.48
Case 10					
FT	885	296	450	425	420
MV	12.97	6.25	10.91	10.55	8.95
Case 11					
FT	498	345	450	356	352
MV	11.2	10.72	5.82	10.97	7.55
Case 12					
FT	998	425	182	522	425
MV	19.81	5.55	5.85	8.1	6.98

Notes: p (baseline- week 24): FT = 0.001 MV = 0.0001
Abbreviations: FT, foveal thickness; MV, and macular volume.

Intravitreal injection of triamcinolone acetonide (TA) is another treatment option aimed to reduce macular edema after RVO. Several recent studies report favorable effects of intravitreal injection (4–20 mg) of TA on the course of RVO (Gregory et al 2006). The extent and duration of the effect of intravitreal injection of TA depends on the dose used and the presence of retinal ischemia (Jonas et al 2005). Repeated intravitreal injections of TA are possible; however, after repeated treatments, the effect on reduction of retinal thickness and increase in visual acuity are reduced (Boyd et al 2002; Kupperman et al 2007). Furthermore, although apparently improving the clinical outcome of RVO, repeated intravitreal injections of TA are associated with many potential complications, such as elevated intraocular pressure and cataract formation, which may ultimately decrease the long-term prognosis of RVO (Goff et al 2006). In contrast to intravitreal injection of TA, several injections of bevacizumab appear to have no drug-related complications. However, complications related to repeated intravitreal injections (eg, endophthalmitis, retinal tear, and lens trauma) must be taken into account (Jaissle et al 2006). Fortunately, none of these complications occurred in the present case series; this may be due to the thorough prophylactic, antiseptic regimen applied in our institution to minimize the likelihood of bacterial contamination.

The use of anti-VEGF agents in retinal disease has become increasingly common since the approval (in 2004 and 2006, respectively) of pegaptanib and ranibizumab for age-related maculopathy. These agents are currently being studied for their efficacy against macular edema due to RVO. The anti-VEGF agent most studied in regard to RVO is bevacizumab. Off-label intravitreal injection of bevacizumab was first reported in 2005 to represent a potential therapy for macular edema secondary to CRVO (Rosenfeld et al 2005b). Since then, several additional publications have reported favorable short-term results for reduction of macular edema and improvement of vision in patients with RVO (Spandau et 2006; Pau et al 2007).

Our results suggest a possible short-term benefit for macular architecture and VA; however, it is also clear that such benefits are transient. Continuous VEGF suppression may be required to sustain beneficial effects observed in the short term and the risks associated with multiple intravitreal injections need to be considered. Our data suggest that patients may require several injections to maintain efficacy. Three to four months after the most recent injection, worsening VA was detected in about half of the cases. The data in this study suggest that a single injection of intravitreal bevacizumab has a limited beneficial effect for approximately two months in most patients.

Although VEGF and its receptors represent potential targets for pharmacologic intervention, several important questions remain. Does VEGF play a role in the formation of vascular shunts across ischemic areas? Does continuous blockage of VEGF have a negative effect over the long term? Furthermore, recurrent macular edema may occur in patients

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with RVO following treatment with bevacizumab; in some cases, the recurrent macular edema may be more severe than the pre-treatment macular edema (a phenomenon known as "rebound" macular edema) (Matsumoto et al 2007).

The changes observed throughout the present study may provide important clues about drug effects and duration. Favorable macular changes, documented by OCT, were evident as soon as day 7 post-injection. While these improvements were maintained at post-injection week 4, there was a clear tendency for macular edema to recur around week 12; this suggests, therefore, that reinjections might be considered at some point during this period when a 1.25 mg dose regimen is used in setting of ischemic or nonischemic RVO.

The present study does have some limitations that must be recognized: there was no control group; we included only 12 patients and there was only a limited follow-up. However, the promising results reported here indicate that further studies of intravitreal bevacizumab injection for the management of ischemic or nonischemic RVO are justified. Future well-designed studies will help to establish the role of antiangiogenic therapy in the management of RVO.

Disclosure

The authors report no conflicts of interest in this work.

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Vascular endothelial growth factor Trap-Eye for diabetic macular oedema

Peter K Kaiser

Diabetic macular oedema (DMO) is the leading cause of visual loss in working-aged Americans, and as such successful treatment is of major public health importance. The gold standard is laser photocoagulation based on the landmark Early Treatment Diabetic Retinopathy Study (ETDRS).[1] In the ETDRS, laser treatment reduced the 3-year risk of moderate visual loss by 50%; however, the standard teaching is that patients in the ETDRS rarely improved vision. In fact, in the published ETDRS manuscripts to date, only around 10% of patients gained more than three lines of vision. This led to the prevailing thinking that laser prevents vision loss, but rarely results in visual improvement. Thus, newer therapies have been explored in an effort to improve outcomes in this common and devastating condition.

Vascular endothelial growth factor (VEGF) was one of the first cytokines implicated in diabetic retinopathy and DMO with elevated VEGF levels found in patients with active disease.[2] Increased retinal capillary permeability due to breakdown of the blood–retina barrier have been shown to be mediated by VEGF.[3] Thus, VEGF appears to be a good target to prevent DMO and progression of diabetic retinopathy.

Several anti-VEGF agents have been evaluated in off-label case series and small-scale clinical trials to treat DMO. In a randomised, phase 2 clinical trial of 172 patients, pegaptanib (Macugen, Eyetech, New York), a VEGF165 specific blocker, resulted in a mean improvement in vision of +4.7 letters with 34% gaining 10 letters of more at 36 weeks.[4] Similarly, the randomised, phase 2 DRCR.net trial of 121 patients with bevacizumab (Avastin, Genentech, South San Francisco, California), a pan-VEGF antibody, reported a mean improvement in vision of +5 letters with 33% having greater than 10 letters of improvement at 12 weeks.[5] Finally, the phase 1/2 Ranibizumab for (O)edema of the Macula in Diabetes (READ) study evaluated ranibizumab (Lucentis, Genentech), an antibody fragment that blocks all forms of VEGF, and reported +12.3 letters of visual improvement at month 7. A pivotal Phase 3 trial testing ranibizumab for DMO is currently under way. In this issue ***(see page 144)***, another VEGF blocker has shown early success in the management of DMO—VEGF Trap-Eye.[6]

Traps consist of two extracellular cytokine receptor domains fused together to a human immunoglobulin G (IgG).[7] VEGF Trap-Eye is a soluble fusion protein that combines ligand-binding elements taken from the extracellular components of VEGF receptors 1 and 2 fused to the Fc portion of IgG1.[8] This protein contains all human amino acid sequences, which minimises the potential for immunogenicity in human patients. Similar to bevacizumab and ranibizumab, VEGF Trap-Eye blocks all isoforms of VEGF and placental growth factor. In the small phase 1, open-label study by Do and colleagues, five patients with DMO were treated with VEGF-Trap Eye with good short-term results and safety.

One may ask why one should develop another extracellular VEGF blocker when we already have bevacizumab and ranibizumab. VEGF Trap-Eye has several features that make it appealing in comparison with the currently available therapeutics. The key feature is the binding constant for VEGF is approximately 0.5 pM Kd, considerably higher than ranibizumab, bevacizumab or even native VEGF receptors. This higher binding affinity translates into greater activity at lower biological levels, and consequently a longer duration of action. Some studies have suggested as long as 10 weeks.[9] This longer duration is very important, as diabetic retinopathy is a chronic condition, and most patients are working. All the anti-VEGF DMO studies to date indicate that when the therapy was stopped, vision returned to baseline, and any gains in retinal thickness and fluorescein leakage were reversed. Thus, continuous treatment may be necessary to maintain the improvements in outcomes. These repeated intravitreal anti-VEGF injections will put a strain on both the healthcare system and patients.

With all anti-VEGF agents, systemic safety needs to be evaluated. All known anti-VEGF therapeutics are detectable in the systemic circulation, often with levels high enough to block all native VEGF. Concerns have been raised about systemic effects including stroke, myocardial infarction and hypertension. Current anti-VEGF studies have been too small to truly evaluate the safety of these drugs in the general population. While a recent meta-analysis with all the randomised ranibizumab studies failed to reveal any increased risk of these events, it also does not mean there is not an increased risk, and we all need to be cognisant of this fact (D Boyer, American Academy of Ophthalmology Meeting, Atlanta, Georgia, 2008).

Finally, one important fact overlooked by many in the ETDRS results and more importantly in the statistical planning for many current clinical trials for DMO is that 85% of the patients in the ETDRS could not improve three lines, since they had vision better than 20/40 at the start of the study.[1] In fact, in a subset of 105 ETDRS patients with definite centre thickening on fundus photographs, less severe retinopathy and a visual acuity letter score <20/32 at baseline, the median change in the visual acuity letter score was +4 letters, with 30% improving 10 or more letters at 2 years.[10] Similarly, the DRCR.net reported at 2 years a mean improvement of 1 letter with 18% gaining three or more lines.[10] So, our old standby, laser, really works better than we thought! All studies with anti-VEGF to date have been too short to truly evaluate the long-term efficacy of this treatment. The DRCR.net showed us that a treatment we thought was better than laser was only better in the short term, and long-term follow-up was necessary to actually show the benefit of laser over steroids in this particular patient population. Thus, we need to wait for the results of ongoing studies with longer follow-up before we declare anti-VEGF therapy a new paradigm in DMO management.

The addition of VEGF-Trap Eye as a possible treatment for DMO is exciting, as it has some appealing features over current anti-VEGF therapies. However, our enthusiasm has to be tempered by

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the short-term nature of this study, the theoretical risks of anti-VEGF therapy and the possible need for continuous therapy to achieve visual gains. Nevertheless, there are many patients who do not respond to laser, and continued exploration into new treatments and even treatment combinations is warranted.

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Competing interests: PKK's employer, the Cole Eye Institute, has received research grant support from Genentech on his behalf. PKK serves on the Scientific Advisory Boards of Genentech and Regeneron. His participation in these boards has been approved and disclosed to the Cleveland Clinic's Conflict of Interest Committee.

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Cover illustration

Lord Shiva's third eye

The cover illustration depicts the Lord Shiva, the third god of the Hindu Trinity (Trimurti), represented by Lord Brahma, Lord Vishnu and Lord Shiva, the Creator, the Preserver and the Destroyer of the universe, respectively. Some contend that the word "destroyer" is used in error as dissolution for creation, as autumn is to spring, is an essential part of the cyclic process of creation, preservation, dissolution and re-creation.

The image of Shiva, as portrayed among Hindus, contains common symbols representative of his superiority. One of these symbols is his third eye, seen in the centre of his forehead; hence he is often referred to as Tryambaka Deva (literally meaning "three-eyed lord"). His right eye is believed to be the sun, the left eye is the moon and his third eye represents fire. His left and right eyes indicate his activity in the physical world. Often Shiva is shown with half open eyes, signifying the never ending, ongoing nature of the birth and destruction of the universe. When the eyes are completely closed it signifies the dissolution of the universe and when it is completely open a new cycle of creation begins.

The third eye can detect evil, even when it is not immediately apparent and the fire that emanates from it can annihilate evil. It also symbolises his activity in the metaphysical, spiritual world and represents the power of knowledge. This eye is seen to be the source of his untamed energy. Once while Shiva was in the midst of worship, the love god, Kama, distracted him. In his anger he opened his third eye, and fire from the eye devoured Kama, until Parvati (Shiva's wife, also known as Kali mata) saved him. For these reasons Shiva is seen as the "destroyer". The power of this eye is so great that it is feared by wrongdoers.

It is said to have appeared when Parvati playfully blindfolded him with her two hands, while he was deep in meditation. Immediately the universe plunged into darkness and chaos reigned supreme. To prevent impending catastrophe, Shiva formed a third eye from which fire emerged to recreate light and order, hence saving the world from inevitable disaster. Throughout imagery of Shiva this eye is depicted as closed or by three horizontal lines in the middle of his forehead. Many Hindus wear a tilak between the eyebrows to represent the third eye, as it is seen as a sign of enlightenment.

Lord Shiva is always shown with a snake (Vasuki Naga, symbol of yogic powers) coiled three times (for the past, present and future) around his neck.

Neeru Dhillon, Arun D Singh, Harminder S Dua

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Vascular endothelial growth factor Trap-Eye for diabetic macular oedema

Peter K Kaiser

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First Named Inventor/Applicant Name:	George D. YANCOPOULOS
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1	Transmittal Letter	0725US6_2020-01-27_Supp_IDS_trans_REGN-008CIPCON5.pdf	51139 825ff5729d58ffff621e277e66a672d99bd5932f	no	2

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INFORMATION DISCLOSURE STATEMENT	Attorney Docket No.	REGN-008CIPCON5
	Confirmation No.	8135
	First Named Inventor	George D. Yancopoulos
	Application Number	16/397,267
	Filing Date	April 29, 2019
	Group Art Unit	
Address to: Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Examiner Name	
	Title: "*Use of a VEGF Antagonist to Treat Angiogenic Eye Disorders*"	

Sir:

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

A listing of the documents is shown on enclosed Form PTO/SB/08A. All documents with the exception of documents (1), (2), (9), (11) and (12) in the non-patent literature were previously submitted and copies are not enclosed. These documents are being relisted on the PTO/SB/08A form to complete the NPL cite from the originally submitted version, for example, article submitted while "In Press".

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

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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-008CIPCON5.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: 27 January 2020

By: /Karl Bozicevic, Reg. No. 28,807/
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	16/397,267
				Filing Date	April 29, 2019
				First Named Inventor	George D. Yancopoulos
				Art Unit	
				Examiner Name	
Sheet	1	of	4	Attorney Docket Number	REGN-008CIPCON5

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				Filing Date	April 29, 2019
				First Named Inventor	George D. Yancopoulos
				Art Unit	
				Examiner Name	
Sheet	4	of	4	Attorney Docket Number	REGN-008CIPCON5

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
	23	Updated Information from ClinicalTrials.gov archive History of Changes for Study: NCT01012973 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)(GALILEO) 12 pages, Latest version submitted October 27, 2014 on ClinicalTrials.gov (NCT01012973_12212010_27443.1)	

Examiner Signature		Date Considered	

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

U.S. National Library of Medicine
ClinicalTrials.gov archive

History of Changes for Study: NCT01012973

Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO) (GALILEO)

Latest version (submitted October 27, 2014) on ClinicalTrials.gov

- A study version is represented by a row in the table.
- Select two study versions to compare. One each from columns A and B.
- Choose either the "Merged" or "Side-by-Side" comparison format to specify how the two study versions are to be displayed. The Side-by-Side format only applies to the Protocol section of the study.
- Click "Compare" to do the comparison and show the differences.
- Select a version's date link to see a rendering of the study for that version.
- Edits or deletions will be displayed in ~~red~~.
- Additions will be displayed in *green*.
- The yellow choices in the table indicate the study versions currently compared below. A yellow row indicates the study version being viewed.
- Hover over the "Recruitment Status" to see how the study's recruitment status changed.

Study Record Versions

Version	A	B	Submitted Date	Changes
1	◉	○	November 12, 2009	Nothing (earliest Version on record)
2	○	○	January 21, 2010	Contacts/Locations, Study Status, Study Identification and Study Description
3	○	○	February 9, 2010	Contacts/Locations and Study Status
4	○	○	March 16, 2010	Contacts/Locations, Study Status and Study Identification
5	○	○	April 16, 2010	Contacts/Locations, Study Status and Study Identification

Version	A	B	Submitted Date	Changes
6	○	○	July 22, 2010	Contacts/Locations, Study Status, Eligibility and Arms and Interventions
7	○	○	August 25, 2010	Study Status and Contacts/Locations
8	○	○	August 26, 2010	Recruitment Status, Study Status and Contacts/Locations
9	○	○	September 8, 2010	Study Status
10	○	○	October 4, 2010	Study Status
11	○	○	November 1, 2010	Study Status
12	○	○	January 25, 2011	Study Status and Contacts/Locations
13	○	○	April 8, 2011	Study Status and Study Design
14	○	○	June 23, 2011	Arms and Interventions, Study Status, Contacts/Locations and Eligibility
15	○	○	September 19, 2011	Study Status
16	○	○	November 29, 2011	Study Status and Study Identification
17	○	○	January 26, 2012	Study Status and Contacts/Locations
18	○	○	February 20, 2012	Recruitment Status, Study Status
19	○	○	October 23, 2012	Outcome Measures, Arms and Interventions, Study Status, More Information, Reported Adverse Events, Baseline Characteristics and Participant Flow
20	○	○	December 18, 2012	More Information, Arms and Interventions, Study Status and Baseline Characteristics
21	○	○	January 18, 2013	Arms and Interventions, More Information, Study Status and Baseline Characteristics
22	○	○	January 30, 2014	Contacts/Locations, Sponsor/Collaborators, More Information, Study Status, Baseline Characteristics and References
23	○	◉	October 27, 2014	More Information, Study Status and References

Compare

Comparison Format: (•) Merged ( ) Side-by-Side

Scroll up to access the controls

Study NCT01012973
on Date: January 18, 2013 (v21)

Study Identification

Unique Protocol ID:	14130
Brief Title:	Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO) (GALILEO)
Official Title:	A Randomized, Double-masked, Sham-controlled Phase 3 Study of the Efficacy, Safety and Tolerability of Repeated Intravitreal Administration of VEGF Trap-Eye in Subjects With Macular Edema Secondary to Central Retinal Vein Occlusion (CRVO)
Secondary IDs:	2009-010973-19 [EudraCT Number]

Study Status

Record Verification:	January 2013
Overall Status:	Completed
Study Start:	October 2009
Primary Completion:	February 2011 [Actual]
Study Completion:	February 2012 [Actual]
First Submitted:	October 30, 2009
First Submitted that Met QC Criteria:	November 12, 2009
First Posted:	November 13, 2009 [Estimate]
Results First Submitted:	October 23, 2012
	October 23, 2012

Results First Submitted that Met QC Criteria:	
Results First Posted:	November 22, 2012 [Estimate]
Certification/Extension First Submitted:	January 26, 2012
Certification/Extension First Submitted that Met QC Criteria:	January 26, 2012
Certification/Extension First Posted:	January 30, 2012 [Estimate]
Last Update Submitted that Met QC Criteria:	January 18, 2013
Last Update Posted:	January 24, 2013 [Estimate]

Sponsor/Collaborators

Sponsor:	Bayer
Responsible Party:	
Collaborators:	Regeneron Pharmaceuticals

Oversight

U.S. FDA-regulated Drug:	
U.S. FDA-regulated Device:	
Data Monitoring:	Yes

Study Description

Brief Summary:	To determine the efficacy of vascular endothelial growth factor (VEGF) Trap-Eye injected into the eye on vision function in subjects with macular edema as a consequence of central retinal vein occlusion
Detailed Description:	

Conditions

Conditions:	Retinal Vein Occlusion
Keywords:	Macular Edema Central Retinal Vein Occlusion

CRVO
VEGF Trap-Eye
best-corrected visual acuity

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	Phase 3
Interventional Study Model:	Parallel Assignment
Number of Arms:	2
Masking:	TripleParticipant, Investigator, Outcomes Assessor
Allocation:	Randomized
Enrollment:	177 [Actual]

Arms and Interventions

Arms	Assigned Interventions
Experimental: Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321) Participants received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered every 4 weeks from Day 1 through Week 20, later as often as every 4 weeks depending on the study retreatment criteria from Week 24 through Week 48. Follow-up phase: Participants on IAI, who continued the study, received 2 mg dose of IAI depending on the study retreatment criteria at Week 60 and 68.	Biological: Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321) Intravitreal injection. Weeks 0 to 20 of Aflibercept Injection every 4 weeks; Weeks 24 to 52 every 4 weeks PRN (pro re nata, on demand); plus additional on Week 60 and 68. Sham treatment Sham treatment. Weeks 0 to 52 sham treatment every 4 weeks; plus additional on Week 60 and 68.
Sham Comparator: Sham treatment Participants received sham treatment administered every 4 weeks from Day 1 through Week 52. Follow-up phase: Participants on sham treatment, who switched to Intravitreal Aflibercept Injection (IAI), received a 2 mg dose of IAI at week 52 and depending on the	Sham treatment Sham treatment. Weeks 0 to 52 sham treatment every 4 weeks; plus additional on Week 60 and 68.

Arms	Assigned Interventions
study retreatment criteria at Week 60 and 68.	

Outcome Measures

[See Results Section.]

Eligibility

Minimum Age: 18 Years

Maximum Age:

Sex: All

Gender Based:

Accepts Healthy Volunteers: No

Criteria: Inclusion Criteria:

- Center-involved macular edema secondary to central retinal vein occlusion (CRVO) for no longer than 9 months with mean central subfield thickness ≥ 250 µm on optical coherence tomography (OCT)
- Adults ≥ 18 years
- Early treatment diabetic retinopathy study (ETDRS) best corrected visual acuity (BCVA) of 20/40 to 20/320 (73 to 24 letters) in the study eye

Exclusion Criteria:

- Any prior treatment with anti-VEGF agents in the study eye (Pegaptanib sodium, anecortave acetate, bevacizumab, ranibizumab, etc.) or previous administration of systemic anti-angiogenic medications
- Prior panretinal laser photocoagulation or macular laser photocoagulation in the study eye
- CRVO disease duration > 9 months from date of diagnosis

- Previous use of intraocular corticosteroids in the study eye or use of periocular corticosteroids in the study eye within the 3 months prior to Day 1
- Iris neovascularization, vitreous hemorrhage, traction retinal detachment, or preretinal fibrosis involving the macula in either the study eye or fellow eye

Contacts/Locations

Study Officials: Bayer Study Director
Study Director
Bayer

Locations: **Australia, New South Wales**

Chatswood, New South Wales, Australia, 2067

Parramatta, New South Wales, Australia, 2150

Sydney, New South Wales, Australia, 2000

Westmead, New South Wales, Australia, 2145

Australia, Victoria

East Melbourne, Victoria, Australia, 3002

Australia, Western Australia

Nedlands, Western Australia, Australia, 6009

Austria

Innsbruck, Austria, 6020

Linz, Austria, 4021

Wien, Austria, 1090

France, Cedex 12

Paris, Cedex 12, France, 75557

France, Cedex 1

Nantes, Cedex 1, France, 44093

France

Bordeaux, France, 33000

Dijon, France, 21033

Marseille, France, 13008

Paris, France, 75015

Germany, Baden-Württemberg

Freiburg, Baden-Württemberg, Germany, 79106

Heidelberg, Baden-Württemberg, Germany, 69120

Tübingen, Baden-Württemberg, Germany, 72076

Germany, Bayern

München, Bayern, Germany, 81675

Regensburg, Bayern, Germany, 93053

Germany, Hessen

Darmstadt, Hessen, Germany, 64297

Frankfurt, Hessen, Germany, 60596

Marburg, Hessen, Germany, 35037

Germany, Niedersachsen

Göttingen, Niedersachsen, Germany, 37075

Germany, Nordrhein-Westfalen

Aachen, Nordrhein-Westfalen, Germany, 52074

Bonn, Nordrhein-Westfalen, Germany, 53105

Essen, Nordrhein-Westfalen, Germany, 45122

Köln, Nordrhein-Westfalen, Germany, 50924

Münster, Nordrhein-Westfalen, Germany, 48145

Germany, Rheinland-Pfalz

Ludwigshafen, Rheinland-Pfalz, Germany, 67063

Mainz, Rheinland-Pfalz, Germany, 55131

Germany, Saarland

Homburg, Saarland, Germany, 66421

Germany, Sachsen

Chemnitz, Sachsen, Germany, 09116

Dresden, Sachsen, Germany, 01307

Dresden, Sachsen, Germany, 06067

Leipzig, Sachsen, Germany, 04103

Germany, Schleswig-Holstein

Kiel, Schleswig-Holstein, Germany, 24105

Lübeck, Schleswig-Holstein, Germany, 23538

Germany

Berlin, Germany, 13353

Hamburg, Germany, 20251

Hungary

Budapest, Hungary, 1089

Budapest, Hungary, 1106

Budapest, Hungary, 1133

Debrecen, Hungary, 4032

Veszprem, Hungary, 8200

Zalaegerszeg, Hungary, H-8900

Italy

Ancona, Italy, 60126

Bari, Italy, 70124

Catania, Italy, 95123

Firenze, Italy, 50134

Milano, Italy, 20122

Milano, Italy, 20132

Milano, Italy, 20157

Padova, Italy, 35128

Roma, Italy, 00133

Roma, Italy, 00198

Torino, Italy, 10122

Japan, Aichi

Nagoya, Aichi, Japan, 466-8560

Nagoya, Aichi, Japan, 467-8602

Japan, Chiba

Urayasu, Chiba, Japan, 279-0021

Japan, Osaka

Suita, Osaka, Japan, 565-0871

Japan, Tokyo

Chiyoda-ku, Tokyo, Japan, 101-8309

Japan

Kyoto, Japan, 606-8507

Korea, Republic of

Incheon, Korea, Republic of, 405-760

Kungki-do, Korea, Republic of, 463-707

Seoul, Korea, Republic of, 110 744

Seoul, Korea, Republic of, 110-744

Seoul, Korea, Republic of, 138-736

Seoul, Korea, Republic of

Latvia

Riga, Latvia, 1002

Riga, Latvia, 1050

Singapore

Singapore, Singapore, 119074

Singapore, Singapore, 168751

IPDSharing

Plan to Share IPD:

References

Citations:

Links:

Available IPD/Information:

Study Results

Participant Flow

Reporting Groups

	Description
Aflibercept Injection First, Then Aflibercept Injection	Participants received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered every 4 weeks from Day 1 through Week 20, later as often as every 4 weeks depending on the study retreatment criteria from Week 24 through Week 48. Follow-up phase: Participants on IAI, who continued the study, received 2 mg dose of IAI depending on the study retreatment criteria at Week 60 and 68.
Sham Treatment First, Then Aflibercept Injection	Participants received sham treatment administered every 4 weeks from Day 1 through Week 52. Follow-up phase: Participants on sham treatment, who switched to Intravitreal Aflibercept Injection (IAI), received a 2 mg dose of IAI at week 52 and depending on the study retreatment criteria at Week 60 and 68.

Overall Study

	Aflibercept Injection First, Then Aflibercept Injection	Sham Treatment First, Then Aflibercept Injection
Started	106	71
Participants Received Treatment	104 [1]	68 [1]
Fulfilled Requirements of FAS Population	103 [2]	68 [2]
Completed Week 24, From FAS	97	57
Completed Week 52, From FAS	91	52
Completed	90	52
Not Completed	16	19
Adverse Event	5	5
Lack of Efficacy	0	5
Lost to Follow-up	1	0

	Aflibercept Injection First, Then Aflibercept Injection	Sham Treatment First, Then Aflibercept Injection
(Overseas travel - indefinite period)		
Increase in vis. acuity, never injected	0	1
Protocol Violation	5	2
Withdrawal by Subject	4	6

[1] Safety Population: Participants received treatment

[2] Full Analysis Set (FAS) Population: Participants received treatment with post baseline measurements

Baseline Characteristics

Reporting Groups

	Description
Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Participants received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered every 4 weeks from Day 1 through Week 20, later as often as every 4 weeks depending on the study retreatment criteria from Week 24 through Week 48. Follow-up phase: Participants on IAI, who continued the study, received 2 mg dose of IAI depending on the study retreatment criteria at Week 60 and 68.
Sham Treatment	Participants received sham treatment administered every 4 weeks from Day 1 through Week 52. Follow-up phase: Participants on sham treatment, who switched to Intravitreal Aflibercept Injection (IAI), received a 2 mg dose of IAI at week 52 and depending on the study retreatment criteria at Week 60 and 68.

Baseline Measures

		Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Sham Treatment	Total
Overall Number of Participants		104	68	172
Age Continuous Mean (Standard Deviation) Unit of measure: Years	Number Analyzed	104 Participants	68 Participants	172 Participants
		60.0 (12.3)	63.8 (13.3)	61.5 (12.8)
Sex: Female, Male Measure type: Count of Participants Unit of measure: Participants	Number Analyzed	104 Participants	68 Participants	172 Participants
	Female	45 43.27%	31 45.59%	76 44.19%
	Male	59 56.73%	37 54.41%	96 55.81%
Ethnicity (NIH/OMB) Measure type: Count of Participants Unit of measure: Participants	Number Analyzed	104 Participants	68 Participants	172 Participants
	Hispanic or Latino	4 3.85%	1 1.47%	5 2.91%
	Not Hispanic or Latino	100 96.15%	66 97.06%	166 96.51%
	Unknown or Not Reported	0 0%	1 1.47%	1 0.58%
Baseline Best Corrected Visual Acuity (BCVA) letter scores [1] Mean (Standard Deviation)	Number Analyzed	104 Participants	68 Participants	172 Participants
		53.5 (15.7)	50.9 (15.4)	52.5 (15.6)
	[1]	Infiormation retrieved from all baseline participants. Only participants with a ETDRS (Early Treatment Diabetic Retinopathy Study) Best Corrected Visual Acuity letter score of 73 to 25 (= Acuity of 20/40 to 20/320) in the study eye at 4 meters were included; a higher score represents better functioning.		
		104 Participants	68 Participants	172 Participants

		Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Sham Treatment	Total
Number of participants with baseline retinal perfusion [1] Measure type: Number Unit of measure: Participants	Number Analyzed			
Perfused		90	54	144
Nonperfused		7	7	14
Indeterminate		7	7	14
	[1] Retinal perfusion defined as less than 10 disc areas of capillary nonperfusion using fluorescein angiography (FA)			
Baseline Retinal Thickness by Optical Coherence Tomography (OCT) Mean (Standard Deviation)	Number Analyzed	104 Participants	68 Participants	172 Participants
		682.78 (233.36)	638.66 (224.69)	665.34 (230.33)
Baseline intraocular pressure Mean (Standard Deviation)	Number Analyzed	104 Participants	68 Participants	172 Participants
		15.2 (2.8)	14.4 (2.7)	14.9 (2.8)
Number of participants with time since Central retinal vein occlusion (CRVO) diagnosis Measure type: Number Unit of measure: Participants	Number Analyzed	104 Participants	68 Participants	172 Participants
>= 2 months		46	33	79
< 2 months		56	35	91
Missing		2	0	2

		Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Sham Treatment	Total
Baseline National Eye Institute 25-item Visual Function Questionnaire (NEI VFQ-25) total score [1]	Number Analyzed	104 Participants	68 Participants	172 Participants
		79.66 (13.06)	78.94 (14.00)	79.38 (13.40)

[1] The NEI VFQ-25 total score ranges from 0-100 with a score of 0 being the worst outcome and 100 being the best outcome. The NEI VFQ questionnaire is organized as a collection of subscales which are all scored from 0-100. To reach the overall composite score, each sub-scale score is averaged in order to give each sub-scale equal weight.

European questionnaire 5 dimensions (EQ-5D) total score [1] Mean (Standard Deviation)	Number Analyzed	104 Participants	68 Participants	172 Participants
		0.87 (0.15)	0.86 (0.16)	0.87 (0.15)

[1] The EQ-5D total score ranges from -0.594 to 1.000 with -0.594 being the worst.

Race Measure type: Number Unit of measure: Participants	Number Analyzed	104 Participants	68 Participants	172 Participants
Asian		26	15	41
White		75	49	124
Unknown or Not Reported		3	4	7

Outcome Measures

1. Primary Outcome Measure:

Measure Title	

	Percentage of Participants Who Gained at Least 15 Letters in BCVA as Measured by ETDRS Letter Score Compared With Baseline at Week 24 With Discontinued Participants Before Week 24 Evaluated as Failures
Measure Description	Defined study baseline range of Early Treatment Diabetic Retinopathy Study (ETDRS) Best Corrected Visual Acuity (BCVA) letter score of 73 to 24 (= Acuity of 20/40 to 20/320) in the study eye; a higher score represents better functioning. Nominator = (Number of participants who maintained vision * 100); Denominator = Number of participants analyzed.
Time Frame	Baseline and Week 24

Analysis Population Description

Full analysis set

Reporting Groups

	Description
Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Participants received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered every 4 weeks from Day 1 through Week 20, later as often as every 4 weeks depending on the study retreatment criteria from Week 24 through Week 48. Follow-up phase: Participants on IAI, who continued the study, received 2 mg dose of IAI depending on the study retreatment criteria at Week 60 and 68.
Sham Treatment	Participants received sham treatment administered every 4 weeks from Day 1 through Week 52. Follow-up phase: Participants on sham treatment, who switched to Intravitreal Aflibercept Injection (IAI), received a 2 mg dose of IAI at week 52 and depending on the study retreatment criteria at Week 60 and 68.

Measured Values

	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Sham Treatment
Overall Number of Participants Analyzed	103	68
Percentage of Participants Who Gained at Least 15 Letters in BCVA as Measured by ETDRS Letter Score Compared With Baseline at Week 24 With Discontinued Participants Before Week 24 Evaluated as Failures Measure Type: Number Unit of Measure: Percentage of participants	60.2	22.1

Statistical Analysis 1 for Percentage of Participants Who Gained at Least 15 Letters in BCVA as Measured by ETDRS Letter Score Compared With Baseline at Week 24 With Discontinued Participants Before Week 24 Evaluated as Failures

Statistical Analysis Overview	Comparison Groups	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321), Sham Treatment
	Comments	Null hypothesis of difference of Eylea minus Sham of 0 was tested. In the database close after Week 24, basis for primary efficacy evaluation, 56 Sham / 96 Eylea subjects were considered as week 24 completers.
	Type of Statistical Test	Superiority or Other (legacy)
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	<.0001
	Comments	[Not specified]
	Method	Cochran-Mantel-Haenszel
	Comments	[Not specified]
	Estimation Parameter	CMH adjusted difference

Method of Estimation	Estimated Value	38.3
	Confidence Interval	(2-sided) 95% 24.4 to 52.1
	Estimation Comments	The estimate is calculated as Eylea minus Sham. A positive value shows Eylea showed a higher BCVA total score compared to Sham.

2. Secondary Outcome Measure:

Measure Title	Change From Baseline in BCVA as Measured by Early Treatment Diabetic Retinopathy Study (ETDRS) Letter Score at Week 24 - Last Observation Carried Forward (LOCF)
Measure Description	Defined study baseline range of ETDRS Best Corrected Visual Acuity letter score of 73 to 24 (= Acuity of 20/40 to 20/320) in the study eye; a higher score represents better functioning. However, because this was assessed at the screening visit, subjects may have had a higher BCVA recorded at the baseline visit and would not have been excluded from the study.
Time Frame	Baseline and Week 24

Analysis Population Description

Full analysis set

Reporting Groups

	Description
Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Participants received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered every 4 weeks from Day 1 through Week 20, later as often as every 4 weeks depending on the study retreatment criteria from Week 24 through Week 48. Follow-up phase: Participants on IAI, who continued the study, received 2 mg dose of IAI

	depending on the study retreatment criteria at Week 60 and 68.
Sham Treatment	Participants received sham treatment administered every 4 weeks from Day 1 through Week 52. Follow-up phase: Participants on sham treatment, who switched to Intravitreal Aflibercept Injection (IAI), received a 2 mg dose of IAI at week 52 and depending on the study retreatment criteria at Week 60 and 68.

Measured Values

	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Sham Treatment
Overall Number of Participants Analyzed	103	68
Change From Baseline in BCVA as Measured by Early Treatment Diabetic Retinopathy Study (ETDRS) Letter Score at Week 24 - Last Observation Carried Forward (LOCF) Measure Type: Mean (Standard Deviation) Unit of Measure: Letters correctly read	71.6 (17.1)	54.3 (20.2)

Statistical Analysis 1 for Change From Baseline in BCVA as Measured by Early Treatment Diabetic Retinopathy Study (ETDRS) Letter Score at Week 24 - Last Observation Carried Forward (LOCF)

Statistical Analysis Overview	Comparison Groups	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321), Sham Treatment
	Comments	Null hypothesis was equality in change from baseline to Week 24 in BCVA total letter score between Eylea and Sham. If primary efficacy was successful, secondary efficacy endpoints were tested in a pre-specified fixed sequence testing procedure. Change in BCVA letter

		score was to be tested first in this sequence.
	Type of Statistical Test	Superiority or Other (legacy)
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	<.0001
	Comments	As primary efficacy evaluation was significant, and this p-value was below significance level of two-sided <.05, the fixed sequence testing did continue with next secondary endpoint.
	Method	ANOVA
	Comments	ANOVA, adjusting for region and baseline BCVA category as fixed factors.

Method of Estimation	Estimation Parameter	Difference in Least square means
	Estimated Value	14.7
	Confidence Interval	(2-sided) 95% 10.8 to 18.7
	Estimation Comments	The difference is calculated as Eylea minus Sham. A positive value indicates Eylea showed a higher change in BCVA total score until week 24 compared to Sham.

3. Secondary Outcome Measure:

Measure Title	Change From Baseline in Central Retinal Thickness (CRT) at Week 24 - LOCF
Measure Description	
Time Frame	Baseline and Week 24

Analysis Population Description

Full-Analysis Set with assessment for this outcome measure; imputation technique: LOCF

Reporting Groups

	Description
Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Participants received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered every 4 weeks from Day 1 through Week 20, later as often as every 4 weeks depending on the study retreatment criteria from Week 24 through Week 48. Follow-up phase: Participants on IAI, who continued the study, received 2 mg dose of IAI depending on the study retreatment criteria at Week 60 and 68.
Sham Treatment	Participants received sham treatment administered every 4 weeks from Day 1 through Week 52. Follow-up phase: Participants on sham treatment, who switched to Intravitreal Aflibercept Injection (IAI), received a 2 mg dose of IAI at week 52 and depending on the study retreatment criteria at Week 60 and 68.

Measured Values

	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Sham Treatment
Overall Number of Participants Analyzed	103	67
Change From Baseline in Central Retinal Thickness (CRT) at Week 24 - LOCF Measure Type: Mean (Standard Deviation) Unit of Measure: microns	-448.58 (256.02)	-169.27 (224.72)

Statistical Analysis 1 for Change From Baseline in Central Retinal Thickness (CRT) at Week 24 - LOCF

	Comparison Groups	

Statistical Analysis Overview		Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321), Sham Treatment
	Comments	Null hypothesis was equality in change from baseline to Week 24 in central retinal thickness between Eylea and Sham. If primary efficacy was successful, secondary efficacy end points were to be tested in a pre-specified fixed sequence testing procedure. Change in central retinal thickness was to be tested at second place in this sequence.
	Type of Statistical Test	Superiority or Other (legacy)
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	<.0001
	Comments	As fixed sequence testing did reject nullhypothesis of change from baseline in BCVA until week 24, and this p-value was below significance level of two-sided <.05, the fixed sequence testing did continue with next secondary endpoint.
	Method	ANCOVA
	Comments	ANCOVA, stratified by region and baseline BCVA category, baseline central retinal thickness added as covariate.

Method of Estimation	Estimation Parameter	Difference in Least square (LS) means
	Estimated Value	-239.42
	Confidence Interval	(2-sided) 95% -286.31 to -192.53

	Estimation Comments	The difference is calculated as Eylea minus Sham. A negative value indicates Eylea showed a higher reduction in change in central retinal thickness until week 24 compared to Sham.

4. Secondary Outcome Measure:

Measure Title	Percentage of Participants Who Developed Neovascularization During the First 24 Weeks
Measure Description	Formation of blood vessels in the anterior segment, optic disc, or elsewhere in the fundus up to Week 24
Time Frame	From baseline until Week 24

Analysis Population Description

Full analysis set

Reporting Groups

	Description
Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Participants received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered every 4 weeks from Day 1 through Week 20, later as often as every 4 weeks depending on the study retreatment criteria from Week 24 through Week 48. Follow-up phase: Participants on IAI, who continued the study, received 2 mg dose of IAI depending on the study retreatment criteria at Week 60 and 68.
Sham Treatment	Participants received sham treatment administered every 4 weeks from Day 1 through Week 52. Follow-up phase: Participants on sham treatment, who switched to Intravitreal Aflibercept Injection (IAI), received a 2 mg dose of IAI at week 52 and depending on the study retreatment criteria at Week 60 and 68.

Measured Values

	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Sham Treatment
Overall Number of Participants Analyzed	103	68
Percentage of Participants Who Developed Neovascularization During the First 24 Weeks Measure Type: Number Unit of Measure: Percentage of participants		
Any neovascularization	2.9	4.4
Anterior segment neovascularization	1.9	1.5
Neovascularization of the optic disc (NVD)	0.0	0.0
Neovascularization elsewhere in the fundus (NVE)	1.0	2.9

Statistical Analysis 1 for Percentage of Participants Who Developed Neovascularization During the First 24 Weeks

Statistical Analysis Overview	Comparison Groups	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321), Sham Treatment
	Comments	Nullhypothesis of no difference in development of neovascularizations between Eylea and Sham group was tested. (Any neovascularization)
	Type of Statistical Test	Superiority or Other (legacy)
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.5947
	Comments	As fixed sequence testing did reject nullhypothesis of change from baseline in CRT until week 24, and this p-value was not below significance level of two-sided <.05,

		the fixed sequence testing did end with this evaluation.
	Method	Cochran-Mantel-Haenszel
	Comments	Cochrane-Mantel-Haenszel test, stratified by region and baseline BCVA category.

Method of Estimation	Estimation Parameter	CMH adjusted Difference
	Estimated Value	-1.5
	Confidence Interval	(2-sided) 95% -7.4 to 4.4
	Estimation Comments	[Not specified]

5. Secondary Outcome Measure:

Measure Title	Change From Baseline in National Eye Institute 25-item Visual Function Questionnaire (NEI VFQ-25) Total Score at Week 24 - LOCF
Measure Description	The NEI VFQ-25 total score ranges from 0-100 with a score of 0 being the worst outcome and 100 being the best outcome. The NEI VFQ questionnaire is organized as a collection of subscales which are all scored from 0-100. To reach the overall composite score, each sub-scale score is averaged in order to give each sub-scale equal weight
Time Frame	Baseline and Week 24

Analysis Population Description

Full-Analysis Set with assessment for this outcome measure; imputation technique: LOCF

Reporting Groups

	Description
Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Participants received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered every 4 weeks from Day 1 through Week 20, later as often

	as every 4 weeks depending on the study retreatment criteria from Week 24 through Week 48. Follow-up phase: Participants on IAI, who continued the study, received 2 mg dose of IAI depending on the study retreatment criteria at Week 60 and 68.
Sham Treatment	Participants received sham treatment administered every 4 weeks from Day 1 through Week 52. Follow-up phase: Participants on sham treatment, who switched to Intravitreal Aflibercept Injection (IAI), received a 2 mg dose of IAI at week 52 and depending on the study retreatment criteria at Week 60 and 68.

Measured Values

	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Sham Treatment
Overall Number of Participants Analyzed	96	65
Change From Baseline in National Eye Institute 25-item Visual Function Questionnaire (NEI VFQ-25) Total Score at Week 24 - LOCF Measure Type: Mean (Standard Deviation) Unit of Measure: Scores on a scale	7.46 (9.55)	3.55 (9.74)

Statistical Analysis 1 for Change From Baseline in National Eye Institute 25-item Visual Function Questionnaire (NEI VFQ-25) Total Score at Week 24 - LOCF

Statistical Analysis Overview	Comparison Groups	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321), Sham Treatment
	Comments	[Not specified]
	Type of Statistical Test	Superiority or Other (legacy)
	Comments	[Not specified]

	Estimation Parameter	Difference in LS means

Method of Estimation	Estimated Value	4.2
	Confidence Interval	(2-sided) 95% 1.7 to 6.8
	Estimation Comments	As the fixed sequence of secondary endpoints stopped with proportion of neovascularizations developed until week 24, 95% confidence interval is only of descriptive nature.

6. Secondary Outcome Measure:

Measure Title	Change From Baseline in European Five-dimensional Health Scale (EQ-5D) Score at Week 24 - LOCF
Measure Description	EQ-5D is a quality of life questionnaire based on a scale from -0.594 (worst) to 1.00 (best).
Time Frame	Baseline and Week 24

Analysis Population Description

Full-Analysis Set with assessment for this outcome measure; imputation technique: LOCF

Reporting Groups

	Description
Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Participants received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered every 4 weeks from Day 1 through Week 20, later as often as every 4 weeks depending on the study retreatment criteria from Week 24 through Week 48. Follow-up phase: Participants on IAI, who continued the study, received 2 mg dose of IAI depending on the study retreatment criteria at Week 60 and 68.
Sham Treatment	Participants received sham treatment administered every 4 weeks from Day 1 through Week 52. Follow-up phase: Participants on sham treatment,

	who switched to Intravitreal Aflibercept Injection (IAI), received a 2 mg dose of IAI at week 52 and depending on the study retreatment criteria at Week 60 and 68.

Measured Values

	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Sham Treatment
Overall Number of Participants Analyzed	95	64
Change From Baseline in European Five-dimensional Health Scale (EQ-5D) Score at Week 24 - LOCF Measure Type: Mean (Standard Deviation) Unit of Measure: Scores on a scale	0.029 (0.139)	-0.002 (0.195)

Statistical Analysis 1 for Change From Baseline in European Five-dimensional Health Scale (EQ-5D) Score at Week 24 - LOCF

Statistical Analysis Overview	Comparison Groups	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321), Sham Treatment
	Comments	[Not specified]
	Type of Statistical Test	Superiority or Other (legacy)
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Difference in LS Means
	Estimated Value	0.044
	Confidence Interval	(2-sided) 95% -0.002 to 0.09
	Estimation Comments	As the fixed sequence of secondary endpoints stopped with proportion of neovascularizations developed until week 24, 95% confidence interval is only of descriptive nature.

Reported Adverse Events

Time Frame	[Not specified]
Adverse Event Reporting Description	[Not specified]

Reporting Groups

	Description
Aflibercept Injection (Until Week 20)	Participants received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered every 4 weeks from Day 1 through Week 20. Participants were observed until Week 24. Participants in the safety population were at risk.
Sham Treatment (Until Week 20)	Participants received sham treatment administered every 4 weeks from Day 1 through Week 20. Participants were observed until Week 24. Participants in the safety population were at risk.
Aflibercept Injection (Until Week 48)	Participants who continued the study drug until Week 24 received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered as often as every 4 weeks depending on the study retreatment criteria from Week 24 through Week 48. Participants were observed from Week 24 until Week 52. Participants in the safety population that completed Week 24 were at risk.
Sham Treatment (Until Week 48)	Participants who continued the study drug until Week 24 received sham treatment administered every 4 weeks from Week 24 to Week 48. Participants were observed from Week 24 until Week 52. Participants in the safety population that completed Week 24 were at risk.
Aflibercept Injection Continued (Until Week 68)	Participants on IAI who continued the study drug until Week 52, received 2 mg dose of IAI depending on the study retreatment criteria at Week 52, 60 and 68. Participants were observed starting from Week 52. Participants in the safety population that completed Week 52 were at risk.

Sham Treatment Then Aflibercept Injection (Until Week 68)	Participants on sham treatment switched to IAI, received a 2 mg dose of IAI at Week 52 and depending on the study retreatment criteria at Week 60 and 68. Participants were observed starting from Week 52. Participants in the safety population that completed Week 52 were at risk.

All-Cause Mortality

	Aflibercept Injection (Until Week 20)	Sham Treatment (Until Week 20)	Aflibercept Injection (Until Week 48)	Sham Treatment (Until Week 48)	Aflibercept Injection Continued (Until Week 68)	Sham Treatment Then Aflibercept Injection (Until Week 68)
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Total	/	/	/	/	/	/

Serious Adverse Events

	Aflibercept Injection (Until Week 20)	Sham Treatment (Until Week 20)	Aflibercept Injection (Until Week 48)	Sham Treatment (Until Week 48)	Aflibercept Injection Continued (Until Week 68)	Sham Treatment Then Aflibercept Injection (Until Week 68)
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Total	8/104 (7.69%)	8/68 (11.76%)	14/97 (14.43%)	7/57 (12.28%)	4/91 (4.4%)	3/52 (5.77%)
Cardiac disorders						
Aortic valve incompetence [A*]	0/104 (0%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	1/52 (1.92%)
Cardiac failure [A*]						

	Aflibercept Injection (Until Week 20)	Sham Treatment (Until Week 20)	Aflibercept Injection (Until Week 48)	Sham Treatment (Until Week 48)	Aflibercept Injection Continued (Until Week 68)	Sham Treatment Then Aflibercept Injection (Until Week 68)
	0/104 (0%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	1/52 (1.92%)
Coronary artery stenosis [A*]	0/104 (0%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	1/52 (1.92%)
Diastolic dysfunction [A*]	0/104 (0%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	1/52 (1.92%)
Mitral valve incompetence [A*]	0/104 (0%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	1/52 (1.92%)
Eye disorders						
Blindness unilateral [A*]	0/104 (0%)	0/68 (0%)	1/97 (1.03%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Glaucoma [A*]	0/104 (0%)	1/68 (1.47%)	0/97 (0%)	1/57 (1.75%)	0/91 (0%)	0/52 (0%)
Iris neovascularisation [A*]	1/104 (0.96%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Macular fibrosis [A*]	0/104 (0%)	0/68 (0%)	1/97 (1.03%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Macular ischaemia [A*]	0/104 (0%)	0/68 (0%)	1/97 (1.03%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Macular oedema [A*]	0/104 (0%)	2/68 (2.94%)	4/97 (4.12%)	0/57 (0%)	1/91 (1.1%)	0/52 (0%)
Retinal vein occlusion [A*]	0/104 (0%)	0/68 (0%)	1/97 (1.03%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Visual acuity reduced [A*]	0/104 (0%)	1/68 (1.47%)	1/97 (1.03%)	0/57 (0%)	2/91 (2.2%)	0/52 (0%)
Vitreous detachment [A*]	1/104	0/68	0/97	0/57	0/91	0/52

	Afliberce Injection (Until Week 20)	Sham Treatme (Until Week 20)	Afliberce Injection (Until Week 48)	Sham Treatme (Until Week 48)	Afliberce Injection Continue (Until Week 68)	Sham Treatme Then Afliberce Injection (Until Week 68)
Vitreous haemorrhage [A*]	0/104 (0%)	1/68 (1.47%)	1/97 (1.03%)	1/57 (1.75%)	0/91 (0%)	0/52 (0%)
Gastrointestinal disorders						
Diverticular perforation [A*]	0/104 (0%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	1/91 (1.1%)	0/52 (0%)
Hepatobiliary disorders						
Hepatic function abnormal [A*]	0/104 (0%)	0/68 (0%)	1/97 (1.03%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Infections and infestations						
Furuncle [A*]	1/104 (0.96%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Gastroenteritis [A*]	0/104 (0%)	1/68 (1.47%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Pneumonia [A*]	0/104 (0%)	1/68 (1.47%)	1/97 (1.03%)	1/57 (1.75%)	0/91 (0%)	0/52 (0%)
Vestibular neuronitis [A*]	0/104 (0%)	0/68 (0%)	0/97 (0%)	1/57 (1.75%)	0/91 (0%)	0/52 (0%)
Injury, poisoning and procedural complications						
Fall [A*]	0/104 (0%)	1/68 (1.47%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Femur fracture [A*]	0/104 (0%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	1/52 (1.92%)
Hand fracture [A*]	1/104 (0.96%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Humerus fracture [A*]	0/104 (0%)	1/68 (1.47%)	1/97 (1.03%)	0/57 (0%)	0/91 (0%)	0/52 (0%)

	Afliberce Injection (Until Week 20)	Sham Treatme (Until Week 20)	Afliberce Injection (Until Week 48)	Sham Treatme (Until Week 48)	Afliberce Injection Continue (Until Week 68)	Sham Treatme Then Afliberce Injection (Until Week 68)
Radius fracture [A*]	0/104 (0%)	1/68 (1.47%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Spinal compression fracture [A*]	1/104 (0.96%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Musculoskeletal and connective tissue disorders						
Intervertebral disc protrusion [A*]	0/104 (0%)	1/68 (1.47%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Spinal column stenosis [A*]	0/104 (0%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	1/91 (1.1%)	0/52 (0%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)						
Breast cancer [A*]	0/104 (0%)	0/68 (0%)	1/97 (1.03%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Oropharyngeal cancer stage unspecified [A*]	1/104 (0.96%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Nervous system disorders						
Paraesthesia [A*]	0/104 (0%)	0/68 (0%)	1/97 (1.03%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Syncope [A*]	0/104 (0%)	0/68 (0%)	1/97 (1.03%)	2/57 (3.51%)	0/91 (0%)	0/52 (0%)
Transient ischaemic attack [A*]	0/104 (0%)	0/68 (0%)	0/97 (0%)	1/57 (1.75%)	0/91 (0%)	0/52 (0%)
Respiratory, thoracic and mediastinal disorders						
Dyspnoea [A*]	0/104 (0%)	0/68 (0%)	0/97 (0%)	1/57 (1.75%)	0/91 (0%)	0/52 (0%)
Laryngeal granuloma [A*]	0/104 (0%)	1/68 (1.47%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)

	Afliberce Injection (Until Week 20)	Sham Treatme (Until Week 20)	Afliberce Injection (Until Week 48)	Sham Treatme (Until Week 48)	Afliberce Injection Continue (Until Week 68)	Sham Treatme Then Afliberce Injection (Until Week 68)
Pulmonary hypertension [A*]	0/104 (0%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	1/52 (1.92%)
Surgical and medical procedures						
Ischaemic heart disease prophylaxis [A*]	1/104 (0.96%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Vascular disorders						
Circulatory collapse [A*]	1/104 (0.96%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)

* Indicates events were collected by non-systematic methods.

A Term from vocabulary, MedDRA (14.1)

Other Adverse Events

Frequency Threshold Above Which Other Adverse Events are Reported: 5%

	Afliberce Injection (Until Week 20)	Sham Treatme (Until Week 20)	Afliberce Injection (Until Week 48)	Sham Treatme (Until Week 48)	Afliberce Injection Continue (Until Week 68)	Sham Treatme Then Afliberce Injection (Until Week 68)
	Affected/A Risk (%)	Affected/A Risk (%)	Affected/A Risk (%)	Affected/A Risk (%)	Affected/A Risk (%)	Affected/A Risk (%)
Total	52/104 (50%)	44/68 (64.71%	66/97 (68.04%	30/57 (52.63%	38/91 (41.76%	19/52 (36.54%
Blood and lymphatic system disorders						
Anaemia [A*]	1/104 (0.96%)	0/68 (0%)	0/97 (0%)	3/57 (5.26%)	0/91 (0%)	0/52 (0%)

	Afliberce Injection (Until Week 20)	Sham Treatme (Until Week 20)	Afliberce Injection (Until Week 48)	Sham Treatme (Until Week 48)	Afliberce Injection Continue (Until Week 68)	Sham Treatme Then Afliberce Injection (Until Week 68)
Eye disorders						
Conjunctival haemorrhage [A*]	10/104 (9.62%)	3/68 (4.41%)	3/97 (3.09%)	0/57 (0%)	9/91 (9.89%)	3/52 (5.77%)
Eye irritation [A*]	3/104 (2.88%)	7/68 (10.29%	4/97 (4.12%)	1/57 (1.75%)	1/91 (1.1%)	2/52 (3.85%)
Eye pain [A*]	12/104 (11.54%	3/68 (4.41%)	6/97 (6.19%)	2/57 (3.51%)	1/91 (1.1%)	0/52 (0%)
Foreign body sensation in eyes [A*]	6/104 (5.77%)	5/68 (7.35%)	2/97 (2.06%)	0/57 (0%)	1/91 (1.1%)	0/52 (0%)
Lacrimation increased [A*]	3/104 (2.88%)	4/68 (5.88%)	3/97 (3.09%)	4/57 (7.02%)	1/91 (1.1%)	2/52 (3.85%)
Macular fibrosis [A*]	1/104 (0.96%)	1/68 (1.47%)	5/97 (5.15%)	4/57 (7.02%)	0/91 (0%)	3/52 (5.77%)
Macular ischaemia [A*]	7/104 (6.73%)	5/68 (7.35%)	3/97 (3.09%)	1/57 (1.75%)	0/91 (0%)	1/52 (1.92%)
Macular oedema [A*]	2/104 (1.92%)	9/68 (13.24%	30/97 (30.93%	7/57 (12.28%	17/91 (18.68%	2/52 (3.85%)
Ocular hyperaemia [A*]	5/104 (4.81%)	4/68 (5.88%)	2/97 (2.06%)	1/57 (1.75%)	4/91 (4.4%)	1/52 (1.92%)
Optic disc vascular disorder [A*]	5/104 (4.81%)	3/68 (4.41%)	3/97 (3.09%)	3/57 (5.26%)	0/91 (0%)	0/52 (0%)
Retinal exudates [A*]	8/104 (7.69%)	5/68 (7.35%)	4/97 (4.12%)	3/57 (5.26%)	0/91 (0%)	0/52 (0%)
Retinal haemorrhage [A*]	4/104 (3.85%)	6/68 (8.82%)	11/97 (11.34%	5/57 (8.77%)	5/91 (5.49%)	2/52 (3.85%)
Retinal vascular disorder [A*]	6/104	7/68	10/97	2/57	0/91	2/52

	Afliberce Injection (Until Week 20)	Sham Treatme (Until Week 20)	Afliberce Injection (Until Week 48)	Sham Treatme (Until Week 48)	Afliberce Injection Continue (Until Week 68)	Sham Treatme Then Afliberce Injection (Until Week 68)
Visual acuity reduced [A*]	2/104 (1.92%)	7/68 (10.29%	10/97 (10.31%	1/57 (1.75%)	7/91 (7.69%)	1/52 (1.92%)
Vitreous detachment [A*]	2/104 (1.92%)	1/68 (1.47%)	7/97 (7.22%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Vitreous floaters [A*]	6/104 (5.77%)	0/68 (0%)	1/97 (1.03%)	1/57 (1.75%)	1/91 (1.1%)	1/52 (1.92%)
Gastrointestinal disorders						
Nausea [A*]	0/104 (0%)	1/68 (1.47%)	0/97 (0%)	3/57 (5.26%)	0/91 (0%)	0/52 (0%)
Infections and infestations						
Influenza [A*]	2/104 (1.92%)	0/68 (0%)	5/97 (5.15%)	1/57 (1.75%)	1/91 (1.1%)	1/52 (1.92%)
Nasopharyngitis [A*]	8/104 (7.69%)	6/68 (8.82%)	10/97 (10.31%	11/57 (19.3%)	4/91 (4.4%)	2/52 (3.85%)
Investigations						
Intraocular pressure increased [A*]	9/104 (8.65%)	4/68 (5.88%)	14/97 (14.43%	2/57 (3.51%)	2/91 (2.2%)	1/52 (1.92%)
Visual acuity tests abnormal [A*]	0/104 (0%)	1/68 (1.47%)	5/97 (5.15%)	0/57 (0%)	1/91 (1.1%)	0/52 (0%)
Musculoskeletal and connective tissue disorders						
Arthralgia [A*]	1/104 (0.96%)	5/68 (7.35%)	2/97 (2.06%)	1/57 (1.75%)	2/91 (2.2%)	0/52 (0%)
Nervous system disorders						
Headache [A*]	7/104 (6.73%)	4/68 (5.88%)	4/97 (4.12%)	1/57 (1.75%)	1/91 (1.1%)	1/52 (1.92%)

	Afliberce Injection (Until Week 20)	Sham Treatme (Until Week 20)	Afliberce Injection (Until Week 48)	Sham Treatme (Until Week 48)	Afliberce Injection Continue (Until Week 68)	Sham Treatme Then Afliberce Injection (Until Week 68)
Vascular disorders						
Hypertension [A*]	4/104 (3.85%)	3/68 (4.41%)	4/97 (4.12%)	4/57 (7.02%)	3/91 (3.3%)	2/52 (3.85%)

* Indicates events were collected by non-systematic methods.

A Term from vocabulary, MedDRA (14.1)

Limitations and Caveats

[Not specified]

More Information

Certain Agreements:

Principal Investigators are NOT employed by the organization sponsoring the study.

There IS an agreement between the Principal Investigator and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed.

Publishing of result communication only after Bayer´s written approval. Manuscript to Bayer sixty days before public release. If no written Bayer comment within 60 days consider approval given. If multi-site study, principal investigator (PI) not do independently publish results before publication of the multi-site paper, but PI not restricted from 24 months from study to completion onwards.

Results Point of Contact:

Name/Official Title: Therapeutic Area Head
Organization: BAYER
Phone:
Email: clinical-trials-contact@bayerhealthcare.com

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ClinicalTrials.gov archive

History of Changes for Study: NCT01012973

Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO) (GALILEO)

Latest version (submitted October 27, 2014) on ClinicalTrials.gov

- A study version is represented by a row in the table.
- Select two study versions to compare. One each from columns A and B.
- Choose either the "Merged" or "Side-by-Side" comparison format to specify how the two study versions are to be displayed. The Side-by-Side format only applies to the Protocol section of the study.
- Click "Compare" to do the comparison and show the differences.
- Select a version's date link to see a rendering of the study for that version.
- Edits or deletions will be displayed in ~~red~~.
- Additions will be displayed in *green*.
- The yellow choices in the table indicate the study versions currently compared below. A yellow row indicates the study version being viewed.
- Hover over the "Recruitment Status" to see how the study's recruitment status changed.

Study Record Versions

Version	A	B	Submitted Date	Changes
1	◉	○	November 12, 2009	Nothing (earliest Version on record)
2	○	○	January 21, 2010	Contacts/Locations, Study Status, Study Identification and Study Description
3	○	○	February 9, 2010	Contacts/Locations and Study Status
4	○	○	March 16, 2010	Contacts/Locations, Study Status and Study Identification
5	○	○	April 16, 2010	Contacts/Locations, Study Status and Study Identification

Version	A	B	Submitted Date	Changes
6	○	○	July 22, 2010	Contacts/Locations, Study Status, Eligibility and Arms and Interventions
7	○	○	August 25, 2010	Study Status and Contacts/Locations
8	○	○	August 26, 2010	Recruitment Status, Study Status and Contacts/Locations
9	○	○	September 8, 2010	Study Status
10	○	○	October 4, 2010	Study Status
11	○	○	November 1, 2010	Study Status
12	○	○	January 25, 2011	Study Status and Contacts/Locations
13	○	○	April 8, 2011	Study Status and Study Design
14	○	○	June 23, 2011	Arms and Interventions, Study Status, Contacts/Locations and Eligibility
15	○	○	September 19, 2011	Study Status
16	○	○	November 29, 2011	Study Status and Study Identification
17	○	○	January 26, 2012	Study Status and Contacts/Locations
18	○	○	February 20, 2012	Recruitment Status, Study Status
19	○	○	October 23, 2012	Outcome Measures, Arms and Interventions, Study Status, More Information, Reported Adverse Events, Baseline Characteristics and Participant Flow
20	○	○	December 18, 2012	More Information, Arms and Interventions, Study Status and Baseline Characteristics
21	○	○	January 18, 2013	Arms and Interventions, More Information, Study Status and Baseline Characteristics
22	○	○	January 30, 2014	Contacts/Locations, Sponsor/Collaborators, More Information, Study Status, Baseline Characteristics and References
23	○	◉	October 27, 2014	More Information, Study Status and References

Compare

Comparison Format: (•) Merged ( ) Side-by-Side

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Study NCT01012973
on Date: January 25, 2011 (v12)

Study Identification

Unique Protocol ID:	14130
Brief Title:	Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO) (GALILEO)
Official Title:	A Randomized, Double-masked, Sham-controlled Phase 3 Study of the Efficacy, Safety and Tolerability of Repeated Intravitreal Administration of VEGF Trap-Eye in Subjects With Macular Edema Secondary to Central Retinal Vein Occlusion (CRVO)
Secondary IDs:	EudraCT: 2009-010973-19

Study Status

Record Verification:	January 2011
Overall Status:	Active, not recruiting
Study Start:	October 2009
Primary Completion:	February 2011 [Anticipated]
Study Completion:	March 2012 [Anticipated]
First Submitted:	October 30, 2009
First Submitted that Met QC Criteria:	November 12, 2009
First Posted:	November 13, 2009 [Estimate]
Last Update Submitted that Met QC Criteria:	January 25, 2011

Last Update Posted:	January 26, 2011 [Estimate]

Sponsor/Collaborators

Sponsor:	Bayer
Responsible Party:	
Collaborators:	Regeneron Pharmaceuticals

Oversight

U.S. FDA-regulated Drug:	
U.S. FDA-regulated Device:	
Data Monitoring:	Yes

Study Description

Brief Summary:	To determine the efficacy of vascular endothelial growth factor (VEGF) Trap-Eye injected into the eye on vision function in subjects with macular edema as a consequence of central retinal vein occlusion
Detailed Description:	

Conditions

Conditions:	Retinal Vein Occlusion
Keywords:	Macular Edema Central Retinal Vein Occlusion CRVO VEGF Trap-Eye best-corrected visual acuity

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	Phase 3
Interventional Study Model:	Parallel Assignment
Number of Arms:	2
Masking:	TripleParticipant, Investigator, Outcomes Assessor
Allocation:	Randomized
Enrollment:	165 [Anticipated]

Arms and Interventions

Arms	Assigned Interventions
Experimental: Arm 1	Drug: VEGF Trap-Eye (BAY86-5321) Intravitreal injection. Weeks 0 to 20 injection of VEGF Trap-Eye every 4 weeks; weeks 24 to 52 every 4 weeks plus additional on week 60 and 68 re-assessment and either (PRN) injection of VEGF Trap-Eye or sham injection; last visit (no treatment) at week 76.
Sham Comparator: Arm 2	Sham treatment Sham treatment. Weeks 0 to 20 sham treatment every 4 weeks; weeks 24 to 48 every 4 weeks re-assessment and sham injection; week 52 VEGF Trap-Eye injection (unless investigator declines for medical reasons), weeks 60 and 68 re-assessment and either (PRN) injection of VEGF Trap-Eye or sham injection; last visit (no treatment) at week 76.

Outcome Measures

Primary Outcome Measures:

1. The proportion of subjects who gain at least 15 letters in BCVA on the EDTRS chart compared with baseline at the Week 24 endpoint
   Week 24

Secondary Outcome Measures:

2. Change from baseline in BCVA score
   Week 24
3. Absolute change from baseline in central retinal thickness, assessed by OCT
   Week 24
4. Proportion of subjects progressing to anterior segment neovascularization, neovascularization of the optic disc (NVD), or neovascularization of the retina elsewhere (NVE) requiring pan-retinal photocoagulation
   Week 24
5.

Change in the NEI-VFQ-25 total score from baseline
Week 24

6. Change in the EQ-5D score from baseline
Week 24

Eligibility

Minimum Age: 18 Years

Maximum Age:

Sex: All

Gender Based:

Accepts Healthy Volunteers: No

Criteria: Inclusion Criteria:

- Center-involved macular edema secondary to central retinal vein occlusion (CRVO) for no longer than 9 months with mean central subfield thickness >= 250 µm on optical coherence tomography (OCT)
- Adults >= 18 years
- Early treatment diabetic retinopathy study (ETDRS) best corrected visual acuity (BCVA) of 20/40 to 20/320 (73 to 24 letters) in the study eye

Exclusion Criteria:

- Any prior treatment with anti-VEGF agents in the study eye (Pegaptanib sodium, anecortave acetate, bevacizumab, ranibizumab, etc.) or previous administration of systemic anti-angiogenic medications
- Prior panretinal laser photocoagulation or macular laser photocoagulation in the study eye
- CRVO disease duration > 9 months from date of diagnosis
- Previous use of intraocular corticosteroids in the study eye or use of periocular corticosteroids in the study eye within the 3 months prior to Day 1

- Iris neovascularization, vitreous hemorrhage, traction retinal detachment, or preretinal fibrosis involving the macula in either the study eye or fellow eye

Contacts/Locations

Study Officials: Bayer Study Director
Study Director
Bayer

Locations:

Australia, New South Wales

Chatswood, New South Wales, Australia, 2067

Parramatta, New South Wales, Australia, 2150

Sydney, New South Wales, Australia, 2000

Westmead, New South Wales, Australia, 2145

Australia, Victoria

East Melbourne, Victoria, Australia, 3002

Australia, Western Australia

Nedlands, Western Australia, Australia, 6009

Austria

Innsbruck, Austria, 6020

Linz, Austria, 4021

Wien, Austria, 1090

France, Cedex 12

Paris, Cedex 12, France, 75557

France, Cedex 1

Nantes, Cedex 1, France, 44093

France

Bordeaux, France, 33000

Dijon, France, 21033

Marseille, France, 13008

Paris, France, 75015

Germany, Baden-Württemberg

Freiburg, Baden-Württemberg, Germany, 79106

Heidelberg, Baden-Württemberg, Germany, 69120

Tübingen, Baden-Württemberg, Germany, 72076

Germany, Bayern

München, Bayern, Germany, 81675

Regensburg, Bayern, Germany, 93053

Germany, Hessen

Darmstadt, Hessen, Germany, 64297

Frankfurt, Hessen, Germany, 60596

Germany, Niedersachsen

Göttingen, Niedersachsen, Germany, 37075

Germany, Nordrhein-Westfalen

Aachen, Nordrhein-Westfalen, Germany, 52074

Bonn, Nordrhein-Westfalen, Germany, 53105

Essen, Nordrhein-Westfalen, Germany, 45122

Köln, Nordrhein-Westfalen, Germany, 50924

Münster, Nordrhein-Westfalen, Germany, 48145

Germany, Rheinland-Pfalz

Ludwigshafen, Rheinland-Pfalz, Germany, 67063

Mainz, Rheinland-Pfalz, Germany, 55131

Germany, Saarland

Homburg, Saarland, Germany, 66424

Germany, Sachsen

Chemnitz, Sachsen, Germany, 09116

Dresden, Sachsen, Germany, 01307

Dresden, Sachsen, Germany, 06067

Leipzig, Sachsen, Germany, 04103

Germany, Schleswig-Holstein

Kiel, Schleswig-Holstein, Germany, 24105

Lübeck, Schleswig-Holstein, Germany, 23538

Germany

Berlin, Germany, 13353

Hamburg, Germany, 20251

Marburg, Germany, 35037

Hungary

Budapest, Hungary, 1089

Budapest, Hungary, 1106

Budapest, Hungary, 1133

Debrecen, Hungary, 4032

Veszprem, Hungary, 8200

Zalaegerszeg, Hungary, H-8900

Italy

Ancona, Italy, 60126

Bari, Italy, 70124

Catania, Italy, 95123

Firenze, Italy, 50134

Milano, Italy, 20122

Milano, Italy, 20132

Milano, Italy, 20157

Padova, Italy, 35128

Roma, Italy, 00133

Roma, Italy, 00198

Torino, Italy, 10122

Japan, Aichi

Nagoya, Aichi, Japan, 466-8560

Nagoya, Aichi, Japan, 467-8602

Japan, Chiba

Urayasu, Chiba, Japan, 279-0021

Japan, Osaka

Suita, Osaka, Japan, 565-0871

Japan, Tokyo

Chiyoda-ku, Tokyo, Japan, 101-8309

Japan

Kyoto, Japan, 606-8507

Korea, Republic of

Incheon, Korea, Republic of, 405-760

Kungki-do, Korea, Republic of, 463-707

Seoul, Korea, Republic of, 110 744

Seoul, Korea, Republic of, 110-744

Seoul, Korea, Republic of, 138-736

Seoul, Korea, Republic of

Latvia

Riga, Latvia, 1002

Riga, Latvia, 1050

Singapore

Singapore, Singapore, 119074

Singapore, Singapore, 168751

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ClinicalTrials.gov archive

History of Changes for Study: NCT01012973

Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO) (GALILEO)

Latest version (submitted October 27, 2014) on ClinicalTrials.gov

- A study version is represented by a row in the table.
- Select two study versions to compare. One each from columns A and B.
- Choose either the "Merged" or "Side-by-Side" comparison format to specify how the two study versions are to be displayed. The Side-by-Side format only applies to the Protocol section of the study.
- Click "Compare" to do the comparison and show the differences.
- Select a version's date link to see a rendering of the study for that version.
- Edits or deletions will be displayed in ~~red~~.
- Additions will be displayed in *green*.
- The yellow choices in the table indicate the study versions currently compared below. A yellow row indicates the study version being viewed.
- Hover over the "Recruitment Status" to see how the study's recruitment status changed.

Study Record Versions

Version	A	B	Submitted Date	Changes
1	◉	○	November 12, 2009	Nothing (earliest Version on record)
2	○	○	January 21, 2010	Contacts/Locations, Study Status, Study Identification and Study Description
3	○	○	February 9, 2010	Contacts/Locations and Study Status
4	○	○	March 16, 2010	Contacts/Locations, Study Status and Study Identification
5	○	○	April 16, 2010	Contacts/Locations, Study Status and Study Identification

Version	A	B	Submitted Date	Changes
6	○	○	July 22, 2010	Contacts/Locations, Study Status, Eligibility and Arms and Interventions
7	○	○	August 25, 2010	Study Status and Contacts/Locations
8	○	○	August 26, 2010	Recruitment Status, Study Status and Contacts/Locations
9	○	○	September 8, 2010	Study Status
10	○	○	October 4, 2010	Study Status
11	○	○	November 1, 2010	Study Status
12	○	○	January 25, 2011	Study Status and Contacts/Locations
13	○	○	April 8, 2011	Study Status and Study Design
14	○	○	June 23, 2011	Arms and Interventions, Study Status, Contacts/Locations and Eligibility
15	○	○	September 19, 2011	Study Status
16	○	○	November 29, 2011	Study Status and Study Identification
17	○	○	January 26, 2012	Study Status and Contacts/Locations
18	○	○	February 20, 2012	Recruitment Status, Study Status
19	○	○	October 23, 2012	Outcome Measures, Arms and Interventions, Study Status, More Information, Reported Adverse Events, Baseline Characteristics and Participant Flow
20	○	○	December 18, 2012	More Information, Arms and Interventions, Study Status and Baseline Characteristics
21	○	○	January 18, 2013	Arms and Interventions, More Information, Study Status and Baseline Characteristics
22	○	○	January 30, 2014	Contacts/Locations, Sponsor/Collaborators, More Information, Study Status, Baseline Characteristics and References
23	○	◉	October 27, 2014	More Information, Study Status and References

Compare

Comparison Format: (•) Merged ( ) Side-by-Side

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Study NCT01012973
on Date: January 26, 2012 (v17)

Study Identification

Unique Protocol ID:	14130
Brief Title:	Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO) (GALILEO)
Official Title:	A Randomized, Double-masked, Sham-controlled Phase 3 Study of the Efficacy, Safety and Tolerability of Repeated Intravitreal Administration of VEGF Trap-Eye in Subjects With Macular Edema Secondary to Central Retinal Vein Occlusion (CRVO)
Secondary IDs:	2009-010973-19 [EudraCT Number]

Study Status

Record Verification:	January 2012
Overall Status:	Active, not recruiting
Study Start:	October 2009
Primary Completion:	February 2011 [Actual]
Study Completion:	March 2012 [Anticipated]
First Submitted:	October 30, 2009
First Submitted that Met QC Criteria:	November 12, 2009
First Posted:	November 13, 2009 [Estimate]
Certification/Extension First Submitted:	January 26, 2012

Certification/Extension First Submitted that Met QC Criteria:	January 26, 2012
Certification/Extension First Posted:	January 30, 2012 [Estimate]
Last Update Submitted that Met QC Criteria:	January 26, 2012
Last Update Posted:	January 30, 2012 [Estimate]

Sponsor/Collaborators

Sponsor:	Bayer
Responsible Party:	
Collaborators:	Regeneron Pharmaceuticals

Oversight

U.S. FDA-regulated Drug:	
U.S. FDA-regulated Device:	
Data Monitoring:	Yes

Study Description

Brief Summary:	To determine the efficacy of vascular endothelial growth factor (VEGF) Trap-Eye injected into the eye on vision function in subjects with macular edema as a consequence of central retinal vein occlusion
Detailed Description:	

Conditions

Conditions:	Retinal Vein Occlusion
Keywords:	Macular Edema Central Retinal Vein Occlusion CRVO VEGF Trap-Eye best-corrected visual acuity

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment

Study Phase:	Phase 3
Interventional Study Model:	Parallel Assignment
Number of Arms:	2
Masking:	TripleParticipant, Investigator, Outcomes Assessor
Allocation:	Randomized
Enrollment:	177 [Actual]

Arms and Interventions

Arms	Assigned Interventions
Experimental: Arm 1	Biological: VEGF Trap-Eye (BAY86-5321) Intravitreal injection. Weeks 0 to 20 injection of VEGF Trap-Eye every 4 weeks; weeks 24 to 52 every 4 weeks plus additional on week 60 and 68 re-assessment and either (PRN) injection of VEGF Trap-Eye or sham injection; last visit (no treatment) at week 76.
Sham Comparator: Arm 2	Sham treatment Sham treatment. Weeks 0 to 20 sham treatment every 4 weeks; weeks 24 to 48 every 4 weeks re-assessment and sham injection; week 52 VEGF Trap-Eye injection (unless investigator declines for medical reasons), weeks 60 and 68 re-assessment and either (PRN) injection of VEGF Trap-Eye or sham injection; last visit (no treatment) at week 76.

Outcome Measures

Primary Outcome Measures:

1. The proportion of subjects who gain at least 15 letters in BCVA on the EDTRS chart compared with baseline at the Week 24 endpoint
   Week 24

Secondary Outcome Measures:

2. Change from baseline in BCVA score
   Week 24

3. Absolute change from baseline in central retinal thickness, assessed by OCT
   Week 24
4. Proportion of subjects progressing to anterior segment neovascularization, neovascularization of the optic disc (NVD), or neovascularization of the retina elsewhere (NVE) requiring pan-retinal photocoagulation
   Week 24
5. Change in the NEI-VFQ-25 total score from baseline
   Week 24
6. Change in the EQ-5D score from baseline
   Week 24

Eligibility

Minimum Age:	18 Years
Maximum Age:	
Sex:	All
Gender Based:	
Accepts Healthy Volunteers:	No

Criteria: Inclusion Criteria:

- Center-involved macular edema secondary to central retinal vein occlusion (CRVO) for no longer than 9 months with mean central subfield thickness ≥ 250 µm on optical coherence tomography (OCT)
- Adults ≥ 18 years
- Early treatment diabetic retinopathy study (ETDRS) best corrected visual acuity (BCVA) of 20/40 to 20/320 (73 to 24 letters) in the study eye

Exclusion Criteria:

- Any prior treatment with anti-VEGF agents in the study eye (Pegaptanib sodium, anecortave acetate, bevacizumab, ranibizumab, etc.) or previous administration of systemic anti-angiogenic medications
- Prior panretinal laser photocoagulation or macular laser photocoagulation in the study eye

- CRVO disease duration > 9 months from date of diagnosis
- Previous use of intraocular corticosteroids in the study eye or use of periocular corticosteroids in the study eye within the 3 months prior to Day 1
- Iris neovascularization, vitreous hemorrhage, traction retinal detachment, or preretinal fibrosis involving the macula in either the study eye or fellow eye

Contacts/Locations

Study Officials: Bayer Study Director
Study Director
Bayer

Locations:

Australia, New South Wales

Chatswood, New South Wales, Australia, 2067

Parramatta, New South Wales, Australia, 2150

Sydney, New South Wales, Australia, 2000

Westmead, New South Wales, Australia, 2145

Australia, Victoria

East Melbourne, Victoria, Australia, 3002

Australia, Western Australia

Nedlands, Western Australia, Australia, 6009

Austria

Innsbruck, Austria, 6020

Linz, Austria, 4021

Wien, Austria, 1090

France, Cedex 12

Paris, Cedex 12, France, 75557

France, Cedex 1

Nantes, Cedex 1, France, 44093

France

Bordeaux, France, 33000

Dijon, France, 21033

Marseille, France, 13008

Paris, France, 75015

Germany, Baden-Württemberg

Freiburg, Baden-Württemberg, Germany, 79106

Heidelberg, Baden-Württemberg, Germany, 69120

Tübingen, Baden-Württemberg, Germany, 72076

Germany, Bayern

München, Bayern, Germany, 81675

Regensburg, Bayern, Germany, 93053

Germany, Hessen

Darmstadt, Hessen, Germany, 64297

Frankfurt, Hessen, Germany, 60596

Marburg, Hessen, Germany, 35037

Germany, Niedersachsen

Göttingen, Niedersachsen, Germany, 37075

Germany, Nordrhein-Westfalen

Aachen, Nordrhein-Westfalen, Germany, 52074

Bonn, Nordrhein-Westfalen, Germany, 53105

Essen, Nordrhein-Westfalen, Germany, 45122

Köln, Nordrhein-Westfalen, Germany, 50924

Münster, Nordrhein-Westfalen, Germany, 48145

Germany, Rheinland-Pfalz

Ludwigshafen, Rheinland-Pfalz, Germany, 67063

Mainz, Rheinland-Pfalz, Germany, 55131

Germany, Saarland

Homburg, Saarland, Germany, 66421

Germany, Sachsen

Chemnitz, Sachsen, Germany, 09116

Dresden, Sachsen, Germany, 01307

Dresden, Sachsen, Germany, 06067

Leipzig, Sachsen, Germany, 04103

Germany, Schleswig-Holstein

Kiel, Schleswig-Holstein, Germany, 24105

Lübeck, Schleswig-Holstein, Germany, 23538

Germany

Berlin, Germany, 13353

Hamburg, Germany, 20251

Hungary

Budapest, Hungary, 1089

Budapest, Hungary, 1106

Budapest, Hungary, 1133

Debrecen, Hungary, 4032

Veszprem, Hungary, 8200

Zalaegerszeg, Hungary, H-8900

Italy

Ancona, Italy, 60126

Bari, Italy, 70124

Catania, Italy, 95123

Firenze, Italy, 50134

Milano, Italy, 20122

Milano, Italy, 20132

Milano, Italy, 20157

Padova, Italy, 35128

Roma, Italy, 00133

Roma, Italy, 00198

Torino, Italy, 10122

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Suita, Osaka, Japan, 565-0871

Japan, Tokyo

Chiyoda-ku, Tokyo, Japan, 101-8309

Japan

Kyoto, Japan, 606-8507

Korea, Republic of

Incheon, Korea, Republic of, 405-760

Kungki-do, Korea, Republic of, 463-707

Seoul, Korea, Republic of, 110 744

Seoul, Korea, Republic of, 110-744

Seoul, Korea, Republic of, 138-736

Seoul, Korea, Republic of

Latvia

Riga, Latvia, 1002

Riga, Latvia, 1050

Singapore

Singapore, Singapore, 119074

Singapore, Singapore, 168751

IPDSharing

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U.S. National Library of Medicine
ClinicalTrials.gov archive

History of Changes for Study: NCT01012973

Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO) (GALILEO)

Latest version (submitted October 27, 2014) on ClinicalTrials.gov

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3	○	○	February 9, 2010	Contacts/Locations and Study Status
4	○	○	March 16, 2010	Contacts/Locations, Study Status and Study Identification
5	○	○	April 16, 2010	Contacts/Locations, Study Status and Study Identification

Version	A	B	Submitted Date	Changes
6	○	○	July 22, 2010	Contacts/Locations, Study Status, Eligibility and Arms and Interventions
7	○	○	August 25, 2010	Study Status and Contacts/Locations
8	○	○	August 26, 2010	Recruitment Status, Study Status and Contacts/Locations
9	○	○	September 8, 2010	Study Status
10	○	○	October 4, 2010	Study Status
11	○	○	November 1, 2010	Study Status
12	○	○	January 25, 2011	Study Status and Contacts/Locations
13	○	○	April 8, 2011	Study Status and Study Design
14	○	○	June 23, 2011	Arms and Interventions, Study Status, Contacts/Locations and Eligibility
15	○	○	September 19, 2011	Study Status
16	○	○	November 29, 2011	Study Status and Study Identification
17	○	○	January 26, 2012	Study Status and Contacts/Locations
18	○	○	February 20, 2012	Recruitment Status, Study Status
19	○	○	October 23, 2012	Outcome Measures, Arms and Interventions, Study Status, More Information, Reported Adverse Events, Baseline Characteristics and Participant Flow
20	○	○	December 18, 2012	More Information, Arms and Interventions, Study Status and Baseline Characteristics
21	○	○	January 18, 2013	Arms and Interventions, More Information, Study Status and Baseline Characteristics
22	○	○	January 30, 2014	Contacts/Locations, Sponsor/Collaborators, More Information, Study Status, Baseline Characteristics and References
23	○	◉	October 27, 2014	More Information, Study Status and References

Compare

Comparison Format: (•) Merged ( ) Side-by-Side

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Study NCT01012973
on Date: January 30, 2014 (v22)

Study Identification

Unique Protocol ID:	14130
Brief Title:	Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO) (GALILEO)
Official Title:	A Randomized, Double-masked, Sham-controlled Phase 3 Study of the Efficacy, Safety and Tolerability of Repeated Intravitreal Administration of VEGF Trap-Eye in Subjects With Macular Edema Secondary to Central Retinal Vein Occlusion (CRVO)
Secondary IDs:	2009-010973-19 [EudraCT Number]

Study Status

Record Verification:	January 2014
Overall Status:	Completed
Study Start:	October 2009
Primary Completion:	February 2011 [Actual]
Study Completion:	February 2012 [Actual]
First Submitted:	October 30, 2009
First Submitted that Met QC Criteria:	November 12, 2009
First Posted:	November 13, 2009 [Estimate]
Results First Submitted:	October 23, 2012
	October 23, 2012

Results First Submitted that Met QC Criteria:	
Results First Posted:	November 22, 2012 [Estimate]
Certification/Extension First Submitted:	January 26, 2012
Certification/Extension First Submitted that Met QC Criteria:	January 26, 2012
Certification/Extension First Posted:	January 30, 2012 [Estimate]
Last Update Submitted that Met QC Criteria:	January 30, 2014
Last Update Posted:	March 5, 2014 [Estimate]

Sponsor/Collaborators

Sponsor:	Bayer
Responsible Party:	Sponsor
Collaborators:	Regeneron Pharmaceuticals

Oversight

U.S. FDA-regulated Drug:	
U.S. FDA-regulated Device:	
Data Monitoring:	Yes

Study Description

Brief Summary:	To determine the efficacy of vascular endothelial growth factor (VEGF) Trap-Eye injected into the eye on vision function in subjects with macular edema as a consequence of central retinal vein occlusion
Detailed Description:	

Conditions

Conditions:	Retinal Vein Occlusion
Keywords:	Macular Edema Central Retinal Vein Occlusion

CRVO
VEGF Trap-Eye
best-corrected visual acuity

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	Phase 3
Interventional Study Model:	Parallel Assignment
Number of Arms:	2
Masking:	TripleParticipant, Investigator, Outcomes Assessor
Allocation:	Randomized
Enrollment:	177 [Actual]

Arms and Interventions

Arms	Assigned Interventions
Experimental: Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321) Participants received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered every 4 weeks from Day 1 through Week 20, later as often as every 4 weeks depending on the study retreatment criteria from Week 24 through Week 48. Follow-up phase: Participants on IAI, who continued the study, received 2 mg dose of IAI depending on the study retreatment criteria at Week 60 and 68.	Biological: Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321) Intravitreal injection. Weeks 0 to 20 of Aflibercept Injection every 4 weeks; Weeks 24 to 52 every 4 weeks PRN (pro re nata, on demand); plus additional on Week 60 and 68. Sham treatment Sham treatment. Weeks 0 to 52 sham treatment every 4 weeks; plus additional on Week 60 and 68.
Sham Comparator: Sham treatment Participants received sham treatment administered every 4 weeks from Day 1 through Week 52. Follow-up phase: Participants on sham treatment, who switched to Intravitreal Aflibercept Injection (IAI), received a 2 mg dose of IAI at week 52 and depending on the	Sham treatment Sham treatment. Weeks 0 to 52 sham treatment every 4 weeks; plus additional on Week 60 and 68.

Arms	Assigned Interventions
study retreatment criteria at Week 60 and 68.	

Outcome Measures

[See Results Section.]

Eligibility

Minimum Age: 18 Years

Maximum Age:

Sex: All

Gender Based:

Accepts Healthy Volunteers: No

Criteria: Inclusion Criteria:

- Center-involved macular edema secondary to central retinal vein occlusion (CRVO) for no longer than 9 months with mean central subfield thickness ≥ 250 µm on optical coherence tomography (OCT)
- Adults ≥ 18 years
- Early treatment diabetic retinopathy study (ETDRS) best corrected visual acuity (BCVA) of 20/40 to 20/320 (73 to 24 letters) in the study eye

Exclusion Criteria:

- Any prior treatment with anti-VEGF agents in the study eye (Pegaptanib sodium, anecortave acetate, bevacizumab, ranibizumab, etc.) or previous administration of systemic anti-angiogenic medications
- Prior panretinal laser photocoagulation or macular laser photocoagulation in the study eye
- CRVO disease duration > 9 months from date of diagnosis

- Previous use of intraocular corticosteroids in the study eye or use of periocular corticosteroids in the study eye within the 3 months prior to Day 1
- Iris neovascularization, vitreous hemorrhage, traction retinal detachment, or preretinal fibrosis involving the macula in either the study eye or fellow eye

Contacts/Locations

Study Officials: Bayer Study Director
Study Director
Bayer

Locations: **Australia, New South Wales**

Chatswood, New South Wales, Australia, 2067

Parramatta, New South Wales, Australia, 2150

Sydney, New South Wales, Australia, 2000

Westmead, New South Wales, Australia, 2145

Australia, Victoria

East Melbourne, Victoria, Australia, 3002

Australia, Western Australia

Nedlands, Western Australia, Australia, 6009

Austria

Innsbruck, Austria, 6020

Linz, Austria, 4021

Wien, Austria, 1090

France, Cedex 12

Paris, Cedex 12, France, 75557

France, Cedex 1

Nantes, Cedex 1, France, 44093

France

Bordeaux, France, 33000

Dijon, France, 21033

Marseille, France, 13008

Paris, France, 75015

Germany, Baden-Württemberg

Freiburg, Baden-Württemberg, Germany, 79106

Heidelberg, Baden-Württemberg, Germany, 69120

Tübingen, Baden-Württemberg, Germany, 72076

Germany, Bayern

München, Bayern, Germany, 81675

Regensburg, Bayern, Germany, 93053

Germany, Hessen

Darmstadt, Hessen, Germany, 64297

Frankfurt, Hessen, Germany, 60596

Marburg, Hessen, Germany, 35037

Germany, Niedersachsen

Göttingen, Niedersachsen, Germany, 37075

Germany, Nordrhein-Westfalen

Aachen, Nordrhein-Westfalen, Germany, 52074

Bonn, Nordrhein-Westfalen, Germany, 53105

Essen, Nordrhein-Westfalen, Germany, 45122

Köln, Nordrhein-Westfalen, Germany, 50924

Münster, Nordrhein-Westfalen, Germany, 48145

Germany, Rheinland-Pfalz

Ludwigshafen, Rheinland-Pfalz, Germany, 67063

Mainz, Rheinland-Pfalz, Germany, 55131

Germany, Saarland

Homburg, Saarland, Germany, 66421

Germany, Sachsen

Chemnitz, Sachsen, Germany, 09116

Dresden, Sachsen, Germany, 01307

Dresden, Sachsen, Germany, 06067

Leipzig, Sachsen, Germany, 04103

Germany, Schleswig-Holstein

Kiel, Schleswig-Holstein, Germany, 24105

Lübeck, Schleswig-Holstein, Germany, 23538

Germany

Berlin, Germany, 13353

Hamburg, Germany, 20251

Hungary

Budapest, Hungary, 1089

Budapest, Hungary, 1106

Budapest, Hungary, 1133

Debrecen, Hungary, 4032

Veszprem, Hungary, 8200

Zalaegerszeg, Hungary, H-8900

Italy

Ancona, Italy, 60126

Bari, Italy, 70124

Catania, Italy, 95123

Firenze, Italy, 50134

Milano, Italy, 20122

Milano, Italy, 20132

Milano, Italy, 20157

Padova, Italy, 35128

Roma, Italy, 00133

Roma, Italy, 00198

Torino, Italy, 10122

Japan, Aichi

Nagoya, Aichi, Japan, 466-8560

Nagoya, Aichi, Japan, 467-8602

Japan, Chiba

Urayasu, Chiba, Japan, 279-0021

Japan, Osaka

Suita, Osaka, Japan, 565-0871

Japan, Tokyo

Chiyoda-ku, Tokyo, Japan, 101-8309

Japan

Kyoto, Japan, 606-8507

Korea, Republic of, Gyeonggido

Seongnam-si, Gyeonggido, Korea, Republic of, 463-707

Korea, Republic of

Incheon, Korea, Republic of, 405-760

Seoul, Korea, Republic of, 110 744

Seoul, Korea, Republic of, 137-701

Seoul, Korea, Republic of, 138-736

Seoul, Korea, Republic of

Latvia

Riga, Latvia, 1002

Riga, Latvia, 1050

Singapore

Singapore, Singapore, 119074

Singapore, Singapore, 168751

IPDSharing

Plan to Share IPD:

References

Citations: [Study Results] Holz FG, Roider J, Ogura Y, Korobelnik JF, Simader C, Groetzbach G, Vitti R, Berliner AJ, Hiemeyer F, Beckmann K, Zeitz O, Sandbrink R. VEGF Trap-Eye for macular oedema secondary to central retinal vein occlusion: 6-month results of the phase III GALILEO study. Br J Ophthalmol. 2013 Mar;97(3):278-84. doi: 10.1136/bjophthalmol-2012-301504. Epub 2013 Jan 7.

Erratum in: Br J Ophthalmol. 2015 Dec;99(12):1746. PubMed 23298885

[Study Results] Korobelnik JF, Holz FG, Roider J, Ogura Y, Simader C, Schmidt-Erfurth U, Lorenz K, Honda M, Vitti R, Berliner AJ, Hiemeyer F, Stemper B, Zeitz O, Sandbrink R; GALILEO Study Group. Intravitreal Aflibercept Injection for Macular Edema Resulting from Central Retinal Vein Occlusion: One-Year Results of the Phase 3 GALILEO Study. Ophthalmology. 2014 Jan;121(1):202-208. doi: 10.1016/j.ophtha.2013.08.012. Epub 2013 Sep 29. PubMed 24084497

Links:

Available IPD/Information:

Study Results

Participant Flow

Reporting Groups

	Description
Aflibercept Injection First, Then Aflibercept Injection	Participants received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered every 4 weeks from Day 1 through Week 20, later as often as every 4 weeks depending on the study retreatment criteria from Week 24 through Week 48. Follow-up phase: Participants on IAI, who continued the study, received 2 mg dose of IAI depending on the study retreatment criteria at Week 60 and 68.
Sham Treatment First, Then Aflibercept Injection	Participants received sham treatment administered every 4 weeks from Day 1 through Week 52. Follow-up phase: Participants on sham treatment, who switched to Intravitreal Aflibercept Injection (IAI), received a 2 mg dose of IAI at week 52 and depending on the study retreatment criteria at Week 60 and 68.

Overall Study

	Aflibercept Injection First, Then Aflibercept Injection	Sham Treatment First, Then Aflibercept Injection
Started	106	71
Participants Received Treatment	104 [1]	68 [1]
Fulfilled Requirements of FAS Population	103 [2]	68 [2]
Completed Week 24, From FAS	97	57
Completed Week 52, From FAS	91	52
Completed	90	52
Not Completed	16	19
Adverse Event	5	5
Lack of Efficacy	0	5
Lost to Follow-up	1	0
(Overseas travel - indefinite period)	1	0
Increase in vis. acuity, never injected	0	1
Protocol Violation	5	2
Withdrawal by Subject	4	6

[1] Safety Population: Participants received treatment

[2] Full Analysis Set (FAS) Population: Participants received treatment with post baseline measurements

Baseline Characteristics

Reporting Groups

	Description
Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Participants received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered every 4 weeks from Day 1 through Week 20, later as often as every

	4 weeks depending on the study retreatment criteria from Week 24 through Week 48. Follow-up phase: Participants on IAI, who continued the study, received 2 mg dose of IAI depending on the study retreatment criteria at Week 60 and 68.
Sham Treatment	Participants received sham treatment administered every 4 weeks from Day 1 through Week 52. Follow-up phase: Participants on sham treatment, who switched to Intravitreal Aflibercept Injection (IAI), received a 2 mg dose of IAI at week 52 and depending on the study retreatment criteria at Week 60 and 68.

Baseline Measures

		Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Sham Treatment	Total
Overall Number of Participants		104	68	172
Age, Continuous Mean (Standard Deviation) Unit of measure: Years	Number Analyzed	104 Participants	68 Participants	172 Participants
		60.0 (12.3)	63.8 (13.3)	61.5 (12.8)
Sex: Female, Male Measure type: Count of Participants Unit of measure: Participants	Number Analyzed	104 Participants	68 Participants	172 Participants
	Female	45 43.27%	31 45.59%	76 44.19%
	Male	59 56.73%	37 54.41%	96 55.81%
Ethnicity (NIH/OMB) Measure type: Count of Participants Unit of measure: Participants	Number Analyzed	104 Participants	68 Participants	172 Participants
	Hispanic or Latino	4 3.85%	1 1.47%	5 2.91%
	Not Hispanic or Latino	100 96.15%	66 97.06%	166 96.51%
		0 0%	1 1.47%	1 0.58%

		Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Sham Treatment	Total
	Unknown or Not Reported			
Baseline Best Corrected Visual Acuity (BCVA) letter scores [1] Mean (Standard Deviation)	Number Analyzed	104 Participants	68 Participants	172 Participants
		53.5 (15.7)	50.9 (15.4)	52.5 (15.6)
	[1] Infiormation retrieved from all baseline participants. Only participants with a ETDRS (Early Treatment Diabetic Retinopathy Study) Best Corrected Visual Acuity letter score of 73 to 25 (= Acuity of 20/40 to 20/320) in the study eye at 4 meters were included; a higher score represents better functioning.			
Number of participants with baseline retinal perfusion [1] Measure type: Number Unit of measure: Participants	Number Analyzed	104 Participants	68 Participants	172 Participants
Perfused		90	54	144
Nonperfused		7	7	14
Indeterminate		7	7	14
	[1] Retinal perfusion defined as less than 10 disc areas of capillary nonperfusion using fluorescein angiography (FA)			
Baseline Retinal Thickness by Optical Coherence Tomography (OCT) Mean (Standard Deviation)	Number Analyzed	104 Participants	68 Participants	172 Participants
		682.78 (233.36)	638.66 (224.69)	665.34 (230.33)

		Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Sham Treatment	Total
Baseline intraocular pressure Mean (Standard Deviation)	Number Analyzed	104 Participants	68 Participants	172 Participants
		15.2 (2.8)	14.4 (2.7)	14.9 (2.8)
Number of participants with time since Central retinal vein occlusion (CRVO) diagnosis Measure type: Number Unit of measure: Participants	Number Analyzed	104 Participants	68 Participants	172 Participants
>= 2 months		46	33	79
< 2 months		56	35	91
Missing		2	0	2
Baseline National Eye Institute 25-item Visual Function Questionnaire (NEI VFQ-25) total score [1]	Number Analyzed	104 Participants	68 Participants	172 Participants
		79.66 (13.06)	78.94 (14.00)	79.38 (13.40)
	[1]	The NEI VFQ-25 total score ranges from 0-100 with a score of 0 being the worst outcome and 100 being the best outcome. The NEI VFQ questionnaire is organized as a collection of subscales which are all scored from 0-100. To reach the overall composite score, each sub-scale score is averaged in order to give each sub-scale equal weight.		
European questionnaire 5 dimensions (EQ-5D) total score [1] Mean (Standard Deviation)	Number Analyzed	104 Participants	68 Participants	172 Participants
		0.87 (0.15)	0.86 (0.16)	0.87 (0.15)

		Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Sham Treatment	Total
Unit of measure: score on a scale				
	[1] The EQ-5D total score ranges from -0.594 to 1.000 with -0.594 being the worst.			
Race Measure type: Number Unit of measure: Participants	Number Analyzed	104 Participants	68 Participants	172 Participants
Asian		26	15	41
White		75	49	124
Unknown or Not Reported		3	4	7

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Percentage of Participants Who Gained at Least 15 Letters in BCVA as Measured by ETDRS Letter Score Compared With Baseline at Week 24 With Discontinued Participants Before Week 24 Evaluated as Failures
Measure Description	Defined study baseline range of Early Treatment Diabetic Retinopathy Study (ETDRS) Best Corrected Visual Acuity (BCVA) letter score of 73 to 24 (= Acuity of 20/40 to 20/320) in the study eye; a higher score represents better functioning. Nominator = (Number of participants who maintained vision * 100); Denominator = Number of participants analyzed.
Time Frame	Baseline and Week 24

Analysis Population Description

Full analysis set

Reporting Groups

	Description
Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Participants received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered every 4 weeks from Day 1 through Week 20, later as often as every 4 weeks depending on the study retreatment criteria from Week 24 through Week 48. Follow-up phase: Participants on IAI, who continued the study, received 2 mg dose of IAI depending on the study retreatment criteria at Week 60 and 68.
Sham Treatment	Participants received sham treatment administered every 4 weeks from Day 1 through Week 52. Follow-up phase: Participants on sham treatment, who switched to Intravitreal Aflibercept Injection (IAI), received a 2 mg dose of IAI at week 52 and depending on the study retreatment criteria at Week 60 and 68.

Measured Values

	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Sham Treatment
Overall Number of Participants Analyzed	103	68
Percentage of Participants Who Gained at Least 15 Letters in BCVA as Measured by ETDRS Letter Score Compared With Baseline at Week 24 With Discontinued Participants Before Week 24 Evaluated as Failures Measure Type: Number Unit of Measure: Percentage of participants	60.2	22.1

Statistical Analysis 1 for Percentage of Participants Who Gained at Least 15 Letters in BCVA as Measured by ETDRS Letter Score Compared With Baseline at Week 24 With Discontinued Participants Before Week 24 Evaluated as Failures

Statistical Analysis Overview	Comparison Groups	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321), Sham Treatment
	Comments	Null hypothesis of difference of Eylea minus Sham of 0 was tested. In the database close after Week 24, basis for primary efficacy evaluation, 56 Sham / 96 Eylea subjects were considered as week 24 completers.
	Type of Statistical Test	Superiority or Other (legacy)
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	<.0001
	Comments	[Not specified]
	Method	Cochran-Mantel-Haenszel
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	CMH adjusted difference
	Estimated Value	38.3
	Confidence Interval	(2-sided) 95% 24.4 to 52.1
	Estimation Comments	The estimate is calculated as Eylea minus Sham. A positive value shows Eylea showed a higher BCVA total score compared to Sham.

2. Secondary Outcome Measure:

Measure Title	Change From Baseline in BCVA as Measured by Early Treatment Diabetic Retinopathy Study (ETDRS) Letter Score at Week 24 - Last Observation Carried Forward (LOCF)
Measure Description	Defined study baseline range of ETDRS Best Corrected Visual Acuity letter score of 73 to 24 (= Acuity of 20/40 to 20/320) in the study eye; a higher score represents better functioning. However, because this was assessed at the screening visit,

	subjects may have had a higher BCVA recorded at the baseline visit and would not have been excluded from the study.
Time Frame	Baseline and Week 24

Analysis Population Description

Full analysis set

Reporting Groups

	Description
Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Participants received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered every 4 weeks from Day 1 through Week 20, later as often as every 4 weeks depending on the study retreatment criteria from Week 24 through Week 48. Follow-up phase: Participants on IAI, who continued the study, received 2 mg dose of IAI depending on the study retreatment criteria at Week 60 and 68.
Sham Treatment	Participants received sham treatment administered every 4 weeks from Day 1 through Week 52. Follow-up phase: Participants on sham treatment, who switched to Intravitreal Aflibercept Injection (IAI), received a 2 mg dose of IAI at week 52 and depending on the study retreatment criteria at Week 60 and 68.

Measured Values

	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Sham Treatment
Overall Number of Participants Analyzed	103	68
Change From Baseline in BCVA as Measured by Early Treatment Diabetic Retinopathy Study (ETDRS) Letter Score at Week 24 - Last Observation Carried Forward (LOCF) Measure Type: Mean (Standard Deviation) Unit of Measure: Letters correctly read	71.6 (17.1)	54.3 (20.2)

Statistical Analysis 1 for Change From Baseline in BCVA as Measured by Early Treatment Diabetic Retinopathy Study (ETDRS) Letter Score at Week 24 - Last Observation Carried Forward (LOCF)

Statistical Analysis Overview	Comparison Groups	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321), Sham Treatment
	Comments	Null hypothesis was equality in change from baseline to Week 24 in BCVA total letter score between Eylea and Sham. If primary efficacy was successful, secondary efficacy endpoints were tested in a pre-specified fixed sequence testing procedure. Change in BCVA letter score was to be tested first in this sequence.
	Type of Statistical Test	Superiority or Other (legacy)
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	<.0001
	Comments	As primary efficacy evaluation was significant, and this p-value was below significance level of two-sided <.05, the fixed sequence testing did continue with next secondary endpoint.
	Method	ANOVA
	Comments	ANOVA, adjusting for region and baseline BCVA category as fixed factors.

Method of Estimation	Estimation Parameter	Difference in Least square means
	Estimated Value	14.7
	Confidence Interval	(2-sided) 95% 10.8 to 18.7
	Estimation Comments	The difference is calculated as Eylea minus Sham. A positive value

		indicates Eylea showed a higher change in BCVA total score until week 24 compared to Sham.

3. Secondary Outcome Measure:

Measure Title	Change From Baseline in Central Retinal Thickness (CRT) at Week 24 - LOCF
Measure Description	
Time Frame	Baseline and Week 24

Analysis Population Description

Full-Analysis Set with assessment for this outcome measure; imputation technique: LOCF

Reporting Groups

	Description
Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Participants received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered every 4 weeks from Day 1 through Week 20, later as often as every 4 weeks depending on the study retreatment criteria from Week 24 through Week 48. Follow-up phase: Participants on IAI, who continued the study, received 2 mg dose of IAI depending on the study retreatment criteria at Week 60 and 68.
Sham Treatment	Participants received sham treatment administered every 4 weeks from Day 1 through Week 52. Follow-up phase: Participants on sham treatment, who switched to Intravitreal Aflibercept Injection (IAI), received a 2 mg dose of IAI at week 52 and depending on the study retreatment criteria at Week 60 and 68.

Measured Values

	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Sham Treatment
Overall Number of Participants Analyzed	103	67

	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Sham Treatment
Change From Baseline in Central Retinal Thickness (CRT) at Week 24 - LOCF Measure Type: Mean (Standard Deviation) Unit of Measure: microns	-448.58 (256.02)	-169.27 (224.72)

Statistical Analysis 1 for Change From Baseline in Central Retinal Thickness (CRT) at Week 24 - LOCF

Statistical Analysis Overview	Comparison Groups	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321), Sham Treatment
	Comments	Null hypothesis was equality in change from baseline to Week 24 in central retinal thickness between Eylea and Sham. If primary efficacy was successful, secondary efficacy end points were to be tested in a pre-specified fixed sequence testing procedure. Change in central retinal thickness was to be tested at second place in this sequence.
	Type of Statistical Test	Superiority or Other (legacy)
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	<.0001
	Comments	As fixed sequence testing did reject nullhypothesis of change from baseline in BCVA until week 24, and this p-value was below significance level of two-sided <.05, the fixed sequence testing did continue with next secondary endpoint.
	Method	ANCOVA
	Comments	ANCOVA, stratified by region and baseline BCVA category, baseline

		central retinal thickness added as covariate.

Method of Estimation	Estimation Parameter	Difference in Least square (LS) means
	Estimated Value	-239.42
	Confidence Interval	(2-sided) 95% -286.31 to -192.53
	Estimation Comments	The difference is calculated as Eylea minus Sham. A negative value indicates Eylea showed a higher reduction in change in central retinal thickness until week 24 compared to Sham.

4. Secondary Outcome Measure:

Measure Title	Percentage of Participants Who Developed Neovascularization During the First 24 Weeks
Measure Description	Formation of blood vessels in the anterior segment, optic disc, or elsewhere in the fundus up to Week 24
Time Frame	From baseline until Week 24

Analysis Population Description

Full analysis set

Reporting Groups

	Description
Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Participants received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered every 4 weeks from Day 1 through Week 20, later as often as every 4 weeks depending on the study retreatment criteria from Week 24 through Week 48. Follow-up phase: Participants on IAI, who continued the study, received 2 mg dose of IAI depending on the study retreatment criteria at Week 60 and 68.
Sham Treatment	Participants received sham treatment administered every 4 weeks from Day 1 through Week 52. Follow-

	up phase: Participants on sham treatment, who switched to Intravitreal Aflibercept Injection (IAI), received a 2 mg dose of IAI at week 52 and depending on the study retreatment criteria at Week 60 and 68.

Measured Values

	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Sham Treatment
Overall Number of Participants Analyzed	103	68
Percentage of Participants Who Developed Neovascularization During the First 24 Weeks Measure Type: Number Unit of Measure: Percentage of participants		
Any neovascularization	2.9	4.4
Anterior segment neovascularization	1.9	1.5
Neovascularization of the optic disc (NVD)	0.0	0.0
Neovascularization elsewhere in the fundus (NVE)	1.0	2.9

Statistical Analysis 1 for Percentage of Participants Who Developed Neovascularization During the First 24 Weeks

Statistical Analysis Overview	Comparison Groups	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321), Sham Treatment
	Comments	Nullhypothesis of no difference in development of neovascularizations between Eylea and Sham group was tested. (Any neovascularization)
	Type of Statistical Test	Superiority or Other (legacy)
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.5947
	Comments	

		As fixed sequence testing did reject nullhypothesis of change from baseline in CRT until week 24, and this p-value was not below significance level of two-sided <.05, the fixed sequence testing did end with this evaluation.
	Method	Cochran-Mantel-Haenszel
	Comments	Cochrane-Mantel-Haenszel test, stratified by region and baseline BCVA category.

Method of Estimation	Estimation Parameter	CMH adjusted Difference
	Estimated Value	-1.5
	Confidence Interval	(2-sided) 95% -7.4 to 4.4
	Estimation Comments	[Not specified]

5. Secondary Outcome Measure:

Measure Title	Change From Baseline in National Eye Institute 25-item Visual Function Questionnaire (NEI VFQ-25) Total Score at Week 24 - LOCF
Measure Description	The NEI VFQ-25 total score ranges from 0-100 with a score of 0 being the worst outcome and 100 being the best outcome. The NEI VFQ questionnaire is organized as a collection of subscales which are all scored from 0-100. To reach the overall composite score, each sub-scale score is averaged in order to give each sub-scale equal weight
Time Frame	Baseline and Week 24

Analysis Population Description

Full-Analysis Set with assessment for this outcome measure; imputation technique: LOCF

Reporting Groups

	Description
Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Participants received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered every 4 weeks from Day 1 through Week 20, later as often as every 4 weeks depending on the study retreatment criteria from Week 24 through Week 48. Follow-up phase: Participants on IAI, who continued the study, received 2 mg dose of IAI depending on the study retreatment criteria at Week 60 and 68.
Sham Treatment	Participants received sham treatment administered every 4 weeks from Day 1 through Week 52. Follow-up phase: Participants on sham treatment, who switched to Intravitreal Aflibercept Injection (IAI), received a 2 mg dose of IAI at week 52 and depending on the study retreatment criteria at Week 60 and 68.

Measured Values

	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Sham Treatment
Overall Number of Participants Analyzed	96	65
Change From Baseline in National Eye Institute 25-item Visual Function Questionnaire (NEI VFQ-25) Total Score at Week 24 - LOCF Measure Type: Mean (Standard Deviation) Unit of Measure: Scores on a scale	7.46 (9.55)	3.55 (9.74)

Statistical Analysis 1 for Change From Baseline in National Eye Institute 25-item Visual Function Questionnaire (NEI VFQ-25) Total Score at Week 24 - LOCF

Statistical Analysis Overview	Comparison Groups	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321), Sham Treatment
	Comments	[Not specified]
	Type of Statistical Test	Superiority or Other (legacy)
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Difference in LS means
	Estimated Value	4.2
	Confidence Interval	(2-sided) 95% 1.7 to 6.8
	Estimation Comments	As the fixed sequence of secondary endpoints stopped with proportion of neovascularizations developed until week 24, 95% confidence interval is only of descriptive nature.

6. Secondary Outcome Measure:

Measure Title	Change From Baseline in European Five-dimensional Health Scale (EQ-5D) Score at Week 24 - LOCF
Measure Description	EQ-5D is a quality of life questionnaire based on a scale from -0.594 (worst) to 1.00 (best).
Time Frame	Baseline and Week 24

Analysis Population Description

Full-Analysis Set with assessment for this outcome measure; imputation technique: LOCF

Reporting Groups

	Description
Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Participants received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered every 4 weeks from Day 1 through Week 20, later as often as every 4 weeks depending on the study retreatment criteria from Week 24 through Week 48. Follow-up phase: Participants on IAI, who continued the study, received 2 mg dose of IAI depending on the study retreatment criteria at Week 60 and 68.
Sham Treatment	Participants received sham treatment administered every 4 weeks from Day 1 through Week 52. Follow-up phase: Participants on sham treatment, who switched to Intravitreal Aflibercept Injection (IAI), received a 2 mg dose of IAI at week 52 and

	depending on the study retreatment criteria at Week 60 and 68.

Measured Values

	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Sham Treatment
Overall Number of Participants Analyzed	95	64
Change From Baseline in European Five-dimensional Health Scale (EQ-5D) Score at Week 24 - LOCF Measure Type: Mean (Standard Deviation) Unit of Measure: Scores on a scale	0.029 (0.139)	-0.002 (0.195)

Statistical Analysis 1 for Change From Baseline in European Five-dimensional Health Scale (EQ-5D) Score at Week 24 - LOCF

Statistical Analysis Overview	Comparison Groups	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321), Sham Treatment
	Comments	[Not specified]
	Type of Statistical Test	Superiority or Other (legacy)
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Difference in LS Means
	Estimated Value	0.044
	Confidence Interval	(2-sided) 95% -0.002 to 0.09
	Estimation Comments	As the fixed sequence of secondary endpoints stopped with proportion of neovascularizations developed until week 24, 95% confidence interval is only of descriptive nature.

Reported Adverse Events

Time Frame	[Not specified]
	[Not specified]

Adverse Event Reporting Description	

Reporting Groups

	Description
Aflibercept Injection (Until Week 20)	Participants received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered every 4 weeks from Day 1 through Week 20. Participants were observed until Week 24. Participants in the safety population were at risk.
Sham Treatment (Until Week 20)	Participants received sham treatment administered every 4 weeks from Day 1 through Week 20. Participants were observed until Week 24. Participants in the safety population were at risk.
Aflibercept Injection (Until Week 48)	Participants who continued the study drug until Week 24 received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered as often as every 4 weeks depending on the study retreatment criteria from Week 24 through Week 48. Participants were observed from Week 24 until Week 52. Participants in the safety population that completed Week 24 were at risk.
Sham Treatment (Until Week 48)	Participants who continued the study drug until Week 24 received sham treatment administered every 4 weeks from Week 24 to Week 48. Participants were observed from Week 24 until Week 52. Participants in the safety population that completed Week 24 were at risk.
Aflibercept Injection Continued (Until Week 68)	Participants on IAI who continued the study drug until Week 52, received 2 mg dose of IAI depending on the study retreatment criteria at Week 52, 60 and 68. Participants were observed starting from Week 52. Participants in the safety population that completed Week 52 were at risk.
Sham Treatment Then Aflibercept Injection (Until Week 68)	Participants on sham treatment switched to IAI, received a 2 mg dose of IAI at Week 52 and depending on the study retreatment criteria at Week

	60 and 68. Participants were observed starting from Week 52. Participants in the safety population that completed Week 52 were at risk.

All-Cause Mortality

	Afliberce Injection (Until Week 20)	Sham Treatme (Until Week 20)	Afliberce Injection (Until Week 48)	Sham Treatme (Until Week 48)	Afliberce Injection Continue (Until Week 68)	Sham Treatme Then Afliberce Injection (Until Week 68)
	Affected/A Risk (%)	Affected/A Risk (%)	Affected/A Risk (%)	Affected/A Risk (%)	Affected/A Risk (%)	Affected/A Risk (%)
Total	/	/	/	/	/	/

Serious Adverse Events

	Afliberce Injection (Until Week 20)	Sham Treatme (Until Week 20)	Afliberce Injection (Until Week 48)	Sham Treatme (Until Week 48)	Afliberce Injection Continue (Until Week 68)	Sham Treatme Then Afliberce Injection (Until Week 68)
	Affected/A Risk (%)	Affected/A Risk (%)	Affected/A Risk (%)	Affected/A Risk (%)	Affected/A Risk (%)	Affected/A Risk (%)
Total	8/104 (7.69%)	8/68 (11.76%	14/97 (14.43%	7/57 (12.28%	4/91 (4.4%)	3/52 (5.77%)
Cardiac disorders						
Aortic valve incompetence [A*]	0/104 (0%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	1/52 (1.92%)
Cardiac failure [A*]	0/104 (0%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	1/52 (1.92%)
Coronary artery stenosis [A*]	0/104 (0%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	1/52 (1.92%)

	Afliberce Injection (Until Week 20)	Sham Treatme (Until Week 20)	Afliberce Injection (Until Week 48)	Sham Treatme (Until Week 48)	Afliberce Injection Continue (Until Week 68)	Sham Treatme Then Afliberce Injection (Until Week 68)
Diastolic dysfunction [A*]	0/104 (0%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	1/52 (1.92%)
Mitral valve incompetence [A*]	0/104 (0%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	1/52 (1.92%)
Eye disorders						
Blindness unilateral [A*]	0/104 (0%)	0/68 (0%)	1/97 (1.03%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Glaucoma [A*]	0/104 (0%)	1/68 (1.47%)	0/97 (0%)	1/57 (1.75%)	0/91 (0%)	0/52 (0%)
Iris neovascularisation [A*]	1/104 (0.96%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Macular fibrosis [A*]	0/104 (0%)	0/68 (0%)	1/97 (1.03%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Macular ischaemia [A*]	0/104 (0%)	0/68 (0%)	1/97 (1.03%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Macular oedema [A*]	0/104 (0%)	2/68 (2.94%)	4/97 (4.12%)	0/57 (0%)	1/91 (1.1%)	0/52 (0%)
Retinal vein occlusion [A*]	0/104 (0%)	0/68 (0%)	1/97 (1.03%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Visual acuity reduced [A*]	0/104 (0%)	1/68 (1.47%)	1/97 (1.03%)	0/57 (0%)	2/91 (2.2%)	0/52 (0%)
Vitreous detachment [A*]	1/104 (0.96%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Vitreous haemorrhage [A*]	0/104 (0%)	1/68 (1.47%)	1/97 (1.03%)	1/57 (1.75%)	0/91 (0%)	0/52 (0%)
Gastrointestinal disorders						

	Afliberce Injection (Until Week 20)	Sham Treatme (Until Week 20)	Afliberce Injection (Until Week 48)	Sham Treatme (Until Week 48)	Afliberce Injection Continue (Until Week 68)	Sham Treatme Then Afliberce Injection (Until Week 68)
Diverticular perforation [A*]	0/104 (0%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	1/91 (1.1%)	0/52 (0%)
Hepatobiliary disorders						
Hepatic function abnormal [A*]	0/104 (0%)	0/68 (0%)	1/97 (1.03%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Infections and infestations						
Furuncle [A*]	1/104 (0.96%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Gastroenteritis [A*]	0/104 (0%)	1/68 (1.47%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Pneumonia [A*]	0/104 (0%)	1/68 (1.47%)	1/97 (1.03%)	1/57 (1.75%)	0/91 (0%)	0/52 (0%)
Vestibular neuronitis [A*]	0/104 (0%)	0/68 (0%)	0/97 (0%)	1/57 (1.75%)	0/91 (0%)	0/52 (0%)
Injury, poisoning and procedural complications						
Fall [A*]	0/104 (0%)	1/68 (1.47%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Femur fracture [A*]	0/104 (0%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	1/52 (1.92%)
Hand fracture [A*]	1/104 (0.96%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Humerus fracture [A*]	0/104 (0%)	1/68 (1.47%)	1/97 (1.03%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Radius fracture [A*]	0/104 (0%)	1/68 (1.47%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Spinal compression fracture [A*]						

	Afliberce Injection (Until Week 20)	Sham Treatme (Until Week 20)	Afliberce Injection (Until Week 48)	Sham Treatme (Until Week 48)	Afliberce Injection Continue (Until Week 68)	Sham Treatme Then Afliberce Injection (Until Week 68)
	1/104 (0.96%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Musculoskeletal and connective tissue disorders						
Intervertebral disc protrusion [A*]	0/104 (0%)	1/68 (1.47%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Spinal column stenosis [A*]	0/104 (0%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	1/91 (1.1%)	0/52 (0%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)						
Breast cancer [A*]	0/104 (0%)	0/68 (0%)	1/97 (1.03%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Oropharyngeal cancer stage unspecified [A*]	1/104 (0.96%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Nervous system disorders						
Paraesthesia [A*]	0/104 (0%)	0/68 (0%)	1/97 (1.03%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Syncope [A*]	0/104 (0%)	0/68 (0%)	1/97 (1.03%)	2/57 (3.51%)	0/91 (0%)	0/52 (0%)
Transient ischaemic attack [A*]	0/104 (0%)	0/68 (0%)	0/97 (0%)	1/57 (1.75%)	0/91 (0%)	0/52 (0%)
Respiratory, thoracic and mediastinal disorders						
Dyspnoea [A*]	0/104 (0%)	0/68 (0%)	0/97 (0%)	1/57 (1.75%)	0/91 (0%)	0/52 (0%)
Laryngeal granuloma [A*]	0/104 (0%)	1/68 (1.47%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Pulmonary hypertension [A*]	0/104 (0%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	1/52 (1.92%)

	Afliberce Injection (Until Week 20)	Sham Treatme (Until Week 20)	Afliberce Injection (Until Week 48)	Sham Treatme (Until Week 48)	Afliberce Injection Continue (Until Week 68)	Sham Treatme Then Afliberce Injection (Until Week 68)
Surgical and medical procedures						
Ischaemic heart disease prophylaxis A*	1/104 (0.96%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Vascular disorders						
Circulatory collapse A*	1/104 (0.96%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)

* Indicates events were collected by non-systematic methods.

A Term from vocabulary, MedDRA (14.1)

Other Adverse Events

Frequency Threshold Above Which Other Adverse Events are Reported: 5%

	Afliberce Injection (Until Week 20)	Sham Treatme (Until Week 20)	Afliberce Injection (Until Week 48)	Sham Treatme (Until Week 48)	Afliberce Injection Continue (Until Week 68)	Sham Treatme Then Afliberce Injection (Until Week 68)
	Affected/A Risk (%)	Affected/A Risk (%)	Affected/A Risk (%)	Affected/A Risk (%)	Affected/A Risk (%)	Affected/A Risk (%)
Total	52/104 (50%)	44/68 (64.71%)	66/97 (68.04%)	30/57 (52.63%)	38/91 (41.76%)	19/52 (36.54%
Blood and lymphatic system disorders						
Anaemia A*	1/104 (0.96%)	0/68 (0%)	0/97 (0%)	3/57 (5.26%)	0/91 (0%)	0/52 (0%)
Eye disorders						
Conjunctival haemorrhage A*						

	Aflibercept Injection (Until Week 20)	Sham Treatment (Until Week 20)	Aflibercept Injection (Until Week 48)	Sham Treatment (Until Week 48)	Aflibercept Injection Continued (Until Week 68)	Sham Treatment Then Aflibercept Injection (Until Week 68)
	10/104 (9.62%)	3/68 (4.41%)	3/97 (3.09%)	0/57 (0%)	9/91 (9.89%)	3/52 (5.77%)
Eye irritation [A*]	3/104 (2.88%)	7/68 (10.29%)	4/97 (4.12%)	1/57 (1.75%)	1/91 (1.1%)	2/52 (3.85%)
Eye pain [A*]	12/104 (11.54%)	3/68 (4.41%)	6/97 (6.19%)	2/57 (3.51%)	1/91 (1.1%)	0/52 (0%)
Foreign body sensation in eyes [A*]	6/104 (5.77%)	5/68 (7.35%)	2/97 (2.06%)	0/57 (0%)	1/91 (1.1%)	0/52 (0%)
Lacrimation increased [A*]	3/104 (2.88%)	4/68 (5.88%)	3/97 (3.09%)	4/57 (7.02%)	1/91 (1.1%)	2/52 (3.85%)
Macular fibrosis [A*]	1/104 (0.96%)	1/68 (1.47%)	5/97 (5.15%)	4/57 (7.02%)	0/91 (0%)	3/52 (5.77%)
Macular ischaemia [A*]	7/104 (6.73%)	5/68 (7.35%)	3/97 (3.09%)	1/57 (1.75%)	0/91 (0%)	1/52 (1.92%)
Macular oedema [A*]	2/104 (1.92%)	9/68 (13.24%)	30/97 (30.93%)	7/57 (12.28%)	17/91 (18.68%)	2/52 (3.85%)
Ocular hyperaemia [A*]	5/104 (4.81%)	4/68 (5.88%)	2/97 (2.06%)	1/57 (1.75%)	4/91 (4.4%)	1/52 (1.92%)
Optic disc vascular disorder [A*]	5/104 (4.81%)	3/68 (4.41%)	3/97 (3.09%)	3/57 (5.26%)	0/91 (0%)	0/52 (0%)
Retinal exudates [A*]	8/104 (7.69%)	5/68 (7.35%)	4/97 (4.12%)	3/57 (5.26%)	0/91 (0%)	0/52 (0%)
Retinal haemorrhage [A*]	4/104 (3.85%)	6/68 (8.82%)	11/97 (11.34%)	5/57 (8.77%)	5/91 (5.49%)	2/52 (3.85%)
Retinal vascular disorder [A*]	6/104 (5.77%)	7/68 (10.29%)	10/97 (10.31%)	2/57 (3.51%)	0/91 (0%)	2/52 (3.85%)

	Aflibercept Injection (Until Week 20)	Sham Treatment (Until Week 20)	Aflibercept Injection (Until Week 48)	Sham Treatment (Until Week 48)	Aflibercept Injection Continued (Until Week 68)	Sham Treatment Then Aflibercept Injection (Until Week 68)
	2/104 (1.92%)	7/68 (10.29%)	10/97 (10.31%)	1/57 (1.75%)	7/91 (7.69%)	1/52 (1.92%)
Vitreous detachment [A*]	2/104 (1.92%)	1/68 (1.47%)	7/97 (7.22%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Vitreous floaters [A*]	6/104 (5.77%)	0/68 (0%)	1/97 (1.03%)	1/57 (1.75%)	1/91 (1.1%)	1/52 (1.92%)
Gastrointestinal disorders						
Nausea [A*]	0/104 (0%)	1/68 (1.47%)	0/97 (0%)	3/57 (5.26%)	0/91 (0%)	0/52 (0%)
Infections and infestations						
Influenza [A*]	2/104 (1.92%)	0/68 (0%)	5/97 (5.15%)	1/57 (1.75%)	1/91 (1.1%)	1/52 (1.92%)
Nasopharyngitis [A*]	8/104 (7.69%)	6/68 (8.82%)	10/97 (10.31%)	11/57 (19.3%)	4/91 (4.4%)	2/52 (3.85%)
Investigations						
Intraocular pressure increased [A*]	9/104 (8.65%)	4/68 (5.88%)	14/97 (14.43%)	2/57 (3.51%)	2/91 (2.2%)	1/52 (1.92%)
Visual acuity tests abnormal [A*]	0/104 (0%)	1/68 (1.47%)	5/97 (5.15%)	0/57 (0%)	1/91 (1.1%)	0/52 (0%)
Musculoskeletal and connective tissue disorders						
Arthralgia [A*]	1/104 (0.96%)	5/68 (7.35%)	2/97 (2.06%)	1/57 (1.75%)	2/91 (2.2%)	0/52 (0%)
Nervous system disorders						
Headache [A*]	7/104 (6.73%)	4/68 (5.88%)	4/97 (4.12%)	1/57 (1.75%)	1/91 (1.1%)	1/52 (1.92%)
Vascular disorders						

	Afliberce Injection (Until Week 20)	Sham Treatme (Until Week 20)	Afliberce Injection (Until Week 48)	Sham Treatme (Until Week 48)	Afliberce Injection Continue (Until Week 68)	Sham Treatme Then Afliberce Injection (Until Week 68)
Hypertension [A]*	4/104 (3.85%)	3/68 (4.41%)	4/97 (4.12%)	4/57 (7.02%)	3/91 (3.3%)	2/52 (3.85%)

* Indicates events were collected by non-systematic methods.

A Term from vocabulary, MedDRA (14.1)

Limitations and Caveats

[Not specified]

More Information

Certain Agreements:

Principal Investigators are NOT employed by the organization sponsoring the study.

There IS an agreement between the Principal Investigator and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed.

Publishing of result communication only after Bayer´s written approval. Manuscript to Bayer sixty days before public release. If no written Bayer comment within 60 days consider approval given. If multi-site study, principal investigator (PI) not do independently publish results before publication of the multi-site paper, but PI not restricted from 24 months from study to completion onwards.

Results Point of Contact:

Name/Official Title: Therapeutic Area Head
Organization: BAYER
Phone:
Email: clinical-trials-contact@bayerhealthcare.com

Scroll up to access the controls Scroll to the Study top

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ClinicalTrials.gov archive

History of Changes for Study: NCT01012973

Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO) (GALILEO)

Latest version (submitted October 27, 2014) on ClinicalTrials.gov

- A study version is represented by a row in the table.
- Select two study versions to compare. One each from columns A and B.
- Choose either the "Merged" or "Side-by-Side" comparison format to specify how the two study versions are to be displayed. The Side-by-Side format only applies to the Protocol section of the study.
- Click "Compare" to do the comparison and show the differences.
- Select a version's date link to see a rendering of the study for that version.
- Edits or deletions will be displayed in ~~red~~.
- Additions will be displayed in *green*.
- The yellow choices in the table indicate the study versions currently compared below. A yellow row indicates the study version being viewed.
- Hover over the "Recruitment Status" to see how the study's recruitment status changed.

Study Record Versions

Version	A	B	Submitted Date	Changes
1	◉	○	November 12, 2009	Nothing (earliest Version on record)
2	○	○	January 21, 2010	Contacts/Locations, Study Status, Study Identification and Study Description
3	○	○	February 9, 2010	Contacts/Locations and Study Status
4	○	○	March 16, 2010	Contacts/Locations, Study Status and Study Identification
5	○	○	April 16, 2010	Contacts/Locations, Study Status and Study Identification

Version	A	B	Submitted Date	Changes
6	○	○	July 22, 2010	Contacts/Locations, Study Status, Eligibility and Arms and Interventions
7	○	○	August 25, 2010	Study Status and Contacts/Locations
8	○	○	August 26, 2010	Recruitment Status, Study Status and Contacts/Locations
9	○	○	September 8, 2010	Study Status
10	○	○	October 4, 2010	Study Status
11	○	○	November 1, 2010	Study Status
12	○	○	January 25, 2011	Study Status and Contacts/Locations
13	○	○	April 8, 2011	Study Status and Study Design
14	○	○	June 23, 2011	Arms and Interventions, Study Status, Contacts/Locations and Eligibility
15	○	○	September 19, 2011	Study Status
16	○	○	November 29, 2011	Study Status and Study Identification
17	○	○	January 26, 2012	Study Status and Contacts/Locations
18	○	○	February 20, 2012	Recruitment Status, Study Status
19	○	○	October 23, 2012	Outcome Measures, Arms and Interventions, Study Status, More Information, Reported Adverse Events, Baseline Characteristics and Participant Flow
20	○	○	December 18, 2012	More Information, Arms and Interventions, Study Status and Baseline Characteristics
21	○	○	January 18, 2013	Arms and Interventions, More Information, Study Status and Baseline Characteristics
22	○	○	January 30, 2014	Contacts/Locations, Sponsor/Collaborators, More Information, Study Status, Baseline Characteristics and References
23	○	◉	October 27, 2014	More Information, Study Status and References

Compare

Comparison Format: (•) Merged ( ) Side-by-Side

Scroll up to access the controls

Study NCT01012973
on Date: February 9, 2010 (v3)

Study Identification

Unique Protocol ID:	14130
Brief Title:	Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO) (GALILEO)
Official Title:	A Randomized, Double-masked, Sham-controlled Phase 3 Study of the Efficacy, Safety and Tolerability of Repeated Intravitreal Administration of VEGF Trap-Eye in Subjects With Macular Edema Secondary to Central Retinal Vein Occlusion (CRVO)
Secondary IDs:	EudraCT: 2009-010973-19

Study Status

Record Verification:	February 2010
Overall Status:	Recruiting
Study Start:	October 2009
Primary Completion:	February 2011 [Anticipated]
Study Completion:	August 2012 [Anticipated]
First Submitted:	October 30, 2009
First Submitted that Met QC Criteria:	November 12, 2009
First Posted:	November 13, 2009 [Estimate]
Last Update Submitted that Met QC Criteria:	February 9, 2010

Last Update Posted:	February 10, 2010 [Estimate]

Sponsor/Collaborators

Sponsor:	Bayer
Responsible Party:	
Collaborators:	Regeneron Pharmaceuticals

Oversight

U.S. FDA-regulated Drug:	
U.S. FDA-regulated Device:	
Data Monitoring:	Yes

Study Description

Brief Summary:	To determine the efficacy of vascular endothelial growth factor (VEGF) Trap-Eye injected into the eye on vision function in subjects with macular edema as a consequence of central retinal vein occlusion
Detailed Description:	

Conditions

Conditions:	Retinal Vein Occlusion
Keywords:	Macular Edema Central Retinal Vein Occlusion CRVO VEGF Trap-Eye best-corrected visual acuity

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	Phase 3
Interventional Study Model:	Parallel Assignment
Number of Arms:	2
Masking:	TripleParticipant, Investigator, Outcomes Assessor
Allocation:	Randomized
Enrollment:	165 [Anticipated]

Arms and Interventions

Arms	Assigned Interventions
Experimental: Arm 1	Drug: VEGF Trap-Eye (BAY86-5321) Intravitreal injection. Weeks 0 to 20 injection of VEGF Trap-Eye every 4 weeks; weeks 24 to 48 every 4 weeks re-assessment and either (PRN) injection of VEGF Trap-Eye or sham injection; weeks 52 to 100 safety follow-up.
Sham Comparator: Arm 2	Sham treatment Sham treatment. Weeks 0 to 20 sham treatment every 4 weeks; weeks 24 to 48 every 4 weeks re-assessment and sham injection; weeks 52 to 100 safety follow-up.

Outcome Measures

Primary Outcome Measures:

1. The proportion of subjects who gain at least 15 letters in BCVA on the EDTRS chart compared with baseline at the Week 24 endpoint
   Week 24

Secondary Outcome Measures:

2. Change from baseline in BCVA score
   Week 24
3. Absolute change from baseline in central retinal thickness, assessed by OCT
   Week 24
4. Proportion of subjects progressing to anterior segment neovascularization, neovascularization of the optic disc (NVD), or neovascularization of the retina elsewhere (NVE) requiring pan-retinal photocoagulation
   Week 24
5. Change in the NEI-VFQ-25 total score from baseline
   Week 24
6. Change in the EQ-5D score from baseline
   Week 24

Eligibility

Minimum Age: 18 Years

Maximum Age:

Sex: All

Gender Based:

Accepts Healthy Volunteers: No

Criteria: Inclusion Criteria:

- Center-involved macular edema secondary to central retinal vein occlusion (CRVO) for no longer than 9 months with mean central subfield thickness >= 250 µm on optical coherence tomography (OCT).
- Adults >= 18 years.
- early treatment diabetic retinopathy study (ETDRS) best corrected visual acuity (BCVA) of 20/40 to 20/320 (73 to 24 letters) in the study eye.

Exclusion Criteria:

- Previous treatment with anti-angiogenic drugs in the study eye (Pegaptanib sodium, anecortave acetate, bevacizumab, ranibizumab, etc.)
- Prior panretinal laser photocoagulation or macular laser photocoagulation in the study eye
- CRVO disease duration > 9 months from date of diagnosis
- Previous use of intraocular corticosteroids in the study eye or use of periocular corticosteroids in the study eye within the 3 months prior to Day 1
- Iris neovascularization, vitreous hemorrhage, traction retinal detachment, or preretinal fibrosis involving the macula in either the study eye or fellow eye

Contacts/Locations

Central Contact: Bayer Clinical Trials Contact
Email: clinical-trials-contact@bayerhealthcare.com

Study Officials:

Bayer Study Director
Study Director
Bayer

Locations: **Australia, New South Wales**

[Not yet recruiting]
Chatswood, New South Wales, Australia, 2067

[Recruiting]
Sydney, New South Wales, Australia, 2000

[Not yet recruiting]
Westmead, New South Wales, Australia, 2145

Australia, Victoria

[Recruiting]
East Melbourne, Victoria, Australia, 3002

Australia, Western Australia

[Recruiting]
Nedlands, Western Australia, Australia, 6009

Australia

[Recruiting]
Parramatta, Australia, 2150

Austria, Oberösterreich

[Not yet recruiting]
Linz, Oberösterreich, Austria, 4020

Austria, Tirol

[Not yet recruiting]
Innsbruck, Tirol, Austria, 6020

Austria

[Recruiting]
Linz, Austria, 4021

[Recruiting]
Wien, Austria, 1090

France, Cedex 12

[Not yet recruiting]
Paris, Cedex 12, France, 75557

France

[Not yet recruiting]
Bordeaux, France, 33000

[Not yet recruiting]
Dijon Cedex, France, BP 1542-21

[Not yet recruiting]
Marseille, France, 13008

[Not yet recruiting]
Nantes Cedex, France, 44035

[Not yet recruiting]
Paris, France, 75015

Germany, Baden-Württemberg

[Recruiting]
Freiburg, Baden-Württemberg, Germany, 79106

[Not yet recruiting]
Heidelberg, Baden-Württemberg, Germany, 69120

[Recruiting]
Tübingen, Baden-Württemberg, Germany, 72076

Germany, Bayern

[Recruiting]
München, Bayern, Germany, 81675

[Recruiting]
Regensburg, Bayern, Germany, 93053

Germany, Hessen

[Recruiting]
Darmstadt, Hessen, Germany, 64276

[Not yet recruiting]
Marburg, Hessen, Germany, 35043

Germany, Niedersachsen

[Not yet recruiting]
Göttingen, Niedersachsen, Germany, 37075

Germany, Nordrhein-Westfalen

[Not yet recruiting]
Aachen, Nordrhein-Westfalen, Germany, 52074

[Recruiting]
Bonn, Nordrhein-Westfalen, Germany, 53105

[Not yet recruiting]
Essen, Nordrhein-Westfalen, Germany, 45147

[Not yet recruiting]
Köln, Nordrhein-Westfalen, Germany, 50931

Germany, Rheinland-Pfalz

[Recruiting]
Ludwigshafen, Rheinland-Pfalz, Germany, 67063

[Recruiting]
Mainz, Rheinland-Pfalz, Germany, 55131

Germany, Saarland

[Not yet recruiting]
Homburg, Saarland, Germany, 66421

Germany, Sachsen

[Not yet recruiting]
Chemnitz, Sachsen, Germany, 09116

[Not yet recruiting]
Dresden, Sachsen, Germany, 01067

[Not yet recruiting]
Dresden, Sachsen, Germany, 01307

[Recruiting]
Leipzig, Sachsen, Germany, 04103

Germany, Schleswig-Holstein

[Not yet recruiting]
Kiel, Schleswig-Holstein, Germany, 24105

[Not yet recruiting]
Lübeck, Schleswig-Holstein, Germany, 23538

Germany

[Not yet recruiting]
Hamburg, Germany, 20251

Hungary

[Not yet recruiting]
Budapest, Hungary, 1036

[Not yet recruiting]
Budapest, Hungary, 1089

[Not yet recruiting]
Budapest, Hungary, 1106

[Recruiting]
Debrecen, Hungary, 4032

[Not yet recruiting]
Veszprem, Hungary, 8200

Italy

[Not yet recruiting]
Ancona, Italy, 60126

[Not yet recruiting]
Bari, Italy, 70124

[Not yet recruiting]
Catania, Italy, 95123

[Not yet recruiting]
Firenze, Italy, 50139

[Not yet recruiting]
Milano, Italy, 20122

[Not yet recruiting]
Milano, Italy, 20132

[Not yet recruiting]
Milano, Italy, 20157

[Not yet recruiting]
Padova, Italy, 35128

[Not yet recruiting]
Roma, Italy, 00133

[Not yet recruiting]
Roma, Italy, 00185

[Not yet recruiting]
Torino, Italy, 10149

Japan, Aichi

[Not yet recruiting]
Nagoya, Aichi, Japan, 466-8560

[Not yet recruiting]
Nagoya, Aichi, Japan, 467-8602

Japan, Chiba

[Recruiting]
Urayasu, Chiba, Japan, 279-0021

Japan, Osaka

[Not yet recruiting]
Suita, Osaka, Japan, 565-0871

Japan, Tokyo

[Not yet recruiting]
Chiyoda-ku, Tokyo, Japan, 101-8309

Japan

[Not yet recruiting]
Kyoto, Japan, 606-8507

Korea, Republic of

[Recruiting]
Ask Contact, Korea, Republic of

[Not yet recruiting]
Incheon, Korea, Republic of, 405-760

[Recruiting]
Kungki-do, Korea, Republic of, 463-707

[Recruiting]
Seoul, Korea, Republic of, 110 744

[Not yet recruiting]
Seoul, Korea, Republic of, 110-744

[Recruiting]
Seoul, Korea, Republic of, 138-736

Latvia

[Not yet recruiting]
Riga, Latvia, 1009

[Recruiting]
Riga, Latvia, LV-1002

Singapore

[Not yet recruiting]
Singapore, Singapore, 119074

[Not yet recruiting]
Singapore, Singapore, 168751

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ClinicalTrials.gov archive

History of Changes for Study: NCT01012973

Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO) (GALILEO)

Latest version (submitted October 27, 2014) on ClinicalTrials.gov

- A study version is represented by a row in the table.
- Select two study versions to compare. One each from columns A and B.
- Choose either the "Merged" or "Side-by-Side" comparison format to specify how the two study versions are to be displayed. The Side-by-Side format only applies to the Protocol section of the study.
- Click "Compare" to do the comparison and show the differences.
- Select a version's date link to see a rendering of the study for that version.
- Edits or deletions will be displayed in ~~red~~.
- Additions will be displayed in *green*.
- The yellow choices in the table indicate the study versions currently compared below. A yellow row indicates the study version being viewed.
- Hover over the "Recruitment Status" to see how the study's recruitment status changed.

Study Record Versions

Version	A	B	Submitted Date	Changes
1	◉	○	November 12, 2009	Nothing (earliest Version on record)
2	○	○	January 21, 2010	Contacts/Locations, Study Status, Study Identification and Study Description
3	○	○	February 9, 2010	Contacts/Locations and Study Status
4	○	○	March 16, 2010	Contacts/Locations, Study Status and Study Identification
5	○	○	April 16, 2010	Contacts/Locations, Study Status and Study Identification

Version	A	B	Submitted Date	Changes
6	○	○	July 22, 2010	Contacts/Locations, Study Status, Eligibility and Arms and Interventions
7	○	○	August 25, 2010	Study Status and Contacts/Locations
8	○	○	August 26, 2010	Recruitment Status, Study Status and Contacts/Locations
9	○	○	September 8, 2010	Study Status
10	○	○	October 4, 2010	Study Status
11	○	○	November 1, 2010	Study Status
12	○	○	January 25, 2011	Study Status and Contacts/Locations
13	○	○	April 8, 2011	Study Status and Study Design
14	○	○	June 23, 2011	Arms and Interventions, Study Status, Contacts/Locations and Eligibility
15	○	○	September 19, 2011	Study Status
16	○	○	November 29, 2011	Study Status and Study Identification
17	○	○	January 26, 2012	Study Status and Contacts/Locations
18	○	○	February 20, 2012	Recruitment Status, Study Status
19	○	○	October 23, 2012	Outcome Measures, Arms and Interventions, Study Status, More Information, Reported Adverse Events, Baseline Characteristics and Participant Flow
20	○	○	December 18, 2012	More Information, Arms and Interventions, Study Status and Baseline Characteristics
21	○	○	January 18, 2013	Arms and Interventions, More Information, Study Status and Baseline Characteristics
22	○	○	January 30, 2014	Contacts/Locations, Sponsor/Collaborators, More Information, Study Status, Baseline Characteristics and References
23	○	◉	October 27, 2014	More Information, Study Status and References

Compare

Comparison Format: (•) Merged ( ) Side-by-Side

Scroll up to access the controls

Study NCT01012973
on Date: February 20, 2012 (v18)

Study Identification

Unique Protocol ID:	14130
Brief Title:	Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO) (GALILEO)
Official Title:	A Randomized, Double-masked, Sham-controlled Phase 3 Study of the Efficacy, Safety and Tolerability of Repeated Intravitreal Administration of VEGF Trap-Eye in Subjects With Macular Edema Secondary to Central Retinal Vein Occlusion (CRVO)
Secondary IDs:	2009-010973-19 [EudraCT Number]

Study Status

Record Verification:	February 2012
Overall Status:	Completed
Study Start:	October 2009
Primary Completion:	February 2011 [Actual]
Study Completion:	February 2012 [Actual]
First Submitted:	October 30, 2009
First Submitted that Met QC Criteria:	November 12, 2009
First Posted:	November 13, 2009 [Estimate]
Certification/Extension First Submitted:	January 26, 2012

Certification/Extension First Submitted that Met QC Criteria:	January 26, 2012
Certification/Extension First Posted:	January 30, 2012 [Estimate]
Last Update Submitted that Met QC Criteria:	February 20, 2012
Last Update Posted:	February 23, 2012 [Estimate]

Sponsor/Collaborators

Sponsor:	Bayer
Responsible Party:	
Collaborators:	Regeneron Pharmaceuticals

Oversight

U.S. FDA-regulated Drug:	
U.S. FDA-regulated Device:	
Data Monitoring:	Yes

Study Description

Brief Summary:	To determine the efficacy of vascular endothelial growth factor (VEGF) Trap-Eye injected into the eye on vision function in subjects with macular edema as a consequence of central retinal vein occlusion
Detailed Description:	

Conditions

Conditions:	Retinal Vein Occlusion
Keywords:	Macular Edema Central Retinal Vein Occlusion CRVO VEGF Trap-Eye best-corrected visual acuity

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment

Study Phase:	Phase 3
Interventional Study Model:	Parallel Assignment
Number of Arms:	2
Masking:	TripleParticipant, Investigator, Outcomes Assessor
Allocation:	Randomized
Enrollment:	177 [Actual]

Arms and Interventions

Arms	Assigned Interventions
Experimental: Arm 1	Biological: VEGF Trap-Eye (BAY86-5321) Intravitreal injection. Weeks 0 to 20 injection of VEGF Trap-Eye every 4 weeks; weeks 24 to 52 every 4 weeks plus additional on week 60 and 68 re-assessment and either (PRN) injection of VEGF Trap-Eye or sham injection; last visit (no treatment) at week 76.
Sham Comparator: Arm 2	Sham treatment Sham treatment. Weeks 0 to 20 sham treatment every 4 weeks; weeks 24 to 48 every 4 weeks re-assessment and sham injection; week 52 VEGF Trap-Eye injection (unless investigator declines for medical reasons), weeks 60 and 68 re-assessment and either (PRN) injection of VEGF Trap-Eye or sham injection; last visit (no treatment) at week 76.

Outcome Measures

Primary Outcome Measures:

1. The proportion of subjects who gain at least 15 letters in BCVA on the EDTRS chart compared with baseline at the Week 24 endpoint
   Week 24

Secondary Outcome Measures:

2. Change from baseline in BCVA score
   Week 24

3. Absolute change from baseline in central retinal thickness, assessed by OCT
   Week 24
4. Proportion of subjects progressing to anterior segment neovascularization, neovascularization of the optic disc (NVD), or neovascularization of the retina elsewhere (NVE) requiring pan-retinal photocoagulation
   Week 24
5. Change in the NEI-VFQ-25 total score from baseline
   Week 24
6. Change in the EQ-5D score from baseline
   Week 24

Eligibility

Minimum Age: 18 Years

Maximum Age:

Sex: All

Gender Based:

Accepts Healthy Volunteers: No

Criteria: Inclusion Criteria:

- Center-involved macular edema secondary to central retinal vein occlusion (CRVO) for no longer than 9 months with mean central subfield thickness ≥ 250 µm on optical coherence tomography (OCT)
- Adults ≥ 18 years
- Early treatment diabetic retinopathy study (ETDRS) best corrected visual acuity (BCVA) of 20/40 to 20/320 (73 to 24 letters) in the study eye

Exclusion Criteria:

- Any prior treatment with anti-VEGF agents in the study eye (Pegaptanib sodium, anecortave acetate, bevacizumab, ranibizumab, etc.) or previous administration of systemic anti-angiogenic medications
- Prior panretinal laser photocoagulation or macular laser photocoagulation in the study eye

- CRVO disease duration > 9 months from date of diagnosis
- Previous use of intraocular corticosteroids in the study eye or use of periocular corticosteroids in the study eye within the 3 months prior to Day 1
- Iris neovascularization, vitreous hemorrhage, traction retinal detachment, or preretinal fibrosis involving the macula in either the study eye or fellow eye

Contacts/Locations

Study Officials: Bayer Study Director
Study Director
Bayer

Locations:

Australia, New South Wales

Chatswood, New South Wales, Australia, 2067

Parramatta, New South Wales, Australia, 2150

Sydney, New South Wales, Australia, 2000

Westmead, New South Wales, Australia, 2145

Australia, Victoria

East Melbourne, Victoria, Australia, 3002

Australia, Western Australia

Nedlands, Western Australia, Australia, 6009

Austria

Innsbruck, Austria, 6020

Linz, Austria, 4021

Wien, Austria, 1090

France, Cedex 12

Paris, Cedex 12, France, 75557

France, Cedex 1

Nantes, Cedex 1, France, 44093

France

Bordeaux, France, 33000

Dijon, France, 21033

Marseille, France, 13008

Paris, France, 75015

Germany, Baden-Württemberg

Freiburg, Baden-Württemberg, Germany, 79106

Heidelberg, Baden-Württemberg, Germany, 69120

Tübingen, Baden-Württemberg, Germany, 72076

Germany, Bayern

München, Bayern, Germany, 81675

Regensburg, Bayern, Germany, 93053

Germany, Hessen

Darmstadt, Hessen, Germany, 64297

Frankfurt, Hessen, Germany, 60596

Marburg, Hessen, Germany, 35037

Germany, Niedersachsen

Göttingen, Niedersachsen, Germany, 37075

Germany, Nordrhein-Westfalen

Aachen, Nordrhein-Westfalen, Germany, 52074

Bonn, Nordrhein-Westfalen, Germany, 53105

Essen, Nordrhein-Westfalen, Germany, 45122

Köln, Nordrhein-Westfalen, Germany, 50924

Münster, Nordrhein-Westfalen, Germany, 48145

Germany, Rheinland-Pfalz

Ludwigshafen, Rheinland-Pfalz, Germany, 67063

Mainz, Rheinland-Pfalz, Germany, 55131

Germany, Saarland

Homburg, Saarland, Germany, 66421

Germany, Sachsen

Chemnitz, Sachsen, Germany, 09116

Dresden, Sachsen, Germany, 01307

Dresden, Sachsen, Germany, 06067

Leipzig, Sachsen, Germany, 04103

Germany, Schleswig-Holstein

Kiel, Schleswig-Holstein, Germany, 24105

Lübeck, Schleswig-Holstein, Germany, 23538

Germany

Berlin, Germany, 13353

Hamburg, Germany, 20251

Hungary

Budapest, Hungary, 1089

Budapest, Hungary, 1106

Budapest, Hungary, 1133

Debrecen, Hungary, 4032

Veszprem, Hungary, 8200

Zalaegerszeg, Hungary, H-8900

Italy

Ancona, Italy, 60126

Bari, Italy, 70124

Catania, Italy, 95123

Firenze, Italy, 50134

Milano, Italy, 20122

Milano, Italy, 20132

Milano, Italy, 20157

Padova, Italy, 35128

Roma, Italy, 00133

Roma, Italy, 00198

Torino, Italy, 10122

Japan, Aichi

Nagoya, Aichi, Japan, 466-8560

Nagoya, Aichi, Japan, 467-8602

Japan, Chiba

Urayasu, Chiba, Japan, 279-0021

Japan, Osaka

Suita, Osaka, Japan, 565-0871

Japan, Tokyo

Chiyoda-ku, Tokyo, Japan, 101-8309

Japan

Kyoto, Japan, 606-8507

Korea, Republic of

Incheon, Korea, Republic of, 405-760

Kungki-do, Korea, Republic of, 463-707

Seoul, Korea, Republic of, 110 744

Seoul, Korea, Republic of, 110-744

Seoul, Korea, Republic of, 138-736

Seoul, Korea, Republic of

Latvia

Riga, Latvia, 1002

Riga, Latvia, 1050

Singapore

Singapore, Singapore, 119074

Singapore, Singapore, 168751

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ClinicalTrials.gov archive

History of Changes for Study: NCT01012973

Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO) (GALILEO)

Latest version (submitted October 27, 2014) on ClinicalTrials.gov

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5	○	○	April 16, 2010	Contacts/Locations, Study Status and Study Identification

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22	○	○	January 30, 2014	Contacts/Locations, Sponsor/Collaborators, More Information, Study Status, Baseline Characteristics and References
23	○	◉	October 27, 2014	More Information, Study Status and References

Compare

Comparison Format: (•) Merged ( ) Side-by-Side

Scroll up to access the controls

Study NCT01012973
on Date: March 16, 2010 (v4)

Study Identification

Unique Protocol ID:	14130
Brief Title:	Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)
Official Title:	A Randomized, Double-masked, Sham-controlled Phase 3 Study of the Efficacy, Safety and Tolerability of Repeated Intravitreal Administration of VEGF Trap-Eye in Subjects With Macular Edema Secondary to Central Retinal Vein Occlusion (CRVO)
Secondary IDs:	EudraCT: 2009-010973-19 GALILEO

Study Status

Record Verification:	March 2010
Overall Status:	Recruiting
Study Start:	October 2009
Primary Completion:	February 2011 [Anticipated]
Study Completion:	August 2012 [Anticipated]
First Submitted:	October 30, 2009
First Submitted that Met QC Criteria:	November 12, 2009
First Posted:	November 13, 2009 [Estimate]
	March 16, 2010

Last Update Submitted that Met QC Criteria:	
Last Update Posted:	March 17, 2010 [Estimate]

Sponsor/Collaborators

Sponsor:	Bayer
Responsible Party:	
Collaborators:	Regeneron Pharmaceuticals

Oversight

U.S. FDA-regulated Drug:	
U.S. FDA-regulated Device:	
Data Monitoring:	Yes

Study Description

Brief Summary:	To determine the efficacy of vascular endothelial growth factor (VEGF) Trap-Eye injected into the eye on vision function in subjects with macular edema as a consequence of central retinal vein occlusion
Detailed Description:	

Conditions

Conditions:	Retinal Vein Occlusion
Keywords:	Macular Edema Central Retinal Vein Occlusion CRVO VEGF Trap-Eye best-corrected visual acuity

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	Phase 3
Interventional Study Model:	Parallel Assignment
Number of Arms:	2
Masking:	TripleParticipant, Investigator, Outcomes Assessor
Allocation:	Randomized

Enrollment: 165 [Anticipated]

Arms and Interventions

Arms	Assigned Interventions
Experimental: Arm 1	Drug: VEGF Trap-Eye (BAY86-5321) Intravitreal injection. Weeks 0 to 20 injection of VEGF Trap-Eye every 4 weeks; weeks 24 to 48 every 4 weeks re-assessment and either (PRN) injection of VEGF Trap-Eye or sham injection; weeks 52 to 100 safety follow-up.
Sham Comparator: Arm 2	Sham treatment Sham treatment. Weeks 0 to 20 sham treatment every 4 weeks; weeks 24 to 48 every 4 weeks re-assessment and sham injection; weeks 52 to 100 safety follow-up.

Outcome Measures

Primary Outcome Measures:

1. The proportion of subjects who gain at least 15 letters in BCVA on the EDTRS chart compared with baseline at the Week 24 endpoint
   Week 24

Secondary Outcome Measures:

2. Change from baseline in BCVA score
   Week 24
3. Absolute change from baseline in central retinal thickness, assessed by OCT
   Week 24
4. Proportion of subjects progressing to anterior segment neovascularization, neovascularization of the optic disc (NVD), or neovascularization of the retina elsewhere (NVE) requiring pan-retinal photocoagulation
   Week 24
5. Change in the NEI-VFQ-25 total score from baseline
   Week 24
6. Change in the EQ-5D score from baseline
   Week 24

Eligibility

Minimum Age: 18 Years

Maximum Age:

Sex: All

Gender Based:

Accepts Healthy Volunteers: No

Criteria: Inclusion Criteria:

- Center-involved macular edema secondary to central retinal vein occlusion (CRVO) for no longer than 9 months with mean central subfield thickness >= 250 µm on optical coherence tomography (OCT).
- Adults >= 18 years.
- early treatment diabetic retinopathy study (ETDRS) best corrected visual acuity (BCVA) of 20/40 to 20/320 (73 to 24 letters) in the study eye.

Exclusion Criteria:

- Previous treatment with anti-angiogenic drugs in the study eye (Pegaptanib sodium, anecortave acetate, bevacizumab, ranibizumab, etc.)
- Prior panretinal laser photocoagulation or macular laser photocoagulation in the study eye
- CRVO disease duration > 9 months from date of diagnosis
- Previous use of intraocular corticosteroids in the study eye or use of periocular corticosteroids in the study eye within the 3 months prior to Day 1
- Iris neovascularization, vitreous hemorrhage, traction retinal detachment, or preretinal fibrosis involving the macula in either the study eye or fellow eye

Contacts/Locations

Central Contact: Bayer Clinical Trials Contact

Email: clinical-trials-contact@bayerhealthcare.com

Study Officials: Bayer Study Director
Study Director
Bayer

Locations: **Australia, New South Wales**

[Not yet recruiting]
Chatswood, New South Wales, Australia, 2067

[Recruiting]
Sydney, New South Wales, Australia, 2000

[Recruiting]
Westmead, New South Wales, Australia, 2145

Australia, Victoria

[Recruiting]
East Melbourne, Victoria, Australia, 3002

Australia, Western Australia

[Recruiting]
Nedlands, Western Australia, Australia, 6009

Australia

[Recruiting]
Parramatta, Australia, 2150

Austria, Oberösterreich

[Not yet recruiting]
Linz, Oberösterreich, Austria, 4020

Austria, Tirol

[Not yet recruiting]
Innsbruck, Tirol, Austria, 6020

Austria

[Recruiting]
Linz, Austria, 4021

[Recruiting]
Wien, Austria, 1090

France, Cedex 12

[Not yet recruiting]
Paris, Cedex 12, France, 75557

France

[Not yet recruiting]
Bordeaux, France, 33000

[Not yet recruiting]
Dijon Cedex, France, BP 1542-21

[Not yet recruiting]
Marseille, France, 13008

[Not yet recruiting]
Nantes Cedex, France, 44035

[Not yet recruiting]
Paris, France, 75015

Germany, Baden-Württemberg

[Recruiting]
Freiburg, Baden-Württemberg, Germany, 79106

[Recruiting]
Heidelberg, Baden-Württemberg, Germany, 69120

[Recruiting]
Tübingen, Baden-Württemberg, Germany, 72076

Germany, Bayern

[Recruiting]
München, Bayern, Germany, 81675

[Recruiting]
Regensburg, Bayern, Germany, 93053

Germany, Hessen

[Recruiting]
Darmstadt, Hessen, Germany, 64276

[Not yet recruiting]
Marburg, Hessen, Germany, 35043

Germany, Niedersachsen

[Recruiting]
Göttingen, Niedersachsen, Germany, 37075

Germany, Nordrhein-Westfalen

[Recruiting]
Aachen, Nordrhein-Westfalen, Germany, 52074

[Recruiting]
Bonn, Nordrhein-Westfalen, Germany, 53105

[Not yet recruiting]
Essen, Nordrhein-Westfalen, Germany, 45147

[Not yet recruiting]
Köln, Nordrhein-Westfalen, Germany, 50931

Germany, Rheinland-Pfalz

[Recruiting]
Ludwigshafen, Rheinland-Pfalz, Germany, 67063

[Recruiting]
Mainz, Rheinland-Pfalz, Germany, 55131

Germany, Saarland

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Homburg, Saarland, Germany, 66421

Germany, Sachsen

[Not yet recruiting]
Chemnitz, Sachsen, Germany, 09116

[Not yet recruiting]
Dresden, Sachsen, Germany, 01067

[Not yet recruiting]
Dresden, Sachsen, Germany, 01307

[Recruiting]
Leipzig, Sachsen, Germany, 04103

Germany, Schleswig-Holstein

[Not yet recruiting]
Kiel, Schleswig-Holstein, Germany, 24105

[Not yet recruiting]
Lübeck, Schleswig-Holstein, Germany, 23538

Germany

[Not yet recruiting]
Hamburg, Germany, 20251

Hungary

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Budapest, Hungary, 1036

[Recruiting]
Budapest, Hungary, 1089

[Recruiting]
Budapest, Hungary, 1106

[Recruiting]
Debrecen, Hungary, 4032

[Not yet recruiting]
Veszprem, Hungary, 8200

Italy

[Not yet recruiting]
Ancona, Italy, 60126

[Not yet recruiting]
Bari, Italy, 70124

[Not yet recruiting]
Catania, Italy, 95123

[Not yet recruiting]
Firenze, Italy, 50139

[Not yet recruiting]
Milano, Italy, 20122

[Not yet recruiting]
Milano, Italy, 20132

[Not yet recruiting]
Milano, Italy, 20157

[Not yet recruiting]
Padova, Italy, 35128

[Not yet recruiting]
Roma, Italy, 00133

[Not yet recruiting]
Roma, Italy, 00185

[Not yet recruiting]
Torino, Italy, 10149

Japan, Aichi

[Recruiting]
Nagoya, Aichi, Japan, 466-8560

[Not yet recruiting]
Nagoya, Aichi, Japan, 467-8602

Japan, Chiba

[Recruiting]
Urayasu, Chiba, Japan, 279-0021

Japan, Osaka

[Recruiting]
Suita, Osaka, Japan, 565-0871

Japan, Tokyo

[Not yet recruiting]
Chiyoda-ku, Tokyo, Japan, 101-8309

Japan

[Not yet recruiting]
Kyoto, Japan, 606-8507

Korea, Republic of

[Not yet recruiting]
Incheon, Korea, Republic of, 405-760

[Recruiting]
Kungki-do, Korea, Republic of, 463-707

[Recruiting]
Seongsanno, Korea, Republic of

[Recruiting]
Seoul, Korea, Republic of, 110 744

[Not yet recruiting]
Seoul, Korea, Republic of, 110-744

[Recruiting]
Seoul, Korea, Republic of, 138-736

Latvia

[Not yet recruiting]
Riga, Latvia, 1009

[Recruiting]
Riga, Latvia, LV-1002

Singapore

[Not yet recruiting]
Singapore, Singapore, 119074

[Recruiting]
Singapore, Singapore, 168751

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Links:

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ClinicalTrials.gov archive

History of Changes for Study: NCT01012973

Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO) (GALILEO)

Latest version (submitted October 27, 2014) on ClinicalTrials.gov

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- Click "Compare" to do the comparison and show the differences.
- Select a version's date link to see a rendering of the study for that version.
- Edits or deletions will be displayed in ~~red~~.
- Additions will be displayed in *green*.
- The yellow choices in the table indicate the study versions currently compared below. A yellow row indicates the study version being viewed.
- Hover over the "Recruitment Status" to see how the study's recruitment status changed.

Study Record Versions

Version	A	B	Submitted Date	Changes
1	◉	○	November 12, 2009	Nothing (earliest Version on record)
2	○	○	January 21, 2010	Contacts/Locations, Study Status, Study Identification and Study Description
3	○	○	February 9, 2010	Contacts/Locations and Study Status
4	○	○	March 16, 2010	Contacts/Locations, Study Status and Study Identification
5	○	○	April 16, 2010	Contacts/Locations, Study Status and Study Identification

Version	A	B	Submitted Date	Changes
6	○	○	July 22, 2010	Contacts/Locations, Study Status, Eligibility and Arms and Interventions
7	○	○	August 25, 2010	Study Status and Contacts/Locations
8	○	○	August 26, 2010	Recruitment Status, Study Status and Contacts/Locations
9	○	○	September 8, 2010	Study Status
10	○	○	October 4, 2010	Study Status
11	○	○	November 1, 2010	Study Status
12	○	○	January 25, 2011	Study Status and Contacts/Locations
13	○	○	April 8, 2011	Study Status and Study Design
14	○	○	June 23, 2011	Arms and Interventions, Study Status, Contacts/Locations and Eligibility
15	○	○	September 19, 2011	Study Status
16	○	○	November 29, 2011	Study Status and Study Identification
17	○	○	January 26, 2012	Study Status and Contacts/Locations
18	○	○	February 20, 2012	Recruitment Status, Study Status
19	○	○	October 23, 2012	Outcome Measures, Arms and Interventions, Study Status, More Information, Reported Adverse Events, Baseline Characteristics and Participant Flow
20	○	○	December 18, 2012	More Information, Arms and Interventions, Study Status and Baseline Characteristics
21	○	○	January 18, 2013	Arms and Interventions, More Information, Study Status and Baseline Characteristics
22	○	○	January 30, 2014	Contacts/Locations, Sponsor/Collaborators, More Information, Study Status, Baseline Characteristics and References
23	○	◉	October 27, 2014	More Information, Study Status and References

Compare

Comparison Format: (•) Merged ( ) Side-by-Side

Scroll up to access the controls

Study NCT01012973
on Date: April 8, 2011 (v13)

Study Identification

Unique Protocol ID:	14130
Brief Title:	Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO) (GALILEO)
Official Title:	A Randomized, Double-masked, Sham-controlled Phase 3 Study of the Efficacy, Safety and Tolerability of Repeated Intravitreal Administration of VEGF Trap-Eye in Subjects With Macular Edema Secondary to Central Retinal Vein Occlusion (CRVO)
Secondary IDs:	EudraCT: 2009-010973-19

Study Status

Record Verification:	April 2011
Overall Status:	Active, not recruiting
Study Start:	October 2009
Primary Completion:	February 2011 [Actual]
Study Completion:	March 2012 [Anticipated]
First Submitted:	October 30, 2009
First Submitted that Met QC Criteria:	November 12, 2009
First Posted:	November 13, 2009 [Estimate]
Last Update Submitted that Met QC Criteria:	April 8, 2011

Last Update Posted:	April 11, 2011 [Estimate]

Sponsor/Collaborators

Sponsor:	Bayer
Responsible Party:	
Collaborators:	Regeneron Pharmaceuticals

Oversight

U.S. FDA-regulated Drug:	
U.S. FDA-regulated Device:	
Data Monitoring:	Yes

Study Description

Brief Summary:	To determine the efficacy of vascular endothelial growth factor (VEGF) Trap-Eye injected into the eye on vision function in subjects with macular edema as a consequence of central retinal vein occlusion
Detailed Description:	

Conditions

Conditions:	Retinal Vein Occlusion
Keywords:	Macular Edema Central Retinal Vein Occlusion CRVO VEGF Trap-Eye best-corrected visual acuity

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	Phase 3
Interventional Study Model:	Parallel Assignment
Number of Arms:	2
Masking:	TripleParticipant, Investigator, Outcomes Assessor
Allocation:	Randomized
Enrollment:	177 [Actual]

Arms and Interventions

Arms	Assigned Interventions
Experimental: Arm 1	Drug: VEGF Trap-Eye (BAY86-5321) Intravitreal injection. Weeks 0 to 20 injection of VEGF Trap-Eye every 4 weeks; weeks 24 to 52 every 4 weeks plus additional on week 60 and 68 re-assessment and either (PRN) injection of VEGF Trap-Eye or sham injection; last visit (no treatment) at week 76.
Sham Comparator: Arm 2	Sham treatment Sham treatment. Weeks 0 to 20 sham treatment every 4 weeks; weeks 24 to 48 every 4 weeks re-assessment and sham injection; week 52 VEGF Trap-Eye injection (unless investigator declines for medical reasons), weeks 60 and 68 re-assessment and either (PRN) injection of VEGF Trap-Eye or sham injection; last visit (no treatment) at week 76.

Outcome Measures

Primary Outcome Measures:

1. The proportion of subjects who gain at least 15 letters in BCVA on the EDTRS chart compared with baseline at the Week 24 endpoint
   Week 24

Secondary Outcome Measures:

2. Change from baseline in BCVA score
   Week 24
3. Absolute change from baseline in central retinal thickness, assessed by OCT
   Week 24
4. Proportion of subjects progressing to anterior segment neovascularization, neovascularization of the optic disc (NVD), or neovascularization of the retina elsewhere (NVE) requiring pan-retinal photocoagulation
   Week 24
5.

Change in the NEI-VFQ-25 total score from baseline
Week 24

6. Change in the EQ-5D score from baseline
Week 24

Eligibility

Minimum Age: 18 Years

Maximum Age:

Sex: All

Gender Based:

Accepts Healthy Volunteers: No

Criteria: Inclusion Criteria:

- Center-involved macular edema secondary to central retinal vein occlusion (CRVO) for no longer than 9 months with mean central subfield thickness >= 250 µm on optical coherence tomography (OCT)
- Adults >= 18 years
- Early treatment diabetic retinopathy study (ETDRS) best corrected visual acuity (BCVA) of 20/40 to 20/320 (73 to 24 letters) in the study eye

Exclusion Criteria:

- Any prior treatment with anti-VEGF agents in the study eye (Pegaptanib sodium, anecortave acetate, bevacizumab, ranibizumab, etc.) or previous administration of systemic anti-angiogenic medications
- Prior panretinal laser photocoagulation or macular laser photocoagulation in the study eye
- CRVO disease duration > 9 months from date of diagnosis
- Previous use of intraocular corticosteroids in the study eye or use of periocular corticosteroids in the study eye within the 3 months prior to Day 1

- Iris neovascularization, vitreous hemorrhage, traction retinal detachment, or preretinal fibrosis involving the macula in either the study eye or fellow eye

Contacts/Locations

Study Officials: Bayer Study Director
Study Director
Bayer

Locations: **Australia, New South Wales**

Chatswood, New South Wales, Australia, 2067

Parramatta, New South Wales, Australia, 2150

Sydney, New South Wales, Australia, 2000

Westmead, New South Wales, Australia, 2145

Australia, Victoria

East Melbourne, Victoria, Australia, 3002

Australia, Western Australia

Nedlands, Western Australia, Australia, 6009

Austria

Innsbruck, Austria, 6020

Linz, Austria, 4021

Wien, Austria, 1090

France, Cedex 12

Paris, Cedex 12, France, 75557

France, Cedex 1

Nantes, Cedex 1, France, 44093

France

Bordeaux, France, 33000

Dijon, France, 21033

Marseille, France, 13008

Paris, France, 75015

Germany, Baden-Württemberg

Freiburg, Baden-Württemberg, Germany, 79106

Heidelberg, Baden-Württemberg, Germany, 69120

Tübingen, Baden-Württemberg, Germany, 72076

Germany, Bayern

München, Bayern, Germany, 81675

Regensburg, Bayern, Germany, 93053

Germany, Hessen

Darmstadt, Hessen, Germany, 64297

Frankfurt, Hessen, Germany, 60596

Germany, Niedersachsen

Göttingen, Niedersachsen, Germany, 37075

Germany, Nordrhein-Westfalen

Aachen, Nordrhein-Westfalen, Germany, 52074

Bonn, Nordrhein-Westfalen, Germany, 53105

Essen, Nordrhein-Westfalen, Germany, 45122

Köln, Nordrhein-Westfalen, Germany, 50924

Münster, Nordrhein-Westfalen, Germany, 48145

Germany, Rheinland-Pfalz

Ludwigshafen, Rheinland-Pfalz, Germany, 67063

Mainz, Rheinland-Pfalz, Germany, 55131

Germany, Saarland

Homburg, Saarland, Germany, 66424

Germany, Sachsen

Chemnitz, Sachsen, Germany, 09116

Dresden, Sachsen, Germany, 01307

Dresden, Sachsen, Germany, 06067

Leipzig, Sachsen, Germany, 04103

Germany, Schleswig-Holstein

Kiel, Schleswig-Holstein, Germany, 24105

Lübeck, Schleswig-Holstein, Germany, 23538

Germany

Berlin, Germany, 13353

Hamburg, Germany, 20251

Marburg, Germany, 35037

Hungary

Budapest, Hungary, 1089

Budapest, Hungary, 1106

Budapest, Hungary, 1133

Debrecen, Hungary, 4032

Veszprem, Hungary, 8200

Zalaegerszeg, Hungary, H-8900

Italy

Ancona, Italy, 60126

Bari, Italy, 70124

Catania, Italy, 95123

Firenze, Italy, 50134

Milano, Italy, 20122

Milano, Italy, 20132

Milano, Italy, 20157

Padova, Italy, 35128

Roma, Italy, 00133

Roma, Italy, 00198

Torino, Italy, 10122

Japan, Aichi

Nagoya, Aichi, Japan, 466-8560

Nagoya, Aichi, Japan, 467-8602

Japan, Chiba

Urayasu, Chiba, Japan, 279-0021

Japan, Osaka

Suita, Osaka, Japan, 565-0871

Japan, Tokyo

Chiyoda-ku, Tokyo, Japan, 101-8309

Japan

Kyoto, Japan, 606-8507

Korea, Republic of

Incheon, Korea, Republic of, 405-760

Kungki-do, Korea, Republic of, 463-707

Seoul, Korea, Republic of, 110 744

Seoul, Korea, Republic of, 110-744

Seoul, Korea, Republic of, 138-736

Seoul, Korea, Republic of

Latvia

Riga, Latvia, 1002

Riga, Latvia, 1050

Singapore

Singapore, Singapore, 119074

Singapore, Singapore, 168751

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U.S. National Library of Medicine
ClinicalTrials.gov archive

History of Changes for Study: NCT01012973

Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO) (GALILEO)

Latest version (submitted October 27, 2014) on ClinicalTrials.gov

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Study Record Versions

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5	○	○	April 16, 2010	Contacts/Locations, Study Status and Study Identification

Version	A	B	Submitted Date	Changes
6	○	○	July 22, 2010	Contacts/Locations, Study Status, Eligibility and Arms and Interventions
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22	○	○	January 30, 2014	Contacts/Locations, Sponsor/Collaborators, More Information, Study Status, Baseline Characteristics and References
23	○	◉	October 27, 2014	More Information, Study Status and References

Compare

Comparison Format: (•) Merged ( ) Side-by-Side

Scroll up to access the controls

Study NCT01012973
on Date: April 16, 2010 (v5)

Study Identification

Unique Protocol ID:	14130
Brief Title:	Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO) (GALILEO)
Official Title:	A Randomized, Double-masked, Sham-controlled Phase 3 Study of the Efficacy, Safety and Tolerability of Repeated Intravitreal Administration of VEGF Trap-Eye in Subjects With Macular Edema Secondary to Central Retinal Vein Occlusion (CRVO)
Secondary IDs:	EudraCT: 2009-010973-19

Study Status

Record Verification:	April 2010
Overall Status:	Recruiting
Study Start:	October 2009
Primary Completion:	February 2011 [Anticipated]
Study Completion:	August 2012 [Anticipated]
First Submitted:	October 30, 2009
First Submitted that Met QC Criteria:	November 12, 2009
First Posted:	November 13, 2009 [Estimate]
Last Update Submitted that Met QC Criteria:	April 16, 2010

Last Update Posted:	April 19, 2010 [Estimate]

Sponsor/Collaborators

Sponsor:	Bayer
Responsible Party:	
Collaborators:	Regeneron Pharmaceuticals

Oversight

U.S. FDA-regulated Drug:	
U.S. FDA-regulated Device:	
Data Monitoring:	Yes

Study Description

Brief Summary:	To determine the efficacy of vascular endothelial growth factor (VEGF) Trap-Eye injected into the eye on vision function in subjects with macular edema as a consequence of central retinal vein occlusion
Detailed Description:	

Conditions

Conditions:	Retinal Vein Occlusion
Keywords:	Macular Edema Central Retinal Vein Occlusion CRVO VEGF Trap-Eye best-corrected visual acuity

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	Phase 3
Interventional Study Model:	Parallel Assignment
Number of Arms:	2
Masking:	TripleParticipant, Investigator, Outcomes Assessor
Allocation:	Randomized
Enrollment:	165 [Anticipated]

Arms and Interventions

Arms	Assigned Interventions
Experimental: Arm 1	Drug: VEGF Trap-Eye (BAY86-5321) Intravitreal injection. Weeks 0 to 20 injection of VEGF Trap-Eye every 4 weeks; weeks 24 to 48 every 4 weeks re-assessment and either (PRN) injection of VEGF Trap-Eye or sham injection; weeks 52 to 100 safety follow-up.
Sham Comparator: Arm 2	Sham treatment Sham treatment. Weeks 0 to 20 sham treatment every 4 weeks; weeks 24 to 48 every 4 weeks re-assessment and sham injection; weeks 52 to 100 safety follow-up.

Outcome Measures

Primary Outcome Measures:

1. The proportion of subjects who gain at least 15 letters in BCVA on the EDTRS chart compared with baseline at the Week 24 endpoint
   Week 24

Secondary Outcome Measures:

2. Change from baseline in BCVA score
   Week 24
3. Absolute change from baseline in central retinal thickness, assessed by OCT
   Week 24
4. Proportion of subjects progressing to anterior segment neovascularization, neovascularization of the optic disc (NVD), or neovascularization of the retina elsewhere (NVE) requiring pan-retinal photocoagulation
   Week 24
5. Change in the NEI-VFQ-25 total score from baseline
   Week 24
6. Change in the EQ-5D score from baseline
   Week 24

Eligibility

Minimum Age: 18 Years

Maximum Age:

Sex: All

Gender Based:

Accepts Healthy Volunteers: No

Criteria: Inclusion Criteria:

- Center-involved macular edema secondary to central retinal vein occlusion (CRVO) for no longer than 9 months with mean central subfield thickness >= 250 µm on optical coherence tomography (OCT).
- Adults >= 18 years.
- early treatment diabetic retinopathy study (ETDRS) best corrected visual acuity (BCVA) of 20/40 to 20/320 (73 to 24 letters) in the study eye.

Exclusion Criteria:

- Previous treatment with anti-angiogenic drugs in the study eye (Pegaptanib sodium, anecortave acetate, bevacizumab, ranibizumab, etc.)
- Prior panretinal laser photocoagulation or macular laser photocoagulation in the study eye
- CRVO disease duration > 9 months from date of diagnosis
- Previous use of intraocular corticosteroids in the study eye or use of periocular corticosteroids in the study eye within the 3 months prior to Day 1
- Iris neovascularization, vitreous hemorrhage, traction retinal detachment, or preretinal fibrosis involving the macula in either the study eye or fellow eye

Contacts/Locations

Central Contact: Bayer Clinical Trials Contact
Email: clinical-trials-contact@bayerhealthcare.com

Study Officials:

Bayer Study Director
Study Director
Bayer

Locations: **Australia, New South Wales**

[Not yet recruiting]
Chatswood, New South Wales, Australia, 2067

[Recruiting]
Sydney, New South Wales, Australia, 2000

[Recruiting]
Westmead, New South Wales, Australia, 2145

Australia, Victoria

[Recruiting]
East Melbourne, Victoria, Australia, 3002

Australia, Western Australia

[Recruiting]
Nedlands, Western Australia, Australia, 6009

Australia

[Recruiting]
Parramatta, Australia, 2150

Austria, Oberösterreich

[Not yet recruiting]
Linz, Oberösterreich, Austria, 4020

Austria, Tirol

[Not yet recruiting]
Innsbruck, Tirol, Austria, 6020

Austria

[Recruiting]
Linz, Austria, 4021

[Recruiting]
Wien, Austria, 1090

France, Cedex 12

[Not yet recruiting]
Paris, Cedex 12, France, 75557

France

[Not yet recruiting]
Bordeaux, France, 33000

[Not yet recruiting]
Dijon Cedex, France, BP 1542-21

[Not yet recruiting]
Marseille, France, 13008

[Not yet recruiting]
Nantes Cedex, France, 44035

[Not yet recruiting]
Paris, France, 75015

Germany, Baden-Württemberg

[Recruiting]
Freiburg, Baden-Württemberg, Germany, 79106

[Recruiting]
Heidelberg, Baden-Württemberg, Germany, 69120

[Recruiting]
Tübingen, Baden-Württemberg, Germany, 72076

Germany, Bayern

[Recruiting]
München, Bayern, Germany, 81675

[Recruiting]
Regensburg, Bayern, Germany, 93053

Germany, Hessen

[Recruiting]
Darmstadt, Hessen, Germany, 64276

[Not yet recruiting]
Marburg, Hessen, Germany, 35043

Germany, Niedersachsen

[Recruiting]
Göttingen, Niedersachsen, Germany, 37075

Germany, Nordrhein-Westfalen

[Recruiting]
Aachen, Nordrhein-Westfalen, Germany, 52074

[Recruiting]
Bonn, Nordrhein-Westfalen, Germany, 53105

[Not yet recruiting]
Essen, Nordrhein-Westfalen, Germany, 45147

[Recruiting]
Köln, Nordrhein-Westfalen, Germany, 50931

Germany, Rheinland-Pfalz

[Recruiting]
Ludwigshafen, Rheinland-Pfalz, Germany, 67063

[Recruiting]
Mainz, Rheinland-Pfalz, Germany, 55131

Germany, Saarland

[Recruiting]
Homburg, Saarland, Germany, 66421

Germany, Sachsen

[Recruiting]
Chemnitz, Sachsen, Germany, 09116

[Not yet recruiting]
Dresden, Sachsen, Germany, 01067

[Not yet recruiting]
Dresden, Sachsen, Germany, 01307

[Recruiting]
Leipzig, Sachsen, Germany, 04103

Germany, Schleswig-Holstein

[Not yet recruiting]
Kiel, Schleswig-Holstein, Germany, 24105

[Not yet recruiting]
Lübeck, Schleswig-Holstein, Germany, 23538

Germany

[Not yet recruiting]
Hamburg, Germany, 20251

Hungary

[Recruiting]
Budapest, Hungary, 1036

[Recruiting]
Budapest, Hungary, 1089

[Recruiting]
Budapest, Hungary, 1106

[Recruiting]
Debrecen, Hungary, 4032

[Suspended]
Veszprem, Hungary, 8200

[Not yet recruiting]
Zalaegerszeg, Hungary, 8900

Italy

[Not yet recruiting]
Ancona, Italy, 60126

[Not yet recruiting]
Bari, Italy, 70124

[Not yet recruiting]
Catania, Italy, 95123

[Not yet recruiting]
Firenze, Italy, 50139

[Recruiting]
Milano, Italy, 20122

[Not yet recruiting]
Milano, Italy, 20132

[Not yet recruiting]
Milano, Italy, 20157

[Not yet recruiting]
Padova, Italy, 35128

[Not yet recruiting]
Roma, Italy, 00133

[Not yet recruiting]
Roma, Italy, 00185

[Not yet recruiting]
Torino, Italy, 10149

Japan, Aichi

[Recruiting]
Nagoya, Aichi, Japan, 466-8560

[Recruiting]
Nagoya, Aichi, Japan, 467-8602

Japan, Chiba

[Recruiting]
Urayasu, Chiba, Japan, 279-0021

Japan, Osaka

[Recruiting]
Suita, Osaka, Japan, 565-0871

Japan, Tokyo

[Not yet recruiting]
Chiyoda-ku, Tokyo, Japan, 101-8309

Japan

[Recruiting]
Kyoto, Japan, 606-8507

Korea, Republic of

[Recruiting]
ask Contact, Korea, Republic of

[Not yet recruiting]
Incheon, Korea, Republic of, 405-760

[Recruiting]
Kungki-do, Korea, Republic of, 463-707

[Recruiting]
Seoul, Korea, Republic of, 110 744

[Recruiting]
Seoul, Korea, Republic of, 110-744

[Recruiting]
Seoul, Korea, Republic of, 138-736

Latvia

[Not yet recruiting]
Riga, Latvia, 1009

[Recruiting]
Riga, Latvia, LV-1002

Singapore

[Recruiting]
Singapore, Singapore, 119074

[Recruiting]
Singapore, Singapore, 168751

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U.S. National Library of Medicine
ClinicalTrials.gov archive

History of Changes for Study: NCT01012973

Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO) (GALILEO)

Latest version (submitted October 27, 2014) on ClinicalTrials.gov

- A study version is represented by a row in the table.
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Version	A	B	Submitted Date	Changes
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Compare

Comparison Format: (•) Merged ( ) Side-by-Side

Scroll up to access the controls

Study NCT01012973
on Date: June 23, 2011 (v14)

Study Identification

Unique Protocol ID:	14130
Brief Title:	Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO) (GALILEO)
Official Title:	A Randomized, Double-masked, Sham-controlled Phase 3 Study of the Efficacy, Safety and Tolerability of Repeated Intravitreal Administration of VEGF Trap-Eye in Subjects With Macular Edema Secondary to Central Retinal Vein Occlusion (CRVO)
Secondary IDs:	EudraCT: 2009-010973-19

Study Status

Record Verification:	June 2011
Overall Status:	Active, not recruiting
Study Start:	October 2009
Primary Completion:	February 2011 [Actual]
Study Completion:	March 2012 [Anticipated]
First Submitted:	October 30, 2009
First Submitted that Met QC Criteria:	November 12, 2009
First Posted:	November 13, 2009 [Estimate]
Last Update Submitted that Met QC Criteria:	June 23, 2011

Last Update Posted:	June 27, 2011 [Estimate]

Sponsor/Collaborators

Sponsor:	Bayer
Responsible Party:	
Collaborators:	Regeneron Pharmaceuticals

Oversight

U.S. FDA-regulated Drug:	
U.S. FDA-regulated Device:	
Data Monitoring:	Yes

Study Description

Brief Summary:	To determine the efficacy of vascular endothelial growth factor (VEGF) Trap-Eye injected into the eye on vision function in subjects with macular edema as a consequence of central retinal vein occlusion
Detailed Description:	

Conditions

Conditions:	Retinal Vein Occlusion
Keywords:	Macular Edema Central Retinal Vein Occlusion CRVO VEGF Trap-Eye best-corrected visual acuity

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	Phase 3
Interventional Study Model:	Parallel Assignment
Number of Arms:	2
Masking:	TripleParticipant, Investigator, Outcomes Assessor
Allocation:	Randomized
Enrollment:	177 [Actual]

Arms and Interventions

Arms	Assigned Interventions
Experimental: Arm 1	Biological: VEGF Trap-Eye (BAY86-5321) Intravitreal injection. Weeks 0 to 20 injection of VEGF Trap-Eye every 4 weeks; weeks 24 to 52 every 4 weeks plus additional on week 60 and 68 re-assessment and either (PRN) injection of VEGF Trap-Eye or sham injection; last visit (no treatment) at week 76.
Sham Comparator: Arm 2	Sham treatment Sham treatment. Weeks 0 to 20 sham treatment every 4 weeks; weeks 24 to 48 every 4 weeks re-assessment and sham injection; week 52 VEGF Trap-Eye injection (unless investigator declines for medical reasons), weeks 60 and 68 re-assessment and either (PRN) injection of VEGF Trap-Eye or sham injection; last visit (no treatment) at week 76.

Outcome Measures

Primary Outcome Measures:

1. The proportion of subjects who gain at least 15 letters in BCVA on the EDTRS chart compared with baseline at the Week 24 endpoint
   Week 24

Secondary Outcome Measures:

2. Change from baseline in BCVA score
   Week 24
3. Absolute change from baseline in central retinal thickness, assessed by OCT
   Week 24
4. Proportion of subjects progressing to anterior segment neovascularization, neovascularization of the optic disc (NVD), or neovascularization of the retina elsewhere (NVE) requiring pan-retinal photocoagulation
   Week 24
5.

Change in the NEI-VFQ-25 total score from baseline
Week 24

6. Change in the EQ-5D score from baseline
Week 24

Eligibility

Minimum Age: 18 Years

Maximum Age:

Sex: All

Gender Based:

Accepts Healthy Volunteers: No

Criteria: Inclusion Criteria:

- Center-involved macular edema secondary to central retinal vein occlusion (CRVO) for no longer than 9 months with mean central subfield thickness ≥ 250 µm on optical coherence tomography (OCT)
- Adults ≥ 18 years
- Early treatment diabetic retinopathy study (ETDRS) best corrected visual acuity (BCVA) of 20/40 to 20/320 (73 to 24 letters) in the study eye

Exclusion Criteria:

- Any prior treatment with anti-VEGF agents in the study eye (Pegaptanib sodium, anecortave acetate, bevacizumab, ranibizumab, etc.) or previous administration of systemic anti-angiogenic medications
- Prior panretinal laser photocoagulation or macular laser photocoagulation in the study eye
- CRVO disease duration > 9 months from date of diagnosis
- Previous use of intraocular corticosteroids in the study eye or use of periocular corticosteroids in the study eye within the 3 months prior to Day 1

- Iris neovascularization, vitreous hemorrhage, traction retinal detachment, or preretinal fibrosis involving the macula in either the study eye or fellow eye

Contacts/Locations

Study Officials: Bayer Study Director
Study Director
Bayer

Locations:

Australia, New South Wales

Chatswood, New South Wales, Australia, 2067

Parramatta, New South Wales, Australia, 2150

Sydney, New South Wales, Australia, 2000

Westmead, New South Wales, Australia, 2145

Australia, Victoria

East Melbourne, Victoria, Australia, 3002

Australia, Western Australia

Nedlands, Western Australia, Australia, 6009

Austria

Innsbruck, Austria, 6020

Linz, Austria, 4021

Wien, Austria, 1090

France, Cedex 12

Paris, Cedex 12, France, 75557

France, Cedex 1

Nantes, Cedex 1, France, 44093

France

Bordeaux, France, 33000

Dijon, France, 21033

Marseille, France, 13008

Paris, France, 75015

Germany, Baden-Württemberg

Freiburg, Baden-Württemberg, Germany, 79106

Heidelberg, Baden-Württemberg, Germany, 69120

Tübingen, Baden-Württemberg, Germany, 72076

Germany, Bayern

München, Bayern, Germany, 81675

Regensburg, Bayern, Germany, 93053

Germany, Hessen

Darmstadt, Hessen, Germany, 64297

Frankfurt, Hessen, Germany, 60596

Germany, Niedersachsen

Göttingen, Niedersachsen, Germany, 37075

Germany, Nordrhein-Westfalen

Aachen, Nordrhein-Westfalen, Germany, 52074

Bonn, Nordrhein-Westfalen, Germany, 53105

Essen, Nordrhein-Westfalen, Germany, 45122

Köln, Nordrhein-Westfalen, Germany, 50924

Münster, Nordrhein-Westfalen, Germany, 48145

Germany, Rheinland-Pfalz

Ludwigshafen, Rheinland-Pfalz, Germany, 67063

Mainz, Rheinland-Pfalz, Germany, 55131

Germany, Saarland

Homburg, Saarland, Germany, 66421

Germany, Sachsen

Chemnitz, Sachsen, Germany, 09116

Dresden, Sachsen, Germany, 01307

Dresden, Sachsen, Germany, 06067

Leipzig, Sachsen, Germany, 04103

Germany, Schleswig-Holstein

Kiel, Schleswig-Holstein, Germany, 24105

Lübeck, Schleswig-Holstein, Germany, 23538

Germany

Berlin, Germany, 13353

Hamburg, Germany, 20251

Marburg, Germany, 35037

Hungary

Budapest, Hungary, 1089

Budapest, Hungary, 1106

Budapest, Hungary, 1133

Debrecen, Hungary, 4032

Veszprem, Hungary, 8200

Zalaegerszeg, Hungary, H-8900

Italy

Ancona, Italy, 60126

Bari, Italy, 70124

Catania, Italy, 95123

Firenze, Italy, 50134

Milano, Italy, 20122

Milano, Italy, 20132

Milano, Italy, 20157

Padova, Italy, 35128

Roma, Italy, 00133

Roma, Italy, 00198

Torino, Italy, 10122

Japan, Aichi

Nagoya, Aichi, Japan, 466-8560

Nagoya, Aichi, Japan, 467-8602

Japan, Chiba

Urayasu, Chiba, Japan, 279-0021

Japan, Osaka

Suita, Osaka, Japan, 565-0871

Japan, Tokyo

Chiyoda-ku, Tokyo, Japan, 101-8309

Japan

Kyoto, Japan, 606-8507

Korea, Republic of

Incheon, Korea, Republic of, 405-760

Kungki-do, Korea, Republic of, 463-707

Seoul, Korea, Republic of, 110 744

Seoul, Korea, Republic of, 110-744

Seoul, Korea, Republic of, 138-736

Seoul, Korea, Republic of

Latvia

Riga, Latvia, 1002

Riga, Latvia, 1050

Singapore

Singapore, Singapore, 119074

Singapore, Singapore, 168751

IPDSharing

Plan to Share IPD:

References

Citations:

Links:

Available IPD/Information:

Scroll up to access the controls | Scroll to the Study top

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U.S. National Library of Medicine
ClinicalTrials.gov archive

History of Changes for Study: NCT01012973

Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO) (GALILEO)

Latest version (submitted October 27, 2014) on ClinicalTrials.gov

- A study version is represented by a row in the table.
- Select two study versions to compare. One each from columns A and B.
- Choose either the "Merged" or "Side-by-Side" comparison format to specify how the two study versions are to be displayed. The Side-by-Side format only applies to the Protocol section of the study.
- Click "Compare" to do the comparison and show the differences.
- Select a version's date link to see a rendering of the study for that version.
- Edits or deletions will be displayed in ~~red~~.
- Additions will be displayed in *green*.
- The yellow choices in the table indicate the study versions currently compared below. A yellow row indicates the study version being viewed.
- Hover over the "Recruitment Status" to see how the study's recruitment status changed.

Study Record Versions

Version	A	B	Submitted Date	Changes
1	◉	○	November 12, 2009	Nothing (earliest Version on record)
2	○	○	January 21, 2010	Contacts/Locations, Study Status, Study Identification and Study Description
3	○	○	February 9, 2010	Contacts/Locations and Study Status
4	○	○	March 16, 2010	Contacts/Locations, Study Status and Study Identification
5	○	○	April 16, 2010	Contacts/Locations, Study Status and Study Identification

Version	A	B	Submitted Date	Changes
6	○	○	July 22, 2010	Contacts/Locations, Study Status, Eligibility and Arms and Interventions
7	○	○	August 25, 2010	Study Status and Contacts/Locations
8	○	○	August 26, 2010	Recruitment Status, Study Status and Contacts/Locations
9	○	○	September 8, 2010	Study Status
10	○	○	October 4, 2010	Study Status
11	○	○	November 1, 2010	Study Status
12	○	○	January 25, 2011	Study Status and Contacts/Locations
13	○	○	April 8, 2011	Study Status and Study Design
14	○	○	June 23, 2011	Arms and Interventions, Study Status, Contacts/Locations and Eligibility
15	○	○	September 19, 2011	Study Status
16	○	○	November 29, 2011	Study Status and Study Identification
17	○	○	January 26, 2012	Study Status and Contacts/Locations
18	○	○	February 20, 2012	Recruitment Status, Study Status
19	○	○	October 23, 2012	Outcome Measures, Arms and Interventions, Study Status, More Information, Reported Adverse Events, Baseline Characteristics and Participant Flow
20	○	○	December 18, 2012	More Information, Arms and Interventions, Study Status and Baseline Characteristics
21	○	○	January 18, 2013	Arms and Interventions, More Information, Study Status and Baseline Characteristics
22	○	○	January 30, 2014	Contacts/Locations, Sponsor/Collaborators, More Information, Study Status, Baseline Characteristics and References
23	○	◉	October 27, 2014	More Information, Study Status and References

Compare

Comparison Format: (•) Merged ( ) Side-by-Side

Scroll up to access the controls

Study NCT01012973
on Date: July 22, 2010 (v6)

Study Identification

Unique Protocol ID:	14130
Brief Title:	Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO) (GALILEO)
Official Title:	A Randomized, Double-masked, Sham-controlled Phase 3 Study of the Efficacy, Safety and Tolerability of Repeated Intravitreal Administration of VEGF Trap-Eye in Subjects With Macular Edema Secondary to Central Retinal Vein Occlusion (CRVO)
Secondary IDs:	EudraCT: 2009-010973-19

Study Status

Record Verification:	July 2010
Overall Status:	Recruiting
Study Start:	October 2009
Primary Completion:	February 2011 [Anticipated]
Study Completion:	March 2012 [Anticipated]
First Submitted:	October 30, 2009
First Submitted that Met QC Criteria:	November 12, 2009
First Posted:	November 13, 2009 [Estimate]
Last Update Submitted that Met QC Criteria:	July 22, 2010

Last Update Posted:	July 23, 2010 [Estimate]

Sponsor/Collaborators

Sponsor:	Bayer
Responsible Party:	
Collaborators:	Regeneron Pharmaceuticals

Oversight

U.S. FDA-regulated Drug:	
U.S. FDA-regulated Device:	
Data Monitoring:	Yes

Study Description

Brief Summary:	To determine the efficacy of vascular endothelial growth factor (VEGF) Trap-Eye injected into the eye on vision function in subjects with macular edema as a consequence of central retinal vein occlusion
Detailed Description:	

Conditions

Conditions:	Retinal Vein Occlusion
Keywords:	Macular Edema Central Retinal Vein Occlusion CRVO VEGF Trap-Eye best-corrected visual acuity

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	Phase 3
Interventional Study Model:	Parallel Assignment
Number of Arms:	2
Masking:	TripleParticipant, Investigator, Outcomes Assessor
Allocation:	Randomized
Enrollment:	165 [Anticipated]

Arms and Interventions

Arms	Assigned Interventions
Experimental: Arm 1	Drug: VEGF Trap-Eye (BAY86-5321) Intravitreal injection. Weeks 0 to 20 injection of VEGF Trap-Eye every 4 weeks; weeks 24 to 52 every 4 weeks plus additional on week 60 and 68 re-assessment and either (PRN) injection of VEGF Trap-Eye or sham injection; last visit (no treatment) at week 76.
Sham Comparator: Arm 2	Sham treatment Sham treatment. Weeks 0 to 20 sham treatment every 4 weeks; weeks 24 to 48 every 4 weeks re-assessment and sham injection; week 52 VEGF Trap-Eye injection (unless investigator declines for medical reasons), weeks 60 and 68 re-assessment and either (PRN) injection of VEGF Trap-Eye or sham injection; last visit (no treatment) at week 76.

Outcome Measures

Primary Outcome Measures:

1. The proportion of subjects who gain at least 15 letters in BCVA on the EDTRS chart compared with baseline at the Week 24 endpoint
   Week 24

Secondary Outcome Measures:

2. Change from baseline in BCVA score
   Week 24
3. Absolute change from baseline in central retinal thickness, assessed by OCT
   Week 24
4. Proportion of subjects progressing to anterior segment neovascularization, neovascularization of the optic disc (NVD), or neovascularization of the retina elsewhere (NVE) requiring pan-retinal photocoagulation
   Week 24
5.

Change in the NEI-VFQ-25 total score from baseline
Week 24

6. Change in the EQ-5D score from baseline
Week 24

Eligibility

Minimum Age: 18 Years

Maximum Age:

Sex: All

Gender Based:

Accepts Healthy Volunteers: No

Criteria: Inclusion Criteria:

- Center-involved macular edema secondary to central retinal vein occlusion (CRVO) for no longer than 9 months with mean central subfield thickness >= 250 µm on optical coherence tomography (OCT)
- Adults >= 18 years
- Early treatment diabetic retinopathy study (ETDRS) best corrected visual acuity (BCVA) of 20/40 to 20/320 (73 to 24 letters) in the study eye

Exclusion Criteria:

- Any prior treatment with anti-VEGF agents in the study eye (Pegaptanib sodium, anecortave acetate, bevacizumab, ranibizumab, etc.) or previous administration of systemic anti-angiogenic medications
- Prior panretinal laser photocoagulation or macular laser photocoagulation in the study eye
- CRVO disease duration > 9 months from date of diagnosis
- Previous use of intraocular corticosteroids in the study eye or use of periocular corticosteroids in the study eye within the 3 months prior to Day 1

- Iris neovascularization, vitreous hemorrhage, traction retinal detachment, or preretinal fibrosis involving the macula in either the study eye or fellow eye

Contacts/Locations

Central Contact: Bayer Clinical Trials Contact
Email: clinical-trials-contact@bayerhealthcare.com

Study Officials: Bayer Study Director
Study Director
Bayer

Locations: **Australia, New South Wales**

[Recruiting]
Chatswood, New South Wales, Australia, 2067

[Recruiting]
Parramatta, New South Wales, Australia, 2150

[Recruiting]
Sydney, New South Wales, Australia, 2000

[Recruiting]
Westmead, New South Wales, Australia, 2145

Australia, Victoria

[Recruiting]
East Melbourne, Victoria, Australia, 3002

Australia, Western Australia

[Recruiting]
Nedlands, Western Australia, Australia, 6009

Austria

[Terminated]
Innsbruck, Austria, 6020

[Recruiting]
Linz, Austria, 4021

[Recruiting]
Wien, Austria, 1090

France, Cedex 12

[Not yet recruiting]
Paris, Cedex 12, France, 75557

France, Cedex 1

[Recruiting]
Nantes, Cedex 1, France, 44093

France

[Recruiting]
Bordeaux, France, 33000

[Recruiting]
Dijon, France, 21033

[Recruiting]
Marseille, France, 13008

[Recruiting]
Paris, France, 75015

Germany, Baden-Württemberg

[Recruiting]
Freiburg, Baden-Württemberg, Germany, 79106

[Recruiting]
Heidelberg, Baden-Württemberg, Germany, 69120

[Recruiting]
Tübingen, Baden-Württemberg, Germany, 72076

Germany, Bayern

[Recruiting]
München, Bayern, Germany, 81675

[Recruiting]
Regensburg, Bayern, Germany, 93053

Germany, Hessen

[Recruiting]
Darmstadt, Hessen, Germany, 64297

[Not yet recruiting]
Frankfurt, Hessen, Germany, 60596

Germany, Niedersachsen

[Recruiting]
Göttingen, Niedersachsen, Germany, 37075

Germany, Nordrhein-Westfalen

[Recruiting]
Aachen, Nordrhein-Westfalen, Germany, 52074

[Recruiting]
Bonn, Nordrhein-Westfalen, Germany, 53105

[Not yet recruiting]
Essen, Nordrhein-Westfalen, Germany, 45122

[Recruiting]
Köln, Nordrhein-Westfalen, Germany, 50924

[Not yet recruiting]
Münster, Nordrhein-Westfalen, Germany, 48145

Germany, Rheinland-Pfalz

[Recruiting]
Ludwigshafen, Rheinland-Pfalz, Germany, 67063

[Recruiting]
Mainz, Rheinland-Pfalz, Germany, 55131

Germany, Saarland

[Recruiting]
Homburg, Saarland, Germany, 66424

Germany, Sachsen

[Recruiting]
Chemnitz, Sachsen, Germany, 09116

[Not yet recruiting]
Dresden, Sachsen, Germany, 01307

[Recruiting]
Dresden, Sachsen, Germany, 06067

[Recruiting]
Leipzig, Sachsen, Germany, 04103

Germany, Schleswig-Holstein

[Not yet recruiting]
Kiel, Schleswig-Holstein, Germany, 24105

[Not yet recruiting]
Lübeck, Schleswig-Holstein, Germany, 23538

Germany

[Not yet recruiting]
Berlin, Germany, 13353

[Recruiting]
Hamburg, Germany, 20251

[Recruiting]
Marburg, Germany, 35037

Hungary

[Recruiting]
Budapest, Hungary, 1036

[Recruiting]
Budapest, Hungary, 1089

[Recruiting]
Budapest, Hungary, 1106

[Recruiting]
Debrecen, Hungary, 4032

[Terminated]
Veszprem, Hungary, 8200

[Not yet recruiting]
Zalaegerszeg, Hungary, H-8900

Italy

[Recruiting]
Ancona, Italy, 60126

[Recruiting]
Bari, Italy, 70124

[Not yet recruiting]
Catania, Italy, 95123

[Recruiting]
Firenze, Italy, 50134

[Recruiting]
Milano, Italy, 20122

[Recruiting]
Milano, Italy, 20132

[Not yet recruiting]
Milano, Italy, 20157

[Terminated]
Padova, Italy, 35128

[Recruiting]
Roma, Italy, 00133

[Recruiting]
Roma, Italy, 00198

[Not yet recruiting]
Torino, Italy, 10122

Japan, Aichi

[Recruiting]
Nagoya, Aichi, Japan, 466-8560

[Recruiting]
Nagoya, Aichi, Japan, 467-8602

Japan, Chiba

[Recruiting]
Urayasu, Chiba, Japan, 279-0021

Japan, Osaka

[Recruiting]
Suita, Osaka, Japan, 565-0871

Japan, Tokyo

[Recruiting]
Chiyoda-ku, Tokyo, Japan, 101-8309

Japan

[Recruiting]
Kyoto, Japan, 606-8507

Korea, Republic of

[Recruiting]
Incheon, Korea, Republic of, 405-760

[Recruiting]
Kungki-do, Korea, Republic of, 463-707

[Recruiting]
Seoul, Korea, Republic of, 110 744

[Recruiting]
Seoul, Korea, Republic of, 110-744

[Recruiting]
Seoul, Korea, Republic of, 138-736

[Recruiting]
Seoul, Korea, Republic of

Latvia

[Recruiting]
Riga, Latvia, 1009

[Recruiting]
Riga, Latvia, LV-1002

Singapore

[Recruiting]
Singapore, Singapore, 119074

[Recruiting]
Singapore, Singapore, 168751

IPDSharing

Plan to Share IPD:

References

Citations:

Links:

Available IPD/Information:

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U.S. National Library of Medicine
ClinicalTrials.gov archive

History of Changes for Study: NCT01012973

Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO) (GALILEO)

Latest version (submitted October 27, 2014) on ClinicalTrials.gov

- A study version is represented by a row in the table.
- Select two study versions to compare. One each from columns A and B.
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- Additions will be displayed in *green*.
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Study Record Versions

Version	A	B	Submitted Date	Changes
1	◉	○	November 12, 2009	Nothing (earliest Version on record)
2	○	○	January 21, 2010	Contacts/Locations, Study Status, Study Identification and Study Description
3	○	○	February 9, 2010	Contacts/Locations and Study Status
4	○	○	March 16, 2010	Contacts/Locations, Study Status and Study Identification
5	○	○	April 16, 2010	Contacts/Locations, Study Status and Study Identification

Version	A	B	Submitted Date	Changes
6	○	○	July 22, 2010	Contacts/Locations, Study Status, Eligibility and Arms and Interventions
7	○	○	August 25, 2010	Study Status and Contacts/Locations
8	○	○	August 26, 2010	Recruitment Status, Study Status and Contacts/Locations
9	○	○	September 8, 2010	Study Status
10	○	○	October 4, 2010	Study Status
11	○	○	November 1, 2010	Study Status
12	○	○	January 25, 2011	Study Status and Contacts/Locations
13	○	○	April 8, 2011	Study Status and Study Design
14	○	○	June 23, 2011	Arms and Interventions, Study Status, Contacts/Locations and Eligibility
15	○	○	September 19, 2011	Study Status
16	○	○	November 29, 2011	Study Status and Study Identification
17	○	○	January 26, 2012	Study Status and Contacts/Locations
18	○	○	February 20, 2012	Recruitment Status, Study Status
19	○	○	October 23, 2012	Outcome Measures, Arms and Interventions, Study Status, More Information, Reported Adverse Events, Baseline Characteristics and Participant Flow
20	○	○	December 18, 2012	More Information, Arms and Interventions, Study Status and Baseline Characteristics
21	○	○	January 18, 2013	Arms and Interventions, More Information, Study Status and Baseline Characteristics
22	○	○	January 30, 2014	Contacts/Locations, Sponsor/Collaborators, More Information, Study Status, Baseline Characteristics and References
23	○	◉	October 27, 2014	More Information, Study Status and References

Compare

Comparison Format: (•) Merged ( ) Side-by-Side

Scroll up to access the controls

Study NCT01012973
on Date: August 25, 2010 (v7)

Study Identification

Unique Protocol ID:	14130
Brief Title:	Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO) (GALILEO)
Official Title:	A Randomized, Double-masked, Sham-controlled Phase 3 Study of the Efficacy, Safety and Tolerability of Repeated Intravitreal Administration of VEGF Trap-Eye in Subjects With Macular Edema Secondary to Central Retinal Vein Occlusion (CRVO)
Secondary IDs:	EudraCT: 2009-010973-19

Study Status

Record Verification:	August 2010
Overall Status:	Recruiting
Study Start:	October 2009
Primary Completion:	February 2011 [Anticipated]
Study Completion:	March 2012 [Anticipated]
First Submitted:	October 30, 2009
First Submitted that Met QC Criteria:	November 12, 2009
First Posted:	November 13, 2009 [Estimate]
Last Update Submitted that Met QC Criteria:	August 25, 2010

Last Update Posted:	August 26, 2010 [Estimate]

Sponsor/Collaborators

Sponsor:	Bayer
Responsible Party:	
Collaborators:	Regeneron Pharmaceuticals

Oversight

U.S. FDA-regulated Drug:	
U.S. FDA-regulated Device:	
Data Monitoring:	Yes

Study Description

Brief Summary:	To determine the efficacy of vascular endothelial growth factor (VEGF) Trap-Eye injected into the eye on vision function in subjects with macular edema as a consequence of central retinal vein occlusion
Detailed Description:	

Conditions

Conditions:	Retinal Vein Occlusion
Keywords:	Macular Edema Central Retinal Vein Occlusion CRVO VEGF Trap-Eye best-corrected visual acuity

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	Phase 3
Interventional Study Model:	Parallel Assignment
Number of Arms:	2
Masking:	TripleParticipant, Investigator, Outcomes Assessor
Allocation:	Randomized
Enrollment:	165 [Anticipated]

Arms and Interventions

Arms	Assigned Interventions
Experimental: Arm 1	Drug: VEGF Trap-Eye (BAY86-5321) Intravitreal injection. Weeks 0 to 20 injection of VEGF Trap-Eye every 4 weeks; weeks 24 to 52 every 4 weeks plus additional on week 60 and 68 re-assessment and either (PRN) injection of VEGF Trap-Eye or sham injection; last visit (no treatment) at week 76.
Sham Comparator: Arm 2	Sham treatment Sham treatment. Weeks 0 to 20 sham treatment every 4 weeks; weeks 24 to 48 every 4 weeks re-assessment and sham injection; week 52 VEGF Trap-Eye injection (unless investigator declines for medical reasons), weeks 60 and 68 re-assessment and either (PRN) injection of VEGF Trap-Eye or sham injection; last visit (no treatment) at week 76.

Outcome Measures

Primary Outcome Measures:

1. The proportion of subjects who gain at least 15 letters in BCVA on the EDTRS chart compared with baseline at the Week 24 endpoint
   Week 24

Secondary Outcome Measures:

2. Change from baseline in BCVA score
   Week 24
3. Absolute change from baseline in central retinal thickness, assessed by OCT
   Week 24
4. Proportion of subjects progressing to anterior segment neovascularization, neovascularization of the optic disc (NVD), or neovascularization of the retina elsewhere (NVE) requiring pan-retinal photocoagulation
   Week 24
5.

Change in the NEI-VFQ-25 total score from baseline
Week 24

6. Change in the EQ-5D score from baseline
Week 24

Eligibility

Minimum Age: 18 Years

Maximum Age:

Sex: All

Gender Based:

Accepts Healthy Volunteers: No

Criteria: Inclusion Criteria:

- Center-involved macular edema secondary to central retinal vein occlusion (CRVO) for no longer than 9 months with mean central subfield thickness >= 250 µm on optical coherence tomography (OCT)
- Adults >= 18 years
- Early treatment diabetic retinopathy study (ETDRS) best corrected visual acuity (BCVA) of 20/40 to 20/320 (73 to 24 letters) in the study eye

Exclusion Criteria:

- Any prior treatment with anti-VEGF agents in the study eye (Pegaptanib sodium, anecortave acetate, bevacizumab, ranibizumab, etc.) or previous administration of systemic anti-angiogenic medications
- Prior panretinal laser photocoagulation or macular laser photocoagulation in the study eye
- CRVO disease duration > 9 months from date of diagnosis
- Previous use of intraocular corticosteroids in the study eye or use of periocular corticosteroids in the study eye within the 3 months prior to Day 1

- Iris neovascularization, vitreous hemorrhage, traction retinal detachment, or preretinal fibrosis involving the macula in either the study eye or fellow eye

Contacts/Locations

Central Contact: Bayer Clinical Trials Contact
Email: clinical-trials-contact@bayerhealthcare.com

Study Officials: Bayer Study Director
Study Director
Bayer

Locations: **Australia, New South Wales**

[Active, not recruiting]
Chatswood, New South Wales, Australia, 2067

[Active, not recruiting]
Parramatta, New South Wales, Australia, 2150

[Active, not recruiting]
Sydney, New South Wales, Australia, 2000

[Active, not recruiting]
Westmead, New South Wales, Australia, 2145

Australia, Victoria

[Active, not recruiting]
East Melbourne, Victoria, Australia, 3002

Australia, Western Australia

[Active, not recruiting]
Nedlands, Western Australia, Australia, 6009

Austria

[Terminated]
Innsbruck, Austria, 6020

[Active, not recruiting]
Linz, Austria, 4021

[Active, not recruiting]
Wien, Austria, 1090

France, Cedex 12

[Terminated]
Paris, Cedex 12, France, 75557

France, Cedex 1

[Active, not recruiting]
Nantes, Cedex 1, France, 44093

France

[Active, not recruiting]
Bordeaux, France, 33000

[Active, not recruiting]
Dijon, France, 21033

[Active, not recruiting]
Marseille, France, 13008

[Active, not recruiting]
Paris, France, 75015

Germany, Baden-Württemberg

[Active, not recruiting]
Freiburg, Baden-Württemberg, Germany, 79106

[Active, not recruiting]
Heidelberg, Baden-Württemberg, Germany, 69120

[Active, not recruiting]
Tübingen, Baden-Württemberg, Germany, 72076

Germany, Bayern

[Active, not recruiting]
München, Bayern, Germany, 81675

[Active, not recruiting]
Regensburg, Bayern, Germany, 93053

Germany, Hessen

[Active, not recruiting]
Darmstadt, Hessen, Germany, 64297

[Active, not recruiting]
Frankfurt, Hessen, Germany, 60596

Germany, Niedersachsen

[Active, not recruiting]
Göttingen, Niedersachsen, Germany, 37075

Germany, Nordrhein-Westfalen

[Active, not recruiting]
Aachen, Nordrhein-Westfalen, Germany, 52074

[Active, not recruiting]
Bonn, Nordrhein-Westfalen, Germany, 53105

[Terminated]
Essen, Nordrhein-Westfalen, Germany, 45122

[Active, not recruiting]
Köln, Nordrhein-Westfalen, Germany, 50924

[Terminated]
Münster, Nordrhein-Westfalen, Germany, 48145

Germany, Rheinland-Pfalz

[Active, not recruiting]
Ludwigshafen, Rheinland-Pfalz, Germany, 67063

[Active, not recruiting]
Mainz, Rheinland-Pfalz, Germany, 55131

Germany, Saarland

[Completed]
Homburg, Saarland, Germany, 66424

Germany, Sachsen

[Active, not recruiting]
Chemnitz, Sachsen, Germany, 09116

[Terminated]
Dresden, Sachsen, Germany, 01307

[Active, not recruiting]
Dresden, Sachsen, Germany, 06067

[Active, not recruiting]
Leipzig, Sachsen, Germany, 04103

Germany, Schleswig-Holstein

[Active, not recruiting]
Kiel, Schleswig-Holstein, Germany, 24105

[Active, not recruiting]
Lübeck, Schleswig-Holstein, Germany, 23538

Germany

[Terminated]
Berlin, Germany, 13353

[Active, not recruiting]
Hamburg, Germany, 20251

[Active, not recruiting]
Marburg, Germany, 35037

Hungary

[Active, not recruiting]
Budapest, Hungary, 1036

[Active, not recruiting]
Budapest, Hungary, 1089

[Active, not recruiting]
Budapest, Hungary, 1106

[Active, not recruiting]
Debrecen, Hungary, 4032

[Terminated]
Veszprem, Hungary, 8200

[Active, not recruiting]
Zalaegerszeg, Hungary, H-8900

Italy

[Active, not recruiting]
Ancona, Italy, 60126

[Active, not recruiting]
Bari, Italy, 70124

[Terminated]
Catania, Italy, 95123

[Active, not recruiting]
Firenze, Italy, 50134

[Active, not recruiting]
Milano, Italy, 20122

[Active, not recruiting]
Milano, Italy, 20132

[Terminated]
Milano, Italy, 20157

[Terminated]
Padova, Italy, 35128

[Active, not recruiting]
Roma, Italy, 00133

[Active, not recruiting]
Roma, Italy, 00198

[Terminated]
Torino, Italy, 10122

Japan, Aichi

[Active, not recruiting]
Nagoya, Aichi, Japan, 466-8560

[Active, not recruiting]
Nagoya, Aichi, Japan, 467-8602

Japan, Chiba

[Active, not recruiting]
Urayasu, Chiba, Japan, 279-0021

Japan, Osaka

[Active, not recruiting]
Suita, Osaka, Japan, 565-0871

Japan, Tokyo

[Active, not recruiting]
Chiyoda-ku, Tokyo, Japan, 101-8309

Japan

[Active, not recruiting]
Kyoto, Japan, 606-8507

Korea, Republic of

[Active, not recruiting]
Incheon, Korea, Republic of, 405-760

[Active, not recruiting]
Kungki-do, Korea, Republic of, 463-707

[Active, not recruiting]
Seoul, Korea, Republic of, 110 744

[Active, not recruiting]
Seoul, Korea, Republic of, 110-744

[Active, not recruiting]
Seoul, Korea, Republic of, 138-736

[Recruiting]
Seoul, Korea, Republic of

Latvia

[Active, not recruiting]
Riga, Latvia, 1009

[Active, not recruiting]
Riga, Latvia, LV-1002

Singapore

[Active, not recruiting]
Singapore, Singapore, 119074

[Active, not recruiting]
Singapore, Singapore, 168751

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History of Changes for Study: NCT01012973

Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO) (GALILEO)

Latest version (submitted October 27, 2014) on ClinicalTrials.gov

- A study version is represented by a row in the table.
- Select two study versions to compare. One each from columns A and B.
- Choose either the "Merged" or "Side-by-Side" comparison format to specify how the two study versions are to be displayed. The Side-by-Side format only applies to the Protocol section of the study.
- Click "Compare" to do the comparison and show the differences.
- Select a version's date link to see a rendering of the study for that version.
- Edits or deletions will be displayed in ~~red~~.
- Additions will be displayed in *green*.
- The yellow choices in the table indicate the study versions currently compared below. A yellow row indicates the study version being viewed.
- Hover over the "Recruitment Status" to see how the study's recruitment status changed.

Study Record Versions

Version	A	B	Submitted Date	Changes
1	◉	○	November 12, 2009	Nothing (earliest Version on record)
2	○	○	January 21, 2010	Contacts/Locations, Study Status, Study Identification and Study Description
3	○	○	February 9, 2010	Contacts/Locations and Study Status
4	○	○	March 16, 2010	Contacts/Locations, Study Status and Study Identification
5	○	○	April 16, 2010	Contacts/Locations, Study Status and Study Identification

Version	A	B	Submitted Date	Changes
6	○	○	July 22, 2010	Contacts/Locations, Study Status, Eligibility and Arms and Interventions
7	○	○	August 25, 2010	Study Status and Contacts/Locations
8	○	○	August 26, 2010	Recruitment Status, Study Status and Contacts/Locations
9	○	○	September 8, 2010	Study Status
10	○	○	October 4, 2010	Study Status
11	○	○	November 1, 2010	Study Status
12	○	○	January 25, 2011	Study Status and Contacts/Locations
13	○	○	April 8, 2011	Study Status and Study Design
14	○	○	June 23, 2011	Arms and Interventions, Study Status, Contacts/Locations and Eligibility
15	○	○	September 19, 2011	Study Status
16	○	○	November 29, 2011	Study Status and Study Identification
17	○	○	January 26, 2012	Study Status and Contacts/Locations
18	○	○	February 20, 2012	Recruitment Status, Study Status
19	○	○	October 23, 2012	Outcome Measures, Arms and Interventions, Study Status, More Information, Reported Adverse Events, Baseline Characteristics and Participant Flow
20	○	○	December 18, 2012	More Information, Arms and Interventions, Study Status and Baseline Characteristics
21	○	○	January 18, 2013	Arms and Interventions, More Information, Study Status and Baseline Characteristics
22	○	○	January 30, 2014	Contacts/Locations, Sponsor/Collaborators, More Information, Study Status, Baseline Characteristics and References
23	○	◉	October 27, 2014	More Information, Study Status and References

Compare

Comparison Format: (•) Merged ( ) Side-by-Side

Scroll up to access the controls

Study NCT01012973
on Date: August 26, 2010 (v8)

Study Identification

Unique Protocol ID:	14130
Brief Title:	Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO) (GALILEO)
Official Title:	A Randomized, Double-masked, Sham-controlled Phase 3 Study of the Efficacy, Safety and Tolerability of Repeated Intravitreal Administration of VEGF Trap-Eye in Subjects With Macular Edema Secondary to Central Retinal Vein Occlusion (CRVO)
Secondary IDs:	EudraCT: 2009-010973-19

Study Status

Record Verification:	August 2010
Overall Status:	Active, not recruiting
Study Start:	October 2009
Primary Completion:	February 2011 [Anticipated]
Study Completion:	March 2012 [Anticipated]
First Submitted:	October 30, 2009
First Submitted that Met QC Criteria:	November 12, 2009
First Posted:	November 13, 2009 [Estimate]
Last Update Submitted that Met QC Criteria:	August 26, 2010

Last Update Posted:	August 27, 2010 [Estimate]

Sponsor/Collaborators

Sponsor:	Bayer
Responsible Party:	
Collaborators:	Regeneron Pharmaceuticals

Oversight

U.S. FDA-regulated Drug:	
U.S. FDA-regulated Device:	
Data Monitoring:	Yes

Study Description

Brief Summary:	To determine the efficacy of vascular endothelial growth factor (VEGF) Trap-Eye injected into the eye on vision function in subjects with macular edema as a consequence of central retinal vein occlusion
Detailed Description:	

Conditions

Conditions:	Retinal Vein Occlusion
Keywords:	Macular Edema Central Retinal Vein Occlusion CRVO VEGF Trap-Eye best-corrected visual acuity

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	Phase 3
Interventional Study Model:	Parallel Assignment
Number of Arms:	2
Masking:	TripleParticipant, Investigator, Outcomes Assessor
Allocation:	Randomized
Enrollment:	165 [Anticipated]

Arms and Interventions

Arms	Assigned Interventions
Experimental: Arm 1	Drug: VEGF Trap-Eye (BAY86-5321) Intravitreal injection. Weeks 0 to 20 injection of VEGF Trap-Eye every 4 weeks; weeks 24 to 52 every 4 weeks plus additional on week 60 and 68 re-assessment and either (PRN) injection of VEGF Trap-Eye or sham injection; last visit (no treatment) at week 76.
Sham Comparator: Arm 2	Sham treatment Sham treatment. Weeks 0 to 20 sham treatment every 4 weeks; weeks 24 to 48 every 4 weeks re-assessment and sham injection; week 52 VEGF Trap-Eye injection (unless investigator declines for medical reasons), weeks 60 and 68 re-assessment and either (PRN) injection of VEGF Trap-Eye or sham injection; last visit (no treatment) at week 76.

Outcome Measures

Primary Outcome Measures:

1. The proportion of subjects who gain at least 15 letters in BCVA on the EDTRS chart compared with baseline at the Week 24 endpoint
   Week 24

Secondary Outcome Measures:

2. Change from baseline in BCVA score
   Week 24
3. Absolute change from baseline in central retinal thickness, assessed by OCT
   Week 24
4. Proportion of subjects progressing to anterior segment neovascularization, neovascularization of the optic disc (NVD), or neovascularization of the retina elsewhere (NVE) requiring pan-retinal photocoagulation
   Week 24
5.

Change in the NEI-VFQ-25 total score from baseline
Week 24

6. Change in the EQ-5D score from baseline
Week 24

Eligibility

Minimum Age: 18 Years

Maximum Age:

Sex: All

Gender Based:

Accepts Healthy Volunteers: No

Criteria: Inclusion Criteria:

- Center-involved macular edema secondary to central retinal vein occlusion (CRVO) for no longer than 9 months with mean central subfield thickness >= 250 µm on optical coherence tomography (OCT)
- Adults >= 18 years
- Early treatment diabetic retinopathy study (ETDRS) best corrected visual acuity (BCVA) of 20/40 to 20/320 (73 to 24 letters) in the study eye

Exclusion Criteria:

- Any prior treatment with anti-VEGF agents in the study eye (Pegaptanib sodium, anecortave acetate, bevacizumab, ranibizumab, etc.) or previous administration of systemic anti-angiogenic medications
- Prior panretinal laser photocoagulation or macular laser photocoagulation in the study eye
- CRVO disease duration > 9 months from date of diagnosis
- Previous use of intraocular corticosteroids in the study eye or use of periocular corticosteroids in the study eye within the 3 months prior to Day 1

- Iris neovascularization, vitreous hemorrhage, traction retinal detachment, or preretinal fibrosis involving the macula in either the study eye or fellow eye

Contacts/Locations

Study Officials: Bayer Study Director
Study Director
Bayer

Locations:

Australia, New South Wales

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Regensburg, Bayern, Germany, 93053

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Frankfurt, Hessen, Germany, 60596

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Köln, Nordrhein-Westfalen, Germany, 50924

Münster, Nordrhein-Westfalen, Germany, 48145

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Mainz, Rheinland-Pfalz, Germany, 55131

Germany, Saarland

Homburg, Saarland, Germany, 66424

Germany, Sachsen

Chemnitz, Sachsen, Germany, 09116

Dresden, Sachsen, Germany, 01307

Dresden, Sachsen, Germany, 06067

Leipzig, Sachsen, Germany, 04103

Germany, Schleswig-Holstein

Kiel, Schleswig-Holstein, Germany, 24105

Lübeck, Schleswig-Holstein, Germany, 23538

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Berlin, Germany, 13353

Hamburg, Germany, 20251

Marburg, Germany, 35037

Hungary

Budapest, Hungary, 1036

Budapest, Hungary, 1089

Budapest, Hungary, 1106

Debrecen, Hungary, 4032

Veszprem, Hungary, 8200

Zalaegerszeg, Hungary, H-8900

Italy

Ancona, Italy, 60126

Bari, Italy, 70124

Catania, Italy, 95123

Firenze, Italy, 50134

Milano, Italy, 20122

Milano, Italy, 20132

Milano, Italy, 20157

Padova, Italy, 35128

Roma, Italy, 00133

Roma, Italy, 00198

Torino, Italy, 10122

Japan, Aichi

Nagoya, Aichi, Japan, 466-8560

Nagoya, Aichi, Japan, 467-8602

Japan, Chiba

Urayasu, Chiba, Japan, 279-0021

Japan, Osaka

Suita, Osaka, Japan, 565-0871

Japan, Tokyo

Chiyoda-ku, Tokyo, Japan, 101-8309

Japan

Kyoto, Japan, 606-8507

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Incheon, Korea, Republic of, 405-760

Kungki-do, Korea, Republic of, 463-707

Seoul, Korea, Republic of, 110 744

Seoul, Korea, Republic of, 110-744

Seoul, Korea, Republic of, 138-736

Seoul, Korea, Republic of

Latvia

Riga, Latvia, 1009

Riga, Latvia, LV-1002

Singapore

Singapore, Singapore, 119074

Singapore, Singapore, 168751

IPDSharing

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ClinicalTrials.gov archive

History of Changes for Study: NCT01012973

Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO) (GALILEO)

Latest version (submitted October 27, 2014) on ClinicalTrials.gov

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- Select a version's date link to see a rendering of the study for that version.
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- Hover over the "Recruitment Status" to see how the study's recruitment status changed.

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3	○	○	February 9, 2010	Contacts/Locations and Study Status
4	○	○	March 16, 2010	Contacts/Locations, Study Status and Study Identification
5	○	○	April 16, 2010	Contacts/Locations, Study Status and Study Identification

Version	A	B	Submitted Date	Changes
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7	○	○	August 25, 2010	Study Status and Contacts/Locations
8	○	○	August 26, 2010	Recruitment Status, Study Status and Contacts/Locations
9	○	○	September 8, 2010	Study Status
10	○	○	October 4, 2010	Study Status
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13	○	○	April 8, 2011	Study Status and Study Design
14	○	○	June 23, 2011	Arms and Interventions, Study Status, Contacts/Locations and Eligibility
15	○	○	September 19, 2011	Study Status
16	○	○	November 29, 2011	Study Status and Study Identification
17	○	○	January 26, 2012	Study Status and Contacts/Locations
18	○	○	February 20, 2012	Recruitment Status, Study Status
19	○	○	October 23, 2012	Outcome Measures, Arms and Interventions, Study Status, More Information, Reported Adverse Events, Baseline Characteristics and Participant Flow
20	○	○	December 18, 2012	More Information, Arms and Interventions, Study Status and Baseline Characteristics
21	○	○	January 18, 2013	Arms and Interventions, More Information, Study Status and Baseline Characteristics
22	○	○	January 30, 2014	Contacts/Locations, Sponsor/Collaborators, More Information, Study Status, Baseline Characteristics and References
23	○	◉	October 27, 2014	More Information, Study Status and References

Compare

Comparison Format: (•) Merged ( ) Side-by-Side

Scroll up to access the controls

Study NCT01012973
on Date: September 8, 2010 (v9)

Study Identification

Unique Protocol ID:	14130
Brief Title:	Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO) (GALILEO)
Official Title:	A Randomized, Double-masked, Sham-controlled Phase 3 Study of the Efficacy, Safety and Tolerability of Repeated Intravitreal Administration of VEGF Trap-Eye in Subjects With Macular Edema Secondary to Central Retinal Vein Occlusion (CRVO)
Secondary IDs:	EudraCT: 2009-010973-19

Study Status

Record Verification:	September 2010
Overall Status:	Active, not recruiting
Study Start:	October 2009
Primary Completion:	February 2011 [Anticipated]
Study Completion:	March 2012 [Anticipated]
First Submitted:	October 30, 2009
First Submitted that Met QC Criteria:	November 12, 2009
First Posted:	November 13, 2009 [Estimate]
Last Update Submitted that Met QC Criteria:	September 8, 2010

Last Update Posted:	September 9, 2010 [Estimate]

Sponsor/Collaborators

Sponsor:	Bayer
Responsible Party:	
Collaborators:	Regeneron Pharmaceuticals

Oversight

U.S. FDA-regulated Drug:	
U.S. FDA-regulated Device:	
Data Monitoring:	Yes

Study Description

Brief Summary:	To determine the efficacy of vascular endothelial growth factor (VEGF) Trap-Eye injected into the eye on vision function in subjects with macular edema as a consequence of central retinal vein occlusion
Detailed Description:	

Conditions

Conditions:	Retinal Vein Occlusion
Keywords:	Macular Edema Central Retinal Vein Occlusion CRVO VEGF Trap-Eye best-corrected visual acuity

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	Phase 3
Interventional Study Model:	Parallel Assignment
Number of Arms:	2
Masking:	TripleParticipant, Investigator, Outcomes Assessor
Allocation:	Randomized
Enrollment:	165 [Anticipated]

Arms and Interventions

Arms	Assigned Interventions
Experimental: Arm 1	Drug: VEGF Trap-Eye (BAY86-5321) Intravitreal injection. Weeks 0 to 20 injection of VEGF Trap-Eye every 4 weeks; weeks 24 to 52 every 4 weeks plus additional on week 60 and 68 re-assessment and either (PRN) injection of VEGF Trap-Eye or sham injection; last visit (no treatment) at week 76.
Sham Comparator: Arm 2	Sham treatment Sham treatment. Weeks 0 to 20 sham treatment every 4 weeks; weeks 24 to 48 every 4 weeks re-assessment and sham injection; week 52 VEGF Trap-Eye injection (unless investigator declines for medical reasons), weeks 60 and 68 re-assessment and either (PRN) injection of VEGF Trap-Eye or sham injection; last visit (no treatment) at week 76.

Outcome Measures

Primary Outcome Measures:

1. The proportion of subjects who gain at least 15 letters in BCVA on the EDTRS chart compared with baseline at the Week 24 endpoint
   Week 24

Secondary Outcome Measures:

2. Change from baseline in BCVA score
   Week 24
3. Absolute change from baseline in central retinal thickness, assessed by OCT
   Week 24
4. Proportion of subjects progressing to anterior segment neovascularization, neovascularization of the optic disc (NVD), or neovascularization of the retina elsewhere (NVE) requiring pan-retinal photocoagulation
   Week 24
5.

Change in the NEI-VFQ-25 total score from baseline
Week 24

6. Change in the EQ-5D score from baseline
Week 24

Eligibility

Minimum Age: 18 Years

Maximum Age:

Sex: All

Gender Based:

Accepts Healthy Volunteers: No

Criteria: Inclusion Criteria:

- Center-involved macular edema secondary to central retinal vein occlusion (CRVO) for no longer than 9 months with mean central subfield thickness >= 250 µm on optical coherence tomography (OCT)
- Adults >= 18 years
- Early treatment diabetic retinopathy study (ETDRS) best corrected visual acuity (BCVA) of 20/40 to 20/320 (73 to 24 letters) in the study eye

Exclusion Criteria:

- Any prior treatment with anti-VEGF agents in the study eye (Pegaptanib sodium, anecortave acetate, bevacizumab, ranibizumab, etc.) or previous administration of systemic anti-angiogenic medications
- Prior panretinal laser photocoagulation or macular laser photocoagulation in the study eye
- CRVO disease duration > 9 months from date of diagnosis
- Previous use of intraocular corticosteroids in the study eye or use of periocular corticosteroids in the study eye within the 3 months prior to Day 1

- Iris neovascularization, vitreous hemorrhage, traction retinal detachment, or preretinal fibrosis involving the macula in either the study eye or fellow eye

Contacts/Locations

Study Officials: Bayer Study Director
Study Director
Bayer

Locations: **Australia, New South Wales**

Chatswood, New South Wales, Australia, 2067

Parramatta, New South Wales, Australia, 2150

Sydney, New South Wales, Australia, 2000

Westmead, New South Wales, Australia, 2145

Australia, Victoria

East Melbourne, Victoria, Australia, 3002

Australia, Western Australia

Nedlands, Western Australia, Australia, 6009

Austria

Innsbruck, Austria, 6020

Linz, Austria, 4021

Wien, Austria, 1090

France, Cedex 12

Paris, Cedex 12, France, 75557

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France

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Marseille, France, 13008

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Germany, Baden-Württemberg

Freiburg, Baden-Württemberg, Germany, 79106

Heidelberg, Baden-Württemberg, Germany, 69120

Tübingen, Baden-Württemberg, Germany, 72076

Germany, Bayern

München, Bayern, Germany, 81675

Regensburg, Bayern, Germany, 93053

Germany, Hessen

Darmstadt, Hessen, Germany, 64297

Frankfurt, Hessen, Germany, 60596

Germany, Niedersachsen

Göttingen, Niedersachsen, Germany, 37075

Germany, Nordrhein-Westfalen

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Germany, Rheinland-Pfalz

Ludwigshafen, Rheinland-Pfalz, Germany, 67063

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Germany, Saarland

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Germany, Sachsen

Chemnitz, Sachsen, Germany, 09116

Dresden, Sachsen, Germany, 01307

Dresden, Sachsen, Germany, 06067

Leipzig, Sachsen, Germany, 04103

Germany, Schleswig-Holstein

Kiel, Schleswig-Holstein, Germany, 24105

Lübeck, Schleswig-Holstein, Germany, 23538

Germany

Berlin, Germany, 13353

Hamburg, Germany, 20251

Marburg, Germany, 35037

Hungary

Budapest, Hungary, 1036

Budapest, Hungary, 1089

Budapest, Hungary, 1106

Debrecen, Hungary, 4032

Veszprem, Hungary, 8200

Zalaegerszeg, Hungary, H-8900

Italy

Ancona, Italy, 60126

Bari, Italy, 70124

Catania, Italy, 95123

Firenze, Italy, 50134

Milano, Italy, 20122

Milano, Italy, 20132

Milano, Italy, 20157

Padova, Italy, 35128

Roma, Italy, 00133

Roma, Italy, 00198

Torino, Italy, 10122

Japan, Aichi

Nagoya, Aichi, Japan, 466-8560

Nagoya, Aichi, Japan, 467-8602

Japan, Chiba

Urayasu, Chiba, Japan, 279-0021

Japan, Osaka

Suita, Osaka, Japan, 565-0871

Japan, Tokyo

Chiyoda-ku, Tokyo, Japan, 101-8309

Japan

Kyoto, Japan, 606-8507

Korea, Republic of

Incheon, Korea, Republic of, 405-760

Kungki-do, Korea, Republic of, 463-707

Seoul, Korea, Republic of, 110 744

Seoul, Korea, Republic of, 110-744

Seoul, Korea, Republic of, 138-736

Seoul, Korea, Republic of

Latvia

Riga, Latvia, 1009

Riga, Latvia, LV-1002

Singapore

Singapore, Singapore, 119074

Singapore, Singapore, 168751

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History of Changes for Study: NCT01012973

Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO) (GALILEO)

Latest version (submitted October 27, 2014) on ClinicalTrials.gov

- A study version is represented by a row in the table.
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- Hover over the "Recruitment Status" to see how the study's recruitment status changed.

Study Record Versions

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1	◉	○	November 12, 2009	Nothing (earliest Version on record)
2	○	○	January 21, 2010	Contacts/Locations, Study Status, Study Identification and Study Description
3	○	○	February 9, 2010	Contacts/Locations and Study Status
4	○	○	March 16, 2010	Contacts/Locations, Study Status and Study Identification
5	○	○	April 16, 2010	Contacts/Locations, Study Status and Study Identification

Version	A	B	Submitted Date	Changes
6	○	○	July 22, 2010	Contacts/Locations, Study Status, Eligibility and Arms and Interventions
7	○	○	August 25, 2010	Study Status and Contacts/Locations
8	○	○	August 26, 2010	Recruitment Status, Study Status and Contacts/Locations
9	○	○	September 8, 2010	Study Status
10	○	○	October 4, 2010	Study Status
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23	○	◉	October 27, 2014	More Information, Study Status and References

Compare

Comparison Format: (•) Merged ( ) Side-by-Side

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Study NCT01012973
on Date: September 19, 2011 (v15)

Study Identification

Unique Protocol ID:	14130
Brief Title:	Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO) (GALILEO)
Official Title:	A Randomized, Double-masked, Sham-controlled Phase 3 Study of the Efficacy, Safety and Tolerability of Repeated Intravitreal Administration of VEGF Trap-Eye in Subjects With Macular Edema Secondary to Central Retinal Vein Occlusion (CRVO)
Secondary IDs:	EudraCT: 2009-010973-19

Study Status

Record Verification:	September 2011
Overall Status:	Active, not recruiting
Study Start:	October 2009
Primary Completion:	February 2011 [Actual]
Study Completion:	March 2012 [Anticipated]
First Submitted:	October 30, 2009
First Submitted that Met QC Criteria:	November 12, 2009
First Posted:	November 13, 2009 [Estimate]
Last Update Submitted that Met QC Criteria:	September 19, 2011

Last Update Posted:	September 20, 2011 [Estimate]

Sponsor/Collaborators

Sponsor:	Bayer
Responsible Party:	
Collaborators:	Regeneron Pharmaceuticals

Oversight

U.S. FDA-regulated Drug:	
U.S. FDA-regulated Device:	
Data Monitoring:	Yes

Study Description

Brief Summary:	To determine the efficacy of vascular endothelial growth factor (VEGF) Trap-Eye injected into the eye on vision function in subjects with macular edema as a consequence of central retinal vein occlusion
Detailed Description:	

Conditions

Conditions:	Retinal Vein Occlusion
Keywords:	Macular Edema Central Retinal Vein Occlusion CRVO VEGF Trap-Eye best-corrected visual acuity

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	Phase 3
Interventional Study Model:	Parallel Assignment
Number of Arms:	2
Masking:	TripleParticipant, Investigator, Outcomes Assessor
Allocation:	Randomized
Enrollment:	177 [Actual]

Arms and Interventions

Arms	Assigned Interventions
Experimental: Arm 1	Biological: VEGF Trap-Eye (BAY86-5321) Intravitreal injection. Weeks 0 to 20 injection of VEGF Trap-Eye every 4 weeks; weeks 24 to 52 every 4 weeks plus additional on week 60 and 68 re-assessment and either (PRN) injection of VEGF Trap-Eye or sham injection; last visit (no treatment) at week 76.
Sham Comparator: Arm 2	Sham treatment Sham treatment. Weeks 0 to 20 sham treatment every 4 weeks; weeks 24 to 48 every 4 weeks re-assessment and sham injection; week 52 VEGF Trap-Eye injection (unless investigator declines for medical reasons), weeks 60 and 68 re-assessment and either (PRN) injection of VEGF Trap-Eye or sham injection; last visit (no treatment) at week 76.

Outcome Measures

Primary Outcome Measures:

1. The proportion of subjects who gain at least 15 letters in BCVA on the EDTRS chart compared with baseline at the Week 24 endpoint
   Week 24

Secondary Outcome Measures:

2. Change from baseline in BCVA score
   Week 24
3. Absolute change from baseline in central retinal thickness, assessed by OCT
   Week 24
4. Proportion of subjects progressing to anterior segment neovascularization, neovascularization of the optic disc (NVD), or neovascularization of the retina elsewhere (NVE) requiring pan-retinal photocoagulation
   Week 24
5.

Change in the NEI-VFQ-25 total score from baseline
Week 24

6. Change in the EQ-5D score from baseline
Week 24

Eligibility

Minimum Age: 18 Years

Maximum Age:

Sex: All

Gender Based:

Accepts Healthy Volunteers: No

Criteria: Inclusion Criteria:

- Center-involved macular edema secondary to central retinal vein occlusion (CRVO) for no longer than 9 months with mean central subfield thickness ≥ 250 µm on optical coherence tomography (OCT)
- Adults ≥ 18 years
- Early treatment diabetic retinopathy study (ETDRS) best corrected visual acuity (BCVA) of 20/40 to 20/320 (73 to 24 letters) in the study eye

Exclusion Criteria:

- Any prior treatment with anti-VEGF agents in the study eye (Pegaptanib sodium, anecortave acetate, bevacizumab, ranibizumab, etc.) or previous administration of systemic anti-angiogenic medications
- Prior panretinal laser photocoagulation or macular laser photocoagulation in the study eye
- CRVO disease duration > 9 months from date of diagnosis
- Previous use of intraocular corticosteroids in the study eye or use of periocular corticosteroids in the study eye within the 3 months prior to Day 1

- Iris neovascularization, vitreous hemorrhage, traction retinal detachment, or preretinal fibrosis involving the macula in either the study eye or fellow eye

Contacts/Locations

Study Officials: Bayer Study Director
Study Director
Bayer

Locations:

Australia, New South Wales

Chatswood, New South Wales, Australia, 2067

Parramatta, New South Wales, Australia, 2150

Sydney, New South Wales, Australia, 2000

Westmead, New South Wales, Australia, 2145

Australia, Victoria

East Melbourne, Victoria, Australia, 3002

Australia, Western Australia

Nedlands, Western Australia, Australia, 6009

Austria

Innsbruck, Austria, 6020

Linz, Austria, 4021

Wien, Austria, 1090

France, Cedex 12

Paris, Cedex 12, France, 75557

France, Cedex 1

Nantes, Cedex 1, France, 44093

France

Bordeaux, France, 33000

Dijon, France, 21033

Marseille, France, 13008

Paris, France, 75015

Germany, Baden-Württemberg

Freiburg, Baden-Württemberg, Germany, 79106

Heidelberg, Baden-Württemberg, Germany, 69120

Tübingen, Baden-Württemberg, Germany, 72076

Germany, Bayern

München, Bayern, Germany, 81675

Regensburg, Bayern, Germany, 93053

Germany, Hessen

Darmstadt, Hessen, Germany, 64297

Frankfurt, Hessen, Germany, 60596

Germany, Niedersachsen

Göttingen, Niedersachsen, Germany, 37075

Germany, Nordrhein-Westfalen

Aachen, Nordrhein-Westfalen, Germany, 52074

Bonn, Nordrhein-Westfalen, Germany, 53105

Essen, Nordrhein-Westfalen, Germany, 45122

Köln, Nordrhein-Westfalen, Germany, 50924

Münster, Nordrhein-Westfalen, Germany, 48145

Germany, Rheinland-Pfalz

Ludwigshafen, Rheinland-Pfalz, Germany, 67063

Mainz, Rheinland-Pfalz, Germany, 55131

Germany, Saarland

Homburg, Saarland, Germany, 66421

Germany, Sachsen

Chemnitz, Sachsen, Germany, 09116

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Nagoya, Aichi, Japan, 467-8602

Japan, Chiba

Urayasu, Chiba, Japan, 279-0021

Japan, Osaka

Suita, Osaka, Japan, 565-0871

Japan, Tokyo

Chiyoda-ku, Tokyo, Japan, 101-8309

Japan

Kyoto, Japan, 606-8507

Korea, Republic of

Incheon, Korea, Republic of, 405-760

Kungki-do, Korea, Republic of, 463-707

Seoul, Korea, Republic of, 110 744

Seoul, Korea, Republic of, 110-744

Seoul, Korea, Republic of, 138-736

Seoul, Korea, Republic of

Latvia

Riga, Latvia, 1002

Riga, Latvia, 1050

Singapore

Singapore, Singapore, 119074

Singapore, Singapore, 168751

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History of Changes for Study: NCT01012973

Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO) (GALILEO)

Latest version (submitted October 27, 2014) on ClinicalTrials.gov

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Version	A	B	Submitted Date	Changes
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23	○	◉	October 27, 2014	More Information, Study Status and References

Compare

Comparison Format: (•) Merged ( ) Side-by-Side

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Study NCT01012973
on Date: October 4, 2010 (v10)

Study Identification

Unique Protocol ID:	14130
Brief Title:	Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO) (GALILEO)
Official Title:	A Randomized, Double-masked, Sham-controlled Phase 3 Study of the Efficacy, Safety and Tolerability of Repeated Intravitreal Administration of VEGF Trap-Eye in Subjects With Macular Edema Secondary to Central Retinal Vein Occlusion (CRVO)
Secondary IDs:	EudraCT: 2009-010973-19

Study Status

Record Verification:	October 2010
Overall Status:	Active, not recruiting
Study Start:	October 2009
Primary Completion:	February 2011 [Anticipated]
Study Completion:	March 2012 [Anticipated]
First Submitted:	October 30, 2009
First Submitted that Met QC Criteria:	November 12, 2009
First Posted:	November 13, 2009 [Estimate]
Last Update Submitted that Met QC Criteria:	October 4, 2010

Last Update Posted:	October 5, 2010 [Estimate]

Sponsor/Collaborators

Sponsor:	Bayer
Responsible Party:	
Collaborators:	Regeneron Pharmaceuticals

Oversight

U.S. FDA-regulated Drug:	
U.S. FDA-regulated Device:	
Data Monitoring:	Yes

Study Description

Brief Summary:	To determine the efficacy of vascular endothelial growth factor (VEGF) Trap-Eye injected into the eye on vision function in subjects with macular edema as a consequence of central retinal vein occlusion
Detailed Description:	

Conditions

Conditions:	Retinal Vein Occlusion
Keywords:	Macular Edema Central Retinal Vein Occlusion CRVO VEGF Trap-Eye best-corrected visual acuity

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	Phase 3
Interventional Study Model:	Parallel Assignment
Number of Arms:	2
Masking:	TripleParticipant, Investigator, Outcomes Assessor
Allocation:	Randomized
Enrollment:	165 [Anticipated]

Arms and Interventions

Arms	Assigned Interventions
Experimental: Arm 1	Drug: VEGF Trap-Eye (BAY86-5321) Intravitreal injection. Weeks 0 to 20 injection of VEGF Trap-Eye every 4 weeks; weeks 24 to 52 every 4 weeks plus additional on week 60 and 68 re-assessment and either (PRN) injection of VEGF Trap-Eye or sham injection; last visit (no treatment) at week 76.
Sham Comparator: Arm 2	Sham treatment Sham treatment. Weeks 0 to 20 sham treatment every 4 weeks; weeks 24 to 48 every 4 weeks re-assessment and sham injection; week 52 VEGF Trap-Eye injection (unless investigator declines for medical reasons), weeks 60 and 68 re-assessment and either (PRN) injection of VEGF Trap-Eye or sham injection; last visit (no treatment) at week 76.

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Primary Outcome Measures:

1. The proportion of subjects who gain at least 15 letters in BCVA on the EDTRS chart compared with baseline at the Week 24 endpoint
   Week 24

Secondary Outcome Measures:

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Change in the NEI-VFQ-25 total score from baseline
Week 24

6. Change in the EQ-5D score from baseline
Week 24

Eligibility

Minimum Age: 18 Years

Maximum Age:

Sex: All

Gender Based:

Accepts Healthy Volunteers: No

Criteria: Inclusion Criteria:

- Center-involved macular edema secondary to central retinal vein occlusion (CRVO) for no longer than 9 months with mean central subfield thickness >= 250 µm on optical coherence tomography (OCT)
- Adults >= 18 years
- Early treatment diabetic retinopathy study (ETDRS) best corrected visual acuity (BCVA) of 20/40 to 20/320 (73 to 24 letters) in the study eye

Exclusion Criteria:

- Any prior treatment with anti-VEGF agents in the study eye (Pegaptanib sodium, anecortave acetate, bevacizumab, ranibizumab, etc.) or previous administration of systemic anti-angiogenic medications
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- Iris neovascularization, vitreous hemorrhage, traction retinal detachment, or preretinal fibrosis involving the macula in either the study eye or fellow eye

Contacts/Locations

Study Officials: Bayer Study Director
Study Director
Bayer

Locations:

Australia, New South Wales

Chatswood, New South Wales, Australia, 2067

Parramatta, New South Wales, Australia, 2150

Sydney, New South Wales, Australia, 2000

Westmead, New South Wales, Australia, 2145

Australia, Victoria

East Melbourne, Victoria, Australia, 3002

Australia, Western Australia

Nedlands, Western Australia, Australia, 6009

Austria

Innsbruck, Austria, 6020

Linz, Austria, 4021

Wien, Austria, 1090

France, Cedex 12

Paris, Cedex 12, France, 75557

France, Cedex 1

Nantes, Cedex 1, France, 44093

France

Bordeaux, France, 33000

Dijon, France, 21033

Marseille, France, 13008

Paris, France, 75015

Germany, Baden-Württemberg

Freiburg, Baden-Württemberg, Germany, 79106

Heidelberg, Baden-Württemberg, Germany, 69120

Tübingen, Baden-Württemberg, Germany, 72076

Germany, Bayern

München, Bayern, Germany, 81675

Regensburg, Bayern, Germany, 93053

Germany, Hessen

Darmstadt, Hessen, Germany, 64297

Frankfurt, Hessen, Germany, 60596

Germany, Niedersachsen

Göttingen, Niedersachsen, Germany, 37075

Germany, Nordrhein-Westfalen

Aachen, Nordrhein-Westfalen, Germany, 52074

Bonn, Nordrhein-Westfalen, Germany, 53105

Essen, Nordrhein-Westfalen, Germany, 45122

Köln, Nordrhein-Westfalen, Germany, 50924

Münster, Nordrhein-Westfalen, Germany, 48145

Germany, Rheinland-Pfalz

Ludwigshafen, Rheinland-Pfalz, Germany, 67063

Mainz, Rheinland-Pfalz, Germany, 55131

Germany, Saarland

Homburg, Saarland, Germany, 66424

Germany, Sachsen

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Berlin, Germany, 13353

Hamburg, Germany, 20251

Marburg, Germany, 35037

Hungary

Budapest, Hungary, 1036

Budapest, Hungary, 1089

Budapest, Hungary, 1106

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Veszprem, Hungary, 8200

Zalaegerszeg, Hungary, H-8900

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Ancona, Italy, 60126

Bari, Italy, 70124

Catania, Italy, 95123

Firenze, Italy, 50134

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Milano, Italy, 20132

Milano, Italy, 20157

Padova, Italy, 35128

Roma, Italy, 00133

Roma, Italy, 00198

Torino, Italy, 10122

Japan, Aichi

Nagoya, Aichi, Japan, 466-8560

Nagoya, Aichi, Japan, 467-8602

Japan, Chiba

Urayasu, Chiba, Japan, 279-0021

Japan, Osaka

Suita, Osaka, Japan, 565-0871

Japan, Tokyo

Chiyoda-ku, Tokyo, Japan, 101-8309

Japan

Kyoto, Japan, 606-8507

Korea, Republic of

Incheon, Korea, Republic of, 405-760

Kungki-do, Korea, Republic of, 463-707

Seoul, Korea, Republic of, 110 744

Seoul, Korea, Republic of, 110-744

Seoul, Korea, Republic of, 138-736

Seoul, Korea, Republic of

Latvia

Riga, Latvia, 1009

Riga, Latvia, LV-1002

Singapore

Singapore, Singapore, 119074

Singapore, Singapore, 168751

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History of Changes for Study: NCT01012973

Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO) (GALILEO)

Latest version (submitted October 27, 2014) on ClinicalTrials.gov

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Version	A	B	Submitted Date	Changes
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19	○	○	October 23, 2012	Outcome Measures, Arms and Interventions, Study Status, More Information, Reported Adverse Events, Baseline Characteristics and Participant Flow
20	○	○	December 18, 2012	More Information, Arms and Interventions, Study Status and Baseline Characteristics
21	○	○	January 18, 2013	Arms and Interventions, More Information, Study Status and Baseline Characteristics
22	○	○	January 30, 2014	Contacts/Locations, Sponsor/Collaborators, More Information, Study Status, Baseline Characteristics and References
23	○	◉	October 27, 2014	More Information, Study Status and References

Compare

Comparison Format: (•) Merged ( ) Side-by-Side

Scroll up to access the controls

Study NCT01012973
on Date: October 23, 2012 (v19)

Study Identification

Unique Protocol ID:	14130
Brief Title:	Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO) (GALILEO)
Official Title:	A Randomized, Double-masked, Sham-controlled Phase 3 Study of the Efficacy, Safety and Tolerability of Repeated Intravitreal Administration of VEGF Trap-Eye in Subjects With Macular Edema Secondary to Central Retinal Vein Occlusion (CRVO)
Secondary IDs:	2009-010973-19 [EudraCT Number]

Study Status

Record Verification:	October 2012
Overall Status:	Completed
Study Start:	October 2009
Primary Completion:	February 2011 [Actual]
Study Completion:	February 2012 [Actual]
First Submitted:	October 30, 2009
First Submitted that Met QC Criteria:	November 12, 2009
First Posted:	November 13, 2009 [Estimate]
Results First Submitted:	October 23, 2012
	October 23, 2012

Results First Submitted that Met QC Criteria:	
Results First Posted:	November 22, 2012 [Estimate]
Certification/Extension First Submitted:	January 26, 2012
Certification/Extension First Submitted that Met QC Criteria:	January 26, 2012
Certification/Extension First Posted:	January 30, 2012 [Estimate]
Last Update Submitted that Met QC Criteria:	October 23, 2012
Last Update Posted:	November 22, 2012 [Estimate]

Sponsor/Collaborators

Sponsor:	Bayer
Responsible Party:	
Collaborators:	Regeneron Pharmaceuticals

Oversight

U.S. FDA-regulated Drug:	
U.S. FDA-regulated Device:	
Data Monitoring:	Yes

Study Description

Brief Summary:	To determine the efficacy of vascular endothelial growth factor (VEGF) Trap-Eye injected into the eye on vision function in subjects with macular edema as a consequence of central retinal vein occlusion
Detailed Description:	

Conditions

Conditions:	Retinal Vein Occlusion
Keywords:	

Macular Edema
Central Retinal Vein Occlusion
CRVO
VEGF Trap-Eye
best-corrected visual acuity

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	Phase 3
Interventional Study Model:	Parallel Assignment
Number of Arms:	2
Masking:	TripleParticipant, Investigator, Outcomes Assessor
Allocation:	Randomized
Enrollment:	177 [Actual]

Arms and Interventions

Arms	Assigned Interventions
Experimental: Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321) Participants received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered every 4 weeks from Day 1 through Week 20, later as often as every 4 weeks depending on the study retreatment criteria from Week 24 through Week 48. Follow-up phase: Participants on IAI, who continued the study, received 2 mg dose of IAI depending on the study retreatment criteria at Week 60 and 68.	Biological: Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321) Intravitreal injection. Weeks 0 to 20 of Aflibercept Injection every 4 weeks; Weeks 24 to 52 every 4 weeks PRN (pro re nata, on demand); plus additional on Week 60 and 68.
Sham Comparator: Sham treatment Participants received sham treatment administered every 4 weeks from Day 1 through Week 52. Follow-up phase: Participants on sham treatment, who switched to Intravitreal Aflibercept	Sham treatment Sham treatment. Weeks 0 to 52 sham treatment every 4 weeks; plus additional on Week 60 and 68.

Arms	Assigned Interventions
Injection (IAI), received a 2 mg dose of IAI at week 52 and depending on the study retreatment criteria at Week 60 and 68.	

Outcome Measures

[See Results Section.]

Eligibility

Minimum Age: 18 Years

Maximum Age:

Sex: All

Gender Based:

Accepts Healthy Volunteers: No

Criteria: Inclusion Criteria:

- Center-involved macular edema secondary to central retinal vein occlusion (CRVO) for no longer than 9 months with mean central subfield thickness ≥ 250 µm on optical coherence tomography (OCT)
- Adults ≥ 18 years
- Early treatment diabetic retinopathy study (ETDRS) best corrected visual acuity (BCVA) of 20/40 to 20/320 (73 to 24 letters) in the study eye

Exclusion Criteria:

- Any prior treatment with anti-VEGF agents in the study eye (Pegaptanib sodium, anecortave acetate, bevacizumab, ranibizumab, etc.) or previous administration of systemic anti-angiogenic medications
- Prior panretinal laser photocoagulation or macular laser photocoagulation in the study eye
- CRVO disease duration > 9 months from date of diagnosis

- Previous use of intraocular corticosteroids in the study eye or use of periocular corticosteroids in the study eye within the 3 months prior to Day 1
- Iris neovascularization, vitreous hemorrhage, traction retinal detachment, or preretinal fibrosis involving the macula in either the study eye or fellow eye

Contacts/Locations

Study Officials: Bayer Study Director
Study Director
Bayer

Locations: **Australia, New South Wales**

Chatswood, New South Wales, Australia, 2067

Parramatta, New South Wales, Australia, 2150

Sydney, New South Wales, Australia, 2000

Westmead, New South Wales, Australia, 2145

Australia, Victoria

East Melbourne, Victoria, Australia, 3002

Australia, Western Australia

Nedlands, Western Australia, Australia, 6009

Austria

Innsbruck, Austria, 6020

Linz, Austria, 4021

Wien, Austria, 1090

France, Cedex 12

Paris, Cedex 12, France, 75557

France, Cedex 1

Nantes, Cedex 1, France, 44093

France

Bordeaux, France, 33000

Dijon, France, 21033

Marseille, France, 13008

Paris, France, 75015

Germany, Baden-Württemberg

Freiburg, Baden-Württemberg, Germany, 79106

Heidelberg, Baden-Württemberg, Germany, 69120

Tübingen, Baden-Württemberg, Germany, 72076

Germany, Bayern

München, Bayern, Germany, 81675

Regensburg, Bayern, Germany, 93053

Germany, Hessen

Darmstadt, Hessen, Germany, 64297

Frankfurt, Hessen, Germany, 60596

Marburg, Hessen, Germany, 35037

Germany, Niedersachsen

Göttingen, Niedersachsen, Germany, 37075

Germany, Nordrhein-Westfalen

Aachen, Nordrhein-Westfalen, Germany, 52074

Bonn, Nordrhein-Westfalen, Germany, 53105

Essen, Nordrhein-Westfalen, Germany, 45122

Köln, Nordrhein-Westfalen, Germany, 50924

Münster, Nordrhein-Westfalen, Germany, 48145

Germany, Rheinland-Pfalz

Ludwigshafen, Rheinland-Pfalz, Germany, 67063

Mainz, Rheinland-Pfalz, Germany, 55131

Germany, Saarland

Homburg, Saarland, Germany, 66421

Germany, Sachsen

Chemnitz, Sachsen, Germany, 09116

Dresden, Sachsen, Germany, 01307

Dresden, Sachsen, Germany, 06067

Leipzig, Sachsen, Germany, 04103

Germany, Schleswig-Holstein

Kiel, Schleswig-Holstein, Germany, 24105

Lübeck, Schleswig-Holstein, Germany, 23538

Germany

Berlin, Germany, 13353

Hamburg, Germany, 20251

Hungary

Budapest, Hungary, 1089

Budapest, Hungary, 1106

Budapest, Hungary, 1133

Debrecen, Hungary, 4032

Veszprem, Hungary, 8200

Zalaegerszeg, Hungary, H-8900

Italy

Ancona, Italy, 60126

Bari, Italy, 70124

Catania, Italy, 95123

Firenze, Italy, 50134

Milano, Italy, 20122

Milano, Italy, 20132

Milano, Italy, 20157

Padova, Italy, 35128

Roma, Italy, 00133

Roma, Italy, 00198

Torino, Italy, 10122

Japan, Aichi

Nagoya, Aichi, Japan, 466-8560

Nagoya, Aichi, Japan, 467-8602

Japan, Chiba

Urayasu, Chiba, Japan, 279-0021

Japan, Osaka

Suita, Osaka, Japan, 565-0871

Japan, Tokyo

Chiyoda-ku, Tokyo, Japan, 101-8309

Japan

Kyoto, Japan, 606-8507

Korea, Republic of

Incheon, Korea, Republic of, 405-760

Kungki-do, Korea, Republic of, 463-707

Seoul, Korea, Republic of, 110 744

Seoul, Korea, Republic of, 110-744

Seoul, Korea, Republic of, 138-736

Seoul, Korea, Republic of

Latvia

Riga, Latvia, 1002

Riga, Latvia, 1050

Singapore

Singapore, Singapore, 119074

Singapore, Singapore, 168751

IPDSharing

Plan to Share IPD:

References

Citations:

Links:

Available IPD/Information:

Study Results

Participant Flow

Reporting Groups

	Description
Aflibercept Injection First, Then Aflibercept Injection	Participants received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered every 4 weeks from Day 1 through Week 20, later as often as every 4 weeks depending on the study retreatment criteria from Week 24 through Week 48. Follow-up phase: Participants on IAI, who continued the study, received 2 mg dose of IAI depending on the study retreatment criteria at Week 60 and 68.
Sham Treatment First, Then Aflibercept Injection	Participants received sham treatment administered every 4 weeks from Day 1 through Week 52. Follow-up phase: Participants on sham treatment, who switched to Intravitreal Aflibercept Injection (IAI), received a 2 mg dose of IAI at week 52 and depending on the study retreatment criteria at Week 60 and 68.

Overall Study

	Aflibercept Injection First, Then Aflibercept Injection	Sham Treatment First, Then Aflibercept Injection
Started	106	71
Participants Received Treatment	104 [1]	68 [1]
Fulfilled Requirements of FAS Population	103 [2]	68 [2]
Completed Week 24, From FAS	97	57
Completed Week 52, From FAS	91	52
Completed	90	52
Not Completed	16	19
Adverse Event	5	5
Lack of Efficacy	0	5
Lost to Follow-up	1	0
	1	0

	Aflibercept Injection First, Then Aflibercept Injection	Sham Treatment First, Then Aflibercept Injection
(Overseas travel - indefinite period)		
Increase in vis. acuity, never injected	0	1
Protocol Violation	5	2
Withdrawal by Subject	4	6

[1] Safety Population: Participants received treatment

[2] Full Analysis Set (FAS) Population: Participants received treatment with post baseline measurements

Baseline Characteristics

Reporting Groups

	Description
Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Participants received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered every 4 weeks from Day 1 through Week 20, later as often as every 4 weeks depending on the study retreatment criteria from Week 24 through Week 48. Follow-up phase: Participants on IAI, who continued the study, received 2 mg dose of IAI depending on the study retreatment criteria at Week 60 and 68.
Sham Treatment	Participants received sham treatment administered every 4 weeks from Day 1 through Week 52. Follow-up phase: Participants on sham treatment, who switched to Intravitreal Aflibercept Injection (IAI), received a 2 mg dose of IAI at week 52 and depending on the study retreatment criteria at Week 60 and 68.

Baseline Measures

		Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Sham Treatment	Total
Overall Number of Participants		104	68	172
Age Continuous Mean (Standard Deviation) Unit of measure: Years	Number Analyzed	104 Participants	68 Participants	172 Participants
		60.0 (12.3)	63.8 (13.3)	61.5 (12.8)
Sex: Female, Male Measure type: Count of Participants Unit of measure: Participants	Number Analyzed	104 Participants	68 Participants	172 Participants
	Female	45 43.27%	31 45.59%	76 44.19%
	Male	59 56.73%	37 54.41%	96 55.81%
Ethnicity (NIH/OMB) Measure type: Count of Participants Unit of measure: Participants	Number Analyzed	104 Participants	68 Participants	172 Participants
	Hispanic or Latino	4 3.85%	1 1.47%	5 2.91%
	Not Hispanic or Latino	100 96.15%	66 97.06%	166 96.51%
	Unknown or Not Reported	0 0%	1 1.47%	1 0.58%
Baseline Best Corrected Visual Acuity (BCVA) letter scores [1] Mean (Standard Deviation)	Number Analyzed	104 Participants	68 Participants	172 Participants
		53.5 (15.7)	50.9 (15.4)	52.5 (15.6)
	[1]	Only participants with a ETDRS (Early Treatment Diabetic Retinopathy Study) Best Corrected Visual Acuity letter score of 73 to 25 (= Acuity of 20/40 to 20/320) in the study eye at 4 meters were included; a higher score represents better functioning.		
	Number Analyzed	104 Participants	68 Participants	172 Participants

		Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Sham Treatment	Total
Number of participants with baseline retinal perfusion [1] Measure type: Number Unit of measure: Participants				
Perfused		90	54	144
Nonperfused		7	7	14
Indeterminate		7	7	14
	[1] Retinal perfusion defined as less than 10 disc areas of capillary nonperfusion using fluorescein angiography (FA)			
Baseline Retinal Thickness by Optical Coherence Tomography (OCT) Mean (Standard Deviation)	Number Analyzed	104 Participants	68 Participants	172 Participants
		682.78 (233.36)	638.66 (224.69)	665.34 (230.33)
Baseline intraocular pressure Mean (Standard Deviation)	Number Analyzed	104 Participants	68 Participants	172 Participants
		15.2 (2.8)	14.4 (2.7)	14.9 (2.8)
Number of participants with time since Central retinal vein occlusion (CRVO) diagnosis Measure type: Number Unit of measure: Participants	Number Analyzed	104 Participants	68 Participants	172 Participants
>= 2 months		46	33	79
< 2 months		56	35	91
Missing		2	0	2

		Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Sham Treatment	Total
Baseline National Eye Institute 25-item Visual Function Questionnaire (NEI VFQ-25) total score [1]	Number Analyzed	104 Participants	68 Participants	172 Participants
		79.66 (13.06)	78.94 (14.00)	79.38 (13.40)

[1] The NEI VFQ-25 total score ranges from 0-100 with a score of 0 being the worst outcome and 100 being the best outcome. The NEI VFQ questionnaire is organized as a collection of subscales which are all scored from 0-100. To reach the overall composite score, each sub-scale score is averaged in order to give each sub-scale equal weight.

European questionnaire 5 dimensions (EQ-5D) total score [1] Mean (Standard Deviation)	Number Analyzed	104 Participants	68 Participants	172 Participants
		0.87 (0.15)	0.86 (0.16)	0.87 (0.15)

[1] The EQ-5D total score ranges from -0.594 to 1.000 with -0.594 being the worst.

Race Measure type: Number Unit of measure: Participants	Number Analyzed	104 Participants	68 Participants	172 Participants
Asian		26	15	41
White		75	49	124
Unknown or Not Reported		3	4	7

Outcome Measures

1. Primary Outcome Measure:

Measure Title	

	Percentage of Participants Who Gained at Least 15 Letters in BCVA as Measured by ETDRS Letter Score Compared With Baseline at Week 24 With Discontinued Participants Before Week 24 Evaluated as Failures
Measure Description	Defined study baseline range of Early Treatment Diabetic Retinopathy Study (ETDRS) Best Corrected Visual Acuity (BCVA) letter score of 73 to 24 (= Acuity of 20/40 to 20/320) in the study eye; a higher score represents better functioning. Nominator = (Number of participants who maintained vision * 100); Denominator = Number of participants analyzed.
Time Frame	Baseline and Week 24

Analysis Population Description

Full analysis set

Reporting Groups

	Description
Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Participants received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered every 4 weeks from Day 1 through Week 20, later as often as every 4 weeks depending on the study retreatment criteria from Week 24 through Week 48. Follow-up phase: Participants on IAI, who continued the study, received 2 mg dose of IAI depending on the study retreatment criteria at Week 60 and 68.
Sham Treatment	Participants received sham treatment administered every 4 weeks from Day 1 through Week 52. Follow-up phase: Participants on sham treatment, who switched to Intravitreal Aflibercept Injection (IAI), received a 2 mg dose of IAI at week 52 and depending on the study retreatment criteria at Week 60 and 68.

Measured Values

	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Sham Treatment
Overall Number of Participants Analyzed	103	68
Percentage of Participants Who Gained at Least 15 Letters in BCVA as Measured by ETDRS Letter Score Compared With Baseline at Week 24 With Discontinued Participants Before Week 24 Evaluated as Failures Measure Type: Number Unit of Measure: Percentage of participants	60.2	22.1

Statistical Analysis 1 for Percentage of Participants Who Gained at Least 15 Letters in BCVA as Measured by ETDRS Letter Score Compared With Baseline at Week 24 With Discontinued Participants Before Week 24 Evaluated as Failures

Statistical Analysis Overview	Comparison Groups	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321), Sham Treatment
	Comments	Null hypothesis of difference of Eylea minus Sham of 0 was tested. In the database close after Week 24, basis for primary efficacy evaluation, 56 Sham / 96 Eylea subjects were considered as week 24 completers.
	Type of Statistical Test	Superiority or Other (legacy)
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	<.0001
	Comments	[Not specified]
	Method	Cochran-Mantel-Haenszel
	Comments	[Not specified]
	Estimation Parameter	CMH adjusted difference

Method of Estimation	Estimated Value	38.3
	Confidence Interval	(2-sided) 95% 24.4 to 52.1
	Estimation Comments	The estimate is calculated as Eylea minus Sham. A positive value shows Eylea showed a higher BCVA total score compared to Sham.

2. Secondary Outcome Measure:

Measure Title	Change From Baseline in BCVA as Measured by Early Treatment Diabetic Retinopathy Study (ETDRS) Letter Score at Week 24 - Last Observation Carried Forward (LOCF)
Measure Description	Defined study baseline range of ETDRS Best Corrected Visual Acuity letter score of 73 to 24 (= Acuity of 20/40 to 20/320) in the study eye; a higher score represents better functioning. However, because this was assessed at the screening visit, subjects may have had a higher BCVA recorded at the baseline visit and would not have been excluded from the study.
Time Frame	Baseline and Week 24

Analysis Population Description

Full analysis set

Reporting Groups

	Description
Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Participants received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered every 4 weeks from Day 1 through Week 20, later as often as every 4 weeks depending on the study retreatment criteria from Week 24 through Week 48. Follow-up phase: Participants on IAI, who continued the study, received 2 mg dose of IAI

	depending on the study retreatment criteria at Week 60 and 68.
Sham Treatment	Participants received sham treatment administered every 4 weeks from Day 1 through Week 52. Follow-up phase: Participants on sham treatment, who switched to Intravitreal Aflibercept Injection (IAI), received a 2 mg dose of IAI at week 52 and depending on the study retreatment criteria at Week 60 and 68.

Measured Values

	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Sham Treatment
Overall Number of Participants Analyzed	103	68
Change From Baseline in BCVA as Measured by Early Treatment Diabetic Retinopathy Study (ETDRS) Letter Score at Week 24 - Last Observation Carried Forward (LOCF) Measure Type: Mean (Standard Deviation) Unit of Measure: Letters correctly read	71.6 (17.1)	54.3 (20.2)

Statistical Analysis 1 for Change From Baseline in BCVA as Measured by Early Treatment Diabetic Retinopathy Study (ETDRS) Letter Score at Week 24 - Last Observation Carried Forward (LOCF)

Statistical Analysis Overview	Comparison Groups	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321), Sham Treatment
	Comments	Null hypothesis was equality in change from baseline to Week 24 in BCVA total letter score between Eylea and Sham. If primary efficacy was successful, secondary efficacy endpoints were tested in a pre-specified fixed sequence testing procedure. Change in BCVA letter

		score was to be tested first in this sequence.
	Type of Statistical Test	Superiority or Other (legacy)
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	<.0001
	Comments	As primary efficacy evaluation was significant, and this p-value was below significance level of two-sided <.05, the fixed sequence testing did continue with next secondary endpoint.
	Method	ANOVA
	Comments	ANOVA, adjusting for region and baseline BCVA category as fixed factors.

Method of Estimation	Estimation Parameter	Difference in Least square means
	Estimated Value	14.7
	Confidence Interval	(2-sided) 95% 10.8 to 18.7
	Estimation Comments	The difference is calculated as Eylea minus Sham. A positive value indicates Eylea showed a higher change in BCVA total score until week 24 compared to Sham.

3. Secondary Outcome Measure:

Measure Title	Change From Baseline in Central Retinal Thickness (CRT) at Week 24 - LOCF
Measure Description	
Time Frame	Baseline and Week 24

Analysis Population Description

Full-Analysis Set with assessment for this outcome measure; imputation technique: LOCF

Reporting Groups

	Description
Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Participants received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered every 4 weeks from Day 1 through Week 20, later as often as every 4 weeks depending on the study retreatment criteria from Week 24 through Week 48. Follow-up phase: Participants on IAI, who continued the study, received 2 mg dose of IAI depending on the study retreatment criteria at Week 60 and 68.
Sham Treatment	Participants received sham treatment administered every 4 weeks from Day 1 through Week 52. Follow-up phase: Participants on sham treatment, who switched to Intravitreal Aflibercept Injection (IAI), received a 2 mg dose of IAI at week 52 and depending on the study retreatment criteria at Week 60 and 68.

Measured Values

	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Sham Treatment
Overall Number of Participants Analyzed	103	67
Change From Baseline in Central Retinal Thickness (CRT) at Week 24 - LOCF Measure Type: Mean (Standard Deviation) Unit of Measure: microns	-448.58 (256.02)	-169.27 (224.72)

Statistical Analysis 1 for Change From Baseline in Central Retinal Thickness (CRT) at Week 24 - LOCF

	Comparison Groups	

Statistical Analysis Overview		Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321), Sham Treatment
	Comments	Null hypothesis was equality in change from baseline to Week 24 in central retinal thickness between Eylea and Sham. If primary efficacy was successful, secondary efficacy end points were to be tested in a pre-specified fixed sequence testing procedure. Change in central retinal thickness was to be tested at second place in this sequence.
	Type of Statistical Test	Superiority or Other (legacy)
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	<.0001
	Comments	As fixed sequence testing did reject nullhypothesis of change from baseline in BCVA until week 24, and this p-value was below significance level of two-sided <.05, the fixed sequence testing did continue with next secondary endpoint.
	Method	ANCOVA
	Comments	ANCOVA, stratified by region and baseline BCVA category, baseline central retinal thickness added as covariate.

Method of Estimation	Estimation Parameter	Difference in Least square (LS) means
	Estimated Value	-239.42
	Confidence Interval	(2-sided) 95% -286.31 to -192.53

	Estimation Comments	The difference is calculated as Eylea minus Sham. A negative value indicates Eylea showed a higher reduction in change in central retinal thickness until week 24 compared to Sham.

4. Secondary Outcome Measure:

Measure Title	Percentage of Participants Who Developed Neovascularization During the First 24 Weeks
Measure Description	Formation of blood vessels in the anterior segment, optic disc, or elsewhere in the fundus up to Week 24
Time Frame	From baseline until Week 24

Analysis Population Description

Full analysis set

Reporting Groups

	Description
Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Participants received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered every 4 weeks from Day 1 through Week 20, later as often as every 4 weeks depending on the study retreatment criteria from Week 24 through Week 48. Follow-up phase: Participants on IAI, who continued the study, received 2 mg dose of IAI depending on the study retreatment criteria at Week 60 and 68.
Sham Treatment	Participants received sham treatment administered every 4 weeks from Day 1 through Week 52. Follow-up phase: Participants on sham treatment, who switched to Intravitreal Aflibercept Injection (IAI), received a 2 mg dose of IAI at week 52 and depending on the study retreatment criteria at Week 60 and 68.

Measured Values

	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Sham Treatment
Overall Number of Participants Analyzed	103	68
Percentage of Participants Who Developed Neovascularization During the First 24 Weeks Measure Type: Number Unit of Measure: Percentage of participants		
Any neovascularization	2.9	4.4
Anterior segment neovascularization	1.9	1.5
Neovascularization of the optic disc (NVD)	0.0	0.0
Neovascularization elsewhere in the fundus (NVE)	1.0	2.9

Statistical Analysis 1 for Percentage of Participants Who Developed Neovascularization During the First 24 Weeks

Statistical Analysis Overview	Comparison Groups	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321), Sham Treatment
	Comments	Nullhypothesis of no difference in development of neovascularizations between Eylea and Sham group was tested. (Any neovascularization)
	Type of Statistical Test	Superiority or Other (legacy)
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.5947
	Comments	As fixed sequence testing did reject nullhypothesis of change from baseline in CRT until week 24, and this p-value was not below significance level of two-sided <.05,

		the fixed sequence testing did end with this evaluation.
	Method	Cochran-Mantel-Haenszel
	Comments	Cochrane-Mantel-Haenszel test, stratified by region and baseline BCVA category.

Method of Estimation	Estimation Parameter	CMH adjusted Difference
	Estimated Value	-1.5
	Confidence Interval	(2-sided) 95% -7.4 to 4.4
	Estimation Comments	[Not specified]

5. Secondary Outcome Measure:

Measure Title	Change From Baseline in National Eye Institute 25-item Visual Function Questionnaire (NEI VFQ-25) Total Score at Week 24 - LOCF
Measure Description	The NEI VFQ-25 total score ranges from 0-100 with a score of 0 being the worst outcome and 100 being the best outcome. The NEI VFQ questionnaire is organized as a collection of subscales which are all scored from 0-100. To reach the overall composite score, each sub-scale score is averaged in order to give each sub-scale equal weight
Time Frame	Baseline and Week 24

Analysis Population Description

Full-Analysis Set with assessment for this outcome measure; imputation technique: LOCF

Reporting Groups

	Description
Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Participants received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered every 4 weeks from Day 1 through Week 20, later as often

	as every 4 weeks depending on the study retreatment criteria from Week 24 through Week 48. Follow-up phase: Participants on IAI, who continued the study, received 2 mg dose of IAI depending on the study retreatment criteria at Week 60 and 68.
Sham Treatment	Participants received sham treatment administered every 4 weeks from Day 1 through Week 52. Follow-up phase: Participants on sham treatment, who switched to Intravitreal Aflibercept Injection (IAI), received a 2 mg dose of IAI at week 52 and depending on the study retreatment criteria at Week 60 and 68.

Measured Values

	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Sham Treatment
Overall Number of Participants Analyzed	96	65
Change From Baseline in National Eye Institute 25-item Visual Function Questionnaire (NEI VFQ-25) Total Score at Week 24 - LOCF Measure Type: Mean (Standard Deviation) Unit of Measure: Scores on a scale	7.46 (9.55)	3.55 (9.74)

Statistical Analysis 1 for Change From Baseline in National Eye Institute 25-item Visual Function Questionnaire (NEI VFQ-25) Total Score at Week 24 - LOCF

Statistical Analysis Overview	Comparison Groups	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321), Sham Treatment
	Comments	[Not specified]
	Type of Statistical Test	Superiority or Other (legacy)
	Comments	[Not specified]

	Estimation Parameter	Difference in LS means

Method of Estimation	Estimated Value	4.2
	Confidence Interval	(2-sided) 95% 1.7 to 6.8
	Estimation Comments	As the fixed sequence of secondary endpoints stopped with proportion of neovascularizations developed until week 24, 95% confidence interval is only of descriptive nature.

6. Secondary Outcome Measure:

Measure Title	Change From Baseline in European Five-dimensional Health Scale (EQ-5D) Score at Week 24 - LOCF
Measure Description	EQ-5D is a quality of life questionnaire based on a scale from -0.594 (worst) to 1.00 (best).
Time Frame	Baseline and Week 24

Analysis Population Description

Full-Analysis Set with assessment for this outcome measure; imputation technique: LOCF

Reporting Groups

	Description
Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Participants received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered every 4 weeks from Day 1 through Week 20, later as often as every 4 weeks depending on the study retreatment criteria from Week 24 through Week 48. Follow-up phase: Participants on IAI, who continued the study, received 2 mg dose of IAI depending on the study retreatment criteria at Week 60 and 68.
Sham Treatment	Participants received sham treatment administered every 4 weeks from Day 1 through Week 52. Follow-up phase: Participants on sham treatment,

	who switched to Intravitreal Aflibercept Injection (IAI), received a 2 mg dose of IAI at week 52 and depending on the study retreatment criteria at Week 60 and 68.

Measured Values

	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Sham Treatment
Overall Number of Participants Analyzed	95	64
Change From Baseline in European Five-dimensional Health Scale (EQ-5D) Score at Week 24 - LOCF Measure Type: Mean (Standard Deviation) Unit of Measure: Scores on a scale	0.029 (0.139)	-0.002 (0.195)

Statistical Analysis 1 for Change From Baseline in European Five-dimensional Health Scale (EQ-5D) Score at Week 24 - LOCF

Statistical Analysis Overview	Comparison Groups	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321), Sham Treatment
	Comments	[Not specified]
	Type of Statistical Test	Superiority or Other (legacy)
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Difference in LS Means
	Estimated Value	0.044
	Confidence Interval	(2-sided) 95% -0.002 to 0.09
	Estimation Comments	As the fixed sequence of secondary endpoints stopped with proportion of neovascularizations developed until week 24, 95% confidence interval is only of descriptive nature.

Reported Adverse Events

Time Frame	[Not specified]
Adverse Event Reporting Description	[Not specified]

Reporting Groups

	Description
Aflibercept Injection (Until Week 20)	Participants received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered every 4 weeks from Day 1 through Week 20. Participants were observed until Week 24. Participants in the safety population were at risk.
Sham Treatment (Until Week 20)	Participants received sham treatment administered every 4 weeks from Day 1 through Week 20. Participants were observed until Week 24. Participants in the safety population were at risk.
Aflibercept Injection (Until Week 48)	Participants who continued the study drug until Week 24 received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered as often as every 4 weeks depending on the study retreatment criteria from Week 24 through Week 48. Participants were observed from Week 24 until Week 52. Participants in the safety population that completed Week 24 were at risk.
Sham Treatment (Until Week 48)	Participants who continued the study drug until Week 24 received sham treatment administered every 4 weeks from Week 24 to Week 48. Participants were observed from Week 24 until Week 52. Participants in the safety population that completed Week 24 were at risk.
Aflibercept Injection Continued (Until Week 68)	Participants on IAI who continued the study drug until Week 52, received 2 mg dose of IAI depending on the study retreatment criteria at Week 52, 60 and 68. Participants were observed starting from Week 52. Participants in the safety population that completed Week 52 were at risk.

Sham Treatment Then Aflibercept Injection (Until Week 68)	Participants on sham treatment switched to IAI, received a 2 mg dose of IAI at Week 52 and depending on the study retreatment criteria at Week 60 and 68. Participants were observed starting from Week 52. Participants in the safety population that completed Week 52 were at risk.

All-Cause Mortality

	Aflibercept Injection (Until Week 20)	Sham Treatment (Until Week 20)	Aflibercept Injection (Until Week 48)	Sham Treatment (Until Week 48)	Aflibercept Injection Continued (Until Week 68)	Sham Treatment Then Aflibercept Injection (Until Week 68)
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Total	/	/	/	/	/	/

Serious Adverse Events

	Aflibercept Injection (Until Week 20)	Sham Treatment (Until Week 20)	Aflibercept Injection (Until Week 48)	Sham Treatment (Until Week 48)	Aflibercept Injection Continued (Until Week 68)	Sham Treatment Then Aflibercept Injection (Until Week 68)
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Total	8/104 (7.69%)	8/68 (11.76%)	14/97 (14.43%)	7/57 (12.28%)	4/91 (4.4%)	3/52 (5.77%)
Cardiac disorders						
Aortic valve incompetence [A*]	0/104 (0%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	1/52 (1.92%)
Cardiac failure [A*]						

	Afliberce Injection (Until Week 20)	Sham Treatme (Until Week 20)	Afliberce Injection (Until Week 48)	Sham Treatme (Until Week 48)	Afliberce Injection Continue (Until Week 68)	Sham Treatme Then Afliberce Injection (Until Week 68)
	0/104 (0%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	1/52 (1.92%)
Coronary artery stenosis [A*]	0/104 (0%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	1/52 (1.92%)
Diastolic dysfunction [A*]	0/104 (0%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	1/52 (1.92%)
Mitral valve incompetence [A*]	0/104 (0%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	1/52 (1.92%)
Eye disorders						
Blindness unilateral [A*]	0/104 (0%)	0/68 (0%)	1/97 (1.03%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Glaucoma [A*]	0/104 (0%)	1/68 (1.47%)	0/97 (0%)	1/57 (1.75%)	0/91 (0%)	0/52 (0%)
Iris neovascularisation [A*]	1/104 (0.96%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Macular fibrosis [A*]	0/104 (0%)	0/68 (0%)	1/97 (1.03%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Macular ischaemia [A*]	0/104 (0%)	0/68 (0%)	1/97 (1.03%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Macular oedema [A*]	0/104 (0%)	2/68 (2.94%)	4/97 (4.12%)	0/57 (0%)	1/91 (1.1%)	0/52 (0%)
Retinal vein occlusion [A*]	0/104 (0%)	0/68 (0%)	1/97 (1.03%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Visual acuity reduced [A*]	0/104 (0%)	1/68 (1.47%)	1/97 (1.03%)	0/57 (0%)	2/91 (2.2%)	0/52 (0%)
Vitreous detachment [A*]	1/104	0/68	0/97	0/57	0/91	0/52

	Afliberce Injection (Until Week 20)	Sham Treatme (Until Week 20)	Afliberce Injection (Until Week 48)	Sham Treatme (Until Week 48)	Afliberce Injection Continue (Until Week 68)	Sham Treatme Then Afliberce Injection (Until Week 68)
Vitreous haemorrhage [A*]	0/104 (0%)	1/68 (1.47%)	1/97 (1.03%)	1/57 (1.75%)	0/91 (0%)	0/52 (0%)
Gastrointestinal disorders						
Diverticular perforation [A*]	0/104 (0%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	1/91 (1.1%)	0/52 (0%)
Hepatobiliary disorders						
Hepatic function abnormal [A*]	0/104 (0%)	0/68 (0%)	1/97 (1.03%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Infections and infestations						
Furuncle [A*]	1/104 (0.96%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Gastroenteritis [A*]	0/104 (0%)	1/68 (1.47%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Pneumonia [A*]	0/104 (0%)	1/68 (1.47%)	1/97 (1.03%)	1/57 (1.75%)	0/91 (0%)	0/52 (0%)
Vestibular neuronitis [A*]	0/104 (0%)	0/68 (0%)	0/97 (0%)	1/57 (1.75%)	0/91 (0%)	0/52 (0%)
Injury, poisoning and procedural complications						
Fall [A*]	0/104 (0%)	1/68 (1.47%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Femur fracture [A*]	0/104 (0%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	1/52 (1.92%)
Hand fracture [A*]	1/104 (0.96%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Humerus fracture [A*]	0/104 (0%)	1/68 (1.47%)	1/97 (1.03%)	0/57 (0%)	0/91 (0%)	0/52 (0%)

	Afliberce Injection (Until Week 20)	Sham Treatme (Until Week 20)	Afliberce Injection (Until Week 48)	Sham Treatme (Until Week 48)	Afliberce Injection Continue (Until Week 68)	Sham Treatme Then Afliberce Injection (Until Week 68)
Radius fracture [A*]	0/104 (0%)	1/68 (1.47%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Spinal compression fracture [A*]	1/104 (0.96%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Musculoskeletal and connective tissue disorders						
Intervertebral disc protrusion [A*]	0/104 (0%)	1/68 (1.47%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Spinal column stenosis [A*]	0/104 (0%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	1/91 (1.1%)	0/52 (0%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)						
Breast cancer [A*]	0/104 (0%)	0/68 (0%)	1/97 (1.03%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Oropharyngeal cancer stage unspecified [A*]	1/104 (0.96%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Nervous system disorders						
Paraesthesia [A*]	0/104 (0%)	0/68 (0%)	1/97 (1.03%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Syncope [A*]	0/104 (0%)	0/68 (0%)	1/97 (1.03%)	2/57 (3.51%)	0/91 (0%)	0/52 (0%)
Transient ischaemic attack [A*]	0/104 (0%)	0/68 (0%)	0/97 (0%)	1/57 (1.75%)	0/91 (0%)	0/52 (0%)
Respiratory, thoracic and mediastinal disorders						
Dyspnoea [A*]	0/104 (0%)	0/68 (0%)	0/97 (0%)	1/57 (1.75%)	0/91 (0%)	0/52 (0%)
Laryngeal granuloma [A*]	0/104 (0%)	1/68 (1.47%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)

	Afliberce Injection (Until Week 20)	Sham Treatme (Until Week 20)	Afliberce Injection (Until Week 48)	Sham Treatme (Until Week 48)	Afliberce Injection Continue (Until Week 68)	Sham Treatme Then Afliberce Injection (Until Week 68)
Pulmonary hypertension [A*]	0/104 (0%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	1/52 (1.92%)
Surgical and medical procedures						
Ischaemic heart disease prophylaxis [A*]	1/104 (0.96%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Vascular disorders						
Circulatory collapse [A*]	1/104 (0.96%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)

∗ Indicates events were collected by non-systematic methods.

A Term from vocabulary, MedDRA (14.1)

Other Adverse Events

Frequency Threshold Above Which Other Adverse Events are Reported: 5%

	Afliberce Injection (Until Week 20)	Sham Treatme (Until Week 20)	Afliberce Injection (Until Week 48)	Sham Treatme (Until Week 48)	Afliberce Injection Continue (Until Week 68)	Sham Treatme Then Afliberce Injection (Until Week 68)
	Affected/A Risk (%)	Affected/A Risk (%)	Affected/A Risk (%)	Affected/A Risk (%)	Affected/A Risk (%)	Affected/A Risk (%)
Total	52/104 (50%)	44/68 (64.71%	66/97 (68.04%	30/57 (52.63%	38/91 (41.76%	19/52 (36.54%
Blood and lymphatic system disorders						
Anaemia [A*]	1/104 (0.96%)	0/68 (0%)	0/97 (0%)	3/57 (5.26%)	0/91 (0%)	0/52 (0%)

	Afliberce Injection (Until Week 20)	Sham Treatme (Until Week 20)	Afliberce Injection (Until Week 48)	Sham Treatme (Until Week 48)	Afliberce Injection Continue (Until Week 68)	Sham Treatme Then Afliberce Injection (Until Week 68)
Eye disorders						
Conjunctival haemorrhage [A*]	10/104 (9.62%)	3/68 (4.41%)	3/97 (3.09%)	0/57 (0%)	9/91 (9.89%)	3/52 (5.77%)
Eye irritation [A*]	3/104 (2.88%)	7/68 (10.29%	4/97 (4.12%)	1/57 (1.75%)	1/91 (1.1%)	2/52 (3.85%)
Eye pain [A*]	12/104 (11.54%	3/68 (4.41%)	6/97 (6.19%)	2/57 (3.51%)	1/91 (1.1%)	0/52 (0%)
Foreign body sensation in eyes [A*]	6/104 (5.77%)	5/68 (7.35%)	2/97 (2.06%)	0/57 (0%)	1/91 (1.1%)	0/52 (0%)
Lacrimation increased [A*]	3/104 (2.88%)	4/68 (5.88%)	3/97 (3.09%)	4/57 (7.02%)	1/91 (1.1%)	2/52 (3.85%)
Macular fibrosis [A*]	1/104 (0.96%)	1/68 (1.47%)	5/97 (5.15%)	4/57 (7.02%)	0/91 (0%)	3/52 (5.77%)
Macular ischaemia [A*]	7/104 (6.73%)	5/68 (7.35%)	3/97 (3.09%)	1/57 (1.75%)	0/91 (0%)	1/52 (1.92%)
Macular oedema [A*]	2/104 (1.92%)	9/68 (13.24%	30/97 (30.93%	7/57 (12.28%	17/91 (18.68%	2/52 (3.85%)
Ocular hyperaemia [A*]	5/104 (4.81%)	4/68 (5.88%)	2/97 (2.06%)	1/57 (1.75%)	4/91 (4.4%)	1/52 (1.92%)
Optic disc vascular disorder [A*]	5/104 (4.81%)	3/68 (4.41%)	3/97 (3.09%)	3/57 (5.26%)	0/91 (0%)	0/52 (0%)
Retinal exudates [A*]	8/104 (7.69%)	5/68 (7.35%)	4/97 (4.12%)	3/57 (5.26%)	0/91 (0%)	0/52 (0%)
Retinal haemorrhage [A*]	4/104 (3.85%)	6/68 (8.82%)	11/97 (11.34%	5/57 (8.77%)	5/91 (5.49%)	2/52 (3.85%)
Retinal vascular disorder [A*]	6/104	7/68	10/97	2/57	0/91	2/52

	Afliberce Injection (Until Week 20)	Sham Treatme (Until Week 20)	Afliberce Injection (Until Week 48)	Sham Treatme (Until Week 48)	Afliberce Injection Continue (Until Week 68)	Sham Treatme Then Afliberce Injection (Until Week 68)
Visual acuity reduced [A*]	2/104 (1.92%)	7/68 (10.29%	10/97 (10.31%	1/57 (1.75%)	7/91 (7.69%)	1/52 (1.92%)
Vitreous detachment [A*]	2/104 (1.92%)	1/68 (1.47%)	7/97 (7.22%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Vitreous floaters [A*]	6/104 (5.77%)	0/68 (0%)	1/97 (1.03%)	1/57 (1.75%)	1/91 (1.1%)	1/52 (1.92%)
Gastrointestinal disorders						
Nausea [A*]	0/104 (0%)	1/68 (1.47%)	0/97 (0%)	3/57 (5.26%)	0/91 (0%)	0/52 (0%)
Infections and infestations						
Influenza [A*]	2/104 (1.92%)	0/68 (0%)	5/97 (5.15%)	1/57 (1.75%)	1/91 (1.1%)	1/52 (1.92%)
Nasopharyngitis [A*]	8/104 (7.69%)	6/68 (8.82%)	10/97 (10.31%	11/57 (19.3%)	4/91 (4.4%)	2/52 (3.85%)
Investigations						
Intraocular pressure increased [A*]	9/104 (8.65%)	4/68 (5.88%)	14/97 (14.43%	2/57 (3.51%)	2/91 (2.2%)	1/52 (1.92%)
Visual acuity tests abnormal [A*]	0/104 (0%)	1/68 (1.47%)	5/97 (5.15%)	0/57 (0%)	1/91 (1.1%)	0/52 (0%)
Musculoskeletal and connective tissue disorders						
Arthralgia [A*]	1/104 (0.96%)	5/68 (7.35%)	2/97 (2.06%)	1/57 (1.75%)	2/91 (2.2%)	0/52 (0%)
Nervous system disorders						
Headache [A*]	7/104 (6.73%)	4/68 (5.88%)	4/97 (4.12%)	1/57 (1.75%)	1/91 (1.1%)	1/52 (1.92%)

	Afliberce Injection (Until Week 20)	Sham Treatme (Until Week 20)	Afliberce Injection (Until Week 48)	Sham Treatme (Until Week 48)	Afliberce Injection Continue (Until Week 68)	Sham Treatme Then Afliberce Injection (Until Week 68)
Vascular disorders						
Hypertension [A*]	4/104 (3.85%)	3/68 (4.41%)	4/97 (4.12%)	4/57 (7.02%)	3/91 (3.3%)	2/52 (3.85%)

* Indicates events were collected by non-systematic methods.

A Term from vocabulary, MedDRA (14.1)

Limitations and Caveats

[Not specified]

More Information

Certain Agreements:

Principal Investigators are NOT employed by the organization sponsoring the study.

There IS an agreement between the Principal Investigator and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed.

Publishing of result communication only after Bayer´s written approval. Manuscript to Bayer sixty days before public release. If no written Bayer comment within 60 days consider approval given. If multi-site study, principal investigator (PI) not do independently publish results before publication of the multi-site paper, but PI not restricted from 24 months from study to completion onwards.

Results Point of Contact:

Name/Official Title: Therapeutic Area Head
Organization: BAYER
Phone:
Email: clinical-trials-contact@bayerhealthcare.com

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U.S. National Library of Medicine
ClinicalTrials.gov archive

History of Changes for Study: NCT01012973

Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO) (GALILEO)

Latest version (submitted October 27, 2014) on ClinicalTrials.gov

- A study version is represented by a row in the table.
- Select two study versions to compare. One each from columns A and B.
- Choose either the "Merged" or "Side-by-Side" comparison format to specify how the two study versions are to be displayed. The Side-by-Side format only applies to the Protocol section of the study.
- Click "Compare" to do the comparison and show the differences.
- Select a version's date link to see a rendering of the study for that version.
- Edits or deletions will be displayed in ~~red~~.
- Additions will be displayed in *green*.
- The yellow choices in the table indicate the study versions currently compared below. A yellow row indicates the study version being viewed.
- Hover over the "Recruitment Status" to see how the study's recruitment status changed.

Study Record Versions

Version	A	B	Submitted Date	Changes
1	◉	○	November 12, 2009	Nothing (earliest Version on record)
2	○	○	January 21, 2010	Contacts/Locations, Study Status, Study Identification and Study Description
3	○	○	February 9, 2010	Contacts/Locations and Study Status
4	○	○	March 16, 2010	Contacts/Locations, Study Status and Study Identification
5	○	○	April 16, 2010	Contacts/Locations, Study Status and Study Identification

Version	A	B	Submitted Date	Changes
6	○	○	July 22, 2010	Contacts/Locations, Study Status, Eligibility and Arms and Interventions
7	○	○	August 25, 2010	Study Status and Contacts/Locations
8	○	○	August 26, 2010	Recruitment Status, Study Status and Contacts/Locations
9	○	○	September 8, 2010	Study Status
10	○	○	October 4, 2010	Study Status
11	○	○	November 1, 2010	Study Status
12	○	○	January 25, 2011	Study Status and Contacts/Locations
13	○	○	April 8, 2011	Study Status and Study Design
14	○	○	June 23, 2011	Arms and Interventions, Study Status, Contacts/Locations and Eligibility
15	○	○	September 19, 2011	Study Status
16	○	○	November 29, 2011	Study Status and Study Identification
17	○	○	January 26, 2012	Study Status and Contacts/Locations
18	○	○	February 20, 2012	Recruitment Status, Study Status
19	○	○	October 23, 2012	Outcome Measures, Arms and Interventions, Study Status, More Information, Reported Adverse Events, Baseline Characteristics and Participant Flow
20	○	○	December 18, 2012	More Information, Arms and Interventions, Study Status and Baseline Characteristics
21	○	○	January 18, 2013	Arms and Interventions, More Information, Study Status and Baseline Characteristics
22	○	○	January 30, 2014	Contacts/Locations, Sponsor/Collaborators, More Information, Study Status, Baseline Characteristics and References
23	○	◉	October 27, 2014	More Information, Study Status and References

Compare

Comparison Format: (•) Merged ( ) Side-by-Side

Scroll up to access the controls

Study NCT01012973
on Date: October 27, 2014 (v23)

Study Identification

Unique Protocol ID:	14130
Brief Title:	Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO) (GALILEO)
Official Title:	A Randomized, Double-masked, Sham-controlled Phase 3 Study of the Efficacy, Safety and Tolerability of Repeated Intravitreal Administration of VEGF Trap-Eye in Subjects With Macular Edema Secondary to Central Retinal Vein Occlusion (CRVO)
Secondary IDs:	2009-010973-19 [EudraCT Number]

Study Status

Record Verification:	October 2014
Overall Status:	Completed
Study Start:	October 2009
Primary Completion:	February 2011 [Actual]
Study Completion:	February 2012 [Actual]
First Submitted:	October 30, 2009
First Submitted that Met QC Criteria:	November 12, 2009
First Posted:	November 13, 2009 [Estimate]
Results First Submitted:	October 23, 2012
	October 23, 2012

Results First Submitted that Met QC Criteria:	
Results First Posted:	November 22, 2012 [Estimate]
Certification/Extension First Submitted:	January 26, 2012
Certification/Extension First Submitted that Met QC Criteria:	January 26, 2012
Certification/Extension First Posted:	January 30, 2012 [Estimate]
Last Update Submitted that Met QC Criteria:	October 27, 2014
Last Update Posted:	November 3, 2014 [Estimate]

Sponsor/Collaborators

Sponsor:	Bayer
Responsible Party:	Sponsor
Collaborators:	Regeneron Pharmaceuticals

Oversight

U.S. FDA-regulated Drug:	
U.S. FDA-regulated Device:	
Data Monitoring:	Yes

Study Description

Brief Summary:	To determine the efficacy of vascular endothelial growth factor (VEGF) Trap-Eye injected into the eye on vision function in subjects with macular edema as a consequence of central retinal vein occlusion
Detailed Description:	

Conditions

Conditions:	Retinal Vein Occlusion
Keywords:	Macular Edema Central Retinal Vein Occlusion

CRVO
VEGF Trap-Eye
best-corrected visual acuity

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	Phase 3
Interventional Study Model:	Parallel Assignment
Number of Arms:	2
Masking:	TripleParticipant, Investigator, Outcomes Assessor
Allocation:	Randomized
Enrollment:	177 [Actual]

Arms and Interventions

Arms	Assigned Interventions
Experimental: Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321) Participants received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered every 4 weeks from Day 1 through Week 20, later as often as every 4 weeks depending on the study retreatment criteria from Week 24 through Week 48. Follow-up phase: Participants on IAI, who continued the study, received 2 mg dose of IAI depending on the study retreatment criteria at Week 60 and 68.	Biological: Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321) Intravitreal injection. Weeks 0 to 20 of Aflibercept Injection every 4 weeks; Weeks 24 to 52 every 4 weeks PRN (pro re nata, on demand); plus additional on Week 60 and 68. Sham treatment Sham treatment. Weeks 0 to 52 sham treatment every 4 weeks; plus additional on Week 60 and 68.
Sham Comparator: Sham treatment Participants received sham treatment administered every 4 weeks from Day 1 through Week 52. Follow-up phase: Participants on sham treatment, who switched to Intravitreal Aflibercept Injection (IAI), received a 2 mg dose of IAI at week 52 and depending on the	Sham treatment Sham treatment. Weeks 0 to 52 sham treatment every 4 weeks; plus additional on Week 60 and 68.

Arms	Assigned Interventions
study retreatment criteria at Week 60 and 68.	

Outcome Measures

[See Results Section.]

Eligibility

Minimum Age: 18 Years

Maximum Age:

Sex: All

Gender Based:

Accepts Healthy Volunteers: No

Criteria: Inclusion Criteria:

- Center-involved macular edema secondary to central retinal vein occlusion (CRVO) for no longer than 9 months with mean central subfield thickness ≥ 250 µm on optical coherence tomography (OCT)
- Adults ≥ 18 years
- Early treatment diabetic retinopathy study (ETDRS) best corrected visual acuity (BCVA) of 20/40 to 20/320 (73 to 24 letters) in the study eye

Exclusion Criteria:

- Any prior treatment with anti-VEGF agents in the study eye (Pegaptanib sodium, anecortave acetate, bevacizumab, ranibizumab, etc.) or previous administration of systemic anti-angiogenic medications
- Prior panretinal laser photocoagulation or macular laser photocoagulation in the study eye
- CRVO disease duration > 9 months from date of diagnosis

- Previous use of intraocular corticosteroids in the study eye or use of periocular corticosteroids in the study eye within the 3 months prior to Day 1
- Iris neovascularization, vitreous hemorrhage, traction retinal detachment, or preretinal fibrosis involving the macula in either the study eye or fellow eye

Contacts/Locations

Study Officials: Bayer Study Director
Study Director
Bayer

Locations:

Australia, New South Wales

Chatswood, New South Wales, Australia, 2067

Parramatta, New South Wales, Australia, 2150

Sydney, New South Wales, Australia, 2000

Westmead, New South Wales, Australia, 2145

Australia, Victoria

East Melbourne, Victoria, Australia, 3002

Australia, Western Australia

Nedlands, Western Australia, Australia, 6009

Austria

Innsbruck, Austria, 6020

Linz, Austria, 4021

Wien, Austria, 1090

France, Cedex 12

Paris, Cedex 12, France, 75557

France, Cedex 1

Nantes, Cedex 1, France, 44093

France

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Dijon, France, 21033

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Paris, France, 75015

Germany, Baden-Württemberg

Freiburg, Baden-Württemberg, Germany, 79106

Heidelberg, Baden-Württemberg, Germany, 69120

Tübingen, Baden-Württemberg, Germany, 72076

Germany, Bayern

München, Bayern, Germany, 81675

Regensburg, Bayern, Germany, 93053

Germany, Hessen

Darmstadt, Hessen, Germany, 64297

Frankfurt, Hessen, Germany, 60596

Marburg, Hessen, Germany, 35037

Germany, Niedersachsen

Göttingen, Niedersachsen, Germany, 37075

Germany, Nordrhein-Westfalen

Aachen, Nordrhein-Westfalen, Germany, 52074

Bonn, Nordrhein-Westfalen, Germany, 53105

Essen, Nordrhein-Westfalen, Germany, 45122

Köln, Nordrhein-Westfalen, Germany, 50924

Münster, Nordrhein-Westfalen, Germany, 48145

Germany, Rheinland-Pfalz

Ludwigshafen, Rheinland-Pfalz, Germany, 67063

Mainz, Rheinland-Pfalz, Germany, 55131

Germany, Saarland

Homburg, Saarland, Germany, 66421

Germany, Sachsen

Chemnitz, Sachsen, Germany, 09116

Dresden, Sachsen, Germany, 01307

Dresden, Sachsen, Germany, 06067

Leipzig, Sachsen, Germany, 04103

Germany, Schleswig-Holstein

Kiel, Schleswig-Holstein, Germany, 24105

Lübeck, Schleswig-Holstein, Germany, 23538

Germany

Berlin, Germany, 13353

Hamburg, Germany, 20251

Hungary

Budapest, Hungary, 1089

Budapest, Hungary, 1106

Budapest, Hungary, 1133

Debrecen, Hungary, 4032

Veszprem, Hungary, 8200

Zalaegerszeg, Hungary, H-8900

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Bari, Italy, 70124

Catania, Italy, 95123

Firenze, Italy, 50134

Milano, Italy, 20122

Milano, Italy, 20132

Milano, Italy, 20157

Padova, Italy, 35128

Roma, Italy, 00133

Roma, Italy, 00198

Torino, Italy, 10122

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Nagoya, Aichi, Japan, 467-8602

Japan, Chiba

Urayasu, Chiba, Japan, 279-0021

Japan, Osaka

Suita, Osaka, Japan, 565-0871

Japan, Tokyo

Chiyoda-ku, Tokyo, Japan, 101-8309

Japan

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Seongnam-si, Gyeonggido, Korea, Republic of, 463-707

Korea, Republic of

Incheon, Korea, Republic of, 405-760

Seoul, Korea, Republic of, 110 744

Seoul, Korea, Republic of, 137-701

Seoul, Korea, Republic of, 138-736

Seoul, Korea, Republic of

Latvia

Riga, Latvia, 1002

Riga, Latvia, 1050

Singapore

Singapore, Singapore, 119074

Singapore, Singapore, 168751

IPDSharing

Plan to Share IPD:

References

Citations: [Study Results] Holz FG, Roider J, Ogura Y, Korobelnik JF, Simader C, Groetzbach G, Vitti R, Berliner AJ, Hiemeyer F, Beckmann K, Zeitz O, Sandbrink R. VEGF Trap-Eye for macular oedema secondary to central retinal vein occlusion: 6-month results of the phase III GALILEO study. Br J Ophthalmol. 2013 Mar;97(3):278-84. doi: 10.1136/bjophthalmol-2012-301504. Epub 2013 Jan 7.

Erratum in: Br J Ophthalmol. 2015 Dec;99(12):1746. PubMed 23298885

[Study Results] Korobelnik JF, Holz FG, Roider J, Ogura Y, Simader C, Schmidt-Erfurth U, Lorenz K, Honda M, Vitti R, Berliner AJ, Hiemeyer F, Stemper B, Zeitz O, Sandbrink R; GALILEO Study Group. Intravitreal Aflibercept Injection for Macular Edema Resulting from Central Retinal Vein Occlusion: One-Year Results of the Phase 3 GALILEO Study. Ophthalmology. 2014 Jan;121(1):202-208. doi: 10.1016/j.ophtha.2013.08.012. Epub 2013 Sep 29. PubMed 24084497

Links:

Available IPD/Information:

Study Results

Participant Flow

Reporting Groups

	Description
Aflibercept Injection First, Then Aflibercept Injection	Participants received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered every 4 weeks from Day 1 through Week 20, later as often as every 4 weeks depending on the study retreatment criteria from Week 24 through Week 48. Follow-up phase: Participants on IAI, who continued the study, received 2 mg dose of IAI depending on the study retreatment criteria at Week 60 and 68.
Sham Treatment First, Then Aflibercept Injection	Participants received sham treatment administered every 4 weeks from Day 1 through Week 52. Follow-up phase: Participants on sham treatment, who switched to Intravitreal Aflibercept Injection (IAI), received a 2 mg dose of IAI at week 52 and depending on the study retreatment criteria at Week 60 and 68.

Overall Study

	Aflibercept Injection First, Then Aflibercept Injection	Sham Treatment First, Then Aflibercept Injection
Started	106	71
Participants Received Treatment	104 [1]	68 [1]
Fulfilled Requirements of FAS Population	103 [2]	68 [2]
Completed Week 24, From FAS	97	57
Completed Week 52, From FAS	91	52
Completed	90	52
Not Completed	16	19
Adverse Event	5	5
Lack of Efficacy	0	5
Lost to Follow-up	1	0
(Overseas travel - indefinite period)	1	0
Increase in vis. acuity, never injected	0	1
Protocol Violation	5	2
Withdrawal by Subject	4	6

[1] Safety Population: Participants received treatment

[2] Full Analysis Set (FAS) Population: Participants received treatment with post baseline measurements

Baseline Characteristics

Reporting Groups

	Description
Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Participants received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered every 4 weeks from Day 1 through Week 20, later as often as every

	4 weeks depending on the study retreatment criteria from Week 24 through Week 48. Follow-up phase: Participants on IAI, who continued the study, received 2 mg dose of IAI depending on the study retreatment criteria at Week 60 and 68.
Sham Treatment	Participants received sham treatment administered every 4 weeks from Day 1 through Week 52. Follow-up phase: Participants on sham treatment, who switched to Intravitreal Aflibercept Injection (IAI), received a 2 mg dose of IAI at week 52 and depending on the study retreatment criteria at Week 60 and 68.

Baseline Measures

		Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Sham Treatment	Total
Overall Number of Participants		104	68	172
Age, Continuous Mean (Standard Deviation) Unit of measure: Years	Number Analyzed	104 Participants	68 Participants	172 Participants
		60.0 (12.3)	63.8 (13.3)	61.5 (12.8)
Sex: Female, Male Measure type: Count of Participants Unit of measure: Participants	Number Analyzed	104 Participants	68 Participants	172 Participants
	Female	45 43.27%	31 45.59%	76 44.19%
	Male	59 56.73%	37 54.41%	96 55.81%
Ethnicity (NIH/OMB) Measure type: Count of Participants Unit of measure: Participants	Number Analyzed	104 Participants	68 Participants	172 Participants
	Hispanic or Latino	4 3.85%	1 1.47%	5 2.91%
	Not Hispanic or Latino	100 96.15%	66 97.06%	166 96.51%
		0 0%	1 1.47%	1 0.58%

		Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Sham Treatment	Total
	Unknown or Not Reported			
Baseline Best Corrected Visual Acuity (BCVA) letter scores [1] Mean (Standard Deviation)	Number Analyzed	104 Participants	68 Participants	172 Participants
		53.5 (15.7)	50.9 (15.4)	52.5 (15.6)
	[1]	Infiormation retrieved from all baseline participants. Only participants with a ETDRS (Early Treatment Diabetic Retinopathy Study) Best Corrected Visual Acuity letter score of 73 to 25 (= Acuity of 20/40 to 20/320) in the study eye at 4 meters were included; a higher score represents better functioning.		
Number of participants with baseline retinal perfusion [1] Measure type: Number Unit of measure: Participants	Number Analyzed	104 Participants	68 Participants	172 Participants
Perfused		90	54	144
Nonperfused		7	7	14
Indeterminate		7	7	14
	[1]	Retinal perfusion defined as less than 10 disc areas of capillary nonperfusion using fluorescein angiography (FA)		
Baseline Retinal Thickness by Optical Coherence Tomography (OCT) Mean (Standard Deviation)	Number Analyzed	104 Participants	68 Participants	172 Participants
		682.78 (233.36)	638.66 (224.69)	665.34 (230.33)

		Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Sham Treatment	Total
Baseline intraocular pressure Mean (Standard Deviation)	Number Analyzed	104 Participants	68 Participants	172 Participants
		15.2 (2.8)	14.4 (2.7)	14.9 (2.8)
Number of participants with time since Central retinal vein occlusion (CRVO) diagnosis Measure type: Number Unit of measure: Participants	Number Analyzed	104 Participants	68 Participants	172 Participants
>= 2 months		46	33	79
< 2 months		56	35	91
Missing		2	0	2
Baseline National Eye Institute 25-item Visual Function Questionnaire (NEI VFQ-25) total score [1]	Number Analyzed	104 Participants	68 Participants	172 Participants
		79.66 (13.06)	78.94 (14.00)	79.38 (13.40)
	[1]	The NEI VFQ-25 total score ranges from 0-100 with a score of 0 being the worst outcome and 100 being the best outcome. The NEI VFQ questionnaire is organized as a collection of subscales which are all scored from 0-100. To reach the overall composite score, each sub-scale score is averaged in order to give each sub-scale equal weight.		
European questionnaire 5 dimensions (EQ-5D) total score [1] Mean (Standard Deviation)	Number Analyzed	104 Participants	68 Participants	172 Participants
		0.87 (0.15)	0.86 (0.16)	0.87 (0.15)

		Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Sham Treatment	Total
Unit of measure: score on a scale				
	[1] The EQ-5D total score ranges from -0.594 to 1.000 with -0.594 being the worst.			
Race Measure type: Number Unit of measure: Participants	Number Analyzed	104 Participants	68 Participants	172 Participants
Asian		26	15	41
White		75	49	124
Unknown or Not Reported		3	4	7

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Percentage of Participants Who Gained at Least 15 Letters in BCVA as Measured by ETDRS Letter Score Compared With Baseline at Week 24 With Discontinued Participants Before Week 24 Evaluated as Failures
Measure Description	Defined study baseline range of Early Treatment Diabetic Retinopathy Study (ETDRS) Best Corrected Visual Acuity (BCVA) letter score of 73 to 24 (= Acuity of 20/40 to 20/320) in the study eye; a higher score represents better functioning. Nominator = (Number of participants who maintained vision * 100); Denominator = Number of participants analyzed.
Time Frame	Baseline and Week 24

Analysis Population Description

Full analysis set

Reporting Groups

	Description
Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Participants received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered every 4 weeks from Day 1 through Week 20, later as often as every 4 weeks depending on the study retreatment criteria from Week 24 through Week 48. Follow-up phase: Participants on IAI, who continued the study, received 2 mg dose of IAI depending on the study retreatment criteria at Week 60 and 68.
Sham Treatment	Participants received sham treatment administered every 4 weeks from Day 1 through Week 52. Follow-up phase: Participants on sham treatment, who switched to Intravitreal Aflibercept Injection (IAI), received a 2 mg dose of IAI at week 52 and depending on the study retreatment criteria at Week 60 and 68.

Measured Values

	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Sham Treatment
Overall Number of Participants Analyzed	103	68
Percentage of Participants Who Gained at Least 15 Letters in BCVA as Measured by ETDRS Letter Score Compared With Baseline at Week 24 With Discontinued Participants Before Week 24 Evaluated as Failures Measure Type: Number Unit of Measure: Percentage of participants	60.2	22.1

Statistical Analysis 1 for Percentage of Participants Who Gained at Least 15 Letters in BCVA as Measured by ETDRS Letter Score Compared With Baseline at Week 24 With Discontinued Participants Before Week 24 Evaluated as Failures

Statistical Analysis Overview	Comparison Groups	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321), Sham Treatment
	Comments	Null hypothesis of difference of Eylea minus Sham of 0 was tested. In the database close after Week 24, basis for primary efficacy evaluation, 56 Sham / 96 Eylea subjects were considered as week 24 completers.
	Type of Statistical Test	Superiority or Other (legacy)
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	<.0001
	Comments	[Not specified]
	Method	Cochran-Mantel-Haenszel
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	CMH adjusted difference
	Estimated Value	38.3
	Confidence Interval	(2-sided) 95% 24.4 to 52.1
	Estimation Comments	The estimate is calculated as Eylea minus Sham. A positive value shows Eylea showed a higher BCVA total score compared to Sham.

2. Secondary Outcome Measure:

Measure Title	Change From Baseline in BCVA as Measured by Early Treatment Diabetic Retinopathy Study (ETDRS) Letter Score at Week 24 - Last Observation Carried Forward (LOCF)
Measure Description	Defined study baseline range of ETDRS Best Corrected Visual Acuity letter score of 73 to 24 (= Acuity of 20/40 to 20/320) in the study eye; a higher score represents better functioning. However, because this was assessed at the screening visit,

	subjects may have had a higher BCVA recorded at the baseline visit and would not have been excluded from the study.
Time Frame	Baseline and Week 24

Analysis Population Description

Full analysis set

Reporting Groups

	Description
Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Participants received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered every 4 weeks from Day 1 through Week 20, later as often as every 4 weeks depending on the study retreatment criteria from Week 24 through Week 48. Follow-up phase: Participants on IAI, who continued the study, received 2 mg dose of IAI depending on the study retreatment criteria at Week 60 and 68.
Sham Treatment	Participants received sham treatment administered every 4 weeks from Day 1 through Week 52. Follow-up phase: Participants on sham treatment, who switched to Intravitreal Aflibercept Injection (IAI), received a 2 mg dose of IAI at week 52 and depending on the study retreatment criteria at Week 60 and 68.

Measured Values

	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Sham Treatment
Overall Number of Participants Analyzed	103	68
Change From Baseline in BCVA as Measured by Early Treatment Diabetic Retinopathy Study (ETDRS) Letter Score at Week 24 - Last Observation Carried Forward (LOCF) Measure Type: Mean (Standard Deviation) Unit of Measure: Letters correctly read	71.6 (17.1)	54.3 (20.2)

Statistical Analysis 1 for Change From Baseline in BCVA as Measured by Early Treatment Diabetic Retinopathy Study (ETDRS) Letter Score at Week 24 - Last Observation Carried Forward (LOCF)

Statistical Analysis Overview	Comparison Groups	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321), Sham Treatment
	Comments	Null hypothesis was equality in change from baseline to Week 24 in BCVA total letter score between Eylea and Sham. If primary efficacy was successful, secondary efficacy endpoints were tested in a pre-specified fixed sequence testing procedure. Change in BCVA letter score was to be tested first in this sequence.
	Type of Statistical Test	Superiority or Other (legacy)
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	<.0001
	Comments	As primary efficacy evaluation was significant, and this p-value was below significance level of two-sided <.05, the fixed sequence testing did continue with next secondary endpoint.
	Method	ANOVA
	Comments	ANOVA, adjusting for region and baseline BCVA category as fixed factors.

Method of Estimation	Estimation Parameter	Difference in Least square means
	Estimated Value	14.7
	Confidence Interval	(2-sided) 95% 10.8 to 18.7
	Estimation Comments	The difference is calculated as Eylea minus Sham. A positive value

		indicates Eylea showed a higher change in BCVA total score until week 24 compared to Sham.

3. Secondary Outcome Measure:

Measure Title	Change From Baseline in Central Retinal Thickness (CRT) at Week 24 - LOCF
Measure Description	
Time Frame	Baseline and Week 24

Analysis Population Description

Full-Analysis Set with assessment for this outcome measure; imputation technique: LOCF

Reporting Groups

	Description
Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Participants received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered every 4 weeks from Day 1 through Week 20, later as often as every 4 weeks depending on the study retreatment criteria from Week 24 through Week 48. Follow-up phase: Participants on IAI, who continued the study, received 2 mg dose of IAI depending on the study retreatment criteria at Week 60 and 68.
Sham Treatment	Participants received sham treatment administered every 4 weeks from Day 1 through Week 52. Follow-up phase: Participants on sham treatment, who switched to Intravitreal Aflibercept Injection (IAI), received a 2 mg dose of IAI at week 52 and depending on the study retreatment criteria at Week 60 and 68.

Measured Values

	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Sham Treatment
Overall Number of Participants Analyzed	103	67

	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Sham Treatment
Change From Baseline in Central Retinal Thickness (CRT) at Week 24 - LOCF Measure Type: Mean (Standard Deviation) Unit of Measure: microns	-448.58 (256.02)	-169.27 (224.72)

Statistical Analysis 1 for Change From Baseline in Central Retinal Thickness (CRT) at Week 24 - LOCF

Statistical Analysis Overview	Comparison Groups	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321), Sham Treatment
	Comments	Null hypothesis was equality in change from baseline to Week 24 in central retinal thickness between Eylea and Sham. If primary efficacy was successful, secondary efficacy end points were to be tested in a pre-specified fixed sequence testing procedure. Change in central retinal thickness was to be tested at second place in this sequence.
	Type of Statistical Test	Superiority or Other (legacy)
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	<.0001
	Comments	As fixed sequence testing did reject nullhypothesis of change from baseline in BCVA until week 24, and this p-value was below significance level of two-sided <.05, the fixed sequence testing did continue with next secondary endpoint.
	Method	ANCOVA
	Comments	ANCOVA, stratified by region and baseline BCVA category, baseline

		central retinal thickness added as covariate.

Method of Estimation	Estimation Parameter	Difference in Least square (LS) means
	Estimated Value	-239.42
	Confidence Interval	(2-sided) 95% -286.31 to -192.53
	Estimation Comments	The difference is calculated as Eylea minus Sham. A negative value indicates Eylea showed a higher reduction in change in central retinal thickness until week 24 compared to Sham.

4. Secondary Outcome Measure:

Measure Title	Percentage of Participants Who Developed Neovascularization During the First 24 Weeks
Measure Description	Formation of blood vessels in the anterior segment, optic disc, or elsewhere in the fundus up to Week 24
Time Frame	From baseline until Week 24

Analysis Population Description

Full analysis set

Reporting Groups

	Description
Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Participants received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered every 4 weeks from Day 1 through Week 20, later as often as every 4 weeks depending on the study retreatment criteria from Week 24 through Week 48. Follow-up phase: Participants on IAI, who continued the study, received 2 mg dose of IAI depending on the study retreatment criteria at Week 60 and 68.
Sham Treatment	Participants received sham treatment administered every 4 weeks from Day 1 through Week 52. Follow-

	up phase: Participants on sham treatment, who switched to Intravitreal Aflibercept Injection (IAI), received a 2 mg dose of IAI at week 52 and depending on the study retreatment criteria at Week 60 and 68.

Measured Values

	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Sham Treatment
Overall Number of Participants Analyzed	103	68
Percentage of Participants Who Developed Neovascularization During the First 24 Weeks Measure Type: Number Unit of Measure: Percentage of participants		
Any neovascularization	2.9	4.4
Anterior segment neovascularization	1.9	1.5
Neovascularization of the optic disc (NVD)	0.0	0.0
Neovascularization elsewhere in the fundus (NVE)	1.0	2.9

Statistical Analysis 1 for Percentage of Participants Who Developed Neovascularization During the First 24 Weeks

Statistical Analysis Overview	Comparison Groups	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321), Sham Treatment
	Comments	Nullhypothesis of no difference in development of neovascularizations between Eylea and Sham group was tested. (Any neovascularization)
	Type of Statistical Test	Superiority or Other (legacy)
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.5947
	Comments	

		As fixed sequence testing did reject nullhypothesis of change from baseline in CRT until week 24, and this p-value was not below significance level of two-sided <.05, the fixed sequence testing did end with this evaluation.
	Method	Cochran-Mantel-Haenszel
	Comments	Cochrane-Mantel-Haenszel test, stratified by region and baseline BCVA category.

Method of Estimation	Estimation Parameter	CMH adjusted Difference
	Estimated Value	-1.5
	Confidence Interval	(2-sided) 95% -7.4 to 4.4
	Estimation Comments	[Not specified]

5. Secondary Outcome Measure:

Measure Title	Change From Baseline in National Eye Institute 25-item Visual Function Questionnaire (NEI VFQ-25) Total Score at Week 24 - LOCF
Measure Description	The NEI VFQ-25 total score ranges from 0-100 with a score of 0 being the worst outcome and 100 being the best outcome. The NEI VFQ questionnaire is organized as a collection of subscales which are all scored from 0-100. To reach the overall composite score, each sub-scale score is averaged in order to give each sub-scale equal weight
Time Frame	Baseline and Week 24

Analysis Population Description

Full-Analysis Set with assessment for this outcome measure; imputation technique: LOCF

Reporting Groups

	Description
Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Participants received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered every 4 weeks from Day 1 through Week 20, later as often as every 4 weeks depending on the study retreatment criteria from Week 24 through Week 48. Follow-up phase: Participants on IAI, who continued the study, received 2 mg dose of IAI depending on the study retreatment criteria at Week 60 and 68.
Sham Treatment	Participants received sham treatment administered every 4 weeks from Day 1 through Week 52. Follow-up phase: Participants on sham treatment, who switched to Intravitreal Aflibercept Injection (IAI), received a 2 mg dose of IAI at week 52 and depending on the study retreatment criteria at Week 60 and 68.

Measured Values

	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Sham Treatment
Overall Number of Participants Analyzed	96	65
Change From Baseline in National Eye Institute 25-item Visual Function Questionnaire (NEI VFQ-25) Total Score at Week 24 - LOCF Measure Type: Mean (Standard Deviation) Unit of Measure: Scores on a scale	7.46 (9.55)	3.55 (9.74)

Statistical Analysis 1 for Change From Baseline in National Eye Institute 25-item Visual Function Questionnaire (NEI VFQ-25) Total Score at Week 24 - LOCF

Statistical Analysis Overview	Comparison Groups	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321), Sham Treatment
	Comments	[Not specified]
	Type of Statistical Test	Superiority or Other (legacy)
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Difference in LS means
	Estimated Value	4.2
	Confidence Interval	(2-sided) 95% 1.7 to 6.8
	Estimation Comments	As the fixed sequence of secondary endpoints stopped with proportion of neovascularizations developed until week 24, 95% confidence interval is only of descriptive nature.

6. Secondary Outcome Measure:

Measure Title	Change From Baseline in European Five-dimensional Health Scale (EQ-5D) Score at Week 24 - LOCF
Measure Description	EQ-5D is a quality of life questionnaire based on a scale from -0.594 (worst) to 1.00 (best).
Time Frame	Baseline and Week 24

Analysis Population Description

Full-Analysis Set with assessment for this outcome measure; imputation technique: LOCF

Reporting Groups

	Description
Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Participants received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered every 4 weeks from Day 1 through Week 20, later as often as every 4 weeks depending on the study retreatment criteria from Week 24 through Week 48. Follow-up phase: Participants on IAI, who continued the study, received 2 mg dose of IAI depending on the study retreatment criteria at Week 60 and 68.
Sham Treatment	Participants received sham treatment administered every 4 weeks from Day 1 through Week 52. Follow-up phase: Participants on sham treatment, who switched to Intravitreal Aflibercept Injection (IAI), received a 2 mg dose of IAI at week 52 and

	depending on the study retreatment criteria at Week 60 and 68.

Measured Values

	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Sham Treatment
Overall Number of Participants Analyzed	95	64
Change From Baseline in European Five-dimensional Health Scale (EQ-5D) Score at Week 24 - LOCF Measure Type: Mean (Standard Deviation) Unit of Measure: Scores on a scale	0.029 (0.139)	-0.002 (0.195)

Statistical Analysis 1 for Change From Baseline in European Five-dimensional Health Scale (EQ-5D) Score at Week 24 - LOCF

Statistical Analysis Overview	Comparison Groups	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321), Sham Treatment
	Comments	[Not specified]
	Type of Statistical Test	Superiority or Other (legacy)
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Difference in LS Means
	Estimated Value	0.044
	Confidence Interval	(2-sided) 95% -0.002 to 0.09
	Estimation Comments	As the fixed sequence of secondary endpoints stopped with proportion of neovascularizations developed until week 24, 95% confidence interval is only of descriptive nature.

Reported Adverse Events

Time Frame	[Not specified]
	[Not specified]

Adverse Event Reporting Description	

Reporting Groups

	Description
Aflibercept Injection (Until Week 20)	Participants received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered every 4 weeks from Day 1 through Week 20. Participants were observed until Week 24. Participants in the safety population were at risk.
Sham Treatment (Until Week 20)	Participants received sham treatment administered every 4 weeks from Day 1 through Week 20. Participants were observed until Week 24. Participants in the safety population were at risk.
Aflibercept Injection (Until Week 48)	Participants who continued the study drug until Week 24 received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered as often as every 4 weeks depending on the study retreatment criteria from Week 24 through Week 48. Participants were observed from Week 24 until Week 52. Participants in the safety population that completed Week 24 were at risk.
Sham Treatment (Until Week 48)	Participants who continued the study drug until Week 24 received sham treatment administered every 4 weeks from Week 24 to Week 48. Participants were observed from Week 24 until Week 52. Participants in the safety population that completed Week 24 were at risk.
Aflibercept Injection Continued (Until Week 68)	Participants on IAI who continued the study drug until Week 52, received 2 mg dose of IAI depending on the study retreatment criteria at Week 52, 60 and 68. Participants were observed starting from Week 52. Participants in the safety population that completed Week 52 were at risk.
Sham Treatment Then Aflibercept Injection (Until Week 68)	Participants on sham treatment switched to IAI, received a 2 mg dose of IAI at Week 52 and depending on the study retreatment criteria at Week

	60 and 68. Participants were observed starting from Week 52. Participants in the safety population that completed Week 52 were at risk.

All-Cause Mortality

	Afliberce Injection (Until Week 20)	Sham Treatme (Until Week 20)	Afliberce Injection (Until Week 48)	Sham Treatme (Until Week 48)	Afliberce Injection Continue (Until Week 68)	Sham Treatme Then Afliberce Injection (Until Week 68)
	Affected/A Risk (%)	Affected/A Risk (%)	Affected/A Risk (%)	Affected/A Risk (%)	Affected/A Risk (%)	Affected/A Risk (%)
Total	/	/	/	/	/	/

Serious Adverse Events

	Afliberce Injection (Until Week 20)	Sham Treatme (Until Week 20)	Afliberce Injection (Until Week 48)	Sham Treatme (Until Week 48)	Afliberce Injection Continue (Until Week 68)	Sham Treatme Then Afliberce Injection (Until Week 68)
	Affected/A Risk (%)	Affected/A Risk (%)	Affected/A Risk (%)	Affected/A Risk (%)	Affected/A Risk (%)	Affected/A Risk (%)
Total	8/104 (7.69%)	8/68 (11.76%	14/97 (14.43%	7/57 (12.28%	4/91 (4.4%)	3/52 (5.77%)
Cardiac disorders						
Aortic valve incompetence [A*]	0/104 (0%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	1/52 (1.92%)
Cardiac failure [A*]	0/104 (0%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	1/52 (1.92%)
Coronary artery stenosis [A*]	0/104 (0%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	1/52 (1.92%)

	Afliberce Injection (Until Week 20)	Sham Treatme (Until Week 20)	Afliberce Injection (Until Week 48)	Sham Treatme (Until Week 48)	Afliberce Injection Continue (Until Week 68)	Sham Treatme Then Afliberce Injection (Until Week 68)
Diastolic dysfunction [A*]	0/104 (0%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	1/52 (1.92%)
Mitral valve incompetence [A*]	0/104 (0%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	1/52 (1.92%)
Eye disorders						
Blindness unilateral [A*]	0/104 (0%)	0/68 (0%)	1/97 (1.03%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Glaucoma [A*]	0/104 (0%)	1/68 (1.47%)	0/97 (0%)	1/57 (1.75%)	0/91 (0%)	0/52 (0%)
Iris neovascularisation [A*]	1/104 (0.96%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Macular fibrosis [A*]	0/104 (0%)	0/68 (0%)	1/97 (1.03%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Macular ischaemia [A*]	0/104 (0%)	0/68 (0%)	1/97 (1.03%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Macular oedema [A*]	0/104 (0%)	2/68 (2.94%)	4/97 (4.12%)	0/57 (0%)	1/91 (1.1%)	0/52 (0%)
Retinal vein occlusion [A*]	0/104 (0%)	0/68 (0%)	1/97 (1.03%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Visual acuity reduced [A*]	0/104 (0%)	1/68 (1.47%)	1/97 (1.03%)	0/57 (0%)	2/91 (2.2%)	0/52 (0%)
Vitreous detachment [A*]	1/104 (0.96%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Vitreous haemorrhage [A*]	0/104 (0%)	1/68 (1.47%)	1/97 (1.03%)	1/57 (1.75%)	0/91 (0%)	0/52 (0%)
Gastrointestinal disorders						

	Afliberce Injection (Until Week 20)	Sham Treatme (Until Week 20)	Afliberce Injection (Until Week 48)	Sham Treatme (Until Week 48)	Afliberce Injection Continue (Until Week 68)	Sham Treatme Then Afliberce Injection (Until Week 68)
Diverticular perforation [A*]	0/104 (0%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	1/91 (1.1%)	0/52 (0%)
Hepatobiliary disorders						
Hepatic function abnormal [A*]	0/104 (0%)	0/68 (0%)	1/97 (1.03%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Infections and infestations						
Furuncle [A*]	1/104 (0.96%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Gastroenteritis [A*]	0/104 (0%)	1/68 (1.47%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Pneumonia [A*]	0/104 (0%)	1/68 (1.47%)	1/97 (1.03%)	1/57 (1.75%)	0/91 (0%)	0/52 (0%)
Vestibular neuronitis [A*]	0/104 (0%)	0/68 (0%)	0/97 (0%)	1/57 (1.75%)	0/91 (0%)	0/52 (0%)
Injury, poisoning and procedural complications						
Fall [A*]	0/104 (0%)	1/68 (1.47%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Femur fracture [A*]	0/104 (0%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	1/52 (1.92%)
Hand fracture [A*]	1/104 (0.96%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Humerus fracture [A*]	0/104 (0%)	1/68 (1.47%)	1/97 (1.03%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Radius fracture [A*]	0/104 (0%)	1/68 (1.47%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Spinal compression fracture [A*]						

	Afliberce Injection (Until Week 20)	Sham Treatme (Until Week 20)	Afliberce Injection (Until Week 48)	Sham Treatme (Until Week 48)	Afliberce Injection Continue (Until Week 68)	Sham Treatme Then Afliberce Injection (Until Week 68)
	1/104 (0.96%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Musculoskeletal and connective tissue disorders						
Intervertebral disc protrusion [A*]	0/104 (0%)	1/68 (1.47%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Spinal column stenosis [A*]	0/104 (0%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	1/91 (1.1%)	0/52 (0%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)						
Breast cancer [A*]	0/104 (0%)	0/68 (0%)	1/97 (1.03%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Oropharyngeal cancer stage unspecified [A*]	1/104 (0.96%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Nervous system disorders						
Paraesthesia [A*]	0/104 (0%)	0/68 (0%)	1/97 (1.03%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Syncope [A*]	0/104 (0%)	0/68 (0%)	1/97 (1.03%)	2/57 (3.51%)	0/91 (0%)	0/52 (0%)
Transient ischaemic attack [A*]	0/104 (0%)	0/68 (0%)	0/97 (0%)	1/57 (1.75%)	0/91 (0%)	0/52 (0%)
Respiratory, thoracic and mediastinal disorders						
Dyspnoea [A*]	0/104 (0%)	0/68 (0%)	0/97 (0%)	1/57 (1.75%)	0/91 (0%)	0/52 (0%)
Laryngeal granuloma [A*]	0/104 (0%)	1/68 (1.47%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Pulmonary hypertension [A*]	0/104 (0%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	1/52 (1.92%)

	Afliberce Injection (Until Week 20)	Sham Treatme (Until Week 20)	Afliberce Injection (Until Week 48)	Sham Treatme (Until Week 48)	Afliberce Injection Continue (Until Week 68)	Sham Treatme Then Afliberce Injection (Until Week 68)
Surgical and medical procedures						
Ischaemic heart disease prophylaxis A*	1/104 (0.96%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Vascular disorders						
Circulatory collapse A*	1/104 (0.96%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)

* Indicates events were collected by non-systematic methods.

A Term from vocabulary, MedDRA (14.1)

Other Adverse Events

Frequency Threshold Above Which Other Adverse Events are Reported: 5%

	Afliberce Injection (Until Week 20)	Sham Treatme (Until Week 20)	Afliberce Injection (Until Week 48)	Sham Treatme (Until Week 48)	Afliberce Injection Continue (Until Week 68)	Sham Treatme Then Afliberce Injection (Until Week 68)
	Affected/A Risk (%)	Affected/A Risk (%)	Affected/A Risk (%)	Affected/A Risk (%)	Affected/A Risk (%)	Affected/A Risk (%)
Total	52/104 (50%)	44/68 (64.71%)	66/97 (68.04%)	30/57 (52.63%)	38/91 (41.76%)	19/52 (36.54%)
Blood and lymphatic system disorders						
Anaemia A*	1/104 (0.96%)	0/68 (0%)	0/97 (0%)	3/57 (5.26%)	0/91 (0%)	0/52 (0%)
Eye disorders						
Conjunctival haemorrhage A*						

	Afliberce Injection (Until Week 20)	Sham Treatme (Until Week 20)	Afliberce Injection (Until Week 48)	Sham Treatme (Until Week 48)	Afliberce Injection Continue (Until Week 68)	Sham Treatme Then Afliberce Injection (Until Week 68)
	10/104 (9.62%)	3/68 (4.41%)	3/97 (3.09%)	0/57 (0%)	9/91 (9.89%)	3/52 (5.77%)
Eye irritation [A*]	3/104 (2.88%)	7/68 (10.29%	4/97 (4.12%)	1/57 (1.75%)	1/91 (1.1%)	2/52 (3.85%)
Eye pain [A*]	12/104 (11.54%	3/68 (4.41%)	6/97 (6.19%)	2/57 (3.51%)	1/91 (1.1%)	0/52 (0%)
Foreign body sensation in eyes [A*]	6/104 (5.77%)	5/68 (7.35%)	2/97 (2.06%)	0/57 (0%)	1/91 (1.1%)	0/52 (0%)
Lacrimation increased [A*]	3/104 (2.88%)	4/68 (5.88%)	3/97 (3.09%)	4/57 (7.02%)	1/91 (1.1%)	2/52 (3.85%)
Macular fibrosis [A*]	1/104 (0.96%)	1/68 (1.47%)	5/97 (5.15%)	4/57 (7.02%)	0/91 (0%)	3/52 (5.77%)
Macular ischaemia [A*]	7/104 (6.73%)	5/68 (7.35%)	3/97 (3.09%)	1/57 (1.75%)	0/91 (0%)	1/52 (1.92%)
Macular oedema [A*]	2/104 (1.92%)	9/68 (13.24%	30/97 (30.93%	7/57 (12.28%	17/91 (18.68%	2/52 (3.85%)
Ocular hyperaemia [A*]	5/104 (4.81%)	4/68 (5.88%)	2/97 (2.06%)	1/57 (1.75%)	4/91 (4.4%)	1/52 (1.92%)
Optic disc vascular disorder [A*]	5/104 (4.81%)	3/68 (4.41%)	3/97 (3.09%)	3/57 (5.26%)	0/91 (0%)	0/52 (0%)
Retinal exudates [A*]	8/104 (7.69%)	5/68 (7.35%)	4/97 (4.12%)	3/57 (5.26%)	0/91 (0%)	0/52 (0%)
Retinal haemorrhage [A*]	4/104 (3.85%)	6/68 (8.82%)	11/97 (11.34%	5/57 (8.77%)	5/91 (5.49%)	2/52 (3.85%)
Retinal vascular disorder [A*]	6/104 (5.77%)	7/68 (10.29%	10/97 (10.31%	2/57 (3.51%)	0/91 (0%)	2/52 (3.85%)

	Aflibercept Injection (Until Week 20)	Sham Treatment (Until Week 20)	Aflibercept Injection (Until Week 48)	Sham Treatment (Until Week 48)	Aflibercept Injection Continued (Until Week 68)	Sham Treatment Then Aflibercept Injection (Until Week 68)
	2/104 (1.92%)	7/68 (10.29%)	10/97 (10.31%)	1/57 (1.75%)	7/91 (7.69%)	1/52 (1.92%)
Vitreous detachment [A*]	2/104 (1.92%)	1/68 (1.47%)	7/97 (7.22%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Vitreous floaters [A*]	6/104 (5.77%)	0/68 (0%)	1/97 (1.03%)	1/57 (1.75%)	1/91 (1.1%)	1/52 (1.92%)
Gastrointestinal disorders						
Nausea [A*]	0/104 (0%)	1/68 (1.47%)	0/97 (0%)	3/57 (5.26%)	0/91 (0%)	0/52 (0%)
Infections and infestations						
Influenza [A*]	2/104 (1.92%)	0/68 (0%)	5/97 (5.15%)	1/57 (1.75%)	1/91 (1.1%)	1/52 (1.92%)
Nasopharyngitis [A*]	8/104 (7.69%)	6/68 (8.82%)	10/97 (10.31%)	11/57 (19.3%)	4/91 (4.4%)	2/52 (3.85%)
Investigations						
Intraocular pressure increased [A*]	9/104 (8.65%)	4/68 (5.88%)	14/97 (14.43%)	2/57 (3.51%)	2/91 (2.2%)	1/52 (1.92%)
Visual acuity tests abnormal [A*]	0/104 (0%)	1/68 (1.47%)	5/97 (5.15%)	0/57 (0%)	1/91 (1.1%)	0/52 (0%)
Musculoskeletal and connective tissue disorders						
Arthralgia [A*]	1/104 (0.96%)	5/68 (7.35%)	2/97 (2.06%)	1/57 (1.75%)	2/91 (2.2%)	0/52 (0%)
Nervous system disorders						
Headache [A*]	7/104 (6.73%)	4/68 (5.88%)	4/97 (4.12%)	1/57 (1.75%)	1/91 (1.1%)	1/52 (1.92%)
Vascular disorders						

	Afliberce Injection (Until Week 20)	Sham Treatme (Until Week 20)	Afliberce Injection (Until Week 48)	Sham Treatme (Until Week 48)	Afliberce Injection Continue (Until Week 68)	Sham Treatme Then Afliberce Injection (Until Week 68)
Hypertension [A]*	4/104 (3.85%)	3/68 (4.41%)	4/97 (4.12%)	4/57 (7.02%)	3/91 (3.3%)	2/52 (3.85%)

* Indicates events were collected by non-systematic methods.

A Term from vocabulary, MedDRA (14.1)

Limitations and Caveats

[Not specified]

More Information

Certain Agreements:

Principal Investigators are NOT employed by the organization sponsoring the study.

There IS an agreement between the Principal Investigator and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed.

Publishing of result communication only after Bayer´s written approval. Manuscript to Bayer sixty days before public release. If no written Bayer comment within 60 days consider approval given. If multi-site study, principal investigator (PI) not do independently publish results before publication of the multi-site paper, but PI not restricted from 24 months from study to completion onwards.

Results Point of Contact:

Name/Official Title: Therapeutic Area Head
Organization: BAYER
Phone:
Email: clinical-trials-contact@bayerhealthcare.com

Scroll up to access the controls Scroll to the Study top

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ClinicalTrials.gov archive

History of Changes for Study: NCT01012973

Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO) (GALILEO)

Latest version (submitted October 27, 2014) on ClinicalTrials.gov

- A study version is represented by a row in the table.
- Select two study versions to compare. One each from columns A and B.
- Choose either the "Merged" or "Side-by-Side" comparison format to specify how the two study versions are to be displayed. The Side-by-Side format only applies to the Protocol section of the study.
- Click "Compare" to do the comparison and show the differences.
- Select a version's date link to see a rendering of the study for that version.
- Edits or deletions will be displayed in ~~red~~.
- Additions will be displayed in *green*.
- The yellow choices in the table indicate the study versions currently compared below. A yellow row indicates the study version being viewed.
- Hover over the "Recruitment Status" to see how the study's recruitment status changed.

Study Record Versions

Version	A	B	Submitted Date	Changes
1	◉	○	November 12, 2009	Nothing (earliest Version on record)
2	○	○	January 21, 2010	Contacts/Locations, Study Status, Study Identification and Study Description
3	○	○	February 9, 2010	Contacts/Locations and Study Status
4	○	○	March 16, 2010	Contacts/Locations, Study Status and Study Identification
5	○	○	April 16, 2010	Contacts/Locations, Study Status and Study Identification

Version	A	B	Submitted Date	Changes
6	○	○	July 22, 2010	Contacts/Locations, Study Status, Eligibility and Arms and Interventions
7	○	○	August 25, 2010	Study Status and Contacts/Locations
8	○	○	August 26, 2010	Recruitment Status, Study Status and Contacts/Locations
9	○	○	September 8, 2010	Study Status
10	○	○	October 4, 2010	Study Status
11	○	○	November 1, 2010	Study Status
12	○	○	January 25, 2011	Study Status and Contacts/Locations
13	○	○	April 8, 2011	Study Status and Study Design
14	○	○	June 23, 2011	Arms and Interventions, Study Status, Contacts/Locations and Eligibility
15	○	○	September 19, 2011	Study Status
16	○	○	November 29, 2011	Study Status and Study Identification
17	○	○	January 26, 2012	Study Status and Contacts/Locations
18	○	○	February 20, 2012	Recruitment Status, Study Status
19	○	○	October 23, 2012	Outcome Measures, Arms and Interventions, Study Status, More Information, Reported Adverse Events, Baseline Characteristics and Participant Flow
20	○	○	December 18, 2012	More Information, Arms and Interventions, Study Status and Baseline Characteristics
21	○	○	January 18, 2013	Arms and Interventions, More Information, Study Status and Baseline Characteristics
22	○	○	January 30, 2014	Contacts/Locations, Sponsor/Collaborators, More Information, Study Status, Baseline Characteristics and References
23	○	◉	October 27, 2014	More Information, Study Status and References

Compare

Comparison Format: (•) Merged ( ) Side-by-Side

Scroll up to access the controls

Study NCT01012973
on Date: November 1, 2010 (v11)

Study Identification

Unique Protocol ID:	14130
Brief Title:	Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO) (GALILEO)
Official Title:	A Randomized, Double-masked, Sham-controlled Phase 3 Study of the Efficacy, Safety and Tolerability of Repeated Intravitreal Administration of VEGF Trap-Eye in Subjects With Macular Edema Secondary to Central Retinal Vein Occlusion (CRVO)
Secondary IDs:	EudraCT: 2009-010973-19

Study Status

Record Verification:	November 2010
Overall Status:	Active, not recruiting
Study Start:	October 2009
Primary Completion:	February 2011 [Anticipated]
Study Completion:	March 2012 [Anticipated]
First Submitted:	October 30, 2009
First Submitted that Met QC Criteria:	November 12, 2009
First Posted:	November 13, 2009 [Estimate]
Last Update Submitted that Met QC Criteria:	November 1, 2010

Last Update Posted:	November 2, 2010 [Estimate]

Sponsor/Collaborators

Sponsor:	Bayer
Responsible Party:	
Collaborators:	Regeneron Pharmaceuticals

Oversight

U.S. FDA-regulated Drug:	
U.S. FDA-regulated Device:	
Data Monitoring:	Yes

Study Description

Brief Summary:	To determine the efficacy of vascular endothelial growth factor (VEGF) Trap-Eye injected into the eye on vision function in subjects with macular edema as a consequence of central retinal vein occlusion
Detailed Description:	

Conditions

Conditions:	Retinal Vein Occlusion
Keywords:	Macular Edema Central Retinal Vein Occlusion CRVO VEGF Trap-Eye best-corrected visual acuity

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	Phase 3
Interventional Study Model:	Parallel Assignment
Number of Arms:	2
Masking:	TripleParticipant, Investigator, Outcomes Assessor
Allocation:	Randomized
Enrollment:	165 [Anticipated]

Arms and Interventions

Arms	Assigned Interventions
Experimental: Arm 1	Drug: VEGF Trap-Eye (BAY86-5321) Intravitreal injection. Weeks 0 to 20 injection of VEGF Trap-Eye every 4 weeks; weeks 24 to 52 every 4 weeks plus additional on week 60 and 68 re-assessment and either (PRN) injection of VEGF Trap-Eye or sham injection; last visit (no treatment) at week 76.
Sham Comparator: Arm 2	Sham treatment Sham treatment. Weeks 0 to 20 sham treatment every 4 weeks; weeks 24 to 48 every 4 weeks re-assessment and sham injection; week 52 VEGF Trap-Eye injection (unless investigator declines for medical reasons), weeks 60 and 68 re-assessment and either (PRN) injection of VEGF Trap-Eye or sham injection; last visit (no treatment) at week 76.

Outcome Measures

Primary Outcome Measures:

1. The proportion of subjects who gain at least 15 letters in BCVA on the EDTRS chart compared with baseline at the Week 24 endpoint
   Week 24

Secondary Outcome Measures:

2. Change from baseline in BCVA score
   Week 24
3. Absolute change from baseline in central retinal thickness, assessed by OCT
   Week 24
4. Proportion of subjects progressing to anterior segment neovascularization, neovascularization of the optic disc (NVD), or neovascularization of the retina elsewhere (NVE) requiring pan-retinal photocoagulation
   Week 24
5.

Change in the NEI-VFQ-25 total score from baseline
Week 24

6. Change in the EQ-5D score from baseline
Week 24

Eligibility

Minimum Age: 18 Years

Maximum Age:

Sex: All

Gender Based:

Accepts Healthy Volunteers: No

Criteria: Inclusion Criteria:

- Center-involved macular edema secondary to central retinal vein occlusion (CRVO) for no longer than 9 months with mean central subfield thickness >= 250 µm on optical coherence tomography (OCT)
- Adults >= 18 years
- Early treatment diabetic retinopathy study (ETDRS) best corrected visual acuity (BCVA) of 20/40 to 20/320 (73 to 24 letters) in the study eye

Exclusion Criteria:

- Any prior treatment with anti-VEGF agents in the study eye (Pegaptanib sodium, anecortave acetate, bevacizumab, ranibizumab, etc.) or previous administration of systemic anti-angiogenic medications
- Prior panretinal laser photocoagulation or macular laser photocoagulation in the study eye
- CRVO disease duration > 9 months from date of diagnosis
- Previous use of intraocular corticosteroids in the study eye or use of periocular corticosteroids in the study eye within the 3 months prior to Day 1

- Iris neovascularization, vitreous hemorrhage, traction retinal detachment, or preretinal fibrosis involving the macula in either the study eye or fellow eye

Contacts/Locations

Study Officials: Bayer Study Director
Study Director
Bayer

Locations:

Australia, New South Wales

Chatswood, New South Wales, Australia, 2067

Parramatta, New South Wales, Australia, 2150

Sydney, New South Wales, Australia, 2000

Westmead, New South Wales, Australia, 2145

Australia, Victoria

East Melbourne, Victoria, Australia, 3002

Australia, Western Australia

Nedlands, Western Australia, Australia, 6009

Austria

Innsbruck, Austria, 6020

Linz, Austria, 4021

Wien, Austria, 1090

France, Cedex 12

Paris, Cedex 12, France, 75557

France, Cedex 1

Nantes, Cedex 1, France, 44093

France

Bordeaux, France, 33000

Dijon, France, 21033

Marseille, France, 13008

Paris, France, 75015

Germany, Baden-Württemberg

Freiburg, Baden-Württemberg, Germany, 79106

Heidelberg, Baden-Württemberg, Germany, 69120

Tübingen, Baden-Württemberg, Germany, 72076

Germany, Bayern

München, Bayern, Germany, 81675

Regensburg, Bayern, Germany, 93053

Germany, Hessen

Darmstadt, Hessen, Germany, 64297

Frankfurt, Hessen, Germany, 60596

Germany, Niedersachsen

Göttingen, Niedersachsen, Germany, 37075

Germany, Nordrhein-Westfalen

Aachen, Nordrhein-Westfalen, Germany, 52074

Bonn, Nordrhein-Westfalen, Germany, 53105

Essen, Nordrhein-Westfalen, Germany, 45122

Köln, Nordrhein-Westfalen, Germany, 50924

Münster, Nordrhein-Westfalen, Germany, 48145

Germany, Rheinland-Pfalz

Ludwigshafen, Rheinland-Pfalz, Germany, 67063

Mainz, Rheinland-Pfalz, Germany, 55131

Germany, Saarland

Homburg, Saarland, Germany, 66424

Germany, Sachsen

Chemnitz, Sachsen, Germany, 09116

Dresden, Sachsen, Germany, 01307

Dresden, Sachsen, Germany, 06067

Leipzig, Sachsen, Germany, 04103

Germany, Schleswig-Holstein

Kiel, Schleswig-Holstein, Germany, 24105

Lübeck, Schleswig-Holstein, Germany, 23538

Germany

Berlin, Germany, 13353

Hamburg, Germany, 20251

Marburg, Germany, 35037

Hungary

Budapest, Hungary, 1036

Budapest, Hungary, 1089

Budapest, Hungary, 1106

Debrecen, Hungary, 4032

Veszprem, Hungary, 8200

Zalaegerszeg, Hungary, H-8900

Italy

Ancona, Italy, 60126

Bari, Italy, 70124

Catania, Italy, 95123

Firenze, Italy, 50134

Milano, Italy, 20122

Milano, Italy, 20132

Milano, Italy, 20157

Padova, Italy, 35128

Roma, Italy, 00133

Roma, Italy, 00198

Torino, Italy, 10122

Japan, Aichi

Nagoya, Aichi, Japan, 466-8560

Nagoya, Aichi, Japan, 467-8602

Japan, Chiba

Urayasu, Chiba, Japan, 279-0021

Japan, Osaka

Suita, Osaka, Japan, 565-0871

Japan, Tokyo

Chiyoda-ku, Tokyo, Japan, 101-8309

Japan

Kyoto, Japan, 606-8507

Korea, Republic of

Incheon, Korea, Republic of, 405-760

Kungki-do, Korea, Republic of, 463-707

Seoul, Korea, Republic of, 110 744

Seoul, Korea, Republic of, 110-744

Seoul, Korea, Republic of, 138-736

Seoul, Korea, Republic of

Latvia

Riga, Latvia, 1009

Riga, Latvia, LV-1002

Singapore

Singapore, Singapore, 119074

Singapore, Singapore, 168751

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U.S. National Library of Medicine

ClinicalTrials.gov archive

History of Changes for Study: NCT01012973

Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO) (GALILEO)

Latest version (submitted October 27, 2014) on ClinicalTrials.gov

- A study version is represented by a row in the table.
- Select two study versions to compare. One each from columns A and B.
- Choose either the "Merged" or "Side-by-Side" comparison format to specify how the two study versions are to be displayed. The Side-by-Side format only applies to the Protocol section of the study.
- Click "Compare" to do the comparison and show the differences.
- Select a version's date link to see a rendering of the study for that version.
- Edits or deletions will be displayed in ~~red~~.
- Additions will be displayed in *green*.
- The yellow choices in the table indicate the study versions currently compared below. A yellow row indicates the study version being viewed.
- Hover over the "Recruitment Status" to see how the study's recruitment status changed.

Study Record Versions

Version	A	B	Submitted Date	Changes
1	◉	○	November 12, 2009	Nothing (earliest Version on record)
2	○	○	January 21, 2010	Contacts/Locations, Study Status, Study Identification and Study Description
3	○	○	February 9, 2010	Contacts/Locations and Study Status
4	○	○	March 16, 2010	Contacts/Locations, Study Status and Study Identification
5	○	○	April 16, 2010	Contacts/Locations, Study Status and Study Identification

Version	A	B	Submitted Date	Changes
6	○	○	July 22, 2010	Contacts/Locations, Study Status, Eligibility and Arms and Interventions
7	○	○	August 25, 2010	Study Status and Contacts/Locations
8	○	○	August 26, 2010	Recruitment Status, Study Status and Contacts/Locations
9	○	○	September 8, 2010	Study Status
10	○	○	October 4, 2010	Study Status
11	○	○	November 1, 2010	Study Status
12	○	○	January 25, 2011	Study Status and Contacts/Locations
13	○	○	April 8, 2011	Study Status and Study Design
14	○	○	June 23, 2011	Arms and Interventions, Study Status, Contacts/Locations and Eligibility
15	○	○	September 19, 2011	Study Status
16	○	○	November 29, 2011	Study Status and Study Identification
17	○	○	January 26, 2012	Study Status and Contacts/Locations
18	○	○	February 20, 2012	Recruitment Status, Study Status
19	○	○	October 23, 2012	Outcome Measures, Arms and Interventions, Study Status, More Information, Reported Adverse Events, Baseline Characteristics and Participant Flow
20	○	○	December 18, 2012	More Information, Arms and Interventions, Study Status and Baseline Characteristics
21	○	○	January 18, 2013	Arms and Interventions, More Information, Study Status and Baseline Characteristics
22	○	○	January 30, 2014	Contacts/Locations, Sponsor/Collaborators, More Information, Study Status, Baseline Characteristics and References
23	○	◉	October 27, 2014	More Information, Study Status and References

Compare

Comparison Format: (•) Merged ( ) Side-by-Side

Scroll up to access the controls

Study NCT01012973
on Date: November 12, 2009 (v1)

Study Identification

Unique Protocol ID:	14130
Brief Title:	Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)
Official Title:	A Randomized, Double-masked, Sham-controlled Phase 3 Study of the Efficacy, Safety and Tolerability of Repeated Intravitreal Administration of VEGF Trap-Eye in Subjects With Macular Edema Secondary to Central Retinal Vein Occlusion (CRVO)
Secondary IDs:	EudraCT: 2009-010973-19 GALILEO

Study Status

Record Verification:	November 2009
Overall Status:	Recruiting
Study Start:	October 2009
Primary Completion:	February 2011 [Anticipated]
Study Completion:	August 2012 [Anticipated]
First Submitted:	October 30, 2009
First Submitted that Met QC Criteria:	November 12, 2009
First Posted:	November 13, 2009 [Estimate]
	November 12, 2009

Last Update Submitted that Met QC Criteria:	
Last Update Posted:	November 13, 2009 [Estimate]

Sponsor/Collaborators

Sponsor:	Bayer
Responsible Party:	
Collaborators:	Regeneron Pharmaceuticals

Oversight

U.S. FDA-regulated Drug:	
U.S. FDA-regulated Device:	
Data Monitoring:	Yes

Study Description

Brief Summary:	To determine the efficacy of vascular endothelial growth factor (VEGF) Trap-Eye injected into the eye on vision function in subjects with macular edema as a consequence of central retinal vein occlusion.
Detailed Description:	

Conditions

Conditions:	Retinal Vein Occlusion
Keywords:	Macular Edema Central Retinal Vein Occlusion CRVO VEGF Trap-Eye best-corrected visual acuity

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	Phase 3
Interventional Study Model:	Parallel Assignment
Number of Arms:	2
Masking:	TripleParticipant, Investigator, Outcomes Assessor

Allocation: Randomized

Enrollment: 165 [Anticipated]

Arms and Interventions

Arms	Assigned Interventions
Experimental: Arm 1	Drug: VEGF Trap-Eye (BAY86-5321) Intravitreal injection. Weeks 0 to 20 injection of VEGF Trap-Eye every 4 weeks; weeks 24 to 48 every 4 weeks re-assessment and either (PRN) injection of VEGF Trap-Eye or sham injection; weeks 52 to 100 safety follow-up.
Sham Comparator: Arm 2	Sham treatment Sham treatment. Weeks 0 to 20 sham treatment every 4 weeks; weeks 24 to 48 every 4 weeks re-assessment and sham injection; weeks 52 to 100 safety follow-up.

Outcome Measures

Primary Outcome Measures:

1. The proportion of subjects who gain at least 15 letters in BCVA on the EDTRS chart compared with baseline at the Week 24 endpoint
   Week 24

Secondary Outcome Measures:

2. Change from baseline in BCVA score
   Week 24
3. Absolute change from baseline in central retinal thickness, assessed by OCT
   Week 24
4. Proportion of subjects progressing to anterior segment neovascularization, neovascularization of the optic disc (NVD), or neovascularization of the retina elsewhere (NVE) requiring pan-retinal photocoagulation
   Week 24
5. Change in the NEI-VFQ-25 total score from baseline
   Week 24
6.

Change in the EQ-5D score from baseline
Week 24

Eligibility

Minimum Age: 18 Years

Maximum Age:

Sex: All

Gender Based:

Accepts Healthy Volunteers: No

Criteria: Inclusion Criteria:

- Center-involved macular edema secondary to central retinal vein occlusion (CRVO) for no longer than 9 months with mean central subfield thickness >= 250 µm on optical coherence tomography (OCT).
- Adults >= 18 years.
- early treatment diabetic retinopathy study (ETDRS) best corrected visual acuity (BCVA) of 20/40 to 20/320 (73 to 24 letters) in the study eye.

Exclusion Criteria:

- Previous treatment with anti-angiogenic drugs in the study eye (Pegaptanib sodium, anecortave acetate, bevacizumab, ranibizumab, etc.)
- Prior panretinal laser photocoagulation or macular laser photocoagulation in the study eye
- CRVO disease duration > 9 months from date of diagnosis
- Previous use of intraocular corticosteroids in the study eye or use of periocular corticosteroids in the study eye within the 3 months prior to Day 1
- Iris neovascularization, vitreous hemorrhage, traction retinal detachment, or preretinal fibrosis involving the macula in either the study eye or fellow eye

Contacts/Locations

Central Contact: Bayer Clinical Trials Contact
Email: clinical-trials-contact@bayerhealthcare.com

Study Officials: Bayer Study Director
Study Director
Bayer

Locations: **Australia, New South Wales**

[Not yet recruiting]
Chatswood, New South Wales, Australia, 2067

[Not yet recruiting]
Sydney, New South Wales, Australia, 2000

[Not yet recruiting]
Sydney, New South Wales, Australia, 2145

Australia, Victoria

[Not yet recruiting]
East Melbourne, Victoria, Australia, 3002

Australia, Western Australia

[Not yet recruiting]
Nedlands, Western Australia, Australia, 6009

Australia

[Not yet recruiting]
Parramatta, Australia, 2150

Austria, Oberösterreich

[Not yet recruiting]
Linz, Oberösterreich, Austria, 4020

Austria, Tirol

[Not yet recruiting]
Innsbruck, Tirol, Austria, 6020

Austria

[Not yet recruiting]
Linz, Austria, 4021

[Not yet recruiting]
Wien, Austria, 1090

France, Cedex 12

[Not yet recruiting]
Paris, Cedex 12, France, 75557

France

[Not yet recruiting]
Bordeaux, France, 33000

[Not yet recruiting]
Dijon Cedex, France, BP 1542-21

[Not yet recruiting]
Marseille, France, 13008

[Not yet recruiting]
Nantes Cedex, France, 44035

[Not yet recruiting]
Paris, France, 75015

Germany, Baden-Württemberg

[Not yet recruiting]
Freiburg, Baden-Württemberg, Germany, 79106

[Not yet recruiting]
Heidelberg, Baden-Württemberg, Germany, 69120

[Not yet recruiting]
Tübingen, Baden-Württemberg, Germany, 72076

Germany, Bayern

[Not yet recruiting]
München, Bayern, Germany, 81675

[Not yet recruiting]
Regensburg, Bayern, Germany, 93053

Germany, Hessen

[Recruiting]
Darmstadt, Hessen, Germany, 64276

[Not yet recruiting]
Marburg, Hessen, Germany, 35043

Germany, Niedersachsen

[Not yet recruiting]
Göttingen, Niedersachsen, Germany, 37075

Germany, Nordrhein-Westfalen

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Aachen, Nordrhein-Westfalen, Germany, 52074

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Bonn, Nordrhein-Westfalen, Germany, 53105

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Essen, Nordrhein-Westfalen, Germany, 45147

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Köln, Nordrhein-Westfalen, Germany, 50931

Germany, Rheinland-Pfalz

[Not yet recruiting]
Ludwigshafen, Rheinland-Pfalz, Germany, 67063

[Not yet recruiting]
Mainz, Rheinland-Pfalz, Germany, 55131

Germany, Saarland

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Homburg, Saarland, Germany, 66421

Germany, Sachsen

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Chemnitz, Sachsen, Germany, 09116

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Dresden, Sachsen, Germany, 01067

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Dresden, Sachsen, Germany, 01307

[Not yet recruiting]
Leipzig, Sachsen, Germany, 04103

Germany, Schleswig-Holstein

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Kiel, Schleswig-Holstein, Germany, 24105

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Lübeck, Schleswig-Holstein, Germany, 23538

Germany

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Hamburg, Germany, 20251

Hungary

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Budapest, Hungary, 1089

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Budapest, Hungary, 1106

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Debrecen, Hungary, 4032

[Not yet recruiting]
Veszprem, Hungary, 8200

Italy

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Ancona, Italy, 60126

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Bari, Italy, 70124

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Catania, Italy, 95123

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Firenze, Italy, 50139

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Milano, Italy, 20122

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Milano, Italy, 20132

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Padova, Italy, 35128

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[Not yet recruiting]
Torino, Italy, 10128

Japan, Aichi

[Not yet recruiting]
Nagoya, Aichi, Japan, 466-8560

[Not yet recruiting]
Nagoya, Aichi, Japan, 467-8602

Japan, Chiba

[Not yet recruiting]
Urayasu, Chiba, Japan, 279-0021

Japan, Osaka

[Not yet recruiting]
Suita, Osaka, Japan, 565-0871

Japan, Tokyo

[Not yet recruiting]
Chiyoda-ku, Tokyo, Japan, 101-8309

Japan

[Not yet recruiting]
Kyoto, Japan, 606-8507

Korea, Republic of, Korea

[Not yet recruiting]
Seoul, Korea, Korea, Republic of, 110 744

Korea, Republic of

[Not yet recruiting]
Ask Contact, Korea, Republic of

[Not yet recruiting]
Incheon, Korea, Republic of, 405-760

[Not yet recruiting]
Kungki-do, Korea, Republic of, 463-707

[Not yet recruiting]
Seoul, Korea, Republic of, 110-744

[Not yet recruiting]
Seoul, Korea, Republic of, 138-736

Latvia

[Not yet recruiting]
Riga, Latvia, 1009

[Not yet recruiting]
Riga, Latvia, LV-1002

Singapore

[Not yet recruiting]
Ask Contact, Singapore, 168751

[Not yet recruiting]
Singapore, Singapore, 119074

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History of Changes for Study: NCT01012973

Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO) (GALILEO)

Latest version (submitted October 27, 2014) on ClinicalTrials.gov

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Study Record Versions

Version	A	B	Submitted Date	Changes
1	◉	○	November 12, 2009	Nothing (earliest Version on record)
2	○	○	January 21, 2010	Contacts/Locations, Study Status, Study Identification and Study Description
3	○	○	February 9, 2010	Contacts/Locations and Study Status
4	○	○	March 16, 2010	Contacts/Locations, Study Status and Study Identification
5	○	○	April 16, 2010	Contacts/Locations, Study Status and Study Identification

Version	A	B	Submitted Date	Changes
6	○	○	July 22, 2010	Contacts/Locations, Study Status, Eligibility and Arms and Interventions
7	○	○	August 25, 2010	Study Status and Contacts/Locations
8	○	○	August 26, 2010	Recruitment Status, Study Status and Contacts/Locations
9	○	○	September 8, 2010	Study Status
10	○	○	October 4, 2010	Study Status
11	○	○	November 1, 2010	Study Status
12	○	○	January 25, 2011	Study Status and Contacts/Locations
13	○	○	April 8, 2011	Study Status and Study Design
14	○	○	June 23, 2011	Arms and Interventions, Study Status, Contacts/Locations and Eligibility
15	○	○	September 19, 2011	Study Status
16	○	○	November 29, 2011	Study Status and Study Identification
17	○	○	January 26, 2012	Study Status and Contacts/Locations
18	○	○	February 20, 2012	Recruitment Status, Study Status
19	○	○	October 23, 2012	Outcome Measures, Arms and Interventions, Study Status, More Information, Reported Adverse Events, Baseline Characteristics and Participant Flow
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21	○	○	January 18, 2013	Arms and Interventions, More Information, Study Status and Baseline Characteristics
22	○	○	January 30, 2014	Contacts/Locations, Sponsor/Collaborators, More Information, Study Status, Baseline Characteristics and References
23	○	◉	October 27, 2014	More Information, Study Status and References

Compare

Comparison Format: (•) Merged ( ) Side-by-Side

Scroll up to access the controls

Study NCT01012973
on Date: November 29, 2011 (v16)

Study Identification

Unique Protocol ID:	14130
Brief Title:	Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO) (GALILEO)
Official Title:	A Randomized, Double-masked, Sham-controlled Phase 3 Study of the Efficacy, Safety and Tolerability of Repeated Intravitreal Administration of VEGF Trap-Eye in Subjects With Macular Edema Secondary to Central Retinal Vein Occlusion (CRVO)
Secondary IDs:	2009-010973-19 [EudraCT Number]

Study Status

Record Verification:	November 2011
Overall Status:	Active, not recruiting
Study Start:	October 2009
Primary Completion:	February 2011 [Actual]
Study Completion:	March 2012 [Anticipated]
First Submitted:	October 30, 2009
First Submitted that Met QC Criteria:	November 12, 2009
First Posted:	November 13, 2009 [Estimate]
Last Update Submitted that Met QC Criteria:	November 29, 2011

Last Update Posted:	November 30, 2011 [Estimate]

Sponsor/Collaborators

Sponsor:	Bayer
Responsible Party:	
Collaborators:	Regeneron Pharmaceuticals

Oversight

U.S. FDA-regulated Drug:	
U.S. FDA-regulated Device:	
Data Monitoring:	Yes

Study Description

Brief Summary:	To determine the efficacy of vascular endothelial growth factor (VEGF) Trap-Eye injected into the eye on vision function in subjects with macular edema as a consequence of central retinal vein occlusion
Detailed Description:	

Conditions

Conditions:	Retinal Vein Occlusion
Keywords:	Macular Edema Central Retinal Vein Occlusion CRVO VEGF Trap-Eye best-corrected visual acuity

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	Phase 3
Interventional Study Model:	Parallel Assignment
Number of Arms:	2
Masking:	TripleParticipant, Investigator, Outcomes Assessor
Allocation:	Randomized
Enrollment:	177 [Actual]

Arms and Interventions

Arms	Assigned Interventions
Experimental: Arm 1	Biological: VEGF Trap-Eye (BAY86-5321) Intravitreal injection. Weeks 0 to 20 injection of VEGF Trap-Eye every 4 weeks; weeks 24 to 52 every 4 weeks plus additional on week 60 and 68 re-assessment and either (PRN) injection of VEGF Trap-Eye or sham injection; last visit (no treatment) at week 76.
Sham Comparator: Arm 2	Sham treatment Sham treatment. Weeks 0 to 20 sham treatment every 4 weeks; weeks 24 to 48 every 4 weeks re-assessment and sham injection; week 52 VEGF Trap-Eye injection (unless investigator declines for medical reasons), weeks 60 and 68 re-assessment and either (PRN) injection of VEGF Trap-Eye or sham injection; last visit (no treatment) at week 76.

Outcome Measures

Primary Outcome Measures:

1. The proportion of subjects who gain at least 15 letters in BCVA on the EDTRS chart compared with baseline at the Week 24 endpoint
   Week 24

Secondary Outcome Measures:

2. Change from baseline in BCVA score
   Week 24
3. Absolute change from baseline in central retinal thickness, assessed by OCT
   Week 24
4. Proportion of subjects progressing to anterior segment neovascularization, neovascularization of the optic disc (NVD), or neovascularization of the retina elsewhere (NVE) requiring pan-retinal photocoagulation
   Week 24
5.

Change in the NEI-VFQ-25 total score from baseline
Week 24

6. Change in the EQ-5D score from baseline
Week 24

Eligibility

Minimum Age: 18 Years

Maximum Age:

Sex: All

Gender Based:

Accepts Healthy Volunteers: No

Criteria: Inclusion Criteria:

- Center-involved macular edema secondary to central retinal vein occlusion (CRVO) for no longer than 9 months with mean central subfield thickness ≥ 250 µm on optical coherence tomography (OCT)
- Adults ≥ 18 years
- Early treatment diabetic retinopathy study (ETDRS) best corrected visual acuity (BCVA) of 20/40 to 20/320 (73 to 24 letters) in the study eye

Exclusion Criteria:

- Any prior treatment with anti-VEGF agents in the study eye (Pegaptanib sodium, anecortave acetate, bevacizumab, ranibizumab, etc.) or previous administration of systemic anti-angiogenic medications
- Prior panretinal laser photocoagulation or macular laser photocoagulation in the study eye
- CRVO disease duration > 9 months from date of diagnosis
- Previous use of intraocular corticosteroids in the study eye or use of periocular corticosteroids in the study eye within the 3 months prior to Day 1

- Iris neovascularization, vitreous hemorrhage, traction retinal detachment, or preretinal fibrosis involving the macula in either the study eye or fellow eye

Contacts/Locations

Study Officials: Bayer Study Director
Study Director
Bayer

Locations: **Australia, New South Wales**

Chatswood, New South Wales, Australia, 2067

Parramatta, New South Wales, Australia, 2150

Sydney, New South Wales, Australia, 2000

Westmead, New South Wales, Australia, 2145

Australia, Victoria

East Melbourne, Victoria, Australia, 3002

Australia, Western Australia

Nedlands, Western Australia, Australia, 6009

Austria

Innsbruck, Austria, 6020

Linz, Austria, 4021

Wien, Austria, 1090

France, Cedex 12

Paris, Cedex 12, France, 75557

France, Cedex 1

Nantes, Cedex 1, France, 44093

France

Bordeaux, France, 33000

Dijon, France, 21033

Marseille, France, 13008

Paris, France, 75015

Germany, Baden-Württemberg

Freiburg, Baden-Württemberg, Germany, 79106

Heidelberg, Baden-Württemberg, Germany, 69120

Tübingen, Baden-Württemberg, Germany, 72076

Germany, Bayern

München, Bayern, Germany, 81675

Regensburg, Bayern, Germany, 93053

Germany, Hessen

Darmstadt, Hessen, Germany, 64297

Frankfurt, Hessen, Germany, 60596

Germany, Niedersachsen

Göttingen, Niedersachsen, Germany, 37075

Germany, Nordrhein-Westfalen

Aachen, Nordrhein-Westfalen, Germany, 52074

Bonn, Nordrhein-Westfalen, Germany, 53105

Essen, Nordrhein-Westfalen, Germany, 45122

Köln, Nordrhein-Westfalen, Germany, 50924

Münster, Nordrhein-Westfalen, Germany, 48145

Germany, Rheinland-Pfalz

Ludwigshafen, Rheinland-Pfalz, Germany, 67063

Mainz, Rheinland-Pfalz, Germany, 55131

Germany, Saarland

Homburg, Saarland, Germany, 66421

Germany, Sachsen

Chemnitz, Sachsen, Germany, 09116

Dresden, Sachsen, Germany, 01307

Dresden, Sachsen, Germany, 06067

Leipzig, Sachsen, Germany, 04103

Germany, Schleswig-Holstein

Kiel, Schleswig-Holstein, Germany, 24105

Lübeck, Schleswig-Holstein, Germany, 23538

Germany

Berlin, Germany, 13353

Hamburg, Germany, 20251

Marburg, Germany, 35037

Hungary

Budapest, Hungary, 1089

Budapest, Hungary, 1106

Budapest, Hungary, 1133

Debrecen, Hungary, 4032

Veszprem, Hungary, 8200

Zalaegerszeg, Hungary, H-8900

Italy

Ancona, Italy, 60126

Bari, Italy, 70124

Catania, Italy, 95123

Firenze, Italy, 50134

Milano, Italy, 20122

Milano, Italy, 20132

Milano, Italy, 20157

Padova, Italy, 35128

Roma, Italy, 00133

Roma, Italy, 00198

Torino, Italy, 10122

Japan, Aichi

Nagoya, Aichi, Japan, 466-8560

Nagoya, Aichi, Japan, 467-8602

Japan, Chiba

Urayasu, Chiba, Japan, 279-0021

Japan, Osaka

Suita, Osaka, Japan, 565-0871

Japan, Tokyo

Chiyoda-ku, Tokyo, Japan, 101-8309

Japan

Kyoto, Japan, 606-8507

Korea, Republic of

Incheon, Korea, Republic of, 405-760

Kungki-do, Korea, Republic of, 463-707

Seoul, Korea, Republic of, 110 744

Seoul, Korea, Republic of, 110-744

Seoul, Korea, Republic of, 138-736

Seoul, Korea, Republic of

Latvia

Riga, Latvia, 1002

Riga, Latvia, 1050

Singapore

Singapore, Singapore, 119074

Singapore, Singapore, 168751

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ClinicalTrials.gov archive

History of Changes for Study: NCT01012973

Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO) (GALILEO)

Latest version (submitted October 27, 2014) on ClinicalTrials.gov

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- Edits or deletions will be displayed in ~~red~~.
- Additions will be displayed in *green*.
- The yellow choices in the table indicate the study versions currently compared below. A yellow row indicates the study version being viewed.
- Hover over the "Recruitment Status" to see how the study's recruitment status changed.

Study Record Versions

Version	A	B	Submitted Date	Changes
1	◉	○	November 12, 2009	Nothing (earliest Version on record)
2	○	○	January 21, 2010	Contacts/Locations, Study Status, Study Identification and Study Description
3	○	○	February 9, 2010	Contacts/Locations and Study Status
4	○	○	March 16, 2010	Contacts/Locations, Study Status and Study Identification
5	○	○	April 16, 2010	Contacts/Locations, Study Status and Study Identification

Version	A	B	Submitted Date	Changes
6	○	○	July 22, 2010	Contacts/Locations, Study Status, Eligibility and Arms and Interventions
7	○	○	August 25, 2010	Study Status and Contacts/Locations
8	○	○	August 26, 2010	Recruitment Status, Study Status and Contacts/Locations
9	○	○	September 8, 2010	Study Status
10	○	○	October 4, 2010	Study Status
11	○	○	November 1, 2010	Study Status
12	○	○	January 25, 2011	Study Status and Contacts/Locations
13	○	○	April 8, 2011	Study Status and Study Design
14	○	○	June 23, 2011	Arms and Interventions, Study Status, Contacts/Locations and Eligibility
15	○	○	September 19, 2011	Study Status
16	○	○	November 29, 2011	Study Status and Study Identification
17	○	○	January 26, 2012	Study Status and Contacts/Locations
18	○	○	February 20, 2012	Recruitment Status, Study Status
19	○	○	October 23, 2012	Outcome Measures, Arms and Interventions, Study Status, More Information, Reported Adverse Events, Baseline Characteristics and Participant Flow
20	○	○	December 18, 2012	More Information, Arms and Interventions, Study Status and Baseline Characteristics
21	○	○	January 18, 2013	Arms and Interventions, More Information, Study Status and Baseline Characteristics
22	○	○	January 30, 2014	Contacts/Locations, Sponsor/Collaborators, More Information, Study Status, Baseline Characteristics and References
23	○	◉	October 27, 2014	More Information, Study Status and References

Compare

Comparison Format: (•) Merged ( ) Side-by-Side

Scroll up to access the controls

Study NCT01012973
on Date: December 18, 2012 (v20)

Study Identification

Unique Protocol ID:	14130
Brief Title:	Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO) (GALILEO)
Official Title:	A Randomized, Double-masked, Sham-controlled Phase 3 Study of the Efficacy, Safety and Tolerability of Repeated Intravitreal Administration of VEGF Trap-Eye in Subjects With Macular Edema Secondary to Central Retinal Vein Occlusion (CRVO)
Secondary IDs:	2009-010973-19 [EudraCT Number]

Study Status

Record Verification:	December 2012
Overall Status:	Completed
Study Start:	October 2009
Primary Completion:	February 2011 [Actual]
Study Completion:	February 2012 [Actual]
First Submitted:	October 30, 2009
First Submitted that Met QC Criteria:	November 12, 2009
First Posted:	November 13, 2009 [Estimate]
Results First Submitted:	October 23, 2012
	October 23, 2012

Results First Submitted that Met QC Criteria:	
Results First Posted:	November 22, 2012 [Estimate]
Certification/Extension First Submitted:	January 26, 2012
Certification/Extension First Submitted that Met QC Criteria:	January 26, 2012
Certification/Extension First Posted:	January 30, 2012 [Estimate]
Last Update Submitted that Met QC Criteria:	December 18, 2012
Last Update Posted:	December 19, 2012 [Estimate]

Sponsor/Collaborators

Sponsor:	Bayer
Responsible Party:	
Collaborators:	Regeneron Pharmaceuticals

Oversight

U.S. FDA-regulated Drug:	
U.S. FDA-regulated Device:	
Data Monitoring:	Yes

Study Description

Brief Summary:	To determine the efficacy of vascular endothelial growth factor (VEGF) Trap-Eye injected into the eye on vision function in subjects with macular edema as a consequence of central retinal vein occlusion
Detailed Description:	

Conditions

Conditions:	Retinal Vein Occlusion
Keywords:	

Macular Edema
Central Retinal Vein Occlusion
CRVO
VEGF Trap-Eye
best-corrected visual acuity

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	Phase 3
Interventional Study Model:	Parallel Assignment
Number of Arms:	2
Masking:	TripleParticipant, Investigator, Outcomes Assessor
Allocation:	Randomized
Enrollment:	177 [Actual]

Arms and Interventions

Arms	Assigned Interventions
Experimental: Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321) Participants received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered every 4 weeks from Day 1 through Week 20, later as often as every 4 weeks depending on the study retreatment criteria from Week 24 through Week 48. Follow-up phase: Participants on IAI, who continued the study, received 2 mg dose of IAI depending on the study retreatment criteria at Week 60 and 68.	Biological: Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321) Intravitreal injection. Weeks 0 to 20 of Aflibercept Injection every 4 weeks; Weeks 24 to 52 every 4 weeks PRN (pro re nata, on demand); plus additional on Week 60 and 68.
Sham Comparator: Sham treatment Participants received sham treatment administered every 4 weeks from Day 1 through Week 52. Follow-up phase: Participants on sham treatment, who switched to Intravitreal Aflibercept	Sham treatment Sham treatment. Weeks 0 to 52 sham treatment every 4 weeks; plus additional on Week 60 and 68. Biological: Sham treatment switched to Aflibercept Injection

Arms	Assigned Interventions
Injection (IAI), received a 2 mg dose of IAI at week 52 and depending on the study retreatment criteria at Week 60 and 68.	Participants on sham treatment, who switched to Intravitreal Aflibercept Injection (IAI), received a 2 mg dose of IAI at week 52 and depending on the study retreatment criteria at Week 60 and 68.

Outcome Measures

[See Results Section.]

Eligibility

Minimum Age: 18 Years

Maximum Age:

Sex: All

Gender Based:

Accepts Healthy Volunteers: No

Criteria: Inclusion Criteria:

- Center-involved macular edema secondary to central retinal vein occlusion (CRVO) for no longer than 9 months with mean central subfield thickness ≥ 250 µm on optical coherence tomography (OCT)
- Adults ≥ 18 years
- Early treatment diabetic retinopathy study (ETDRS) best corrected visual acuity (BCVA) of 20/40 to 20/320 (73 to 24 letters) in the study eye

Exclusion Criteria:

- Any prior treatment with anti-VEGF agents in the study eye (Pegaptanib sodium, anecortave acetate, bevacizumab, ranibizumab, etc.) or previous administration of systemic anti-angiogenic medications
- Prior panretinal laser photocoagulation or macular laser photocoagulation in the study eye

- CRVO disease duration > 9 months from date of diagnosis
- Previous use of intraocular corticosteroids in the study eye or use of periocular corticosteroids in the study eye within the 3 months prior to Day 1
- Iris neovascularization, vitreous hemorrhage, traction retinal detachment, or preretinal fibrosis involving the macula in either the study eye or fellow eye

Contacts/Locations

Study Officials: Bayer Study Director
Study Director
Bayer

Locations:

Australia, New South Wales

Chatswood, New South Wales, Australia, 2067

Parramatta, New South Wales, Australia, 2150

Sydney, New South Wales, Australia, 2000

Westmead, New South Wales, Australia, 2145

Australia, Victoria

East Melbourne, Victoria, Australia, 3002

Australia, Western Australia

Nedlands, Western Australia, Australia, 6009

Austria

Innsbruck, Austria, 6020

Linz, Austria, 4021

Wien, Austria, 1090

France, Cedex 12

Paris, Cedex 12, France, 75557

France, Cedex 1

Nantes, Cedex 1, France, 44093

France

Bordeaux, France, 33000

Dijon, France, 21033

Marseille, France, 13008

Paris, France, 75015

Germany, Baden-Württemberg

Freiburg, Baden-Württemberg, Germany, 79106

Heidelberg, Baden-Württemberg, Germany, 69120

Tübingen, Baden-Württemberg, Germany, 72076

Germany, Bayern

München, Bayern, Germany, 81675

Regensburg, Bayern, Germany, 93053

Germany, Hessen

Darmstadt, Hessen, Germany, 64297

Frankfurt, Hessen, Germany, 60596

Marburg, Hessen, Germany, 35037

Germany, Niedersachsen

Göttingen, Niedersachsen, Germany, 37075

Germany, Nordrhein-Westfalen

Aachen, Nordrhein-Westfalen, Germany, 52074

Bonn, Nordrhein-Westfalen, Germany, 53105

Essen, Nordrhein-Westfalen, Germany, 45122

Köln, Nordrhein-Westfalen, Germany, 50924

Münster, Nordrhein-Westfalen, Germany, 48145

Germany, Rheinland-Pfalz

Ludwigshafen, Rheinland-Pfalz, Germany, 67063

Mainz, Rheinland-Pfalz, Germany, 55131

Germany, Saarland

Homburg, Saarland, Germany, 66421

Germany, Sachsen

Chemnitz, Sachsen, Germany, 09116

Dresden, Sachsen, Germany, 01307

Dresden, Sachsen, Germany, 06067

Leipzig, Sachsen, Germany, 04103

Germany, Schleswig-Holstein

Kiel, Schleswig-Holstein, Germany, 24105

Lübeck, Schleswig-Holstein, Germany, 23538

Germany

Berlin, Germany, 13353

Hamburg, Germany, 20251

Hungary

Budapest, Hungary, 1089

Budapest, Hungary, 1106

Budapest, Hungary, 1133

Debrecen, Hungary, 4032

Veszprem, Hungary, 8200

Zalaegerszeg, Hungary, H-8900

Italy

Ancona, Italy, 60126

Bari, Italy, 70124

Catania, Italy, 95123

Firenze, Italy, 50134

Milano, Italy, 20122

Milano, Italy, 20132

Milano, Italy, 20157

Padova, Italy, 35128

Roma, Italy, 00133

Roma, Italy, 00198

Torino, Italy, 10122

Japan, Aichi

Nagoya, Aichi, Japan, 466-8560

Nagoya, Aichi, Japan, 467-8602

Japan, Chiba

Urayasu, Chiba, Japan, 279-0021

Japan, Osaka

Suita, Osaka, Japan, 565-0871

Japan, Tokyo

Chiyoda-ku, Tokyo, Japan, 101-8309

Japan

Kyoto, Japan, 606-8507

Korea, Republic of

Incheon, Korea, Republic of, 405-760

Kungki-do, Korea, Republic of, 463-707

Seoul, Korea, Republic of, 110 744

Seoul, Korea, Republic of, 110-744

Seoul, Korea, Republic of, 138-736

Seoul, Korea, Republic of

Latvia

Riga, Latvia, 1002

Riga, Latvia, 1050

Singapore

Singapore, Singapore, 119074

Singapore, Singapore, 168751

IPDSharing

Plan to Share IPD:

References

Citations:

Links:

Available IPD/Information:

Study Results

Participant Flow

Reporting Groups

	Description
Aflibercept Injection First, Then Aflibercept Injection	Participants received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered every 4 weeks from Day 1 through Week 20, later as often as every 4 weeks depending on the study retreatment criteria from Week 24 through Week 48. Follow-up phase: Participants on IAI, who continued the study, received 2 mg dose of IAI depending on the study retreatment criteria at Week 60 and 68.
Sham Treatment First, Then Aflibercept Injection	Participants received sham treatment administered every 4 weeks from Day 1 through Week 52. Follow-up phase: Participants on sham treatment, who switched to Intravitreal Aflibercept Injection (IAI), received a 2 mg dose of IAI at week 52 and depending on the study retreatment criteria at Week 60 and 68.

Overall Study

	Aflibercept Injection First, Then Aflibercept Injection	Sham Treatment First, Then Aflibercept Injection
Started	106	71
Participants Received Treatment	104 [1]	68 [1]
Fulfilled Requirements of FAS Population	103 [2]	68 [2]
Completed Week 24, From FAS	97	57
Completed Week 52, From FAS	91	52
Completed	90	52
Not Completed	16	19
Adverse Event	5	5
Lack of Efficacy	0	5

	Aflibercept Injection First, Then Aflibercept Injection	Sham Treatment First, Then Aflibercept Injection
Lost to Follow-up	1	0
(Overseas travel - indefinite period)	1	0
Increase in vis. acuity, never injected	0	1
Protocol Violation	5	2
Withdrawal by Subject	4	6

[1] Safety Population: Participants received treatment

[2] Full Analysis Set (FAS) Population: Participants received treatment with post baseline measurements

Baseline Characteristics

Reporting Groups

	Description
Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Participants received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered every 4 weeks from Day 1 through Week 20, later as often as every 4 weeks depending on the study retreatment criteria from Week 24 through Week 48. Follow-up phase: Participants on IAI, who continued the study, received 2 mg dose of IAI depending on the study retreatment criteria at Week 60 and 68.
Sham Treatment	Participants received sham treatment administered every 4 weeks from Day 1 through Week 52. Follow-up phase: Participants on sham treatment, who switched to Intravitreal Aflibercept Injection (IAI), received a 2 mg dose of IAI at week 52 and depending on the study retreatment criteria at Week 60 and 68.

Baseline Measures

		Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Sham Treatment	Total
Overall Number of Participants		104	68	172
Age Continuous Mean (Standard Deviation) Unit of measure: Years	Number Analyzed	104 Participants	68 Participants	172 Participants
		60.0 (12.3)	63.8 (13.3)	61.5 (12.8)
Sex: Female, Male Measure type: Count of Participants Unit of measure: Participants	Number Analyzed	104 Participants	68 Participants	172 Participants
	Female	45 43.27%	31 45.59%	76 44.19%
	Male	59 56.73%	37 54.41%	96 55.81%
Ethnicity (NIH/OMB) Measure type: Count of Participants Unit of measure: Participants	Number Analyzed	104 Participants	68 Participants	172 Participants
	Hispanic or Latino	4 3.85%	1 1.47%	5 2.91%
	Not Hispanic or Latino	100 96.15%	66 97.06%	166 96.51%
	Unknown or Not Reported	0 0%	1 1.47%	1 0.58%
Baseline Best Corrected Visual Acuity (BCVA) letter scores [1] Mean (Standard Deviation)	Number Analyzed	104 Participants	68 Participants	172 Participants
		53.5 (15.7)	50.9 (15.4)	52.5 (15.6)
	[1]	Only participants with a ETDRS (Early Treatment Diabetic Retinopathy Study) Best Corrected Visual Acuity letter score of 73 to 25 (= Acuity of 20/40 to 20/320) in the study eye at 4 meters were included, Safety Analysis Set (EYLEA n=104, Sham n=68); a higher score represents better functioning.		
		104 Participants	68 Participants	172 Participants

		Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Sham Treatment	Total
Number of participants with baseline retinal perfusion [1] Measure type: Number Unit of measure: Participants	Number Analyzed			
Perfused		90	54	144
Nonperfused		7	7	14
Indeterminate		7	7	14
	[1] Retinal perfusion defined as less than 10 disc areas of capillary nonperfusion using fluorescein angiography (FA)			
Baseline Retinal Thickness by Optical Coherence Tomography (OCT) Mean (Standard Deviation)	Number Analyzed	104 Participants	68 Participants	172 Participants
		682.78 (233.36)	638.66 (224.69)	665.34 (230.33)
Baseline intraocular pressure Mean (Standard Deviation)	Number Analyzed	104 Participants	68 Participants	172 Participants
		15.2 (2.8)	14.4 (2.7)	14.9 (2.8)
Number of participants with time since Central retinal vein occlusion (CRVO) diagnosis Measure type: Number Unit of measure: Participants	Number Analyzed	104 Participants	68 Participants	172 Participants
>= 2 months		46	33	79
< 2 months		56	35	91
Missing		2	0	2

		Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Sham Treatment	Total
Baseline National Eye Institute 25-item Visual Function Questionnaire (NEI VFQ-25) total score [1]	Number Analyzed	104 Participants	68 Participants	172 Participants
		79.66 (13.06)	78.94 (14.00)	79.38 (13.40)

[1] The NEI VFQ-25 total score ranges from 0-100 with a score of 0 being the worst outcome and 100 being the best outcome. The NEI VFQ questionnaire is organized as a collection of subscales which are all scored from 0-100. To reach the overall composite score, each sub-scale score is averaged in order to give each sub-scale equal weight.

European questionnaire 5 dimensions (EQ-5D) total score [1] Mean (Standard Deviation)	Number Analyzed	104 Participants	68 Participants	172 Participants
		0.87 (0.15)	0.86 (0.16)	0.87 (0.15)

[1] The EQ-5D total score ranges from -0.594 to 1.000 with -0.594 being the worst.

Race Measure type: Number Unit of measure: Participants	Number Analyzed	104 Participants	68 Participants	172 Participants
Asian		26	15	41
White		75	49	124
Unknown or Not Reported		3	4	7

Outcome Measures

1. Primary Outcome Measure:

Measure Title	

	Percentage of Participants Who Gained at Least 15 Letters in BCVA as Measured by ETDRS Letter Score Compared With Baseline at Week 24 With Discontinued Participants Before Week 24 Evaluated as Failures
Measure Description	Defined study baseline range of Early Treatment Diabetic Retinopathy Study (ETDRS) Best Corrected Visual Acuity (BCVA) letter score of 73 to 24 (= Acuity of 20/40 to 20/320) in the study eye; a higher score represents better functioning. Nominator = (Number of participants who maintained vision * 100); Denominator = Number of participants analyzed.
Time Frame	Baseline and Week 24

Analysis Population Description

Full analysis set

Reporting Groups

	Description
Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Participants received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered every 4 weeks from Day 1 through Week 20, later as often as every 4 weeks depending on the study retreatment criteria from Week 24 through Week 48. Follow-up phase: Participants on IAI, who continued the study, received 2 mg dose of IAI depending on the study retreatment criteria at Week 60 and 68.
Sham Treatment	Participants received sham treatment administered every 4 weeks from Day 1 through Week 52. Follow-up phase: Participants on sham treatment, who switched to Intravitreal Aflibercept Injection (IAI), received a 2 mg dose of IAI at week 52 and depending on the study retreatment criteria at Week 60 and 68.

Measured Values

	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Sham Treatment
Overall Number of Participants Analyzed	103	68
Percentage of Participants Who Gained at Least 15 Letters in BCVA as Measured by ETDRS Letter Score Compared With Baseline at Week 24 With Discontinued Participants Before Week 24 Evaluated as Failures Measure Type: Number Unit of Measure: Percentage of participants	60.2	22.1

Statistical Analysis 1 for Percentage of Participants Who Gained at Least 15 Letters in BCVA as Measured by ETDRS Letter Score Compared With Baseline at Week 24 With Discontinued Participants Before Week 24 Evaluated as Failures

Statistical Analysis Overview	Comparison Groups	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321), Sham Treatment
	Comments	Null hypothesis of difference of Eylea minus Sham of 0 was tested. In the database close after Week 24, basis for primary efficacy evaluation, 56 Sham / 96 Eylea subjects were considered as week 24 completers.
	Type of Statistical Test	Superiority or Other (legacy)
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	<.0001
	Comments	[Not specified]
	Method	Cochran-Mantel-Haenszel
	Comments	[Not specified]
	Estimation Parameter	CMH adjusted difference

Method of Estimation	Estimated Value	38.3
	Confidence Interval	(2-sided) 95% 24.4 to 52.1
	Estimation Comments	The estimate is calculated as Eylea minus Sham. A positive value shows Eylea showed a higher BCVA total score compared to Sham.

2. Secondary Outcome Measure:

Measure Title	Change From Baseline in BCVA as Measured by Early Treatment Diabetic Retinopathy Study (ETDRS) Letter Score at Week 24 - Last Observation Carried Forward (LOCF)
Measure Description	Defined study baseline range of ETDRS Best Corrected Visual Acuity letter score of 73 to 24 (= Acuity of 20/40 to 20/320) in the study eye; a higher score represents better functioning. However, because this was assessed at the screening visit, subjects may have had a higher BCVA recorded at the baseline visit and would not have been excluded from the study.
Time Frame	Baseline and Week 24

Analysis Population Description

Full analysis set

Reporting Groups

	Description
Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Participants received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered every 4 weeks from Day 1 through Week 20, later as often as every 4 weeks depending on the study retreatment criteria from Week 24 through Week 48. Follow-up phase: Participants on IAI, who continued the study, received 2 mg dose of IAI

	depending on the study retreatment criteria at Week 60 and 68.
Sham Treatment	Participants received sham treatment administered every 4 weeks from Day 1 through Week 52. Follow-up phase: Participants on sham treatment, who switched to Intravitreal Aflibercept Injection (IAI), received a 2 mg dose of IAI at week 52 and depending on the study retreatment criteria at Week 60 and 68.

Measured Values

	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Sham Treatment
Overall Number of Participants Analyzed	103	68
Change From Baseline in BCVA as Measured by Early Treatment Diabetic Retinopathy Study (ETDRS) Letter Score at Week 24 - Last Observation Carried Forward (LOCF) Measure Type: Mean (Standard Deviation) Unit of Measure: Letters correctly read	71.6 (17.1)	54.3 (20.2)

Statistical Analysis 1 for Change From Baseline in BCVA as Measured by Early Treatment Diabetic Retinopathy Study (ETDRS) Letter Score at Week 24 - Last Observation Carried Forward (LOCF)

Statistical Analysis Overview	Comparison Groups	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321), Sham Treatment
	Comments	Null hypothesis was equality in change from baseline to Week 24 in BCVA total letter score between Eylea and Sham. If primary efficacy was successful, secondary efficacy endpoints were tested in a pre-specified fixed sequence testing procedure. Change in BCVA letter

		score was to be tested first in this sequence.
	Type of Statistical Test	Superiority or Other (legacy)
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	<.0001
	Comments	As primary efficacy evaluation was significant, and this p-value was below significance level of two-sided <.05, the fixed sequence testing did continue with next secondary endpoint.
	Method	ANOVA
	Comments	ANOVA, adjusting for region and baseline BCVA category as fixed factors.

Method of Estimation	Estimation Parameter	Difference in Least square means
	Estimated Value	14.7
	Confidence Interval	(2-sided) 95% 10.8 to 18.7
	Estimation Comments	The difference is calculated as Eylea minus Sham. A positive value indicates Eylea showed a higher change in BCVA total score until week 24 compared to Sham.

3. Secondary Outcome Measure:

Measure Title	Change From Baseline in Central Retinal Thickness (CRT) at Week 24 - LOCF
Measure Description	
Time Frame	Baseline and Week 24

Analysis Population Description

Full-Analysis Set with assessment for this outcome measure; imputation technique: LOCF

Reporting Groups

	Description
Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Participants received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered every 4 weeks from Day 1 through Week 20, later as often as every 4 weeks depending on the study retreatment criteria from Week 24 through Week 48. Follow-up phase: Participants on IAI, who continued the study, received 2 mg dose of IAI depending on the study retreatment criteria at Week 60 and 68.
Sham Treatment	Participants received sham treatment administered every 4 weeks from Day 1 through Week 52. Follow-up phase: Participants on sham treatment, who switched to Intravitreal Aflibercept Injection (IAI), received a 2 mg dose of IAI at week 52 and depending on the study retreatment criteria at Week 60 and 68.

Measured Values

	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Sham Treatment
Overall Number of Participants Analyzed	103	67
Change From Baseline in Central Retinal Thickness (CRT) at Week 24 - LOCF Measure Type: Mean (Standard Deviation) Unit of Measure: microns	-448.58 (256.02)	-169.27 (224.72)

Statistical Analysis 1 for Change From Baseline in Central Retinal Thickness (CRT) at Week 24 - LOCF

	Comparison Groups	

Statistical Analysis Overview		Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321), Sham Treatment
	Comments	Null hypothesis was equality in change from baseline to Week 24 in central retinal thickness between Eylea and Sham. If primary efficacy was successful, secondary efficacy end points were to be tested in a pre-specified fixed sequence testing procedure. Change in central retinal thickness was to be tested at second place in this sequence.
	Type of Statistical Test	Superiority or Other (legacy)
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	<.0001
	Comments	As fixed sequence testing did reject nullhypothesis of change from baseline in BCVA until week 24, and this p-value was below significance level of two-sided <.05, the fixed sequence testing did continue with next secondary endpoint.
	Method	ANCOVA
	Comments	ANCOVA, stratified by region and baseline BCVA category, baseline central retinal thickness added as covariate.

Method of Estimation	Estimation Parameter	Difference in Least square (LS) means
	Estimated Value	-239.42
	Confidence Interval	(2-sided) 95% -286.31 to -192.53

	Estimation Comments	The difference is calculated as Eylea minus Sham. A negative value indicates Eylea showed a higher reduction in change in central retinal thickness until week 24 compared to Sham.

4. Secondary Outcome Measure:

Measure Title	Percentage of Participants Who Developed Neovascularization During the First 24 Weeks
Measure Description	Formation of blood vessels in the anterior segment, optic disc, or elsewhere in the fundus up to Week 24
Time Frame	From baseline until Week 24

Analysis Population Description

Full analysis set

Reporting Groups

	Description
Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Participants received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered every 4 weeks from Day 1 through Week 20, later as often as every 4 weeks depending on the study retreatment criteria from Week 24 through Week 48. Follow-up phase: Participants on IAI, who continued the study, received 2 mg dose of IAI depending on the study retreatment criteria at Week 60 and 68.
Sham Treatment	Participants received sham treatment administered every 4 weeks from Day 1 through Week 52. Follow-up phase: Participants on sham treatment, who switched to Intravitreal Aflibercept Injection (IAI), received a 2 mg dose of IAI at week 52 and depending on the study retreatment criteria at Week 60 and 68.

Measured Values

	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Sham Treatment
Overall Number of Participants Analyzed	103	68
Percentage of Participants Who Developed Neovascularization During the First 24 Weeks Measure Type: Number Unit of Measure: Percentage of participants		
Any neovascularization	2.9	4.4
Anterior segment neovascularization	1.9	1.5
Neovascularization of the optic disc (NVD)	0.0	0.0
Neovascularization elsewhere in the fundus (NVE)	1.0	2.9

Statistical Analysis 1 for Percentage of Participants Who Developed Neovascularization During the First 24 Weeks

Statistical Analysis Overview	Comparison Groups	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321), Sham Treatment
	Comments	Nullhypothesis of no difference in development of neovascularizations between Eylea and Sham group was tested. (Any neovascularization)
	Type of Statistical Test	Superiority or Other (legacy)
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.5947
	Comments	As fixed sequence testing did reject nullhypothesis of change from baseline in CRT until week 24, and this p-value was not below significance level of two-sided <.05,

		the fixed sequence testing did end with this evaluation.
	Method	Cochran-Mantel-Haenszel
	Comments	Cochrane-Mantel-Haenszel test, stratified by region and baseline BCVA category.

Method of Estimation	Estimation Parameter	CMH adjusted Difference
	Estimated Value	-1.5
	Confidence Interval	(2-sided) 95% -7.4 to 4.4
	Estimation Comments	[Not specified]

5. Secondary Outcome Measure:

Measure Title	Change From Baseline in National Eye Institute 25-item Visual Function Questionnaire (NEI VFQ-25) Total Score at Week 24 - LOCF
Measure Description	The NEI VFQ-25 total score ranges from 0-100 with a score of 0 being the worst outcome and 100 being the best outcome. The NEI VFQ questionnaire is organized as a collection of subscales which are all scored from 0-100. To reach the overall composite score, each sub-scale score is averaged in order to give each sub-scale equal weight
Time Frame	Baseline and Week 24

Analysis Population Description

Full-Analysis Set with assessment for this outcome measure; imputation technique: LOCF

Reporting Groups

	Description
Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Participants received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered every 4 weeks from Day 1 through Week 20, later as often

	as every 4 weeks depending on the study retreatment criteria from Week 24 through Week 48. Follow-up phase: Participants on IAI, who continued the study, received 2 mg dose of IAI depending on the study retreatment criteria at Week 60 and 68.
Sham Treatment	Participants received sham treatment administered every 4 weeks from Day 1 through Week 52. Follow-up phase: Participants on sham treatment, who switched to Intravitreal Aflibercept Injection (IAI), received a 2 mg dose of IAI at week 52 and depending on the study retreatment criteria at Week 60 and 68.

Measured Values

	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Sham Treatment
Overall Number of Participants Analyzed	96	65
Change From Baseline in National Eye Institute 25-item Visual Function Questionnaire (NEI VFQ-25) Total Score at Week 24 - LOCF Measure Type: Mean (Standard Deviation) Unit of Measure: Scores on a scale	7.46 (9.55)	3.55 (9.74)

Statistical Analysis 1 for Change From Baseline in National Eye Institute 25-item Visual Function Questionnaire (NEI VFQ-25) Total Score at Week 24 - LOCF

Statistical Analysis Overview	Comparison Groups	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321), Sham Treatment
	Comments	[Not specified]
	Type of Statistical Test	Superiority or Other (legacy)
	Comments	[Not specified]

	Estimation Parameter	Difference in LS means

Method of Estimation	Estimated Value	4.2
	Confidence Interval	(2-sided) 95% 1.7 to 6.8
	Estimation Comments	As the fixed sequence of secondary endpoints stopped with proportion of neovascularizations developed until week 24, 95% confidence interval is only of descriptive nature.

6. Secondary Outcome Measure:

Measure Title	Change From Baseline in European Five-dimensional Health Scale (EQ-5D) Score at Week 24 - LOCF
Measure Description	EQ-5D is a quality of life questionnaire based on a scale from -0.594 (worst) to 1.00 (best).
Time Frame	Baseline and Week 24

Analysis Population Description

Full-Analysis Set with assessment for this outcome measure; imputation technique: LOCF

Reporting Groups

	Description
Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Participants received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered every 4 weeks from Day 1 through Week 20, later as often as every 4 weeks depending on the study retreatment criteria from Week 24 through Week 48. Follow-up phase: Participants on IAI, who continued the study, received 2 mg dose of IAI depending on the study retreatment criteria at Week 60 and 68.
Sham Treatment	Participants received sham treatment administered every 4 weeks from Day 1 through Week 52. Follow-up phase: Participants on sham treatment,

	who switched to Intravitreal Aflibercept Injection (IAI), received a 2 mg dose of IAI at week 52 and depending on the study retreatment criteria at Week 60 and 68.

Measured Values

	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Sham Treatment
Overall Number of Participants Analyzed	95	64
Change From Baseline in European Five-dimensional Health Scale (EQ-5D) Score at Week 24 - LOCF Measure Type: Mean (Standard Deviation) Unit of Measure: Scores on a scale	0.029 (0.139)	-0.002 (0.195)

Statistical Analysis 1 for Change From Baseline in European Five-dimensional Health Scale (EQ-5D) Score at Week 24 - LOCF

Statistical Analysis Overview	Comparison Groups	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321), Sham Treatment
	Comments	[Not specified]
	Type of Statistical Test	Superiority or Other (legacy)
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Difference in LS Means
	Estimated Value	0.044
	Confidence Interval	(2-sided) 95% -0.002 to 0.09
	Estimation Comments	As the fixed sequence of secondary endpoints stopped with proportion of neovascularizations developed until week 24, 95% confidence interval is only of descriptive nature.

Reported Adverse Events

Time Frame	[Not specified]
Adverse Event Reporting Description	[Not specified]

Reporting Groups

	Description
Aflibercept Injection (Until Week 20)	Participants received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered every 4 weeks from Day 1 through Week 20. Participants were observed until Week 24. Participants in the safety population were at risk.
Sham Treatment (Until Week 20)	Participants received sham treatment administered every 4 weeks from Day 1 through Week 20. Participants were observed until Week 24. Participants in the safety population were at risk.
Aflibercept Injection (Until Week 48)	Participants who continued the study drug until Week 24 received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered as often as every 4 weeks depending on the study retreatment criteria from Week 24 through Week 48. Participants were observed from Week 24 until Week 52. Participants in the safety population that completed Week 24 were at risk.
Sham Treatment (Until Week 48)	Participants who continued the study drug until Week 24 received sham treatment administered every 4 weeks from Week 24 to Week 48. Participants were observed from Week 24 until Week 52. Participants in the safety population that completed Week 24 were at risk.
Aflibercept Injection Continued (Until Week 68)	Participants on IAI who continued the study drug until Week 52, received 2 mg dose of IAI depending on the study retreatment criteria at Week 52, 60 and 68. Participants were observed starting from Week 52. Participants in the safety population that completed Week 52 were at risk.

Sham Treatment Then Aflibercept Injection (Until Week 68)	Participants on sham treatment switched to IAI, received a 2 mg dose of IAI at Week 52 and depending on the study retreatment criteria at Week 60 and 68. Participants were observed starting from Week 52. Participants in the safety population that completed Week 52 were at risk.

All-Cause Mortality

	Aflibercept Injection (Until Week 20)	Sham Treatment (Until Week 20)	Aflibercept Injection (Until Week 48)	Sham Treatment (Until Week 48)	Aflibercept Injection Continued (Until Week 68)	Sham Treatment Then Aflibercept Injection (Until Week 68)
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Total	/	/	/	/	/	/

Serious Adverse Events

	Aflibercept Injection (Until Week 20)	Sham Treatment (Until Week 20)	Aflibercept Injection (Until Week 48)	Sham Treatment (Until Week 48)	Aflibercept Injection Continued (Until Week 68)	Sham Treatment Then Aflibercept Injection (Until Week 68)
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Total	8/104 (7.69%)	8/68 (11.76%)	14/97 (14.43%)	7/57 (12.28%)	4/91 (4.4%)	3/52 (5.77%)
Cardiac disorders						
Aortic valve incompetence [A*]	0/104 (0%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	1/52 (1.92%)
Cardiac failure [A*]						

	Afliberce Injection (Until Week 20)	Sham Treatme (Until Week 20)	Afliberce Injection (Until Week 48)	Sham Treatme (Until Week 48)	Afliberce Injection Continue (Until Week 68)	Sham Treatme Then Afliberce Injection (Until Week 68)
	0/104 (0%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	1/52 (1.92%)
Coronary artery stenosis [A*]	0/104 (0%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	1/52 (1.92%)
Diastolic dysfunction [A*]	0/104 (0%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	1/52 (1.92%)
Mitral valve incompetence [A*]	0/104 (0%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	1/52 (1.92%)
Eye disorders						
Blindness unilateral [A*]	0/104 (0%)	0/68 (0%)	1/97 (1.03%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Glaucoma [A*]	0/104 (0%)	1/68 (1.47%)	0/97 (0%)	1/57 (1.75%)	0/91 (0%)	0/52 (0%)
Iris neovascularisation [A*]	1/104 (0.96%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Macular fibrosis [A*]	0/104 (0%)	0/68 (0%)	1/97 (1.03%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Macular ischaemia [A*]	0/104 (0%)	0/68 (0%)	1/97 (1.03%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Macular oedema [A*]	0/104 (0%)	2/68 (2.94%)	4/97 (4.12%)	0/57 (0%)	1/91 (1.1%)	0/52 (0%)
Retinal vein occlusion [A*]	0/104 (0%)	0/68 (0%)	1/97 (1.03%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Visual acuity reduced [A*]	0/104 (0%)	1/68 (1.47%)	1/97 (1.03%)	0/57 (0%)	2/91 (2.2%)	0/52 (0%)
Vitreous detachment [A*]	1/104	0/68	0/97	0/57	0/91	0/52

	Afliberce Injection (Until Week 20)	Sham Treatme (Until Week 20)	Afliberce Injection (Until Week 48)	Sham Treatme (Until Week 48)	Afliberce Injection Continue (Until Week 68)	Sham Treatme Then Afliberce Injection (Until Week 68)
Vitreous haemorrhage [A*]	0/104 (0%)	1/68 (1.47%)	1/97 (1.03%)	1/57 (1.75%)	0/91 (0%)	0/52 (0%)
Gastrointestinal disorders						
Diverticular perforation [A*]	0/104 (0%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	1/91 (1.1%)	0/52 (0%)
Hepatobiliary disorders						
Hepatic function abnormal [A*]	0/104 (0%)	0/68 (0%)	1/97 (1.03%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Infections and infestations						
Furuncle [A*]	1/104 (0.96%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Gastroenteritis [A*]	0/104 (0%)	1/68 (1.47%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Pneumonia [A*]	0/104 (0%)	1/68 (1.47%)	1/97 (1.03%)	1/57 (1.75%)	0/91 (0%)	0/52 (0%)
Vestibular neuronitis [A*]	0/104 (0%)	0/68 (0%)	0/97 (0%)	1/57 (1.75%)	0/91 (0%)	0/52 (0%)
Injury, poisoning and procedural complications						
Fall [A*]	0/104 (0%)	1/68 (1.47%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Femur fracture [A*]	0/104 (0%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	1/52 (1.92%)
Hand fracture [A*]	1/104 (0.96%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Humerus fracture [A*]	0/104 (0%)	1/68 (1.47%)	1/97 (1.03%)	0/57 (0%)	0/91 (0%)	0/52 (0%)

	Afliberce Injection (Until Week 20)	Sham Treatme (Until Week 20)	Afliberce Injection (Until Week 48)	Sham Treatme (Until Week 48)	Afliberce Injection Continue (Until Week 68)	Sham Treatme Then Afliberce Injection (Until Week 68)
Radius fracture [A*]	0/104 (0%)	1/68 (1.47%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Spinal compression fracture [A*]	1/104 (0.96%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Musculoskeletal and connective tissue disorders						
Intervertebral disc protrusion [A*]	0/104 (0%)	1/68 (1.47%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Spinal column stenosis [A*]	0/104 (0%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	1/91 (1.1%)	0/52 (0%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)						
Breast cancer [A*]	0/104 (0%)	0/68 (0%)	1/97 (1.03%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Oropharyngeal cancer stage unspecified [A*]	1/104 (0.96%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Nervous system disorders						
Paraesthesia [A*]	0/104 (0%)	0/68 (0%)	1/97 (1.03%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Syncope [A*]	0/104 (0%)	0/68 (0%)	1/97 (1.03%)	2/57 (3.51%)	0/91 (0%)	0/52 (0%)
Transient ischaemic attack [A*]	0/104 (0%)	0/68 (0%)	0/97 (0%)	1/57 (1.75%)	0/91 (0%)	0/52 (0%)
Respiratory, thoracic and mediastinal disorders						
Dyspnoea [A*]	0/104 (0%)	0/68 (0%)	0/97 (0%)	1/57 (1.75%)	0/91 (0%)	0/52 (0%)
Laryngeal granuloma [A*]	0/104 (0%)	1/68 (1.47%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)

	Afliberce Injection (Until Week 20)	Sham Treatme (Until Week 20)	Afliberce Injection (Until Week 48)	Sham Treatme (Until Week 48)	Afliberce Injection Continue (Until Week 68)	Sham Treatme Then Afliberce Injection (Until Week 68)
Pulmonary hypertension [A*]	0/104 (0%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	1/52 (1.92%)
Surgical and medical procedures						
Ischaemic heart disease prophylaxis [A*]	1/104 (0.96%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Vascular disorders						
Circulatory collapse [A*]	1/104 (0.96%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)

* Indicates events were collected by non-systematic methods.

A Term from vocabulary, MedDRA (14.1)

Other Adverse Events

Frequency Threshold Above Which Other Adverse Events are Reported: 5%

	Afliberce Injection (Until Week 20)	Sham Treatme (Until Week 20)	Afliberce Injection (Until Week 48)	Sham Treatme (Until Week 48)	Afliberce Injection Continue (Until Week 68)	Sham Treatme Then Afliberce Injection (Until Week 68)
	Affected/A Risk (%)	Affected/A Risk (%)	Affected/A Risk (%)	Affected/A Risk (%)	Affected/A Risk (%)	Affected/A Risk (%)
Total	52/104 (50%)	44/68 (64.71%	66/97 (68.04%	30/57 (52.63%	38/91 (41.76%	19/52 (36.54%
Blood and lymphatic system disorders						
Anaemia [A*]	1/104 (0.96%)	0/68 (0%)	0/97 (0%)	3/57 (5.26%)	0/91 (0%)	0/52 (0%)

	Aflibercept Injection (Until Week 20)	Sham Treatment (Until Week 20)	Aflibercept Injection (Until Week 48)	Sham Treatment (Until Week 48)	Aflibercept Injection Continued (Until Week 68)	Sham Treatment Then Aflibercept Injection (Until Week 68)
Eye disorders						
Conjunctival haemorrhage [A*]	10/104 (9.62%)	3/68 (4.41%)	3/97 (3.09%)	0/57 (0%)	9/91 (9.89%)	3/52 (5.77%)
Eye irritation [A*]	3/104 (2.88%)	7/68 (10.29%)	4/97 (4.12%)	1/57 (1.75%)	1/91 (1.1%)	2/52 (3.85%)
Eye pain [A*]	12/104 (11.54%)	3/68 (4.41%)	6/97 (6.19%)	2/57 (3.51%)	1/91 (1.1%)	0/52 (0%)
Foreign body sensation in eyes [A*]	6/104 (5.77%)	5/68 (7.35%)	2/97 (2.06%)	0/57 (0%)	1/91 (1.1%)	0/52 (0%)
Lacrimation increased [A*]	3/104 (2.88%)	4/68 (5.88%)	3/97 (3.09%)	4/57 (7.02%)	1/91 (1.1%)	2/52 (3.85%)
Macular fibrosis [A*]	1/104 (0.96%)	1/68 (1.47%)	5/97 (5.15%)	4/57 (7.02%)	0/91 (0%)	3/52 (5.77%)
Macular ischaemia [A*]	7/104 (6.73%)	5/68 (7.35%)	3/97 (3.09%)	1/57 (1.75%)	0/91 (0%)	1/52 (1.92%)
Macular oedema [A*]	2/104 (1.92%)	9/68 (13.24%)	30/97 (30.93%)	7/57 (12.28%)	17/91 (18.68%)	2/52 (3.85%)
Ocular hyperaemia [A*]	5/104 (4.81%)	4/68 (5.88%)	2/97 (2.06%)	1/57 (1.75%)	4/91 (4.4%)	1/52 (1.92%)
Optic disc vascular disorder [A*]	5/104 (4.81%)	3/68 (4.41%)	3/97 (3.09%)	3/57 (5.26%)	0/91 (0%)	0/52 (0%)
Retinal exudates [A*]	8/104 (7.69%)	5/68 (7.35%)	4/97 (4.12%)	3/57 (5.26%)	0/91 (0%)	0/52 (0%)
Retinal haemorrhage [A*]	4/104 (3.85%)	6/68 (8.82%)	11/97 (11.34%)	5/57 (8.77%)	5/91 (5.49%)	2/52 (3.85%)
Retinal vascular disorder [A*]	6/104	7/68	10/97	2/57	0/91	2/52

	Afliberce Injection (Until Week 20)	Sham Treatme (Until Week 20)	Afliberce Injection (Until Week 48)	Sham Treatme (Until Week 48)	Afliberce Injection Continue (Until Week 68)	Sham Treatme Then Afliberce Injection (Until Week 68)
Visual acuity reduced [A*]	2/104 (1.92%)	7/68 (10.29%	10/97 (10.31%	1/57 (1.75%)	7/91 (7.69%)	1/52 (1.92%)
Vitreous detachment [A*]	2/104 (1.92%)	1/68 (1.47%)	7/97 (7.22%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Vitreous floaters [A*]	6/104 (5.77%)	0/68 (0%)	1/97 (1.03%)	1/57 (1.75%)	1/91 (1.1%)	1/52 (1.92%)
Gastrointestinal disorders						
Nausea [A*]	0/104 (0%)	1/68 (1.47%)	0/97 (0%)	3/57 (5.26%)	0/91 (0%)	0/52 (0%)
Infections and infestations						
Influenza [A*]	2/104 (1.92%)	0/68 (0%)	5/97 (5.15%)	1/57 (1.75%)	1/91 (1.1%)	1/52 (1.92%)
Nasopharyngitis [A*]	8/104 (7.69%)	6/68 (8.82%)	10/97 (10.31%	11/57 (19.3%)	4/91 (4.4%)	2/52 (3.85%)
Investigations						
Intraocular pressure increased [A*]	9/104 (8.65%)	4/68 (5.88%)	14/97 (14.43%	2/57 (3.51%)	2/91 (2.2%)	1/52 (1.92%)
Visual acuity tests abnormal [A*]	0/104 (0%)	1/68 (1.47%)	5/97 (5.15%)	0/57 (0%)	1/91 (1.1%)	0/52 (0%)
Musculoskeletal and connective tissue disorders						
Arthralgia [A*]	1/104 (0.96%)	5/68 (7.35%)	2/97 (2.06%)	1/57 (1.75%)	2/91 (2.2%)	0/52 (0%)
Nervous system disorders						
Headache [A*]	7/104 (6.73%)	4/68 (5.88%)	4/97 (4.12%)	1/57 (1.75%)	1/91 (1.1%)	1/52 (1.92%)

	Afliberce Injection (Until Week 20)	Sham Treatme (Until Week 20)	Afliberce Injection (Until Week 48)	Sham Treatme (Until Week 48)	Afliberce Injection Continue (Until Week 68)	Sham Treatme Then Afliberce Injection (Until Week 68)
Vascular disorders						
Hypertension [A*]	4/104 (3.85%)	3/68 (4.41%)	4/97 (4.12%)	4/57 (7.02%)	3/91 (3.3%)	2/52 (3.85%)

* Indicates events were collected by non-systematic methods.

A Term from vocabulary, MedDRA (14.1)

Limitations and Caveats

[Not specified]

More Information

Certain Agreements:

Principal Investigators are NOT employed by the organization sponsoring the study.

There IS an agreement between the Principal Investigator and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed.

Publishing of result communication only after Bayer´s written approval. Manuscript to Bayer sixty days before public release. If no written Bayer comment within 60 days consider approval given. If multi-site study, principal investigator (PI) not do independently publish results before publication of the multi-site paper, but PI not restricted from 24 months from study to completion onwards.

Results Point of Contact:

Name/Official Title: Therapeutic Area Head
Organization: BAYER
Phone:
Email: clinical-trials-contact@bayerhealthcare.com

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U.S. National Library of Medicine
ClinicalTrials.gov archive

History of Changes for Study: NCT01012973

Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO) (GALILEO)

Latest version (submitted October 27, 2014) on ClinicalTrials.gov

- A study version is represented by a row in the table.
- Select two study versions to compare. One each from columns A and B.
- Choose either the "Merged" or "Side-by-Side" comparison format to specify how the two study versions are to be displayed. The Side-by-Side format only applies to the Protocol section of the study.
- Click "Compare" to do the comparison and show the differences.
- Select a version's date link to see a rendering of the study for that version.
- Edits or deletions will be displayed in ~~red~~.
- Additions will be displayed in *green*.
- The yellow choices in the table indicate the study versions currently compared below. A yellow row indicates the study version being viewed.
- Hover over the "Recruitment Status" to see how the study's recruitment status changed.

Study Record Versions

Version	A	B	Submitted Date	Changes
1	◉	○	November 12, 2009	Nothing (earliest Version on record)
2	○	○	January 21, 2010	Contacts/Locations, Study Status, Study Identification and Study Description
3	○	○	February 9, 2010	Contacts/Locations and Study Status
4	○	○	March 16, 2010	Contacts/Locations, Study Status and Study Identification
5	○	○	April 16, 2010	Contacts/Locations, Study Status and Study Identification

Version	A	B	Submitted Date	Changes
6	○	○	July 22, 2010	Contacts/Locations, Study Status, Eligibility and Arms and Interventions
7	○	○	August 25, 2010	Study Status and Contacts/Locations
8	○	○	August 26, 2010	Recruitment Status, Study Status and Contacts/Locations
9	○	○	September 8, 2010	Study Status
10	○	○	October 4, 2010	Study Status
11	○	○	November 1, 2010	Study Status
12	○	○	January 25, 2011	Study Status and Contacts/Locations
13	○	○	April 8, 2011	Study Status and Study Design
14	○	○	June 23, 2011	Arms and Interventions, Study Status, Contacts/Locations and Eligibility
15	○	○	September 19, 2011	Study Status
16	○	○	November 29, 2011	Study Status and Study Identification
17	○	○	January 26, 2012	Study Status and Contacts/Locations
18	○	○	February 20, 2012	Recruitment Status, Study Status
19	○	○	October 23, 2012	Outcome Measures, Arms and Interventions, Study Status, More Information, Reported Adverse Events, Baseline Characteristics and Participant Flow
20	○	○	December 18, 2012	More Information, Arms and Interventions, Study Status and Baseline Characteristics
21	○	○	January 18, 2013	Arms and Interventions, More Information, Study Status and Baseline Characteristics
22	○	○	January 30, 2014	Contacts/Locations, Sponsor/Collaborators, More Information, Study Status, Baseline Characteristics and References
23	○	◉	October 27, 2014	More Information, Study Status and References

Compare

Comparison Format: (•) Merged ( ) Side-by-Side

Scroll up to access the controls

Study NCT01012973
on Date: January 21, 2010 (v2)

Study Identification

Unique Protocol ID:	14130
Brief Title:	Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO) (GALILEO)
Official Title:	A Randomized, Double-masked, Sham-controlled Phase 3 Study of the Efficacy, Safety and Tolerability of Repeated Intravitreal Administration of VEGF Trap-Eye in Subjects With Macular Edema Secondary to Central Retinal Vein Occlusion (CRVO)
Secondary IDs:	EudraCT: 2009-010973-19

Study Status

Record Verification:	January 2010
Overall Status:	Recruiting
Study Start:	October 2009
Primary Completion:	February 2011 [Anticipated]
Study Completion:	August 2012 [Anticipated]
First Submitted:	October 30, 2009
First Submitted that Met QC Criteria:	November 12, 2009
First Posted:	November 13, 2009 [Estimate]
Last Update Submitted that Met QC Criteria:	January 21, 2010

Last Update Posted:	January 22, 2010 [Estimate]

Sponsor/Collaborators

Sponsor:	Bayer
Responsible Party:	
Collaborators:	Regeneron Pharmaceuticals

Oversight

U.S. FDA-regulated Drug:	
U.S. FDA-regulated Device:	
Data Monitoring:	Yes

Study Description

Brief Summary:	To determine the efficacy of vascular endothelial growth factor (VEGF) Trap-Eye injected into the eye on vision function in subjects with macular edema as a consequence of central retinal vein occlusion
Detailed Description:	

Conditions

Conditions:	Retinal Vein Occlusion
Keywords:	Macular Edema Central Retinal Vein Occlusion CRVO VEGF Trap-Eye best-corrected visual acuity

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	Phase 3
Interventional Study Model:	Parallel Assignment
Number of Arms:	2
Masking:	TripleParticipant, Investigator, Outcomes Assessor
Allocation:	Randomized
Enrollment:	165 [Anticipated]

Arms and Interventions

Arms	Assigned Interventions
Experimental: Arm 1	Drug: VEGF Trap-Eye (BAY86-5321) Intravitreal injection. Weeks 0 to 20 injection of VEGF Trap-Eye every 4 weeks; weeks 24 to 48 every 4 weeks re-assessment and either (PRN) injection of VEGF Trap-Eye or sham injection; weeks 52 to 100 safety follow-up.
Sham Comparator: Arm 2	Sham treatment Sham treatment. Weeks 0 to 20 sham treatment every 4 weeks; weeks 24 to 48 every 4 weeks re-assessment and sham injection; weeks 52 to 100 safety follow-up.

Outcome Measures

Primary Outcome Measures:

1. The proportion of subjects who gain at least 15 letters in BCVA on the EDTRS chart compared with baseline at the Week 24 endpoint
   Week 24

Secondary Outcome Measures:

2. Change from baseline in BCVA score
   Week 24
3. Absolute change from baseline in central retinal thickness, assessed by OCT
   Week 24
4. Proportion of subjects progressing to anterior segment neovascularization, neovascularization of the optic disc (NVD), or neovascularization of the retina elsewhere (NVE) requiring pan-retinal photocoagulation
   Week 24
5. Change in the NEI-VFQ-25 total score from baseline
   Week 24
6. Change in the EQ-5D score from baseline
   Week 24

Eligibility

Minimum Age: 18 Years

Maximum Age:

Sex: All

Gender Based:

Accepts Healthy Volunteers: No

Criteria: Inclusion Criteria:

- Center-involved macular edema secondary to central retinal vein occlusion (CRVO) for no longer than 9 months with mean central subfield thickness >= 250 µm on optical coherence tomography (OCT).
- Adults >= 18 years.
- early treatment diabetic retinopathy study (ETDRS) best corrected visual acuity (BCVA) of 20/40 to 20/320 (73 to 24 letters) in the study eye.

Exclusion Criteria:

- Previous treatment with anti-angiogenic drugs in the study eye (Pegaptanib sodium, anecortave acetate, bevacizumab, ranibizumab, etc.)
- Prior panretinal laser photocoagulation or macular laser photocoagulation in the study eye
- CRVO disease duration > 9 months from date of diagnosis
- Previous use of intraocular corticosteroids in the study eye or use of periocular corticosteroids in the study eye within the 3 months prior to Day 1
- Iris neovascularization, vitreous hemorrhage, traction retinal detachment, or preretinal fibrosis involving the macula in either the study eye or fellow eye

Contacts/Locations

Central Contact: Bayer Clinical Trials Contact
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Study Officials:

Bayer Study Director
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Locations: **Australia, New South Wales**

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[Not yet recruiting]
Budapest, Hungary, 1106

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Singapore, Singapore, 119074

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Singapore, Singapore, 168751

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Electronic Acknowledgement Receipt

EFS ID:	38658587
Application Number:	16397267
International Application Number:	
Confirmation Number:	8135
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-008CIPCON5
Receipt Date:	21-FEB-2020
Filing Date:	29-APR-2019
Time Stamp:	15:49:41
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	0725US06_2020-02-21_Supp_IDS_trans_REGN-008CIPCON5.pdf	50616 e578c05302b0e045db959d29256dfcd642590263	no	2

Warnings:

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2	Information Disclosure Statement (IDS) Form (SB08)	0725US06__2020-02-21_Supp_IDS_SB08A.pdf	42471 9d842d7c3da23e345620c4e504381603a0ec824d	no	4
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Information:					
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3	Non Patent Literature	NCT01012973_01182013_27424_1a.pdf	387850 3611596cbf2c3151497ab7f1023827335e74dfd0	no	38
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4	Non Patent Literature	NCT01012973_01252011_27433_1a.pdf	202886 863ea430a0b1a1cd4db6546121ce51493c626a14	no	10
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5	Non Patent Literature	NCT01012973_01262012_27428_1a.pdf	204978 9da69fc33b0b54b02ac3a5bc75335ad9b67f02a0	no	11
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Information:					
6	Non Patent Literature	NCT01012973_01302013_27423_1a.pdf	393002 e94c0f2f9b72f0c70de9124d70f494ad9963edb0	no	38
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7	Non Patent Literature	NCT01012973_02092010_27442_1a.pdf	205517 146573f030447d3e752726652930460f5a8e115	no	12
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8	Non Patent Literature	NCT01012973_02202012_27427_1a.pdf	205076 0b34980c7a0f3e5e341d6b0c58b7346829ae9b16	no	11
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9	Non Patent Literature	NCT01012973_03162010_27441_1a.pdf	205838 0b335c9cac34627988ae78c5fadd06e351e30197	no	12
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10	Non Patent Literature	NCT01012973_04082011_27432_1a.pdf	202854 2b6eaff33edab7147db38435285f46f2b6befc80	no	10
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11	Non Patent Literature	NCT01012973_04162010_27440_1a.pdf	206353 115b4761e50f4e965b2b6bf7a18f495e2e3732bd	no	12
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12	Non Patent Literature	NCT01012973_06232011_27431_1a.pdf	202913 73584750b04b8b43d9c186c24e32a6a739d61557	no	10
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13	Non Patent Literature	NCT01012973_07222010_27439_1a.pdf	206587 945460bfe03ce65f025e72290b2a2aa0ec6e18dd	no	12
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14	Non Patent Literature	NCT01012973_08252010_27438_1a.pdf	207066 582fe282007a1d7a122b245830b5a0cef56595e9	no	12
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15	Non Patent Literature	NCT01012973_08262010_27437_1a.pdf	203139 fa7f94b3e8de7bb3ef65f3adac4d9145c4736123	no	10
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16	Non Patent Literature	NCT01012973_09082010_27436_1a.pdf	202787 10f24e5ee4809b91556b3959a04af8002920bbf1	no	10
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17	Non Patent Literature	NCT01012973_09192011_27430_1a.pdf	202833 f8c01baf26e9d562dae1246e3590022a470d2e8e	no	10
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Information:					
18	Non Patent Literature	NCT01012973_10042010_27435_1a.pdf	202793 947ae692be386b88631fedf064a2933898a81924	no	10
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19	Non Patent Literature	NCT01012973_10232012_27426_1a.pdf	387280 baa1f57c36ac7107700b3484197711e18792a8c9	no	38
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20	Non Patent Literature	NCT01012973_10272013_27422_1a.pdf	393007 96988a4c0bc0506e694fab39a1198e4a2bcce693	no	38
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21	Non Patent Literature	NCT01012973_11012010_27434_1a.pdf	202609 419a169b77875f93570ffb485e599399b6d350d5	no	10
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22	Non Patent Literature	NCT01012973_11132009_27444_1a.pdf	205352 2014c1892ab17afd7ae36889f0cbf4f35d3a8e28	no	12
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Information:					

23	Non Patent Literature	NCT01012973_11292011_27429_1a.pdf	202738 1e20bf11575dd80b56a6cc6d51744682dc430bd4	no	10
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Information:					
24	Non Patent Literature	NCT01012973_12182012_27425_1a.pdf	387906 1b275ad8ebcdd13b7008bbb387c8d249babeabd7	no	38
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Information:					
25	Non Patent Literature	NCT01012973_12212010_27443_1a.pdf	205393 69eca39829ebf95d6eadd663cc3719a86ca210b9	no	12
Warnings:					
Information:					
		Total Files Size (in bytes):	5719844		

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New Applications Under 35 U.S.C. 111

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

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

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

New International Application Filed with the USPTO as a Receiving Office

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

Electronically Filed

INFORMATION DISCLOSURE STATEMENT	Attorney Docket No.	REGN-008CIPCON5
	Confirmation No.	8135
	First Named Inventor	George D. Yancopoulos
	Application Number	16/397,267
	Filing Date	April 29, 2019
	Group Art Unit	
	Examiner Name	
Address to: Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Title: "*Use of a VEGF Antagonist to Treat Angiogenic Eye Disorders*"	

Sir:

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

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-008CIPCON5.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: 21 February 2020

By: /Karl Bozicevic, Reg. No. 28,807/
Karl Bozicevic
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	16/397,267
				Filing Date	April 29, 2019
				First Named Inventor	George D. Yancopoulos
				Art Unit	
				Examiner Name	
Sheet	1	of	2	Attorney Docket Number	REGN-008CIPCON5

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	7070959	2006-07-04	Papadopoulos	
	2	8092803	2012-01-10	Furfine et al.	
	3	10406226	2019-09-10	Dix et al.	
	4	10464992	2019-11-05	Furfine 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	2019/0388539	2019-12-26	Dix et al.	
	2	2020/0017572	2020-01-16	Furfine et al.	

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					
	2					

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 "Anti-VEGF 2019: The State of the Art" Review of Ophthalmology (published August 5, 2019)	
	2	CHATZIRALLI et al. "Intravitreal aflibercept for neovascular age-related macular degeneration in patients aged 90 years or older: 2-year visual acuity outcomes" Eye (2018) 32:1523-1529	
	3	CHUNG et al. "Ziv-aflibercept: A novel angiogenesis inhibitor for the treatment of metastatic colorectal cancer" Am J Heath-Syst Pharm (November 1, 2013) 70:1887-1896	
	4	COOPER et al., "Increased Renal Expression of Vascular Endothelial Growth Factor (VEGF) and Its Receptor VEGFR-2 in Experimental Diabetes" Diabetes (1999) 48:2229-2239	
	5	CROLL et al., "VEGF-mediated inflammation precedes angiogenesis in adult brain" Experimental Neurology (2004) 187:388-402	
	6	DeVRIESE et al., "Antibodies against Vascular Endothelial Growth Factor Improve Early Renal Dysfunction in Experimental Diabetes" J. Am. Soc. Nephrol (2001) 12:993-1000	
	7	EREMINA et al., "Glomerular-specific alterations of VEGF-A expression lead to distinct congenital and acquired renal diseases" Journal of Clinical Investigation (March 2003) 111(5):707-716	
	8	ERIKSSON et al., "Structure, Expression and Receptor-Binding Properties of Novel Vascular Endothelial Growth Factors" Vascular Growth Factors and Angiogenesis, Springer (1999) pp. 41-57	

Examiner Signature		Date Considered	

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

INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	16/397,267
				Filing Date	April 29, 2019
				First Named Inventor	George D. Yancopoulos
				Art Unit	
				Examiner Name	
Sheet	2	of	2	Attorney Docket Number	REGN-008CIPCON5

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
	9	FERRARA, N. "Vascular Endothelial Growth Factor: Molecular and Biological Aspects" Advances in Organ Biology (1999) pp. 1-30	
	10	FERRARA et al., "Clinical applications of angiogenic growth factors and their inhibitors" Nature Medicine (December 1999) 5(12):1359-1364	
	11	FLYVBJERG et al., "Amelioration of Long-Term Renal Changes in Obese Type 2 Diabetic Mice by a Neutralizing Vascular Endothelial Growth Factor Antibody" Diabetes (October 2002) 51:3090-3094	
	12	HOLASH et al., "Vessel Cooption, Regression, and Growth in Tumors Mediated by Angiopoietins and VEGF" Science (June 18, 1999) 284(5422):1994-1998	
	13	KOROBELNIK et al., "Intravitreal Aflibercept Injection for Macular Edema Resulting from Central Retinal Vein Occlusion" American Academy of Ophthalmology (2014) 121(1):202-208	
	14	MITCHELL, Edith P. "Targeted Therapy for Metastatic Colorectal Cancer: Role of Aflibercept" Clinical Colorectal Cancer (2013) 12(2):73-85	
	15	NOGUERA-TROISE et al., "Blockade of D114 inhibits tumour growth by promoting non-productive angiogenesis" Nature (December 2006) 444:1032-1037	
	16	RUDGE et al., "VEGF Trap complex formation measures production rates of VEGF, providing a biomarker for predicting efficacious angiogenic blockade" PNAS (November 20, 2007) 104(47):18363-18370	
	17	SCHMIDT-ERFURTH et al., "Intravitreal Aflibercept Injection for Neovascular Age-related Macular Degeneration" Ophthalmology (2014) 121:193-201	
	18	SEMERARO et al., "Aflibercept in wet AMD: specific role and optimal use" Drug Design, Development and Therapy (August 2, 2013) 7:711-722	
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	20	THURSTON, Gavin "Complementary actions of VEGF and Angiopoietin-1 on blood vessel growth and leakage" J. Anat. (2002) 200:575-580	
	21	XIA et al., "Transgenic delivery of VEGF to mouse skin leads to an inflammatory condition resembling human psoriasis" Blood (July 1, 2003) 102(1):161-168	

Examiner Signature		Date Considered	

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

REVIEW of OPHTHALMOLOGY

Christopher Kent, Senior Editor

PUBLISHED 5 AUGUST 2019

Anti-VEGF 2019: The State of the Art

Surgeons share the latest thinking about the benefits and risks of anti-VEGF therapy, and what lies ahead.

There's no question that anti-VEGF drugs have caused a sea-change in the treatment of several retinal diseases. Conditions that were basically untreatable have now become manageable, preventing what was once almost inevitable blindness. Yet there's still plenty of room for improvement; results vary, and not all patients avoid vision loss.

"When I started my career, neovascular age-related macular degeneration was a horrible disease," recalls K. Bailey Freund, MD, a retina specialist and a clinical professor of ophthalmology at the New York University School of Medicine. (Dr. Freund has been a principal investigator in several pivotal trials of novel treatments for retinal diseases.) "Nothing we could do would really help our patients. Today, certain patients do extremely well—particularly the ones that have Type 1 (subretinal pigment epithelium) neovascularization under the fovea. Others do well initially, but eventually the non-neovascular aspect of the disease kicks in and they ultimately end up losing vision, more from macular atrophy than exudative complications."

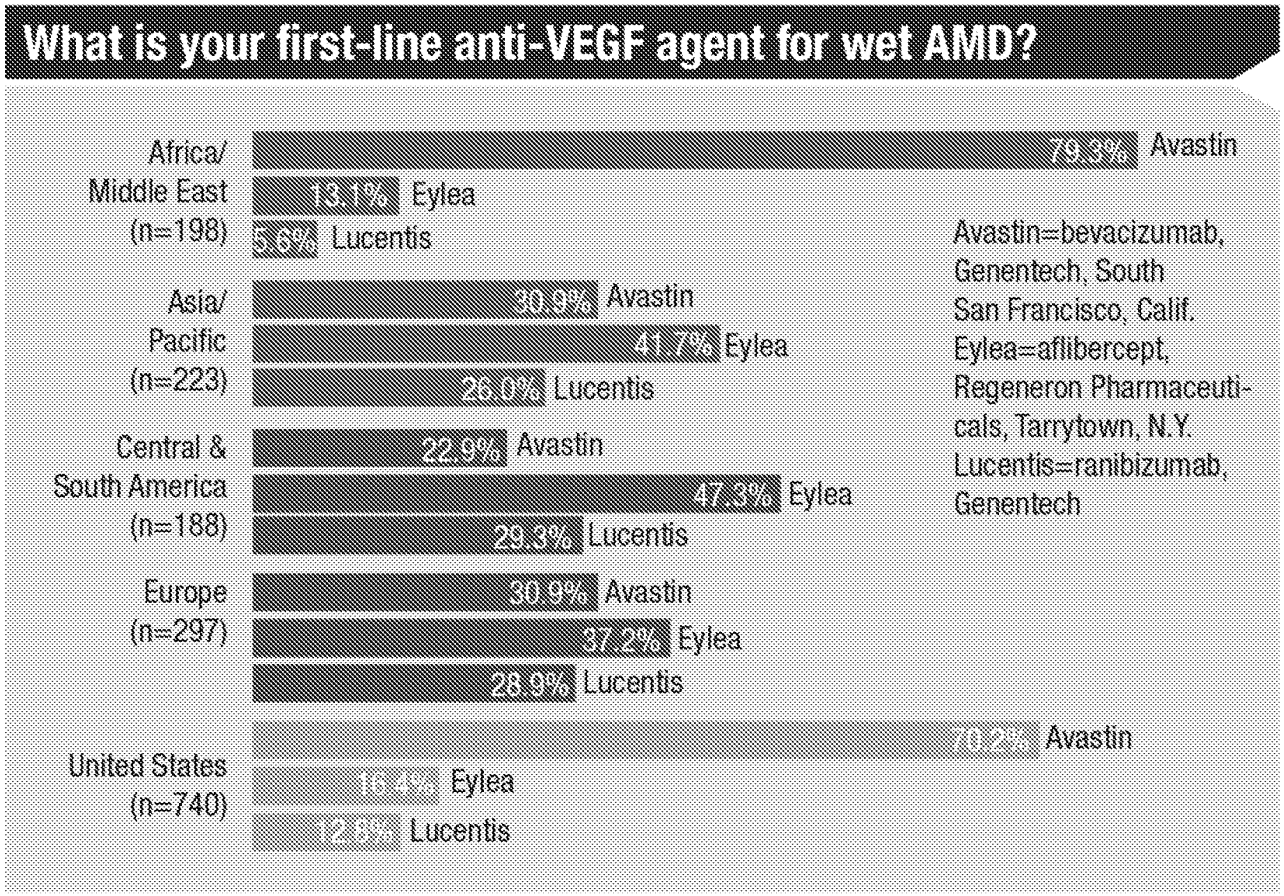
Here, retina specialists answer key questions about the current state of anti-VEGF drug treatments for macular degeneration and other retinal diseases; share the latest insights, which suggest that neovascularization and subretinal fluid are not always a bad thing; and discuss what the upcoming years may hold.

Anti-VEGF Drug Choice

"Each anti-VEGF option has an advantage that certain people prefer," notes Philip Rosenfeld, MD, PhD, professor of ophthalmology at the Bascom Palmer Eye Institute at the University of Miami Miller School of Medicine. "For example, bevacizumab is cheap. In certain countries surgeons can get a rebate for using ranibizumab, so some doctors use it because it's financially rewarding for the practice. Aflibercept is the preferred drug for certain neovascular types of disease; for example, I think it works best in fibrovascular retinal pigment epithelial detachments with a significant serous component.

"Personally, I treat with bevacizumab and aflibercept," he says. "In my non-hospital-based setting, I always start with bevacizumab and try to get a durability that exceeds six, eight or 10 weeks. If I can't get beyond that six-to-eight week interval, then I switch to aflibercept. Some surgeons prefer ranibizumab, and others prefer to use aflibercept exclusively. However, many times when patients are in Medicare Advantage plans, the choice of drug is decided by the provider."

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Data from the Global Trends in Retina Survey, conducted by the American Society of Retina Specialists, in conjunction with the 20th Annual ASRS Preferences and Trends (PAT) Survey.[3] Members of 42 retina societies around the world participated in the 2018 Global Trends in Retina Survey. (Reprinted with permission.)

Dr. Rosenfeld notes that The American Society of Retina Specialists runs an annual Patterns and Trends survey, in which they ask about anti-VEGF drug choices every year. “We don’t have the results for 2019 as we speak,” he says, “but the replies for 2018 indicated that in the U.S., bevacizumab is the first-line choice for treating wet AMD for about 70 percent of retina specialists. Ranibizumab is first-line for 12 percent, and aflibercept is first-line for 16 percent. Outside the U.S.—except in Africa and the Middle East—it looks like aflibercept wins. However, treating physicians are litigating for access to bevacizumab in the U.K. In France, it’s still very hard to get.” (He notes that at a recent retina meeting in Italy, most treating physicians said that they’ve used all three drug options—ranibizumab, bevacizumab and aflibercept.)

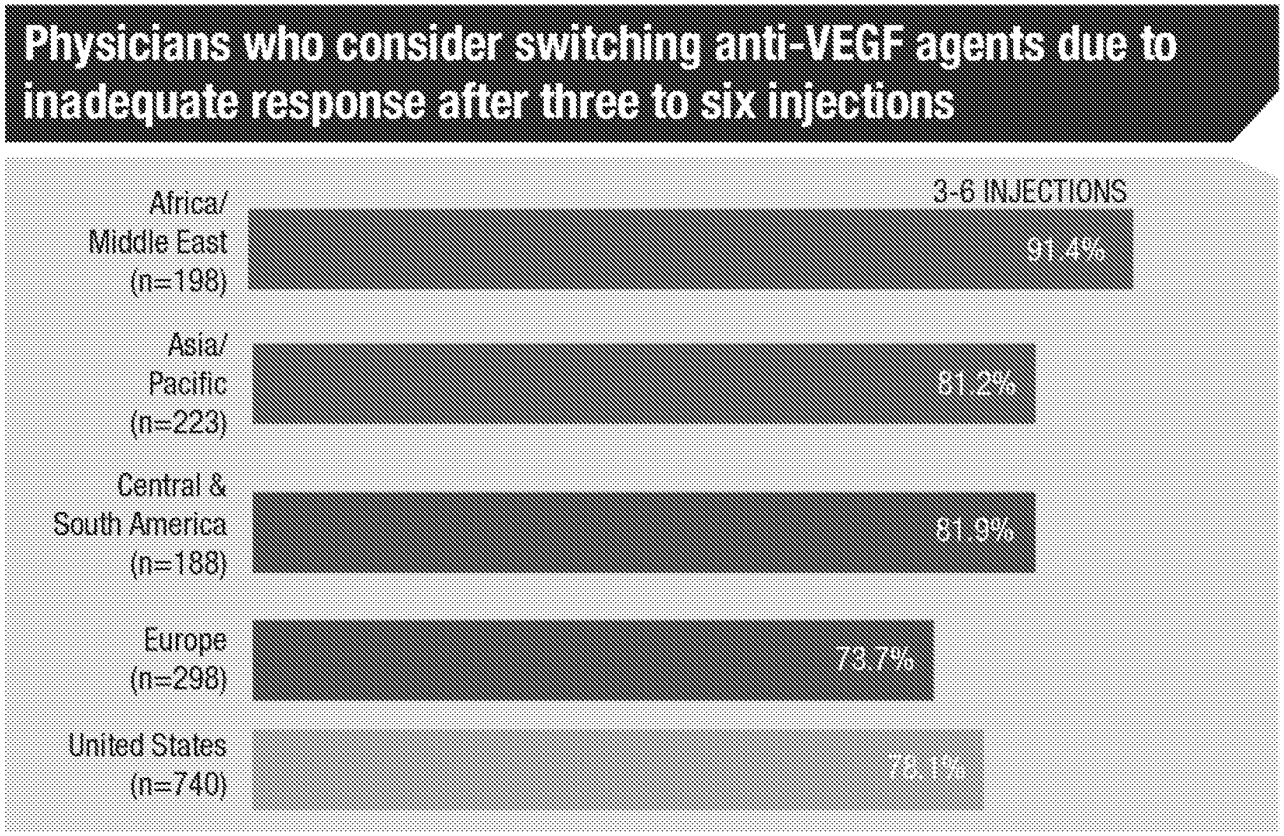
Dr. Freund says he finds the current anti-VEGF agents to be fairly similar in terms of efficacy and safety, so he chooses his drug regimen based on the individual patient’s presentation. “I might choose one drug over another when a patient is somewhat refractory to treatment,” he says. “This is particularly true for eyes that have what I currently refer to as aneurysmal Type 1 neovascularization, more commonly known as polypoidal choroidal vasculopathy. I see many patients with this lesion growth pattern because it was first described in our practice, and I’ve published on it extensively.

“Eyes with this lesion growth pattern may have a more robust response to aflibercept,” he continues. “Clinical trial evidence from the PLANET study showed that many of these eyes respond well to aflibercept monotherapy, while data from the EVEREST II trial indicates that eyes with aneurysmal Type 1 neovascularization receiving

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ranibizumab may require the addition of photodynamic therapy in order to optimize visual outcomes.

"There's another form of neovascular AMD that I call pachychoroid neovasculopathy," he notes. "These eyes have choroidal findings that are similar to those seen in eyes with central serous chorioretinopathy. Also, they lack some of the characteristic clinical findings we associate with typical macular degeneration in elderly Caucasian patients, such as soft drusen. Those eyes may benefit from aflibercept, since aflibercept has been shown to decrease choroidal thickness more than the other agents. I find that eyes which are somewhat refractory to anti-VEGF therapy may not respond as well to bevacizumab, compared to the other agents.



More data from the 2018 Global Trends in Retina Survey, conducted by the American Society of Retina Specialists.[3] (For more information, see the caption for the chart on page 27.)

"In the final analysis, a typical patient responds well to all of these agents," he says. "Numerous studies show that bevacizumab is noninferior to the alternative FDA-approved options. However, for patients managed on a treat-and-extend regimen, I'm less comfortable extending my dosing interval beyond eight weeks with bevacizumab. So, for patients with no out-of-pocket drug expense, we may choose a different agent that could require fewer injections, particularly when frequent office visits would be very difficult."

Of course, some patients don't respond to the first drug the treating physician tries, but Dr. Freund points out that switching refractory patients to an alternative anti-VEGF is not a cure-all. "When aflibercept was approved, many practices did what we then called 'switcher' studies," notes Dr. Freund. "We took patients who were poorly controlled with monthly bevacizumab or ranibizumab and switched them to aflibercept, expecting that because most eyes in the aflibercept trials could be maintained on injections every eight weeks, the same might happen with these refractory cases. But the eyes we were switching were very different from the type of newly-diagnosed cases

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enrolled in clinical trials. All we typically found was that aflibercept might get rid of more fluid for a little longer than the prior agents. We did not find that eyes showing persistent fluid with monthly ranibizumab were fluid-free for eight weeks with aflibercept."

Regarding the treatment protocol, Dr. Rosenfeld says he believes that most clinicians treat their patients using a treat-and-extend or modified treat-and-extend regimen. "This usually means performing monthly dosing until the macular fluid is resolved, and then extending the interval until macular fluid recurs," he explains. "At that point the interval is shortened, and eventually a treatment interval is defined for that particular patient. When I attended the FLORetina meeting in Florence, Italy recently, this protocol seemed to be the general consensus among the attendees."

Is Neovascularization Bad?

Clearly, neovascularization can be part of the problem in retinal diseases such as macular degeneration. However, many researchers note that anti-VEGF drugs aren't really treating the neovascularization—and they're beginning to suspect that neovascularization may actually be a good thing in some patients.

"There are three types of macular neovascularization," Dr. Rosenfeld explains. "The major type is what's called Type 1, which occurs under the retinal pigment epithelium. Today, with OCTA, particularly swept-source OCTA, we can identify Type 1 neovascularization long before exudation occurs. For that reason there's been some debate about whether we should treat Type 1 lesions with anti-VEGF therapy before exudation starts.

"I think the consensus is that we should not," he says. "Instead, we should watch the lesions and treat when symptomatic exudation develops. The reason is that those lesions don't go away because of treatment. What we're doing is training them not to leak. We calm the lesion down, but we don't make it go away.

Do Anti-VEGF Drugs Cause Atrophy?

Philip Rosenfeld, MD, PhD, professor of ophthalmology at the Bascom Palmer Eye Institute at the University of Miami Miller School of Medicine, believes the concern about anti-VEGF therapy possibly promoting the formation of macular atrophy is still present, but receding. "There's still some debate about whether the drugs themselves are influencing the formation of macular atrophy," he notes, "or whether it's just normal disease progression, or whether it's a characteristic of certain lesion types, such as Type 3 macular neovascularization, also known as retinal angiomatous proliferation, which tends to form atrophy."

K. Bailey Freund, MD, a retina specialist and a clinical professor of ophthalmology at the New York University School of Medicine, admits that a connection between anti-VEGF treatment and atrophy is biologically plausible. "Continuous VEGF suppression could do that, but we're not actually providing continuous suppression," he points out. "We give a large bolus of the drug, and over time the concentration drops to a very low level. Then we give another bolus. This may be one reason that the studies suggesting a possible link between anti-VEGF therapy and atrophy have really only shown this association when patients were treated continuously every month. Even these studies haven't really proven that the anti-VEGF treatment is causing the atrophy."

Dr. Freund advises clinicians to use their judgment. "Look at the data and use common sense," he says. "It might be reasonable to reduce injection frequency for eyes with Type 3 lesions, but not in eyes with large vascularized pigment epithelial detachments, particularly those with aneurysms—more commonly known as polyps—as these eyes appear resistant to macular atrophy, but are at risk for catastrophic hemorrhages if undertreated. So, look closely at the type of eye you're treating and adjust your protocol accordingly.

"The data indicate that more patients in the United States and around the world lose vision to undertreatment than to overtreatment," he adds. "So, while I think retina specialists should be concerned about causing atrophy, they should also be concerned about the disease itself, and make sure it's kept under control."

Dr. Rosenfeld agrees. "When patients come to us with exudative disease, not treating them isn't an option," he says. "So they get the injections, and we try to balance the need for reinjection and eliminating macular fluid against our concern about the possibility that overtreatment may exacerbate atrophy."

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"In fact, we're starting to believe that when the Type 1 lesions go away, you're left with macular atrophy," he says. "Many of my colleagues believe that you need to manage the neovascularization, but you don't want to overtreat it. You want the neovascularization to stay there and just stop leaking. To put it another way, the field has evolved to believe that neovascularization is not the enemy; exudation and hemorrhage are the enemy. The neovascularization may actually be serving a very important function—providing nutritional support for the retinal pigment epithelium. Its appearance may be a normal physiologic response to a pathological condition in which you're losing the choriocapillaris and there's low-grade inflammation in the back of the eye. You need this neovascular complex. You just don't want the exudation."

"We know that patients that look clinically dry can harbor 'non-exudative' Type 1 neovascular tissue, which proliferates beneath the RPE with little clinical or optical coherence tomography evidence of its presence," says Dr. Freund. "There's no fluid and no hemorrhage. Today, however, we have tools like OCTA that let us detect these vessels. The most notable fact is that some of these patients never develop pathologic exudation. The challenge is that we don't know exactly what percentage of those patients will eventually develop vision-threatening fluid and hemorrhage."

Dr. Freund frequently collaborates with Christine A. Curcio, PhD, a professor of ophthalmology at the University of Alabama at Birmingham, who is an expert in the histology of macular degeneration. "We've been performing clinicopathologic correlations for AMD for close to a decade," he says. "If patients from my practice consent, we enroll them in our donor program, and the eye bank recovers the whole globe following their death. Our mission is to correlate the histology with the retinal imaging done in the clinic.

"We're currently studying the eyes of a patient followed for 10 years," he says. "When she first presented, she was in her late 70s, and she'd already lost central vision in one eye from scarring due to neovascular AMD. Surprisingly, even though fluorescein angiography and OCT documented Type 1 neovascularization in her other eye, this eye never developed sight-threating exudation, and retained excellent visual acuity for more than a decade. This unusual disease course was documented with multimodal retinal imaging, which we're now correlating with high-resolution histology. Unexpectedly, it turns out that more than half of her macula was sitting on top of neovascular tissue, and the overlying photoreceptors maintained a healthy structure. The neovascular tissue appears to have maintained nutritional support to the fovea as the patient's native choriocapillaris failed due to aging. So, by the time she died, the health of her outer retina appears to have been maintained by the very same tissue that we all fear is going to cause patients to lose vision—tissue that we often do everything in our power to suppress with our anti-VEGF agents."

Dr. Freund notes that the idea that Type 1 neovascularization could be beneficial isn't new. "This idea was first proposed by Hans E. Grossniklaus, MD and Richard Green, MD," says Dr. Freund. "They hypothesized that Type 1 neovascularization had the potential to recapitulate the normal choriocapillaris, and this concept appears to be supported by the findings in our current donor. In some patients, these non-exudative vessels may actually be helping to preserve the overlying retina. So, the goal may not be to destroy or completely inhibit their growth but to carefully monitor eyes with these vessels so that pathologic exudation can be caught and treated early.

"That means we need to have the right balance," he concludes. "We shouldn't be so aggressive that we destroy a potentially protective mechanism that could benefit our patients in future, but we also shouldn't let it get out of control and damage vision quickly with catastrophic bleeding."

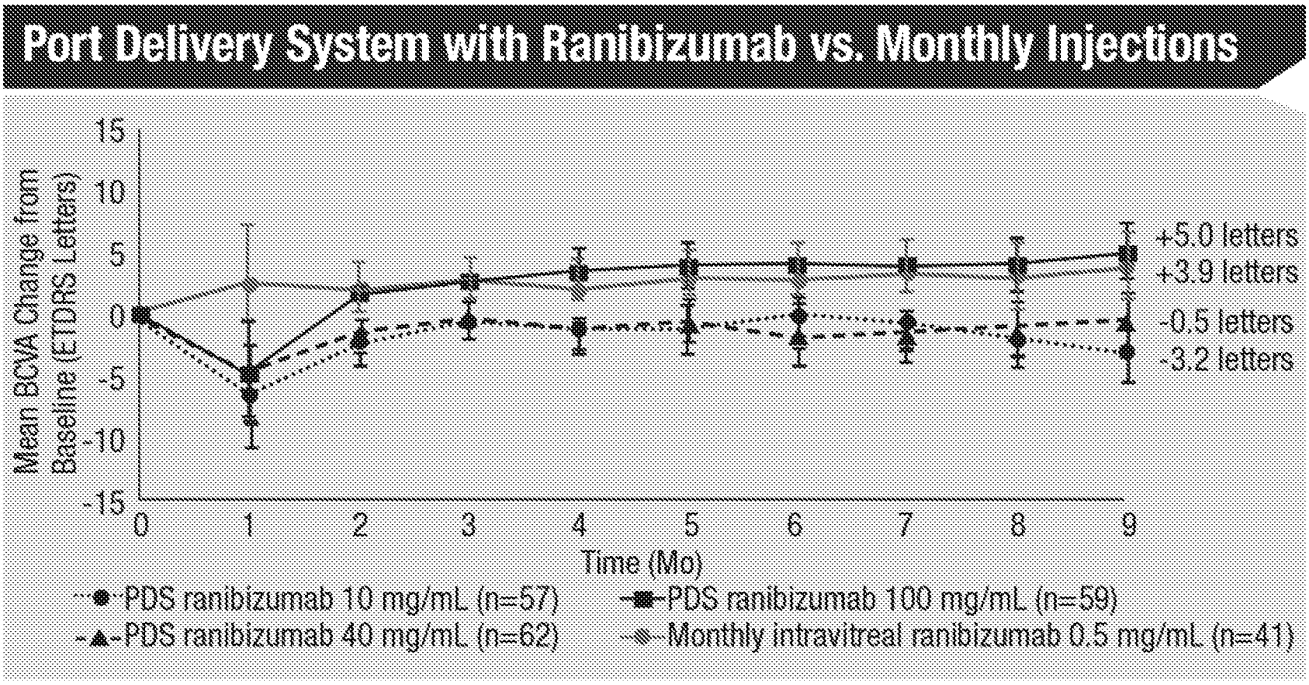
Is Fluid Always a Bad Thing?

"Studies have shown that eyes treated with intravitreal anti-VEGF therapy which continue to manifest subretinal fluid —eyes that don't go completely dry—may do as well, or even better, than eyes which dry up completely," notes Dr. Freund. "So, a little bit of fluid may not be such a bad thing."

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Dr. Freund refers to the three main types of neovascularization occurring in exudative AMD, and says evidence is mounting that they may warrant different treatment regimens. “I believe retinal specialists should look at the eye’s presenting imaging characteristics, which define a lesion’s subtype,” he says. “Different subtypes seem to respond differently to treatment and call for different levels of monitoring. For example, it’s my strong belief that eyes presenting with Type 1 neovascularization beneath the fovea that continue to show a small amount of subretinal fluid, despite frequent dosing, are more resistant to geographic atrophy than eyes with other neovascular lesion patterns. In these eyes, a little bit of fluid is probably not such a bad thing. The main threat to vision in eyes like this appears to be the occurrence of subretinal hemorrhage if treatment is discontinued.

“In contrast, atrophy is a greater concern in eyes that have intraretinal neovascularization known as a Type 3 neovascularization or RAP (retinal angiomatous proliferation) pattern,” he continues. “Greater susceptibility to macular atrophy in eyes with Type 3 lesions has been observed in several large clinical trials. Patients presenting with Type 3 neovascularization are often older individuals with thin choroids and focal areas of macular hyperpigmentation, both of which increase susceptibility to macular atrophy. For eyes presenting with Type 3 neovascularization, I’ll often first try PRN dosing, for three reasons: lesion quiescence may be long-lasting; recurrences predictably occur at the initial site of activity; and recurrent exudation with Type 3 lesions is rarely accompanied by large hemorrhages.”



Data from the Phase II LADDER clinical trial. All patients were previously treated with and were responsive to anti-VEGF therapy. (Vertical bars=95% confidence intervals.)[4]

Dr. Freund notes that Type 1 and Type 3 are the two most common variants of neovascular AMD. “Type 2 and mixed lesions with a component of Type 2 are less common, but the vessels in these eyes have broken through the RPE to proliferate in the subretinal space,” he says. “You have to be careful with these cases, since recurrent exudation from Type 2 lesions is in direct contact with the vulnerable photoreceptors. In that situation irreversible vision loss can occur quickly.”

Dr. Freund points out that the implication is that different types of lesions should be treated differently. “Don’t simply assume that all neovascular AMD is the same and should be treated with the same regimen,” he says. “Over the short term, these slight variations in regimen may not seem to make a difference, but we often treat patients for the

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rest of their lives. Little differences in how a patient does on one regimen versus another end up making a big difference over five, 10 or 15 years of treatment."

Dr. Freund says that OCT may provide clues to the best treatment protocol. "If you see a shallow, irregular PED with heterogeneous internal contents in a patient with other findings of AMD, there's a high probability that this finding represents neovascular tissue," he says. "If there's no exudation, eyes with this finding should be monitored closely, and the patient should be instructed to use an Amsler grid to monitor for conversion to active wet disease.

"When this type of vascularized pigment epithelial detachment, or Type 1 pattern, is subfoveal and associated with exudation, I use a treat-and-extend regimen of anti-VEGF therapy to control exudation," he continues. "However, my goal is not to flatten the PED itself. I believe that intense treatment has the potential to convert a vascularized PED into avascular fibrotic tissue—tissue that will no longer be able to support the overlying retina. If there's no hemorrhage, I'm not concerned about a little bit of persistent subretinal fluid, as long as it's not increasing over time."

Dr. Freund says that many of his patients have demonstrated the wisdom of this approach. "I have many patients I've been treating with anti-VEGF therapy for 10 or more years, some of whom have had as many as 100 injections," he says. "Many eyes still have close to 20/20 vision."

How Important is OCTA?

"Right now we treat based on exudation—the fluid that's visible on structural OCT," notes Dr. Rosenfeld. "However, people are working hard to see if the information we pick up with OCTA may be able to influence how we treat. Many papers have been published about using OCTA to look at different types of neovascular structures that exist in these eyes with wet AMD, hoping that some of what they find would be predictive of how often we need to treat, and/or the outcome of treatment. The results have been underwhelming, which is probably because the anti-VEGF drugs treat the exudation, not the neovascularization. Thus, changes in the vasculature revealed by OCTA may be less important than the presence of exudation on structural OCT.

"However, OCTA does have a role," he says. "It's a very powerful way to identify eyes with dry macular degeneration that are at higher risk of exudation, so we can follow them differently. With OCTA—in particular SS-OCTA—you can see the neovascularization many months before patients actually develop exudation. It's growing silently. This has been known since the 1970s, when autopsy eyes with dry macular degeneration were shown to harbor neovascularization; it just wasn't leaking or bleeding. Using ICG angiography in the 1990s, retina specialists also showed that this neovascularization existed in their living patients. However, we couldn't routinely screen patients with ICG angiography, so this discovery was largely forgotten until OCTA came along.

"Knowing that this neovascularization is present, via OCTA, is valuable information," he says. "We recently conducted a two-year study involving 227 patients, which is currently in press. We compared eyes with and without this nonexudative neovascularization and found that there's a 14-fold increased risk of exudation over a period of two years when neovascularization is present. So OCTA serves a purpose—just not for monitoring lesions once you start treating. Instead, it can help to identify these lesions before exudation develops.

"For this reason, I use OCTA to check all of my dry AMD patients to see if they have these lesions," he says. "It changes how I manage my patients. If they have the lesions, I usually follow them every two months. If they don't have the lesions, I usually follow them every six months. It also helps me educate patients so they understand what's going on and become partners in their own management."

Dr. Freund says he uses OCTA frequently, but doesn't believe it's essential for diagnosing or treating AMD. "Often, OCT alone is sufficient to diagnose neovascular AMD or to arouse high suspicion that there's a problem," he notes. "In some cases, when there's a characteristic OCT pattern of specific neovascular features, dye angiography may

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not be needed, especially if there's a hemorrhage. I think OCTA is helpful if, like myself, you're interested in identifying the neovascular lesion type to help individualize your treatment algorithm.

"Does individualizing the treatment regimen necessarily lead to better outcomes?" he adds. "I think so, but this remains to be proven. For now, I'd say that OCTA is a valuable research tool. In the future, it may become essential for a clinician managing macular degeneration."

Dr. Rosenfeld believes clinicians will benefit from using OCTA. "I think everyone who practices retinal care needs access to OCTA, whether it's for diabetes or AMD or vein occlusions," he says. "It's a remarkable tool that allows us to see the full extent of the underlying disease, and in certain situations helps us manage it better. OCTA is now our number one tool for diagnosing proliferative diabetic retinopathy. It helps us determine the extent of vascular nonperfusion in diabetics and vein occlusion, and it's particularly useful for identifying the subclinical, nonexudative lesions in dry AMD. Furthermore, patients love it compared with dye-based angiograms. Meanwhile, of course, structural OCT is very useful for managing all of these conditions as well. But with OCTA scans, you get both the structural OCT and the angiographic OCT."

Dr. Rosenfeld points out one big problem with OCTA, however, at least in the United States. "We don't have a unique billing code for OCTA," he explains. "The scan time is about the same as routine OCT, but the time it takes for the physician to interact with the instrument, look at the scans and extract the information by manipulating the segmentation boundaries to get the best possible image isn't currently reimbursed. So, while the equipment is more expensive and it takes more time to evaluate the scans, the reimbursement is the same as for the more typical OCT. Outside the U.S., OCTA has a higher reimbursement, so the technology has become very popular. But in the U.S., it's a difficult product to sell, because doctors want the revenue from dye-based angiography.

"Despite that concern, I believe it's worth using OCTA," he concludes. "With it, you achieve increased patient satisfaction and patient wait time is decreased. You can see more patients, because dye-based angiography takes a long time to perform—and it's risky. So from an economic standpoint I think OCTA wins, even without the unique billing code."

The Syringe Factor

K. Bailey Freund, MD, a retina specialist and a clinical professor of ophthalmology at the New York University School of Medicine, notes that the type of syringe used to deliver the anti-VEGF medication has become a point of consideration. "Unless a syringe is silicone-free, droplets of silicone can end up in the medication," he explains. "Then, if you use syringes that don't have reservoir at the tip, which can trap the silicone as it's pushed down by the plunger, you're more likely to inject some of that silicone into the eye. Compounding pharmacies often use fixed-needle insulin syringes which lack a reservoir at the tip. As a result, some silicone oil often gets into the vitreous.

"Lucentis now offers a pre-filled syringe that's been designed, in part, to minimize this problem," he continues. "Also, with aflibercept, or ranibizumab dispensed in a vial, most retinal specialists use syringes with either a Luer-Lock or Luer-Slip design. These syringes have a dead space at the tip, so when the plunger is pushed all the way down, not all of the fluid in the syringe is injected into the vitreous. However, that type of syringe is frequently not used for bevacizumab, in part because the presence of a dead space requires that more drug be added, which increases the cost.

"The SCORE trial investigators reported this issue with fixed-needle syringes when they were looking at a syringe pre-filled with an Allergan steroid," he says. "Furthermore, a study published in 2017 compared the amount of silicone expressed from syringes of different types.[1] It showed quite convincingly that when you use syringes with fixed needles, you're more likely to see silicone droplets expressed from the needle tip. I'm also a co-author of a recently published editorial in *Retina* which discusses this topic.[2]"

Dr. Freund admits that the number of incidents related to this problem and compounded bevacizumab is very small. "Nevertheless, there are potential issues with a compounded drug," he says. "All of those factors weigh into which drug you choose, even if you think there's not much of a difference between the drugs."

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What's Next?

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As effective as the current options are, new drugs and technology in the pipeline have surgeons hoping for even better outcomes—and a reduced injection burden.

• ***Brolucizumab***. This is an investigational anti-VEGF drug from Novartis. "We hope it will provide a greater duration of action," Dr. Rosenfeld explains.

Dr. Freund notes that brolucizumab was compared head to head with aflibercept in a trial. "The trial compared the labeled dosing of Eylea—every four weeks times three, extended to once every eight weeks—to brolucizumab, which is given every four weeks for three injections and then extended to every 12 weeks," he explains. "With brolucizumab, a little more than half of the eyes could be maintained on the 12-week dosing to the final 48-week endpoint. Unfortunately, the trial design makes it hard to do a direct comparison between the drugs because patients treated with aflibercept were never extended beyond eight weeks. However, during the first three months, all the eyes were dosed every four weeks. During that period, there was more improvement in OCT thickness with brolucizumab than with aflibercept. "Part of the reason for this finding is that brolucizumab is a smaller molecule in a more concentrated formulation," he points out. "When you inject the same volume of both drugs, the molar concentration of brolucizumab is approximately 10 times that of aflibercept. That means you're getting a lot more drug in the eye with each injection of brolucizumab."

One reason surgeons look forward to new options is the possibility that they'll help to treat refractory patients. However, Dr. Freund points out that it could be problematic to use brolucizumab for this purpose, at least at the outset, because of the trial design. "Let's say you have a patient that doesn't dry up as much as you hope using one of the other agents," he says. "In the trials of the other drugs there were arms in which patients were treated monthly to the endpoint. Brolucizumab didn't have that, so it seems unlikely that the initial approval will include long-term monthly dosing. The reality is, if a refractory patient can't go for four or five weeks on the other agents, they'll probably have trouble going for eight or 12 weeks with brolucizumab. That may limit how much you can use that drug for these difficult, refractory patients.

"I believe the company is doing other studies that may eventually get a label allowing monthly treatment," he adds, "but at the launch that could be a bit of an issue."

• ***Abicipar pegol***. Another drug being tested is Allergan's abicipar pegol. "The trial design was basically 12-month dosing head-to-head between abicipar pegol and monthly ranibizumab," Dr. Freund explains. "The new drug met its noninferiority endpoint, which is fairly impressive. Patients went to 12 weeks and seemed to do just as well as patients getting ranibizumab every month.

"The issue is that there's been some inflammation with abicipar pegol," he continues. "Initially about 15 percent of patients had inflammation. However, the company subsequently released data from a trial called MAPLE, where a change in the manufacturing of the drug reduced the inflammation rate to 8 or 9 percent, and so far, there's no evidence that the inflammation caused in any of these patients was of much concern. So, you could decide to try abicipar pegol on your patient once. If the patient develops inflammation, you could stop. The risk/benefit ratio would be pretty good: There may be only a 9-percent chance that that the patient will have inflammation, but there's close to a 90-percent chance that the patient will be able to be dosed once every 12 weeks. With brolucizumab you'd only have a 50-50 chance of reaching every 12 weeks. That's one way to look at the data."

• ***Sustained delivery.*** A key way to reduce the injection burden, of course, is via sustained delivery. "No one likes injections," notes Dr. Freund. "But now Genentech has an implantable port that's a refillable reservoir. Theoretically, you'd only have to do two refills a year."

Dr. Rosenfeld says that data from the LADDER study, involving Genentech's Port Delivery System with ranibizumab, was presented at the FLORetina meeting. "It appears to provide some extended benefit for patients," he says. "Less-frequent dosing was needed. In addition, there's a sustained-release tyrosine kinase inhibitor from Graybug Vision (Redwood City, California) that may or may not prove to be a long-term solution for this problem."

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• ***Home monitoring.*** "The key to monitoring those lesions is going to be some kind of home monitoring that's reliable," notes Dr. Rosenfeld. "Our dream device would be an OCT that a patient could use every day, or every other day. That would allow us to identify exudation as soon as it develops. Home OCT monitoring would be useful for following patients who have non-exudative, neovascular lesions that we can identify with OCT angiography, who are at high risk for exudation, as well as patients on a treat-and-extend regimen. If they were testing themselves with home OCT monitoring, we'd know as soon as the fluid develops or recurs.

"Notal Vision has a prototype that's being tested that uses an AI algorithm capable of picking up exudation," he continues. "There are other strategies being developed as well, but the Notal Vision device may become available within a year or two. Patients wouldn't buy the instrument; it would be more of a lease situation. Medicare currently covers the cost of home monitoring, so for a nominal fee, perhaps in addition to Medicare coverage, you'd be able to have your patients monitored at home."

• ***Gene therapy.*** "Two companies have gene therapies that involve injecting a viral vector into the eye," says Dr. Freund. "Adverum Biotechnologies is in a Phase I trial with an intravitreal injection, and Regenxbio will soon be conducting a Phase II trial involving subretinal delivery of gene therapy. The viral vector inserts DNA into cells in the eye, so they start to produce either ranibizumab or aflibercept on their own. Theoretically, you could inject it once and you'd be done. To me that's very exciting." REVIEW

Dr. Freund is a consultant for Allergan, Novartis, Zeiss, OptoVue and Heidelberg Engineering, and receives research support from Genentech Roche. Dr. Rosenfeld has received research funding from and is a consultant for Carl Zeiss Meditec.

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ARTICLE

Intravitreal aflibercept for neovascular age-related macular degeneration in patients aged 90 years or older: 2-year visual acuity outcomes

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Abstract

Purpose The purpose of this study was to investigate the efficacy of intravitreal aflibercept for neovascular age-related macular degeneration (nAMD) in very elderly patients aged 90 years or older at 2 years after treatment initiation.

Methods In this multicentre retrospective data analysis from electronic medical record, consecutive treatment-naive patients with nAMD treated with aflibercept with at least 2 years follow-up were stratified into those aged < 90 years (Group I) and an older cohort aged 90 and over (Group II). We compared the visual acuity (EDTRS letters) outcomes at 4 weekly intervals between the two groups over a 2-year period.

Results The mean visual acuity of Group I at presentation was 56.3 ETDRS letters versus 52.8 letters in Group II. Maximal visual acuity was achieved in both the groups by 6 months after initiating treatment (4.7 vs. 4.0 letters gain). By 2 years, the mean visual acuity of the older cohort fell marginally below their baseline visual acuity (0.8 letter loss), while Group I presented +2.1 letters gain. The number of injections given and the retention rate of the older cohort were no different to the rest of the patients.

Conclusions Very old patients with nAMD benefited from aflibercept, but not to the same degree as the younger patients. The study showed that, on an average, the very elderly patients were able to adhere to the intensive anti-VEGF treatment regimens.

Introduction

Age-related macular degeneration (AMD) is broadly classified into early and late forms. Late AMD is the leading cause of visual loss in the elderly. AMD is a perfect example of an aging-dependent condition, where the prevalence of the disease increases monotonically with age [1]. The prevalence of late AMD increases from 1% at 70 years to as high as 12% in patients over 80 years [2–4]. This condition is an outcome of a multitude of accumulating degenerative changes in the various layers of the outer retina and the choroid. Although there have been many well-conducted epidemiological studies on AMD, the proportions of patients aged 90 years or older in these cohorts were small. Therefore, there is a paucity of information on AMD in the very elderly patients.

Late AMD is further classified into "dry" and "wet or neovascular" (nAMD). The former is responsible for the majority of cases, but there are no treatment options available for this condition as yet. Only 10–15% of patients exhibit nAMD and these patients present with sudden decrease in vision, and if left untreated, this condition results in profound irreversible visual impairment [5, 6]. AMD is a bilateral disease and the risk of developing nAMD in the fellow eye of patients with unilateral AMD

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increases by 10% per year from the date of diagnosis, albeit this is dependent on features of the eye and other risk factors [7]. Furthermore, if a patient develops nAMD in one eye at the age of 80, the risk of nAMD in the fellow eye is 48% at 10 years [6]. Therefore, we would expect most patients with nAMD at 90 years to have bilateral nAMD. Determining the outcome of treatment in this cohort, compared to those in the younger age group, has implications, as it estimates the burden of this disease in this age group that is also at risk of other aging-dependent co-morbidities. Studying the treatment outcomes in this group will also provide us with better estimates of age-dependent outcomes of treatments for health economic evaluation. Ultimately, this has significant implications for future service provision, and treatment planning in the very elderly.

Intravitreal injections of inhibitors of vascular endothelial growth factor (VEGF) have been the mainstay of treatment for nAMD for over a decade [8–12] The three anti-VEGF agents commonly used for this condition include ranibizumab, bevacizumab and aflibercept. The treatment regimens are intensive with monthly intravitreal injections for 3 months, followed by varying re-treatment regimens depending on the anti-VEGF agent. On an average, a patient requires 7–8 injections in the first year and six injections from the second year. A comprehensive assessment of baseline predictive factors for visual outcomes at month 12 in Comparison of Age-related macular degeneration Treatment Trials (CATT) demonstrated that older age was associated with poor outcomes in both ranibizumab and bevacizumab groups, while the exact cause for this observation remains unknown [10]. Aflibercept is the newest FDA-approved anti-VEGF agent against nAMD, which binds tightly to VEGF-A, having a longer half-life than both ranibizumab and bevacizumab, a property which can be exploited by ophthalmologists to allow greater intervals between intravitreal treatments [12] The VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD studies (VIEW 1 and VIEW 2) showed that intravitreal aflibercept given bimonthly after 3 initial monthly doses had comparable improvement in visual acuity as monthly ranibizumab in treatment-naive patients with nAMD [12]

To our knowledge, the specific effect of older age on the efficacy of aflibercept in nAMD has not been addressed in the scientific literature, while older age has been shown to adversely affect the outcomes in patients treated with both bevacizumab and ranibizumab [10, 11] In addition, since it is difficult to study the outcomes in an elderly population due to several issues, including follow-up retention, large study samples are needed in order to reach reliable conclusions. Consequently, analysis of a large database system seems to be a good option. In fact, the use of electronic databases to estimate the outcomes in retinal disorders is becoming increasingly common, and they have been used to provide estimates for national and regional population outcomes [13, 14]. We have recently utilized a national dataset from 16 centres in the United Kingdom (UK) to report that the "real world" clinical outcomes of aflibercept in nAMD are similar to that of the randomized control trials of aflibercept in AMD [13] Therefore, this dataset is ideal to examine the influence of advanced age on visual outcomes in patients with nAMD treated with aflibercept. In this study, we compared aflibercept the outcomes in very elderly patients with nAMD (≥90 years) with the rest of the cohort treated with aflibercept for nAMD to evaluate the treatment's outcomes in the very old population.

Materials and methods

In this retrospective study, anonymised data was extracted from 16 UK National Health Service (NHS) hospitals forall treatment-naive eyes with nAMD initiated on aflibercept between March 2013 and April 2015, to ensure a minimum of 24-month follow-up. All the data were recorded using a single electronic medical record (EMR) system (Medisoft Ophthalmology; Medisoft Limited, Leeds, UK), which mandated the collection of a standardized dataset throughout the nAMD care pathway. Written approval for anonymised data extraction was received from each participating hospital. Ethical approval was not required, since a study of this nature is considered as an audit or service evaluation. The study was conducted in accordance with the tenets of Helsinki Declaration and the UK's Data Protection Act.

Sites were selected based on the confirmation that they used aflibercept to treat nAMD according to the VIEW protocol, consisting of 3-monthly intravitreal aflibercept injections (loading phase), followed by repeated bimonthly injections thereafter during theentire year 1 . All included centers were using a treat and extend approach after year 1. To determine the influence of age on visual acuity (VA) outcomes, patients were divided into two groups: Group I consisted of a younger cohort aged 0–89 years, while Group II consisted of very elderly patients aged 90 years and over.

All patients underwent optical coherence tomography (OCT) and fluorescein angiography to confirm the diagnosis of nAMD, while indocyanine green angiography was used at the discretion of the physician when needed. Eyes with polypoidal choroidal vasculopathy, choroidal neovascularization of other cause than nAMD, other co-morbidities that may confound visual outcomes and those treated previously with anti-VEGF were excluded. At each visit, visual acuity, injection history and follow-up date were recorded and entered into the EMR system by all staff members as part of routine clinical care. Potential operative and postoperative ocular and systemic complications were also documented at each visit.

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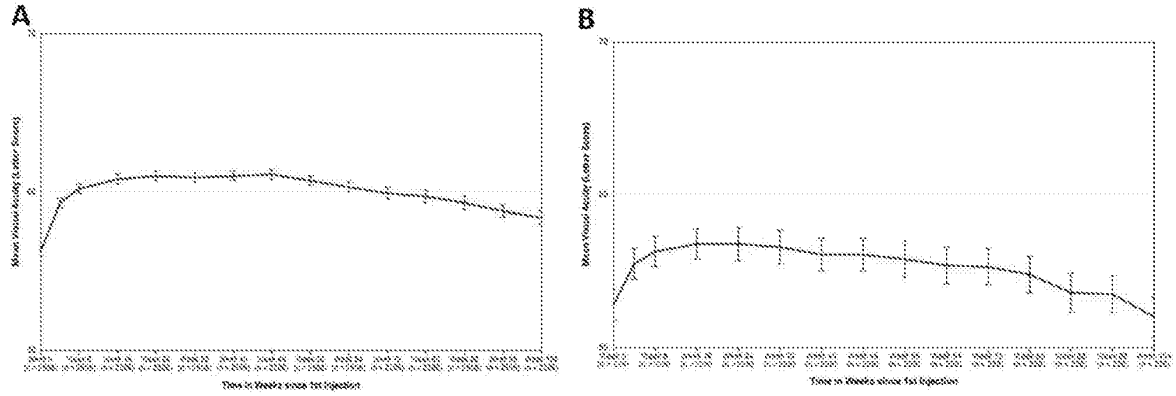


Fig. 1 Mean change in visual acuity over time in patients aged <90 years (**a**) and ≥90 years (**b**)

Visual acuity and missing value imputation

Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity letter scores at 2 meters were recorded at each visit at all sites, and represented the primary outcome of the study. In cases when alternatives measures were used conversion to ETDRS letters was performed. The visual acuity at each clinical visit was used for the analysis. When visual acuity recorded was counting figures, hand movements, light perception or no light perception, zero ETDRS letter score was ascribed.

Since in real-world studies, patients tend not to attend at the precisely intended intervals, the visual acuity of all attendees at 4-week intervals were utilized for the analysis over a 2-year period, having ensured that the sample size in each month reflected all patients who were being followed up continually. If there were gaps in the visual acuity data, they were imputed using the mean of the observations before and after the missing period. No observations were carried forward beyond the last recorded VA value, because loss to follow-up is more common in clinical practice than in proper clinical trials.

Results

Data were extracted from 16 NHS centers for 2734 treatment-naive eyes initiating aflibercept treatment for nAMD between March 2013 and April 2015, to allow a minimum follow-up of 2 years. Group I (aged < 90 years) comprised 2506 eyes and Group II (aged ≥ 90 years) included 228 (8.3%) eyes.

Mean change in visual acuity at 2 years

The mean change in VA over time for both the groups is shown in Fig. 1. In patients aged < 90 years, the mean VA at baseline was 56.3 ETDRS letters (standard error, 0.3 letter), improving significantly to 60.9 ETDRS letter at year 1 (standard error, 0.3 letter; + 4.6 letters gain) and to 58.4 ETDRS letter at year 2 (standard error, 0.4 letter; + 2.1 letters gain), compared to baseline. In patients aged ≥ 90 years, the VA at baseline was 52.8 ETDRS letters (standard error, 1 letter) and improved to 55.9 ETDRS letters at year 1 (standard error, 1.2 letter; + 3.1 letters gain), but dropped to 52 ETDRS letters at year 2 (standard error, 1.3 letter; −0.8 letters loss), compared to baseline. The maximum change in VA was achieved at 6 months for both the groups (+4.7 and +4.0 letters gain respectively).

First eye involvement

If analysis was restricted to first-treated eyes (eyes with normal vision in the other eye), in Group I the mean baseline VA for first-treated eyes was 55.2 ETDRS letters (standard error, 0.4 letter), which increased to 60.6 letters at year 1 (standard error, 0.4 letter; +5.4 letters gain) and to 58.1 letters (standard error, 0.5 letter; +5 letters gain) at year 2. In Group II, the mean baseline VA in first-treated eyes was 50.0 ETDRS letters (standard error, 1.2 letter), increasing to 52.4 letters at year 1 (standard error, 1.5 letter; +2.4 letters gain), but dropping to 48.8 letters at year 2 (standard error, 1.7 letter; −1.2 letters loss).

Second eye involvement

For second-treated eye (eyes with visual loss in other eye) in Group I, the mean baseline VA was 63.5 ETDRS letters (standard error, 0.7 letter), increasing to 65.1 letters at year 1 (standard error, 0.8 letter; +1.6 letters gain) and to 63.4 letters at year 2 (standard error, 0.8 letter; −0.1 letter loss). In Group II, the mean baseline VA for second-treated eye was 59.2 ETDRS letters (standard error, 2.4 letter), which increased to 63.0 letters at year 1 (standard error, 2.2 letter;

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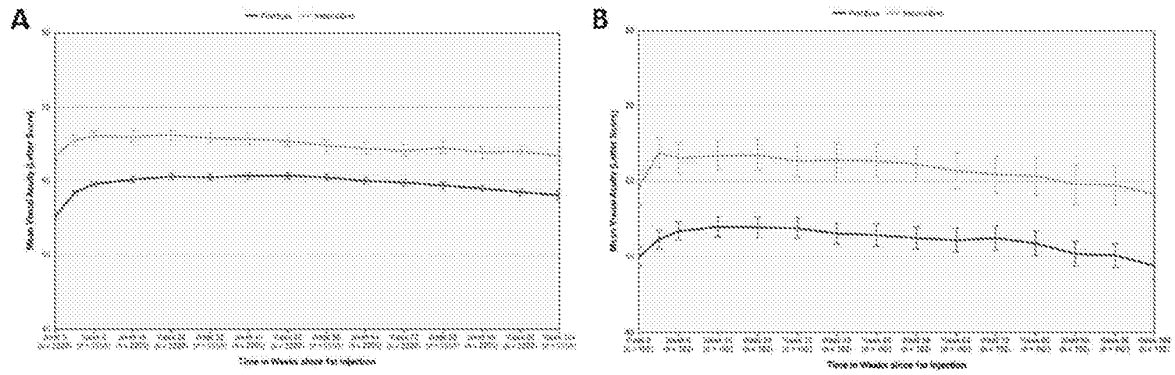


Fig. 2 Mean change in visual acuity over time regarding first-treated and second-treated eyes in patients aged <90 years (**a**) and ≥90 years (**b**)

+3.8 letters gain) and dropped to 58.3 letters at year 2 (standard error, 2.5 letter; −0.9 letter loss), as it is shown in Fig. 2.

Patients presenting poor visual acuity

There were 218 eyes (13.0%) in Group I, compared to 24 eyes (10.5%) in Group 2 that presented with VA < 35 ETDRS letters. For both the groups, the largest VA gains were achieved in eyes that started with the worst vision. In patients aged < 90 years, eyes with baseline VA < 35 ETDRS letters gained a mean of 11.6 letters (standard error, 1.1 letter) and 9.2 letters (standard error, 1.2 letter) at year 1 and 2 respectively. A similar trend was observed in patients aged ≥ 90 years with eyes commencing aflibercept treatment, with the worst VA attaining the largest VA gains, but to a lesser degree. Specifically, patients in Group II with baseline VA < 35 ETDRS letters gained a mean of 7.4 letters (standard error, 1.9 letter) and 3.9 letters (standard error, 3.4 letter) at year 1 and 2, respectively.

Patients presenting good vision

There were 397 patients (15.8%) in Group I, compared to 24 (10.5%) patients in Group II who presented VA > 70 ETDRS letters. In Group I, there was a mean decline of 0.6 letters (standard error, 0.4 letter) and 3.5 letters (standard error, 0.6 letter) at year 1 and 2, respectively, as it is depicted in Fig. 3a. In Group II, patients with baseline VA > 70 ETDRS letters (24 eyes) experienced a significant drop in VA of 3.8 letters at 1 year (standard error, 1.7 letter) and 13.3 letters at year 2 (standard error, 3.4 letter), as shown in Fig. 3b.

Gains in visual acuity

In Group I, the proportions of the 2147 eyes (85.7%) with follow-up at year 1 that gained 5, 10 and 15 letters were 52.3%, 35.2% and 20.6%, respectively. At year 2, the proportions of the 2102 eyes (83.9%) with a gain of 5, 10 and 15 letters were 46.7%, 31.5% and 20.7%, respectively. In patients aged ≥ 90 years, the proportions of 186 eyes (81.6%) with follow-up at 1 year that gained 5, 10 and 15 letters were 49.5%, 32.8% and 22.6%, respectively. At year 2, the proportions of the 192 eyes (84.2%) gaining 5, 10 and 15 letters were 37.5%, 27.6% and 17.7%, respectively (Fig. 4).

Losers in visual acuity

Over the first year, the proportions of those losing 5, 10 and 15 letters in Group I were 18.8%, 10% and 5.8%, respectively and at 2 years, 26.3%, 18.3% and 13% lost 5, 10 and 15 letters. In Group II, the proportions losing 5, 10 and 15 letters were 26%, 14% and 7%, respectively at year 1 and 37%, 24% and 16% of eyes in year 2, respectively.

Discussion

This study evaluated aflibercept outcomes in nAMD in the largest series of patients aged 90 years or over. The principal message of this study is that intravitreal aflibercept is effective in the very elderly population with nAMD and they are able to adhere to rigorous anti-VEGF treatment regimens.

There are half a million people aged 90 years or older in the UK. Owen et al reported ~40,000 new nAMD cases a year in the UK, with an estimated 7700 people beingin this age group (19%) [4]. This study shows that the oldest people constituted 8% of the new cases presented, and were treated with aflibercept over 2 years. Therefore, approximately half the expected number of the very elderly patients with new onset nAMD were present for the treatment. Considering those who presented for diagnosis and

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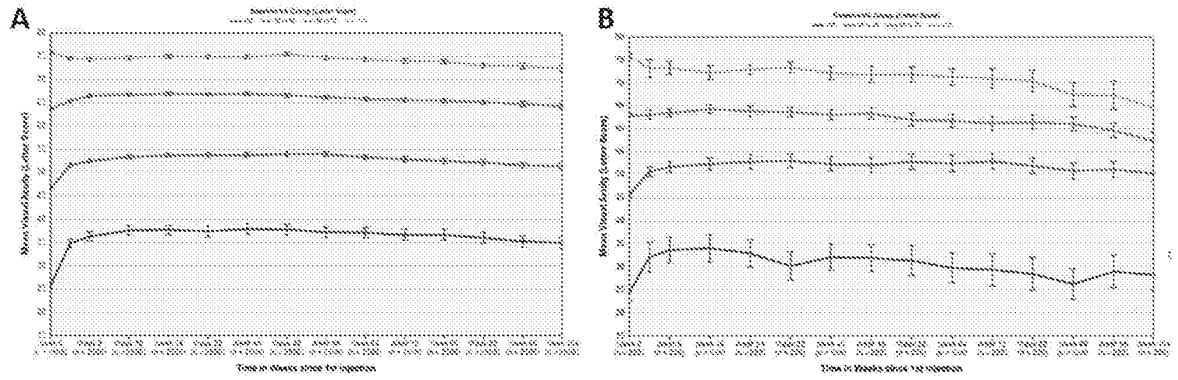


Fig. 3 Mean change in visual acuity over time based on baseline visual acuity groups in patients aged <90 years (**a**) and ≥90 years (**b**)

treatment, their baseline VA was similar to the rest of the cohort. Therefore, those were the patients who were able to access the NHS benefit from the treatment received for nAMD.

The proportion of patients with final VA records at 2 years was also similar between the two the groups, suggesting that the drop out rate was not higher in the very old patients. The study is limited to 2-year follow-up. Longer follow-up of these patients will provide insight into any deviations between the two cohorts on clinic attendance with time. The outcome measured in various ways show that very elderly patients with nAMD benefit from aflibercept therapy. However, it is more challenging for the patients aged 90 years or above to achieve the driving vision, defined as more than 70 letters in the treated eyes. In addition, the older patients who presented good vision (>70 letters) showed a larger decline in VA over the 2 years, compared to the rest of the cohort. These outcomes in this age group may contribute to the higher risk of falls and fractures, need for nursing home support and mortality.

Interestingly, we also observed that 80% of patients presented first eye involvement in the 90 years and above group. We postulate that this group may indeed represent a unique "special" group that has avoided conversion to nAMD, probably having a lower predisposition for the development of nAMD. It would be useful to interrogate this group of patients further in terms of both functional and structural changes in the retina to study the disease mechanism.

The VA outcomes of the present study were not as favorable as the clinical trials outcomes, but were similar to the other real-life studies [13, 15, 16] The mean gain in VA in our study in patients aged < 90 years was +4.6 and +2.1 letters at year 1 and 2, respectively. In patients aged ≥ 90 years, the mean gain in VA at year 1 was +3.1 letters, while patients lost 0.8 letters at year 2. The integrated analysis of VIEW 1 and VIEW 2 studies showed 8.4 letters gain at year 1 (7.9 letters for VIEW 1 and 8.9 letters for VIEW 2 study [12], whereas Talks et al found 5.1 letters gain at year 1 in patients with nAMD treated with intravitreal aflibercept in real-life conditions, based on the VIEW protocol [13]. Additionally, previous audits using PRN ranibizumab in clinical practice reported VA gains of 2–3.8 letters at year 1 [15, 16]. It is worthy to note that reduced VA in the older group may represent more prevalent concurrent atrophic changes than in the younger group. In addition, the aged outer retinal tissue may be less responsive to anti-VEGF therapy.

The discrepancy in the VA outcomes between clinical trials and real-life studies may be explained by the fact that in the real-world, data measurement techniques may differ. Specifically, VA is usually measured with the patients' habitual correction and not with the subjective refraction at each visit as in clinical trials. Although this may underestimate the actual changes in vision, it may reflect better patients' vision experience [13]. Moreover, patients in clinical trials are strictly selected and may have different characteristics than those of daily practice, while treatment is administered within tight timelines. It is also worthy to note that this older patient cohort is often not included in the clinical trials, even though these diseases are aging dependent. They represented 8% of this cohort. Therefore, this is an example where the answers to a research question are better derived from real-life datasets than clinical trials.

Another interesting observation of our study was that maximal VA gain was obtained at month 6 after initiation of treatment, irrespective of the age. In addition, the initial VA gain achieved after the 3-monthly loading phase was maintained at the end of year 1 in both the groups and by year 2 in patients aged < 90 years. In contrast, in the very elderly patients, the rate of decline in VA was more pronounced after year 1, with patients presenting loss of 0.8 letters at year 2 and falling below the baseline VA. However, the outcome is still better than the natural history of the disease. Although treatment after 6 months did not result in further VA gains in either group, continuous treatment may halt further visual deteriorations in both the groups.

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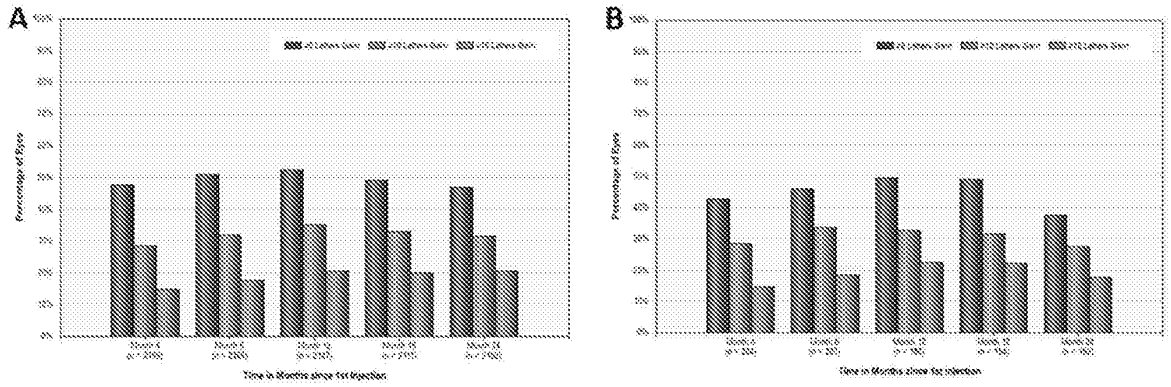


Fig. 4 Percentage of patients gaining at least 5, 10 and 15 letters in patients aged <90 years (**a**) and ≥90 years (**b**)

In conclusion, our study showed that very old patients with nAMD benefited from aflibercept therapy, but not to the same degree as the younger patients. The reason why elderly patients do not achieve the same outcomes as their younger counterparts despite adhering to the treatment regimen is unclear. An understanding of the morphological differences in patients with nAMD across different age profiles should shed more light on the disease mechanisms. The information provided in this study may also be of value to health economists for incorporation in future cost-effectiveness models.

Summary

What was known before

- Intravitreal aflibercept is safe and effective for the treatment of age-related macular degeneration.
- The so-far studies regarding the effectiveness of aflibercept in patients over 90 years are scarce.

What this study adds

- Very old patients with nAMD benefited from aflibercept, but not to the same degree as younger the patients.
- The study showed that on an average, the very elderly patients are able to adhere to the intensive anti-VEGF treatment regimens.

UK Aflibercept Users Group A. J. Lotery, F. Ghanchi, N. Patel, C. Bailey, S. Mahmood, A. Lobo, B. Paul, Q. Kashif, C. Santiago, G. Walters, M. Tahir, B. Mushtaq, K. Ahmed, M. McKibbin, S. Sivaprasad, and J. Talks

Compliance with ethical standards

Conflict of interest Irini Chatziralli, James Talks and Sobha Sivaprasad have received travel grants, research grants and speaker fees, and attended advisory board meetings of Bayer, Allergan and Novartis. The remaining authors declare that they have no conflict of interest.

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CLINICAL REVIEW

Ziv-aflibercept: A novel angiogenesis inhibitor for the treatment of metastatic colorectal cancer

CLEMENT CHUNG AND NISHA PHERWANI

Purpose. The pharmacology, pharmacokinetics, clinical efficacy, safety, and administration of ziv-aflibercept in combination therapy for metastatic colorectal cancer (mCRC) are reviewed.

Summary. Ziv-aflibercept (Zaltrap, Regeneron Pharmaceuticals and sanofi-aventis) is a novel recombinant fusion protein that targets the angiogenesis signaling pathway of tumor cells by blocking vascular endothelial growth factor (VEGF) receptors that play a key role in tumor growth and metastasis; it is a more potent VEGF blocker than bevacizumab. Ziv-aflibercept is approved by the Food and Drug Administration for use in combination with fluorouracil, irinotecan, and leucovorin (the FOLFIRI regimen) for second-line treatment of patients with mCRC who have disease progression during first-line oxaliplatin-based chemotherapy. A Phase III trial demonstrated that relative to FOLFIRI therapy alone, the use of ziv-aflibercept was associated with significantly improved patient response, overall survival, and progression-free survival in patients with good performance status at baseline, including some who had received prior bevacizumab therapy. The most common grade 3 or 4 adverse effects associated with ziv-aflibercept use in clinical studies were neutropenia, hypertension, and diarrhea; the U.S. product labeling warns of potential hemorrhage and other treatment-related risks.

Conclusion. Current clinical data are insufficient to directly compare ziv-aflibercept and bevacizumab when used with standard combination chemotherapy as first- or second-line regimens for mCRC. The role of ziv-aflibercept is currently limited to the second-line setting in combination with irinotecan-based regimens in mCRC patients who have not received irinotecan previously. The role of ziv-aflibercept in chemotherapy for other tumor types is yet to be determined.

Am J Health-Syst Pharm. 2013; 70:1887-96

Cancers of the colon and rectum (collectively, colorectal cancer) comprise the third most common tumor type worldwide, with the former being more prevalent than the latter.[1] Colorectal cancer is the third most common form of cancer in the United States and the second most common cause of cancer-related deaths[2]; an estimated 143,460 new cases and 51,690 deaths occurred in 2012.[3] It is estimated that 20% of patients with colorectal cancer have metastatic disease at the time of diagnosis. Despite optimal treatment with adequate surgery and adjuvant chemotherapy, 30–50% of patients with primary colon cancer relapse and die from metastatic disease.[4,5] For most patients with metastatic colorectal cancer (mCRC), treatment remains palliative and the five-year survival rate is disappointing, at approximately 10%.[4]

First-line treatment of mCRC typically consists of fluorouracil and leucovorin (abbreviated FO, for folinic acid, in regimen acronyms) combined with either an oxaliplatin-based regimen (i.e., FOLFOX chemotherapy) or an irinotecan-based regimen (i.e., FOLFIRI), with crossover to the alternative regimen for second-line treatment (i.e., first-line FOLFOX followed by second-line FOLFIRI chemotherapy or vice versa).[6] Various trials have demonstrated no significant difference between FOLFOX and FOLFIRI chemotherapy in terms of the average response rate (54% and 56%, respectively), progression-free survival (PFS) (8.0 months versus 8.5 months), and overall survival (OS) (20.6 months versus 21.5 months) in patients with mCRC.[7-9] However,

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the trial results indicated differences in the toxicity profiles of the two regimens, with relatively more frequent grade 3 or 4 mucositis, nausea and vomiting, and grade 2 alopecia with FOLFIRI chemotherapy and more frequent grade 3 or 4 neutropenia and neurotoxicity with FOLFOX chemotherapy.[10,11]

In the last decade, the introduction of targeted biological therapy has transformed the paradigm for treatment of mCRC. Antiangiogenesis agents, such as bevacizumab,[12] and epidermal growth factor receptor antagonists, such as cetuximab,[13] have been added to the standard combination chemotherapy (FOLFOX or FOLFIRI), with improved survival outcomes reported in patients with mCRC. Angiogenesis, the process by which new blood and lymphatic vessels are formed, is required to support growth in the embryo and young animals, as well as to allow tissue repair and remodeling in adults.[14] For tumors, as with normal tissues, oxygen and nutrients are obtained and waste products are removed via the vasculature. Although tumors can grow in part by co-opting existing host vessels,[15] most tumors induce new vessel formation (neovascularization), suggesting that angiogenesis is a hallmark of tumor growth and function throughout the tumor's life cycle. The predominant growth factor, or proangiogenic factor, of the angiogenesis pathway is vascular endothelial growth factor (VEGF).[16,17] Its continuous expression by the tumor makes VEGF a rational target for cancer therapy.[17]

This article focuses on the clinical review of ziv-aflibercept (ziv″ - a flib′ er sept; Zaltrap, Regeneron Pharmaceuticals and sanofi-aventis), a novel fully humanized monoclonal antibody with antiangiogenic activity recently approved by the Food and Drug Administration (FDA) for use in combination with second-line FOLFIRI chemotherapy for patients with mCRC who have not responded to an oxaliplatin-containing first-line regimen.

Pharmacology

The mammalian VEGF family[14,18] consists of six distinct glycoproteins, or growth factors: VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E, and placental growth factor (PlGF). These growth factors are ligands that bind to VEGF receptors that mediate tumor angiogenesis. Among these, VEGF-A (or simply VEGF) is considered the principal driving force in tumor angiogenesis.[18] Each ligand has specific affinity for different receptors.

There are three VEGF receptors: VEGFR-1, VEGFR-2, and VEGFR-3. All of these VEGF receptors are characterized by seven immunoglobulin (Ig)-like domains in the extracellular region, a single transmembrane domain, and an intracellular tyrosine kinase domain.[19] These VEGF receptors are high-affinity (denoted by low dissociation constant) receptors, with tyrosine kinase activity expressed in normal and tumor vasculature (i.e., vascular endothelial cells).[18,20] The major receptor for VEGF-A is VEGFR-2 (flk1/KDR). Although VEGF-A binds to VEGFR-1 with 10 times higher affinity than does VEGFR-2, the higher tyrosine kinase activity of VEGFR-2 makes it the most important effector in VEGF signaling.[18,20] Of note, PlGF, which binds to VEGFR-1 but not VEGFR-2, also contributes to tumor angiogenesis.[19]

Ziv-aflibercept, a fully humanized soluble recombinant fusion protein, is created by fusing extracellular Ig domain 2 of VEGFR-1 and extracellular Ig domain 3 of VEGFR-2 to the Fc (constant) region of human IgG1, resulting in the formation of a more potent and high-affinity VEGF blocker than bevacizumab.[19] This fusion protein has been demonstrated to have pharmacologically improved activity over bevacizumab (Table 1).[21-23] Since this fusion protein blocks the angiogenesis pathway by binding to all isoforms of VEGF-A, VEGF-B, and PlGF, it is also known as a "VEGF trap" or a composite decoy receptor (due to the fusion of both VEGFR-1 and VEGFR-2 to IgG1).[21] By binding to these endogenous ligands, ziv-aflibercept inhibits the binding and activation of their cognate receptors, resulting in inhibition of downstream signaling events that mediate neovascularization and vascular permeability. This process results in maintenance of a more functional and normal vasculature,[18,19] inhibition of tumor growth and tumor metastasis, and potentially improved drug delivery (due to "normalization" of tumor vasculature that enables tumor cells to become more sensitive to cytotoxic chemotherapy).[24]

Table 1.
Key Differences in Biological Properties of Ziv-aflibercept and Bevacizumab[21-23,a]

Property	Ziv-aflibercept	Bevacizumab
Binding target(s)	VEGF-A, VEGF-B, PlGF	VEGF-A
Equilibrium dissociation constant,[b] pM	0.49	58
Elimination half-life, days	5–6	20

[a]VEGF = vascular endothelial growth factor, PlGF = placental growth factor.
[b]A measure of binding affinity, with smaller values indicating stronger binding.

Pharmacokinetics and pharmacodynamics

Ziv-aflibercept binds 1:1 to endogenous VEGF to form stable inert complexes, which appear in the circulation at a maximum level within 24–48 hours of treatment.[25]

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These complexes are retained in the systemic circulation. Clearance occurs via a receptor- or pinocyte-mediated pathway that results in proteolysis.

Pharmacokinetic studies of ziv-aflibercept involved the measurement of plasma concentrations of free and VEGF-bound ziv-aflibercept.[26-28] The level of VEGF-bound ziv-aflibercept indicates the amount of endogenous VEGF produced in normal and tumor tissues, whereas free ziv-aflibercept is available for binding with newly secreted VEGF. Free ziv-aflibercept concentrations exhibit linear kinetics at a dose range of 2–9 mg/kg, with steady-state concentrations of free ziv-aflibercept reached by the second dose. Maximum VEGF-bound ziv-aflibercept levels are reached at doses of 2 mg/kg i.v. or greater, indicating complete blockade of the ligand. In pharmacokinetic studies, the half-life of ziv-aflibercept increased (from 1.7 to 5.1 days) as doses were increased from 0.3 to 7.0 mg/kg i.v. Clearance was stable at doses in the range of 2–7 mg/kg. There was no accumulation of free ziv-aflibercept between treatment cycles.

Some studies also demonstrated that the biological effects of ziv-aflibercept correlated closely with free ziv-aflibercept levels in excess of VEGF-bound ziv-aflibercept levels.[26-29] The mean maximum observed plasma concentration of free ziv-aflibercept, at doses ranging from 0.3 to 7.0 mg/kg (0.3 mg/kg is about a tenth of the biologically effective dose in humans), varied from 4 to 159 μg/mL.[29] Following the administration of ziv-aflibercept at 2- and 3-mg/kg doses, free drug concentrations were similar to VEGF-bound ziv-aflibercept concentrations. With doses of ≥4 mg/kg, free ziv-aflibercept concentrations were in excess of bound ziv-aflibercept concentrations throughout the dosing intervals in most patients. Thus, a 4-mg/kg i.v. dose provides a sufficient ziv-aflibercept concentration to block endogenous production of VEGF.

Van Cutsem and colleagues[26] showed that clearance and concentrations of free and bound ziv-aflibercept at steady state in patients treated with irinotecan-based combination chemotherapy were comparable to those observed with ziv-aflibercept monotherapy. No clinically significant pharmacokinetic drug–drug interactions were found between ziv-aflibercept, irinotecan, and SN-38 the active metabolite of irinotecan).

Clinical trials

Phase I research. The safety and dose determination of single-agent ziv-aflibercept therapy were explored in a dose-escalation trial conducted by Lockhart and colleagues[29] that included 7 patients with mCRC among a total of 47 patients with refractory solid tumors. Seven dose levels were evaluated (0.3, 1.0, 2.0, 3.0, 4.0, 5.0, and 7.0 mg/kg); 3, 7, 6, 7, 7, 4, and 13 patients were treated at each respective dose level. The investigators also evaluated the safety and maximum tolerable dose (MTD) of ziv-aflibercept at doses ranging from 0.3 to 7.0 mg/kg i.v. every two weeks. The MTD was defined as the highest dose at which 2 of 3–6 treated patients experienced a dose-limiting toxicity (DLT): uncontrolled hypertension, grade 3 or 4 proteinuria, febrile neutropenia, grade 4 neutropenia, grade 3 or 4 thrombocytopenia, and any toxicity of any grade that led to drug discontinuation. DLTs were evaluated during each dose-escalation phase. Tumor response was evaluated after every two cycles (or four treatments per eight-week interval) according to the RECIST (Response Evaluation Criteria In Solid Tumors, version 1.0) scheme. Patients could elect to continue treatment until disease progression or intolerable toxicity or until they chose to withdraw consent.

Results showed that single-agent ziv-aflibercept was generally well tolerated, with a rate of partial response of 6% and a rate of stable disease for greater than one year of 4%. The types of treatment-related toxicities observed (e.g., fatigue, hypertension, proteinuria) were consistent with those reported in other trials evaluating antiangiogenic therapies.[30-34] The median times to the onset of hypertension or proteinuria were 3.5 days (range, 1–21 days) and 15 days (range, 14–16 days), respectively. These adverse events were reversible on drug discontinuation or initiation of supportive care. Based on these observations and observed increases in the frequency and severity of adverse events at doses of ≥4 mg/kg, single-agent ziv-aflibercept 4 mg/kg i.v. every two weeks was determined to be the recommended dosage for use in Phase II trials.

In another study, investigators evaluated the safety, efficacy, DLT profile, and recommended dose of ziv-aflibercept in combination with irinotecan-based chemotherapy for second-line treatment of Japanese patients with mCRC, 10 (63%) of whom had received prior bevacizumab therapy.[28,35] Ziv-aflibercept was administered at two dosage levels (2 and 4 mg/kg i.v. every two weeks, administered to 3 and 13 patients, respectively). The median numbers of cycles administered were 6 (range, 3–9) and 10 (range, 1–23), and the total numbers of cycles of the 2- and 4-mg/kg doses were 18 and 131, respectively. No DLTs were observed at either dosing level. The response rate and PFS for patients receiving the 4-mg/kg i.v. dose were 8% and 7.6 months, respectively. At both dosing levels, the most common adverse events (occurring in ≥40% of patients) included bone marrow suppression (e.g., neutropenia) and gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea, stomatitis, decreased appetite); these toxicities are known to be associated with FOLFIRI regimens. In addition, toxicities known to be associated with

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the antiangiogenesis therapy, such as hypertension and epistaxis, were also frequently observed (rates of ≥40%) with use of the 4-mg/kg dose. The most common grade 3 or 4 adverse events were neutropenia and hypertension. This study established the recommended dose and schedule of ziv-aflibercept (i.e., 4 mg/kg i.v. every two weeks) to be used in combination with irinotecan-based chemotherapy for mCRC.

Of note, ziv-aflibercept has been evaluated extensively for the treatment of patients with other advanced solid tumors.[30-34] Most of the patients involved had received prior chemotherapy regimens, either as first- or higher-line therapies. Ziv-aflibercept was found to have very modest clinical activity as a monotherapy; however, when it was used as a component of combination therapies, partial-response rates ranged from 4% to 18%.

Phase II research. Tang and colleagues[36] conducted a multicenter open-label Phase II trial in 75 heavily treated mCRC patients with good performance status (i.e., Eastern Cooperative Oncology Group [ECOG] performance status of 2 or less). Patients had received a median of two prior regimens and were stratified as having received (n = 51) or not received (n = 24) prior bevacizumab therapy. The primary endpoints were response rate and PFS. After a median of 4 treatment cycles (range, 1–16 cycles) of single-agent ziv-aflibercept therapy (4 mg/kg i.v. every 2 weeks), median PFS was 2.4 months among patients who had received prior bevacizumab therapy and 2.0 months in the bevacizumab-naive group. The efficacy of ziv-aflibercept did not seem to be affected by prior bevacizumab therapy (duration not specified). In the prior-bevacizumab cohort, 1 patient had a partial response and 6 patients (12%) had stable disease for greater than 16 weeks. In the bevacizumab-naive cohort, the best response was stable disease for greater than 16 weeks in 5 of 24 patients (21%). Overall, the most common adverse events of any grade were fatigue (68%), hypertension (51%), proteinuria (49%), headache (42%), voice alteration (31%), anorexia (24%), and joint pain (18%). Single-agent ziv-aflibercept appeared to be tolerated and to have modest antitumor activity in pretreated patients with mCRC, including those who had received prior bevacizumab therapy.

A notable limitation of the trial of Tang et al.[36] was that the activity of ziv-aflibercept against mCRC has never been directly compared with that of bevacizumab. The best conclusion that one can draw from this study is that ziv-aflibercept appears to be neither dramatically better nor worse than bevacizumab; this underlines the need for more studies with different drug combinations and direct comparisons with bevacizumab-based therapies.

Phase III research. Because of the acceptable clinical activity of ziv-aflibercept when used in combination therapies,[28-31,35] a Phase III prospective, multinational, double-blind, parallel-arm trial (the VELOUR trial) was conducted in patients with mCRC who had experienced disease progression while receiving oxaliplatin-based chemotherapy (e.g., FOLFOX).[37]

The primary study endpoint was OS, as determined by the planned subgroup analysis. Secondary endpoints were PFS and response rate. A total of 1226 patients with mCRC and an ECOG score of 2 or less were randomly assigned in a 1:1 fashion to receive ziv-aflibercept (n = 612) or a placebo (n = 614) followed by FOLFIRI chemotherapy every two weeks. Patients were stratified based on prior bevacizumab treatment and performance status (an ECOG score of 0 or 1 versus a score of 2). The study had a power of 90% to detect a 20% improvement in OS in the ziv-aflibercept group. All patients had received prior oxaliplatin therapy.

Ziv-aflibercept was given as a 4-mg/kg i.v. infusion prior to FOLFIRI chemotherapy. The FOLFIRI regimen was administered according to the National Comprehensive Cancer Network (NCCN) colon cancer guideline (irinotecan hydrochloride 180 mg/m^2 i.v. on day 1 of each two-week cycle, to be administered concurrently with leucovorin 400 mg/m^2 i.v., followed by fluorouracil 400 mg/m^2 by i.v. bolus and then fluorouracil 2400 mg/m^2 by continuous i.v. infusion over 46 hours[38]). The use of supportive care medications, including atropine (for prophylaxis of acute diarrhea due to irinotecan) and colony-stimulating factor (for prophylaxis of neutropenia) was permitted. Disease response was evaluated radiologically every six weeks. Treatment continued until disease progression or intolerable toxicity. The study groups were well balanced in terms of performance status and prior bevacizumab therapy. Approximately 30% of patients (186 of 612) in the ziv-aflibercept group had received bevacizumab, compared with 31% of patients (187 of 614) in the placebo group. The overall median age was 61 years; the majority of patients (87%) were white, 7% were Asians, and 3.5% were black.

At a median follow-up of 22.3 months, the two-year survival rates were 28.0% and 18.7% in the ziv-aflibercept and control groups, respectively. Relative to placebo users, patients treated with ziv-aflibercept had longer OS (13.5 months versus 12.1 months; hazard ratio, 0.817; 95% confidence interval, 0.71–0.94 months; p = 0.0032), a higher response rate (19.8% versus 11.1%, $p <$ 0.001), and longer PFS (6.9 months versus 4.7 months, $p <$ 0.0001). Patients receiving antiangiogenic therapy were given a median of seven cycles of ziv-aflibercept (the numbers of cycles of FOLFIRI and ziv-aflibercept varied among these patients); those in the control group received eight cycles

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of placebo administration. Irinotecan and fluorouracil were administered for a median of 21 weeks in the ziv-aflibercept group and 18.1 weeks in the control group.

Cycle delays and dose modifications were more common among patients receiving ziv-aflibercept. Dose intensity (defined as the ratio of the delivered chemotherapy dose to the standard full dose, expressed as a percentage) was 83% in the ziv-aflibercept group versus 92% in the control group. No significant relationship was observed between treatment outcomes and prior bevacizumab exposure. In a subgroup analysis, a greater OS benefit related to ziv-aflibercept therapy was observed only in patients with liver metastasis as opposed to metastasis to other organs. The benefits in OS and PFS seen in the bevacizumab-pretreated group were consistent with those observed in the overall population.

Adverse events among VELOUR trial participants included diarrhea, asthenia, stomatitis, ulceration, nausea, and infections. These adverse events were primarily grade 1 or 2 and were more common in patients treated with ziv-aflibercept.

Overall, adverse events of all grades were similar in both study groups. Grade 3 or 4 adverse events related to antiangiogenesis therapy that occurred more frequently in the ziv-aflibercept group relative to the control group included hypertension (19% versus 1.5%), hemorrhage (2.9% versus 1.7%), arterial thromboembolic events (1.8% versus 0.5%), venous thromboembolic events (8% versus 6%), and proteinuria (8% versus 1%). Surprisingly, a significant increase in chemotherapy-induced grade 3 or 4 toxicities—particularly diarrhea (19% versus 8%), asthenia (17% versus 11%), stomatitis (13% versus 5%), and infections (12% versus 7%)—was also observed with antiangiogenesis therapy (Table 2). This apparent increase in ziv-aflibercept-associated toxicities was not in line with Phase III study results on bevacizumab use in patients with mCRC.[38] However, prior bevacizumab treatment did not seem to impact the safety profile of ziv-aflibercept. The most common adverse events that led to treatment discontinuation included asthenia, infections, diarrhea, and hypertension.

Based on the results that demonstrated statistically significant improvement in OS, PFS, and response rate in patients with mCRC who received ziv-aflibercept as a second-line therapy with or without prior bevacizumab therapy, FDA approved ziv-aflibercept for use in this patient population in 2012.[22]

Safety

Overall, ziv-aflibercept appears to be tolerated, even in heavily pretreated mCRC populations. In the VELOUR trial, the most common adverse effects observed in patients receiving ziv-aflibercept in combination with the FOLFIRI regimen were leucopenia, neutropenia, thrombocytopenia, diarrhea, proteinuria, and hypertension.[22,37] These adverse effects were mostly grade 1 or 2 and reversible. Of note, some of these common adverse effects (hypertension and proteinuria) were among the most common DLTs identified in Phase I and II trials[26-29] and were consistent with the inhibition of the angiogenesis pathway. Other adverse effects occurring more commonly in ziv-aflibercept versus control groups (e.g., increases in liver function enzymes, stomatitis, fatigue, decreased appetite) may not be related to ziv-aflibercept's antiangiogenic effect.

Class-related adverse effects. Hypertension, proteinuria, and thromboembolism are recognized as the

Table 2.
Most Common Adverse Effects of Ziv-aflibercept in Phase III Trial[37,a]

Adverse Effect	% Patients Affected			
	FOLFIRI + Ziv-aflibercept (n = 611)		FOLFIRI + Placebo (n = 605)	
	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4
Leukopenia	78	16	72	12
Neutropenia	67	37	57	30
Thrombocytopenia	48	3	35	2
Hypertension	41	19	11	2
Diarrhea	69	19	57	8
Stomatitis	50	13	33	5
Proteinuria	62	8	41	1
Fatigue	48	13	39	8
AST elevation	62	3	54	2
ALT elevation	50	3	39	2

[a]FOLFIRI = leucovorin, fluorouracil, and irinotecan; AST = aspartate transaminase; ALT = alanine transaminase.

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hallmark class-related adverse effects associated with antiangiogenic therapy.[39-42] Hypertension associated with antiangiogenic therapy is often of low grade (1 or 2). Even grade 3 or 4 hypertension may still be reversible, and patients are managed with angiotensin-converting enzyme inhibitors, calcium channel blockers, or diuretics.[43]

Proteinuria (all grades) was reported in 49% of patients in the VELOUR trial.[37] The frequency of grade 3 or 4 proteinuria was 7.8%; dose modification may be necessary for patients who develop this complication. The drug manufacturer recommends monitoring for proteinuria by urine dipstick (or urinalysis) and determination of the urinary protein-to-creatinine ratio (UPCR) prior to each dose of ziv-aflibercept.[22] For patients with a UPCR greater than 1, analysis of a 24-hour urine collection is recommended.

In addition, inhibition of the VEGF signaling pathway leads to dysfunctional endothelial cells in the vascular endothelium, causing activation of tissue factor and an increased risk of thrombosis. Experience with bevacizumab demonstrated that bevacizumab–VEGF complexes induced platelet aggregation and led to the thromboembolic events observed in clinical trials.[23,44] Currently, it remains unclear whether the biologically inert ziv-aflibercept–VEGF complex is associated with a lower frequency of thromboembolic events. In the VELOUR trial, grade 3 or 4 thromboembolic complications occurred in less than 1% of patients.[37] It is, however, important to note that cancer patients in general are at an increased risk for thrombosis due to their procoagulant disease state and that antiangiogenic therapy marginally increases this risk.[44]

Black-box warning. Ziv-aflibercept carries an FDA-mandated black-box warning on treatment-related hemorrhage, gastrointestinal perforation, and compromised wound healing.[22] In clinical trials, the rate of bleeding and hemorrhage together was 37.8% in the ziv-aflibercept groups versus 19% in the control groups[35,37]; the occurrence of grade 3 or 4 hemorrhage, including severe intracranial hemorrhage, was also slightly higher with ziv-aflibercept use (3% versus 1.7%).[22] Patients receiving ziv-aflibercept should be monitored for signs and symptoms of bleeding. Therapy should be discontinued in patients who develop severe hemorrhage. Although the rates of gastrointestinal perforation were similar in both study groups in the VELOUR trial, patients receiving antiangiogenic therapy should be monitored and treatment should be discontinued if gastrointestinal perforation develops.

Pregnancy consideration. Ziv-aflibercept is classified as a pregnancy category D agent. It should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus.[22] Both female and male patients of reproductive potential must use effective contraception during treatment and for a minimum of three months after the last dose of ziv-aflibercept.

Immunogenicity and hypersensitivity. During clinical research, the frequency of development of antibodies to ziv-aflibercept was 3.1% in patients receiving ziv-aflibercept versus 1.7% in patients receiving a placebo[22]; among patients who tested positive for anti-ziv-aflibercept antibody, neutralizing antibodies were detected in 17 of 48 patients administered ziv-aflibercept and in 2 of 40 placebo users. The impact of neutralizing antibodies on treatment efficacy and safety remains unclear. Since the antibody assay may be influenced by many factors, direct comparison of the frequency of anti-ziv-aflibercept antibody formation with the corresponding rate for other protein-based medications may be misleading. Currently, it is not known if such antibody formation is persistent enough to cause infusion-related reactions or reduced ziv-aflibercept exposure. No data are available on the usefulness of routine screening for positive antibody.

In regard to the frequency of severe (grade 3 or 4) hypersensitivity reactions, no difference was found in ziv-aflibercept versus control patients in the VELOUR trial (0.3% versus 0.5%).[37]

Other safety considerations. Ziv-aflibercept, known simply as aflibercept in European and other countries, is specifically named with the prefix "ziv" (derived from the brand name Zaltrap and the abbreviation i.v.) in the United States in accordance with the FDA requirement that drug manufacturers reduce the potential for confusion related to sound-alike and look-alike medication names. The World Health Organization's international nonproprietary name for Zaltrap is aflibercept.

FDA required that the U.S. generic name ziv-aflibercept be used to clearly differentiate the formulation approved for use in managing mCRC from its ophthalmic counterpart, aflibercept, which is marketed under the proprietary name Eylea (Regeneron Pharmaceuticals) in a different strength.[22] The scientific literature still uses aflibercept as the generic name for ziv-aflibercept. It is recommended that ziv-aflibercept be stored, segregated, and labeled with a specific warning to help distinguish the product from the ophthalmic product.

Dosage, preparation, and administration

The recommended dosage of ziv-aflibercept is 4 mg/kg i.v. administered every two weeks prior to FOLFIRI combination chemotherapy. Treatment is continued until disease progression or intolerable toxicity. Ziv-aflibercept is supplied as a ready-to-use single-dose vial

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of either 200 or 100 mg (solution concentration, 25 mg/mL). After the withdrawal of the calculated dose from the vial, the drug is further diluted in a vehicle of 0.9% sodium chloride injection or 5% dextrose injection to yield a final ziv-aflibercept concentration of 0.6–8 mg/mL. Diluted solution must be refrigerated and used within four hours.[22]

Ziv-aflibercept should be administered as an intermittent infusion over one hour through a 0.2-μm polyethersulfone filter.[22] An administration set made of one of the following materials may be used: polyvinyl chloride (PVC)-containing diethylhexyl phthalate (DEHP), DEHP-free PVC containing trioctyl trimellitate, polypropylene, polyethylene-lined PVC, and polyurethane. Ziv-aflibercept is administered alone prior to any component of FOLFIRI combination chemotherapy.

Ziv-aflibercept has not been shown to have clinically significant interactions with irinotecan, SN-38, and fluorouracil.[26,37] The manufacturer has not conducted dedicated drug–drug interaction studies.[22]

The dosage of ziv-aflibercept does not need to be adjusted for renal impairment.[22] The VELOUR trial data indicated that no dosage adjustment is needed for mild hepatic impairment; however, no information is available on the potential need for dosage adjustments in severe hepatic impairment (defined in the VELOUR trial as a total bilirubin level greater than three times the upper limit of normal).[37]

Ziv-aflibercept should be discontinued for any of the following toxicities: arterial thromboembolic events, fistula formation, gastrointestinal perforation, severe hemorrhage, hypertensive crisis, hypertensive encephalopathy, nephrotic syndrome, thrombotic microangiopathy, and reversible posterior leukoencephalopathy syndrome.[22,44]

Dosage modifications should be made for patients with severe or uncontrolled hypertension; ziv-aflibercept should be withheld until blood pressure is controlled, with the dose subsequently reduced to 2 mg/kg.[22] For patient with substantial proteinuria (i.e., ≥2 g in 24 hours), ziv-aflibercept should be withheld and only administered when the protein level declines below that level. If proteinuria recurs, ziv-aflibercept must be discontinued until the urine protein level falls below 2 g in 24 hours, with therapy resumed at a reduced dose of 2 mg/kg.

Patients must be monitored for hematologic toxicity at baseline and prior to each cycle of ziv-aflibercept.[22] Treatment with ziv-aflibercept and FOLFIRI chemotherapy must be delayed until the neutrophil count is $\geq 1.5 \times 10^9$ cells/L. Furthermore, ziv-aflibercept has been shown to delay and compromise wound healing. Treatment should be stopped at least four weeks prior to elective surgery and should not be resumed until at least four weeks after surgery or until the surgical wound is fully healed.

No dosage adjustment is necessary for the elderly. Based on a population pharmacokinetic analysis,[22] race and sex did not have a clinically significant effect on exposure to free ziv-aflibercept. Currently, there is no recommendation for ziv-aflibercept dosing in obese patients. In one of the Phase I studies summarized above, patients weighing more than 100 kg had a 29% increase in systemic exposure to ziv-aflibercept compared with patients weighing 50–100 kg.[35] Furthermore, no recommendation for a maximum total dose of ziv-aflibercept has been made. In the VELOUR trial, a maximum patient weight was not specified.[22,37]

The use of FOLFIRI combination chemotherapy requires the calculation of body surface area (BSA).[22] In the VELOUR trial, if a patient's BSA was greater than 2 m^2, the amounts of irinotecan and fluorouracil used were adjusted downward to the doses corresponding to a BSA of 2 m^2 for safety purposes.[22,37]

Cost considerations

The average wholesale acquisition cost (WAC) of ziv-aflibercept is $1,600 per 100-mg vial or $3,200 per 200-mg vial.[45] Recently, the drug manufacturer discounted the cost by 50% for hospitals and clinics through its wholesalers and through group purchasing organizations. With a dose of 4 mg/kg and an average patient weight of 72 kg, an estimated dose for each treatment would be about 288 mg. Thus, each dose would cost approximately $4,800. Based on the clinical trial data, the median treatment duration of ziv-aflibercept was 6.9 months (PFS).[37] The cost of ziv-aflibercept alone for this treatment course is about $66,240. Since the drug was approved as an add-on to the standard second-line chemotherapy combination for mCRC (FOLFIRI), the total cost of the ziv-aflibercept–FOLFIRI regimen is approximately $80,000 for a patient with an average BSA (1.73 m^2). It is apparent that the use of ziv-aflibercept will result in a significant increase in overall mCRC treatment expenditure that may raise concerns among payers about the growing cost of oncology treatment.

On the other hand, the WAC of bevacizumab is $596 for a 100-mg vial or $2387 for a 400-mg vial.[45] Given the recommended dose of 5 mg/kg with standard chemotherapy, each dose of bevacizumab costs approximately $2387—only half the cost of ziv-aflibercept. The significant difference in cost between bevacizumab and ziv-aflibercept has brought renewed attention to cost issues in cancer care.[46] Whether an increased cost is justified by additional clinical efficacy is a robust area of comparative effectiveness research that is likely to continue.

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Place in therapy and future directions

The Phase III VELOUR trial demonstrated a statistically significant OS benefit, with improved PFS, in favor of ziv-aflibercept in combination with FOLFIRI chemotherapy relative to FOLFIRI chemotherapy alone in patients with mCRC that has progressed with an oxaliplatin-based regimen.[37] Common adverse effects are related to the mechanism-based effect of antiangiogenic therapy. Currently, there are no data to suggest that FOLFIRI plus ziv-aflibercept therapy has significant antitumor activity in patients whose disease has progressed during treatment with FOLFIRI plus bevacizumab. Ziv-aflibercept has only been shown to have antitumor activity when given in combination with FOLFIRI in FOLFIRI-naive patients. Therefore, NCCN recommends ziv-aflibercept as a second-line option to be used in combination with FOLFIRI or irinotecan only in patients with disease progression while receiving therapy not containing irinotecan.[38]

Considerable strides have been made regarding the use of bevacizumab beyond disease progression in the metastatic setting. In the setting of second-line chemotherapy that does not consist of FOLFIRI, current opinion seems to favor bevacizumab.[47-50] Ziv-aflibercept has yet to show safety and efficacy with chemotherapy regimens other than FOLFIRI in the second-line setting. Recently, a large Phase II trial (AFFIRM) of FOLFOX with or without ziv-aflibercept therapy for first-line treatment demonstrated no improvement in efficacy outcomes with ziv-aflibercept use.[51] In contrast, the activity of bevacizumab in the second-line treatment of patients with disease progression during first-line or even maintenance bevacizumab therapy is supported by some studies.[47-50] Similar efficacy, however, cannot be assumed for ziv-aflibercept based on current data.[22,37]

Ziv-aflibercept has the broad pharmacologic advantage of targeting endogenous ligands that are pro-angiogenic: VEGF-A, VEGF-B, and PlGF. How much of this advantage is translated to real clinical benefits is yet to be determined. On the other hand, the survival benefits conferred by bevacizumab have been clearly demonstrated in first-line, second-line, and maintenance treatment settings.[47-50] Bevacizumab also seems to have a more favorable safety profile than ziv-aflibercept (i.e., a lower potential to induce proteinuria and minimal constitutional toxicities).[23]

Ziv-aflibercept is appropriate for use as an add-on therapy in combination with irinotecan-based regimens in patients with mCRC who have not received irinotecan previously. At the time of writing, it cannot be recommended as first-line therapy, but an ongoing trial (NCT016522196) that is investigating the role of ziv-aflibercept in combination with FOLFOX chemotherapy in patients with previously untreated mCRC may shed light on the place of therapy for ziv-aflibercept.[52]

Like bevacizumab, ziv-aflibercept may be complementary to other cytotoxic chemotherapy agents. It has been studied in several tumor types and may be useful in various combinations.[26-31,40] Its distinctive mechanism of action may allow its use against other advanced solid tumors.[53] A Phase III trial of ziv-aflibercept plus docetaxel therapy for locally advanced or metastatic non-small-cell lung cancer demonstrated efficacy in terms of PFS and response rate but no major improvement in OS.[54] In another Phase III trial, combination therapy with ziv-aflibercept and gemcitabine was shown to produce no significant improvement in metastatic pancreatic cancer.[55] In metastatic prostate cancer refractory to hormonal therapy, recently published data from a Phase III study (the VENICE trial) showed that ziv-aflibercept plus docetaxel and prednisone failed to improve survival outcomes.[56] Until more study results are available, due to the aforementioned cost and reimbursement issues, ziv-aflibercept is indicated for selected patients with mCRC who have good performance status and whose disease is refractory to first-line oxaliplatin-based chemotherapy.

Conclusion

Current clinical data are insufficient to directly compare ziv-aflibercept and bevacizumab when used with standard combination chemotherapy as first- or second-line regimens for mCRC. The role of ziv-aflibercept is currently limited to the second-line setting in combination with irinotecan-based regimens in mCRC patients who have not received irinotecan previously. The role of ziv-aflibercept for other tumor types is yet to be determined.

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Increased Renal Expression of Vascular Endothelial Growth Factor (VEGF) and Its Receptor VEGFR-2 in Experimental Diabetes

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It has been suggested that the cytokine vascular endothelial growth factor (VEGF) has an important role in the pathogenesis of diabetic retinopathy, but its role in nephropathy has not been clearly demonstrated. Assessment of VEGF, ^{125}I-VEGF binding, and vascular endothelial growth factor receptor–2 (VEGFR-2) in the kidney was performed after 3 and 32 weeks of streptozotocin-induced diabetes. Gene expression of both VEGF and VEGFR-2 was assessed by Northern blot analysis and the localization of the ligand and receptor was examined by in situ hybridization. VEGF and VEGFR-2 protein were also evaluated by immunohistochemistry. Binding of the radioligand ^{125}I-VEGF was evaluated by in vitro and in vivo autoradiography. Diabetes was associated with increased renal VEGF gene expression. VEGF mRNA and protein were localized to the visceral epithelial cells of the glomerulus and to distal tubules and collecting ducts in both diabetic and nondiabetic rats. Renal VEGFR-2 mRNA was increased after 3 weeks of diabetes but not in long-term diabetes. In situ hybridization and immunohistochemical studies revealed that glomerular endothelial cells were the major site of VEGFR-2 expression. In addition, VEGFR-2 gene expression was detected in cortical and renomedullary interstitial cells and on endothelial cells of peritubular capillaries. There was an increase in ^{125}I-VEGF binding sites after 3 but not 32 weeks of diabetes. The major VEGF binding sites were in the glomeruli. ^{125}I-VEGF binding was also observed in medullary rays and in the renal papillae. These studies indicate an early and persistent increase in renal VEGF gene expression in association with experimental diabetes. In addition, an early and transient increase in renal VEGF receptors was also observed in diabetic rats. These findings are consistent with a role for VEGF in mediating some of the changes observed in the diabetic kidney. *Diabetes* **48:2229–2239, 1999**

Vascular endothelial growth factor (VEGF), also known as vascular permeability factor, is a term used to describe a family of potent multifunctional cytokines (1). The VEGF-A gene produces five closely related species by alternative splicing. VEGF-A_{165} is the most abundantly expressed species and is a 165–amino acid glycoprotein with 20% homology to the A and B chains of platelet-derived growth factor (1). At least two high-affinity receptor-binding sites have been reported for VEGF. These receptors have been cloned and named flt-1 (vascular endothelial growth factor receptor [VEGFR]-1) and flk-1/KDR/NYK (VEGFR-2) and were initially viewed to be endothelial-specific tyrosine kinases (2,3). More recently, it has been determined that these receptors are present on other cell types (4). Recent studies suggest that it is the biological interaction of VEGF with VEGFR-2 that is involved in inducing the spectrum of biological responses of VEGF (1,5). VEGF also has a selective action of promoting vascular permeability (6), being 50,000 times more potent than histamine on a molar basis (7). Radioligand binding studies with iodinated recombinant VEGF have confirmed a wide distribution of VEGF binding sites in the rat, including the kidney (8). More recently, VEGF binding has also been detected in the adult and fetal human kidney (9).

Recent studies have emphasized the potential role of VEGF in diabetic retinopathy (10,11), with several groups reporting an increase in VEGF and its receptors in the diabetic retina (12,13). It has been shown that there is a close relationship between proliferative diabetic retinopathy and nephropathy (14). Furthermore, several of the putative pathways implicated in the pathogenesis of diabetic retinopathy are also viewed to be involved in the development of diabetic nephropathy (15,16). However, the status of VEGF and its receptors in the kidney in experimental diabetes has not been previously characterized.

RESEARCH DESIGN AND METHODS

Experimental plan. Diabetes was induced by streptozotocin (Sigma, St. Louis, MO) injection (diabetic, 60 mg/kg i.v.) or sham injection with citrate buffer injection (control) after an overnight fast in Sprague-Dawley rats weighing 200–250 g. Before the rats were killed, blood was collected for determination of plasma glucose by the glucose oxidase technique (17) and systolic blood pressure was measured by tail cuff plethysmography (18). The animals were anesthetized with

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AGE, advanced glycated end product; IC_{50}, concentration of unlabeled ligand required to displace 50% of the radioligand; NSB, nonspecific binding; PBS, phosphate-buffered saline; PKC, protein kinase C; ROD, relative optical density; SSC, sodium chloride–sodium citrate; TGF, transforming growth factor; VEGF, vascular endothelial growth factor; VEGFR-2, vascular endothelial growth factor receptor–2.

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pentobarbital sodium (Nembutal 50 mg/kg body weight i.v.; Bomac Laboratories, Asquith, Australia) and killed after 3 or 32 weeks of diabetes. Both kidneys were then removed. One kidney was snap frozen in liquid nitrogen–cooled isopentane for use in extracting RNA for Northern hybridization and for in vitro autoradiographic binding studies. The other kidney was bissected and immediately fixed in freshly prepared 4% paraformaldehyde in preparation for in situ hybridization. A separate group of control and diabetic rats were prepared in a manner similar to that described above, except that both kidneys were removed after infusion of radioactive VEGF tracer for the in vivo autoradiographic binding studies.

Northern hybridization of VEGF and its receptors

Preparation of RNA and synthesis of probes. Total RNA was isolated from the kidney at the time when the animals were killed using the acid guanidium thiocynate-phenol-chloroform extraction method (19). RNA purity and concentration were determined spectrophotometrically. Twenty-microgram samples were denatured and electrophoresed through 0.8% agarose formaldehyde gels. RNA integrity was verified by examination of the 28S and 18S ribosomal bands of ethidium bromide–stained material under ultraviolet light. RNA was then transferred by capillary action onto nylon filters (Hybond-N; Amersham, Bucks, U.K.) and fixed under ultraviolet light. Filters were then probed with the cDNA coding for either VEGF or its receptors, VEGFR-1 and VEGFR-2 (13). The probes were then labeled with [^{32}P]dCTP by randomly primed DNA synthesis (Boehringer Mannheim, Mannheim, Germany). Hybridization was performed at 42°C for 16 h in 50% formamide, 45 mmol/l Na_2HPO_4, 5× Denhardt's solution, 0.5% SDS, and sonicated salmon sperm DNA. After hybridization, filters were washed in solutions of decreasing ionic strength and increasing temperature, followed by exposure of filters to X-ray film for 5–14 days.

In situ hybridization of VEGF and VEGFR-2

Synthesis of riboprobes. Sense and antisense RNA probes for VEGF and VEGFR-2 were generated by in vitro transcription (Promega, Madison, WI), as previously described (13). In brief, linearized template (500 ng) was added to a reaction mixture of transcription buffer (final volume 20 µl) containing 6 mmol/l dithiothreitol, 333 µmol/l each of ATP, CTP, and GTP, 12 µmol/l UTP, 100 µCi [^{33}P]UTP (2,000 Ci/mmol, New-Dupont, Boston, MA), 20 U RNAsin (Boehringer-Mannheim), and 20 U RNA polymerase (Boehringer-Mannheim). The reaction mixture was incubated at 37°C for 90 min, after which the DNA template was digested with 1 U RNAse-free DNAse for 15 min. The riboprobe was precipitated by ammonium acetate and ethanol using yeast tRNA as a carrier and then reconstituted in 100 µl of water. Purified riboprobe length was adjusted to ~150 bases by alkaline hydrolysis.

In situ hybridization. Four-micrometer-thick sections cut from paraformaldehyde-fixed paraffin-embedded kidney tissue were placed onto slides precoated with 3-aminopropyltriethoxysilane and left overnight at 37°C. Tissue sections were dewaxed in histolene, rehydrated in graded ethanols to deionized milliQ water, equilibrated in P buffer (50 mmol/l Tris-HCl, pH 7.5, 5 mmol/l EDTA), and incubated in 125 µg/ml Pronase E (Sigma) in P buffer for 10 min at 37°C. Sections were then washed in 0.1 mol/l sodium phosphate buffer (pH 7.2), briefly refixed in 4% paraformaldehyde for 10 min, rinsed in milliQ water, dehydrated in 70% ethanol, and air dried.

Hybridization buffer containing 2×10^4 cpm/µl riboprobe in 300 mmol/l NaCl, 10 mmol/l Tris-HCl (pH 7.5), 10 mmol/l Na_2HPO_4, 5 mmol/l EDTA (pH 8.0), 1× Denhardt's solution, 50% formamide, 17 mg/ml yeast RNA, and 10% wt/vol dextran sulfate was heated to 85°C for 5 min. A 25-µl aliquot of this solution was then applied to each tissue section under coverslips. Hybridization of tissue to the riboprobe was performed overnight at 60°C in 50% formamide-humidified chambers. Sense probes for VEGF and its receptor, neuroepithelial tyrosine kinase (NYK), were used on a further set of tissue sections as controls for nonspecific binding.

After hybridization, slides were washed in 2× sodium chloride–sodium citrate (SSC) containing 50% formamide prewarmed to 50°C to remove coverslips. Sections were then washed in the above-mentioned solution for 1 h at 55°C, rinsed three times in RNAse buffer (10 mmol/l Tris-HCl, pH 7.5, 1 mmol/l EDTA, pH 8.0, 0.5 mol/l NaCl), and then incubated with RNAse A (150 µg/ml) for 1 h at 37°C. Sections were later washed in 2× SSC for 45 min at 55°C, dehydrated in graded ethanol, air dried, and exposed to Kodak X-Omat autoradiographic film (Kodak, Rochester, NY) for 1–3 days. Slides were then dipped in Ilford K5 nuclear emulsion (Ilford, Mobberley, U.K.), stored in a light-free box with desiccant at room temperature for 2–3 weeks, and developed in Kodak D19, followed by fixation with Ilford Hypam. Sections were then stained with hematoxylin and eosin for examination under light microscopy.

Quantitation of Northern and in situ hybridization X-ray films. The relative intensity of autoradiograms of the Northern blots was determined by scanning densitometry (Ultrocan XL; LKB, Bromma, Sweden). All results were corrected for differences in RNA loading by rehybridization with an oligonucleotide probe for 18S rRNA. Densitometry of autoradiographic images from kidney sections, obtained by in situ hybridization, was performed as previously described (20), using a Micro Computer Imaging Device (MCID; Imaging Research, St. Catharines, Ontario, Canada), according to the methods of Baskin and Stahl (21). In brief, in situ autoradiographic images were placed on a uniformly illuminating fluorescent light box (Northern Light Precision Luminator Model C60; Image Research) and captured using a video camera (Sony Video Camera Module CCD; Tokyo) connected to an IBM AT computer with a 512-by-512 pixel array imaging board with 256 gray levels. In view of the focal nature of glomerular [^{125}I]VEGF binding, the mean of 20–25 quantitations of these areas was assessed for each kidney section (22). After calibration, construction of a curve of optical versus radioactivity density was possible and quantitation of digitalized autoradiographic images is performed using MCID software (22). Results were then expressed as relative optical density (ROD) (23). All measurements were performed by an independent observer (B.R.) in a masked manner.

Immunohistochemistry. Sections 4 µm thick were placed onto slides, rehydrated, and treated with 1% H_2O_2/methanol followed by incubation in Protein Blocking Agent (Lipshaw-Immunon, Pittsburgh, PA) for 20 min at room temperature, as previously described (13). Sections were next incubated with a polyclonal rabbit antibody directed against the NH_2-terminal 21 amino acids of human VEGF (Santa Cruz Biotechnology, Santa Cruz, CA) overnight at 4°C, washed in phosphate-buffered saline (PBS), and incubated with biotinylated goat anti–rabbit IgG (DAKO, Carpinteria, CA). After washing with PBS, sections were incubated with avidin-biotin complex (Vector, Burlingame, CA). Peroxidase conjugates were subsequently localized by diaminobenzidine tetrahydrochloride as a chromogen. Sections were counterstained with hematoxylin. Antibody specificity had been previously confirmed by preabsorption of antibody with recombinant VEGF and by incubation without the primary antiserum (13). A similar procedure was used for assessment of VEGFR-2 protein using a polyclonal rabbit antibody directed against the COOH-terminal 20 amino acids of the mouse flk-1 protein (3).

VEGF binding in the kidney

Iodination of VEGF-165. Recombinant human VEGF (R + D Systems, Minneapolis, MN) (0.5 µg) was iodinated with ^{125}I using the chloramine T method (24). A 5-µl (0.5 mCi) aliquot of ^{125}I was added to the recombinant VEGF. Next, 50 µl of Chloramine T at a concentration of 5 mg/10 ml was added and the mixture allowed to react for 60 s. To halt the reaction, 50 µl of sodium metabisulphite (5 mg/ml) was added. After iodination, the labeled protein was separated on a Sep-pak C18 column (Millipore, Milford, MA).

In vitro autoradiography. Frozen 20-µm sections were cut on a cryostat and placed onto gelatin-coated slides. Tissue sections were washed twice for 7.5 min in preincubation buffer containing 10 mmol/l HEPES, 100 mmol/l NaCl, 5 mmol/l KCl, 5 mmol/l $MgCl_2$, 1 mmol/l EGTA, 0.1% bovine serum albumin, and 0.5 mg/ml bacitracin. Tissue sections were then incubated for 3 h in incubation buffer, consisting of preincubation buffer and ^{125}I-VEGF tracer. The final amount of radioactivity in the incubation buffer was ~300 cpm/µl; a total of 2.4×10^6 cpm was used with a final concentration of ~2 pmol/l ^{125}I-VEGF. Tissue sections were washed first in preincubation buffer for 4 min, followed by two 4-min washes in postincubation buffer consisting of 10 mmol/l HEPES, 100 mmol/l NaCl, 5 mmol/l KCl, 5 mmol/l $MgCl_2$, 1 mmol/l EGTA, and 0.5 mg/ml bacitracin. Once sections were dry, they were placed against X-ray film (Kodak X-o-Mat; Kodak, Rochester, NY) for 2 weeks. Competitive binding studies were performed with varying concentrations (10^{-12} to 10^{-8} mol/l) of unlabeled VEGF. Nonspecific binding was determined by addition of 1 nmol/l of unlabeled VEGF. Radioactive standards were made by using known dilutions of ^{125}I-VEGF onto standard disks of rat kidney slices, which were included in each slide cassette to allow calculation of autoradiographic density into units of radioactivity, as previously described (22). Quantitation of binding was performed using a computerized imaging system (MCID; Imaging Research), and one kidney from five rats per group was examined. By means of this imaging system, the density of radioactive VEGF that binds to each kidney section can be calculated. In view of the focal nature of ^{125}I-detected rat VEGF glomerular binding, the mean of 20–25 quantitations of these areas was assessed for each kidney section (22). At least five sections per rat were analyzed. The data were then analyzed by SIGMAPLOT (Jandel Scientific, San Rafael, CA) to yield a value for the concentration of unlabeled ligand required to displace 50% of the radioligand ^{125}I-VEGF (IC_{50}) (22).

In vivo autoradiography. To further define cellular localization of ^{125}I-VEGF binding in the renal cortex, the tracer was infused in vivo in separate groups of rats (control, $n = 6$; diabetic, $n = 5$). This approach has been used when characterizing other binding sites, since it is associated with better preservation of renal morphology (25,26). Rats were anesthetized with pentobarbital sodium (Nembutal 50 mg/kg body weight) and the abdominal cavity was opened with a midline incision. For infusion of ^{125}I-VEGF, a 22-gauge catheter was inserted into the abdominal aorta below the renal arteries. For total binding studies, rats were infused with ~15 µCi ^{125}I-VEGF in 1 ml of 0.1 mol/l PBS at pH 7.4. After 10–15 min of circulation, the rats were perfused at systolic blood pressure (~140 mmHg) with PBS for 1 min followed by 2% glutaraldehyde for 2 min. After perfusion fixation, one kidney was removed and fixed in 10% neutral buffered formalin overnight before it was embedded in paraffin and sections pre-

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TABLE 1
Metabolic parameters

	Short-term (3 weeks)		Long-term (32 weeks)	
	Control	Diabetic	Control	Diabetic
n	10	6	10	8
Glucose (mmol/l)	7.9 ± 0.4	17.7 ± 1.2*	8.2 ± 0.4	19.8 ± 1.5*
Blood pressure (mmHg)	129 ± 4	122 ± 8	135 ± 3	137 ± 2
Body weight (g)				
Week 0	232 ± 5	228 ± 8	230 ± 4	220 ± 6
End of study	316 ± 12	220 ± 6*	495 ± 16	344 ± 9*

Data are means ± SE. *P < 0.01 vs. control.

pared for emulsion autoradiography. Nonspecific binding (NSB) was determined in separate animals by infusion of excess (10^{-9} mol/l) unlabeled VEGF proteins 3 min before infusion of ^{125}I-VEGF tracer. The procedure was then followed as described above. The other kidney was frozen in liquid nitrogen–cooled isopentane, and 20-µm sections were cut on a cryostat and then dried and placed against X-ray film. Between 8 and 13 sections per animal were quantitated using the MCID imaging system as described above.

Statistical analysis. All data were compared by analysis of variance using the statistical package Statview SE+Graphics on an Apple Macintosh computer (Apple Computer, Cupertino, CA) and are shown as means ± SE. Differences between groups were assessed using Fisher's least significant differences test (27).

RESULTS

At the end of both short-term (3 weeks) and long-term (32 weeks) studies, all streptozotocin-induced diabetic animals had hyperglycemia (plasma glucose >15 mmol/l) and decreased body weight compared with the control groups (Table 1). In the short-term diabetic group, no weight gain was observed over the 3-week period. No difference in blood pressure was observed between control and diabetic groups.

Northern analysis. Representative Northern hybridization blots for both VEGF and VEGFR-2 in the short-term and long-term studies are shown in Fig. 1. By Northern analysis, short-term diabetes was associated with a threefold increase in VEGF mRNA when compared with control rats (Fig. 2*A*). There was also a twofold increase in VEGFR-2 gene expression with short-term diabetes (Fig. 2*A*). Long-term diabetes was associated with a twofold increase in VEGF mRNA (Fig. 2*B*). VEGFR-2 mRNA levels were not different between con-

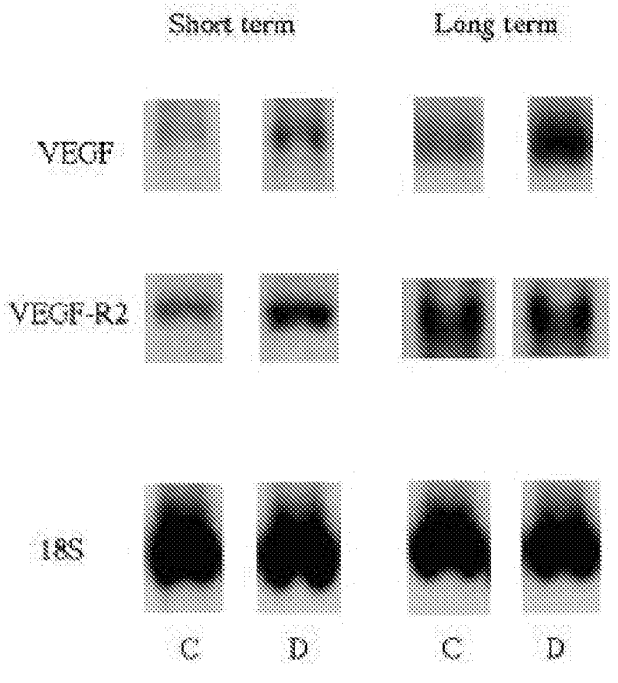


FIG. 1. Northern blot of VEGF, VEGFR-2, and 18S in control (C) and diabetic (D) rat kidneys. Increased gene expression of VEGF and VEGFR-2 is seen in kidneys of short-term diabetic rats. Increased gene expression of VEGF but not VEGFR-2 is seen in kidneys of long-term diabetic rats. 18S rRNA is similar in control and diabetic groups.

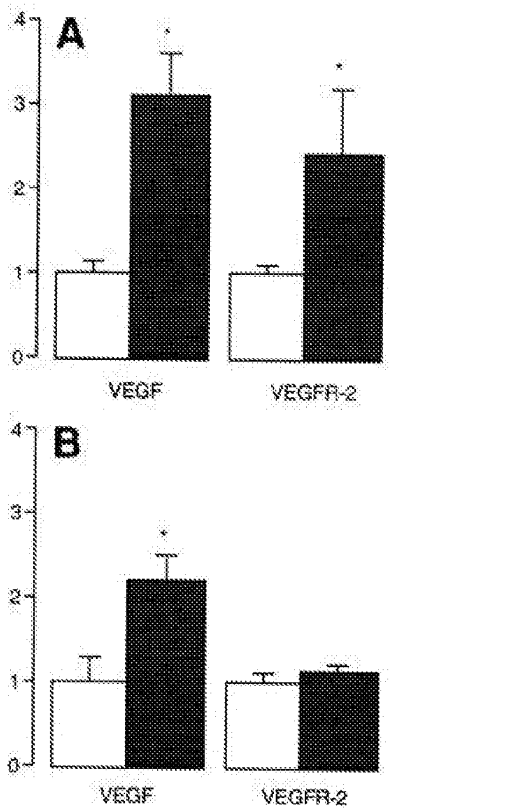


FIG. 2. Quantitation of kidney VEGF and VEGFR-2 mRNA in control (□) and diabetic (■) rats from short-term (*A*) and long-term (*B*) studies. Data are means ± SE of the ratio of optical density of VEGF and VEGFR-2 mRNA to that of 18S rRNA relative to control values (designated an arbitrary value of 1). *P < 0.01; diabetic versus control.

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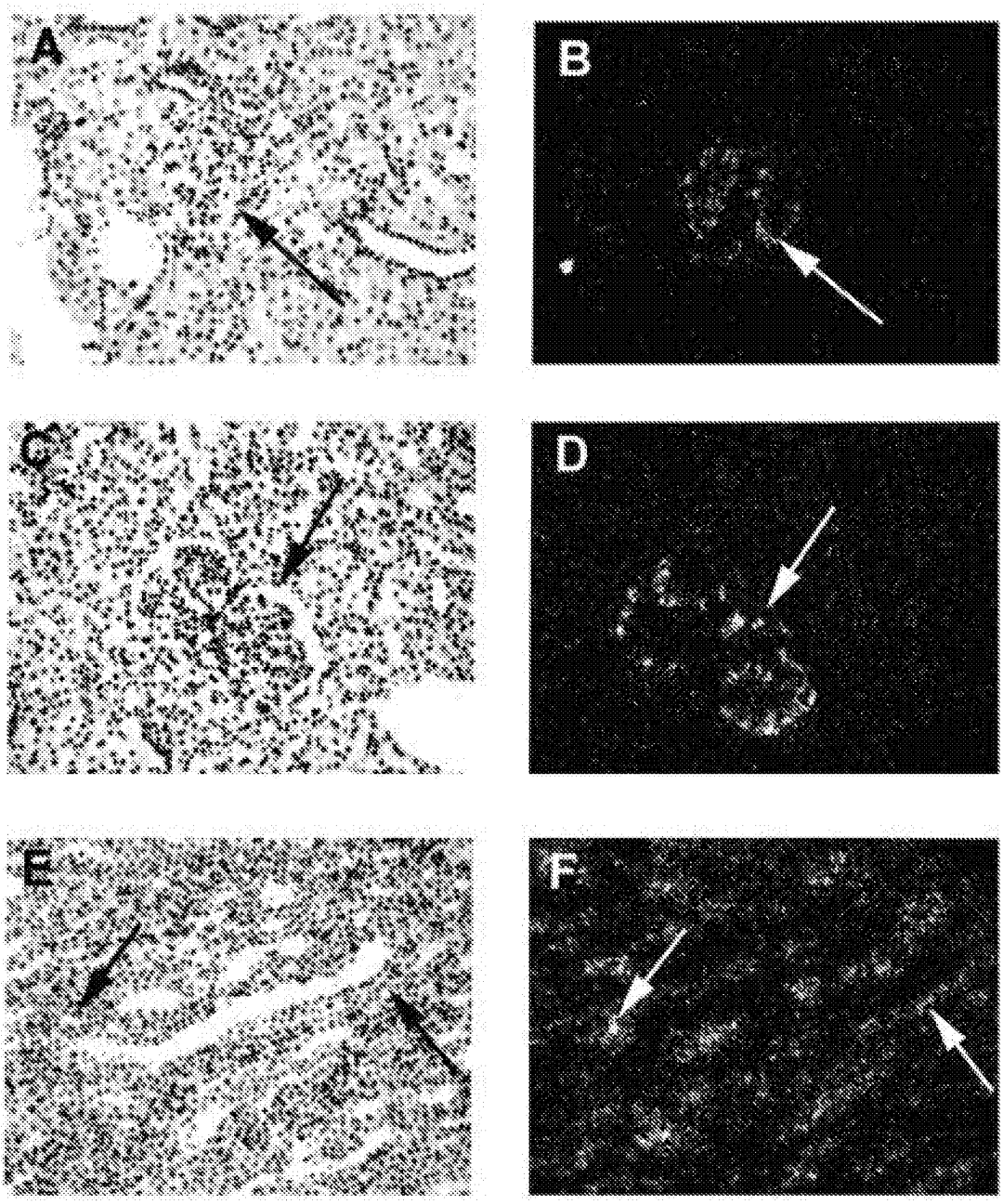


FIG. 3. In situ hybridization photomicrographs of VEGF mRNA. In the cortex, hybridization is present in the glomerular epithelial cells (arrow) in control (*A*: light field; *B*: dark field) and in greater abundance in diabetic (*C*: light field; *D*: dark field) rat kidneys. In both control and diabetic kidneys, collecting ducts expressed VEGF (control rats, *E*: light field; *F*: dark field). Original magnification 200×.

trol and diabetic rats (Fig. 2*B*). By contrast, there was no evidence of hybridization to a VEGFR-1 riboprobe in either control or diabetic rat kidney.

Localization of VEGF and VEGFR-2. Light microscopy following in situ hybridization of sections revealed abundant expression of VEGF mRNA in the visceral epithelial cells of glomeruli (Fig. 3*A–D*) and in distal tubules and collecting ducts (Fig. 3*E* and *F*). Gene expression for the VEGF receptor, VEGFR-2, was detected in glomerular endothelial cells (Fig. 4*A–D*). In addition, VEGFR-2 mRNA was noted in cortical interstitial fibroblasts and endothelial cells of peritubular capillaries (Fig. 4*E*) and renomedullary interstitial cells (Fig. 4*F*). No difference in the pattern of distribution between control and diabetic rats was noted for either VEGF (Fig. 3*A–D*) or VEGFR-2 mRNA (Fig. 4*A–D*). No hybridization was observed with sense probes (Fig. 5).

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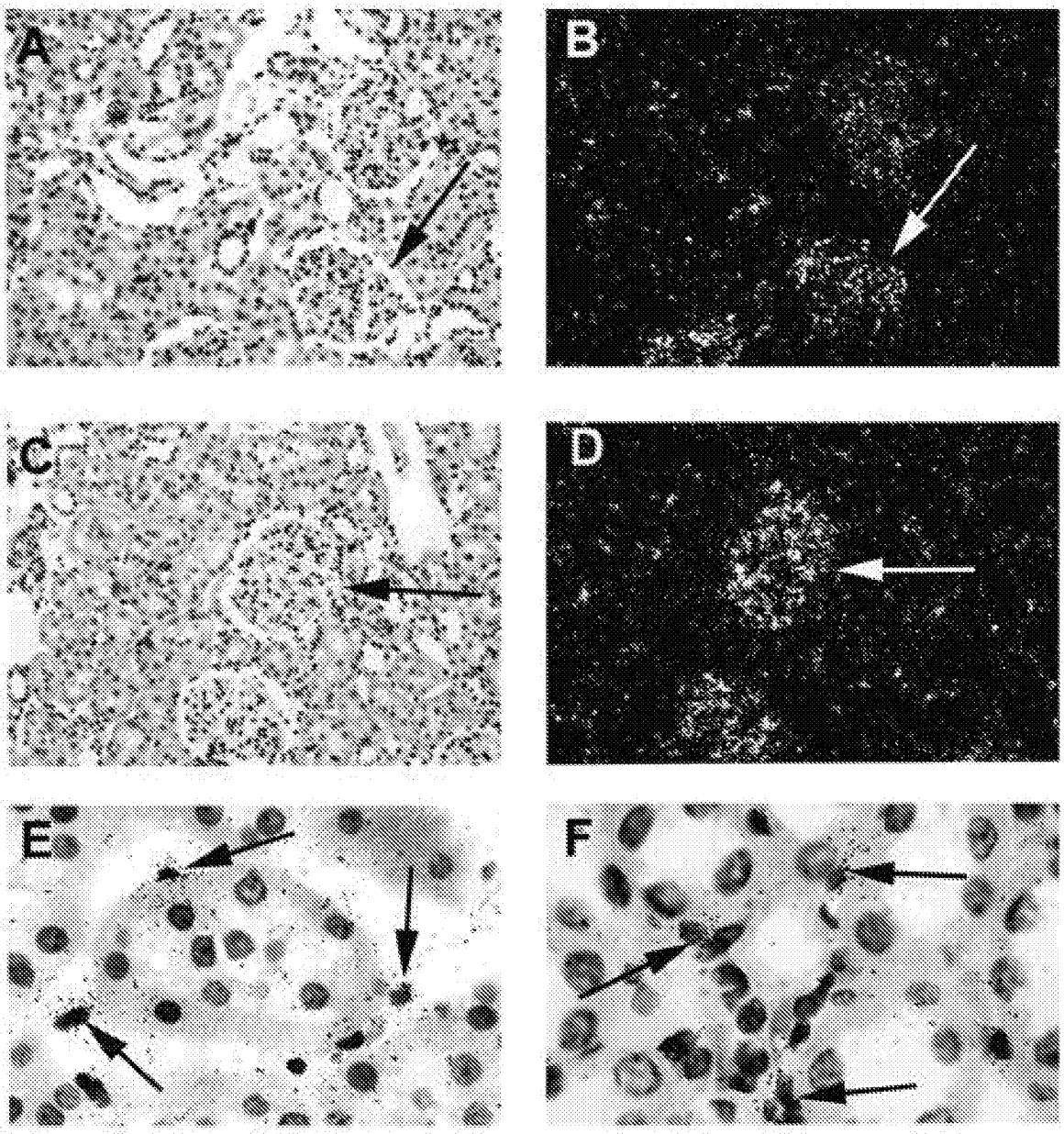


FIG. 4. In situ hybridization photomicrographs of VEGFR-2 mRNA. In the cortex, hybridization is present in the glomerular endothelial cells in control (*A*: light field; *B*: dark field) and in greater abundance in diabetic (*C*: light field; *D*: dark field) rat kidneys. Original magnification 200×. In both control and diabetic kidneys, VEGFR-2 was expressed in cortical fibroblasts, in endothelial cells of peritubular capillaries (*E*), and in renomedullary interstitial cells (*F*). Original magnification 1,000×.

Quantitation of in situ hybridization autoradiography. Kidney sections labeled with the VEGF probe showed that hybridization within glomeruli was more intense in the short-term diabetic group compared with the age-matched nondiabetic group (control, $n = 10$; 0.213 ± 0.006 vs. diabetic, $n = 6$; 0.314 ± 0.006, ROD units, mean ± SE, $P = 0.002$).

Quantitation of glomerular VEGF mRNA expression in long-term diabetic rats showed similar results to that observed in the short-term diabetic animals. Glomerular VEGF mRNA expression in the diabetic group was increased when compared with the nondiabetic group (control, $n = 5$; 0.247 ± 0.016 vs. diabetic, $n = 5$; 0.314 ± 0.020 ROD, $P = 0.03$).

Immunohistochemistry. VEGF protein was detected in glomerular epithelial cells, distal tubules, and collecting ducts (Fig. 6*A*). A similar distribution of VEGF protein was observed in diabetic rats, although the immunostaining appeared to be increased at these sites (Fig. 6*B*). There was only minimal VEGFR-2 protein detected in glomerular endothelial cells in control rats (Fig. 7*A*). Immunostaining of glomerular endothelial cells was increased in short-term diabetic rats (Fig. 7*B*).

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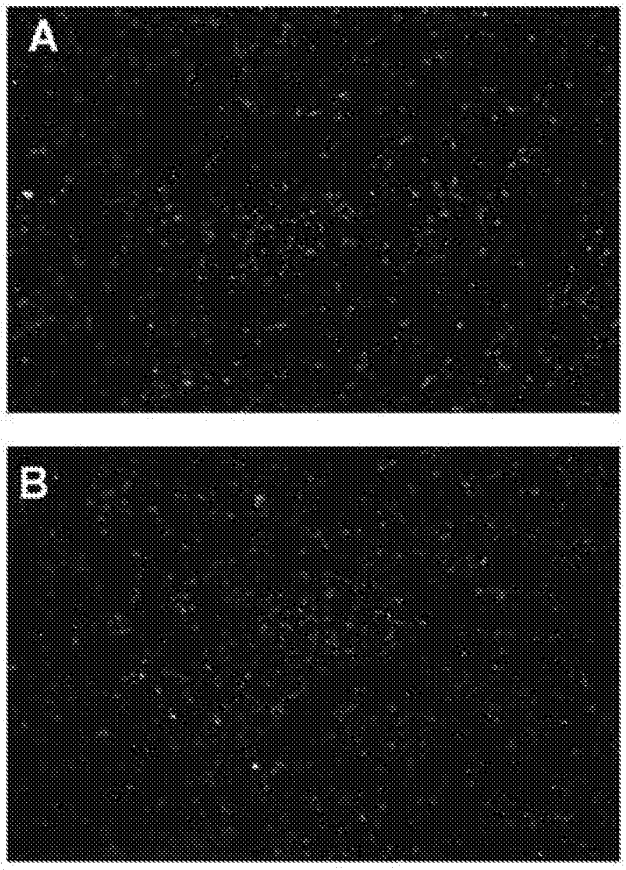


FIG. 5. In situ hybridization photomicrographs of sense VEGF (*A*) and VEGFR-2 (*B*) mRNA. No specific hybridization was detected in sections exposed to the VEGF and VEGFR-2 sense probes. Original magnification 300×.

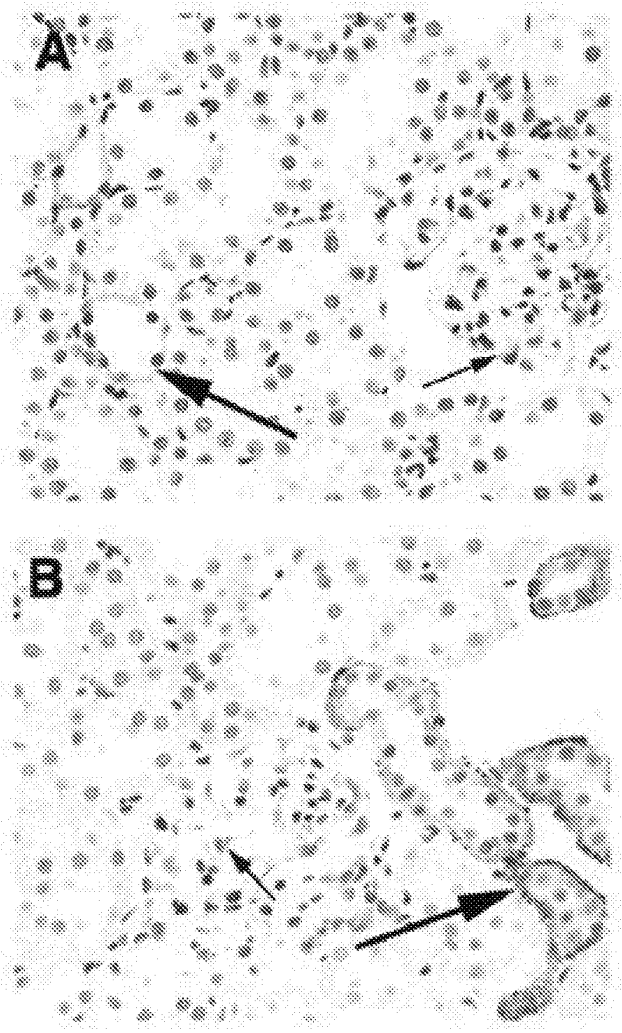


FIG. 6. Paraffin sections (4-μm thick) of control (*A*) and diabetic (*B*) rat kidney were immunostained for VEGF and counterstained with hematoxylin. Original magnification 320×. The arrows identify immunolabeling to distal tubules and glomerular epithelial cells. There appeared to be increased immunostaining in the diabetic kidney.

^{125}I-VEGF binding in the diabetic kidney

In vitro studies. Maximal receptor binding of iodinated VEGF-165 was seen after 5 h at a concentration of ~2 pmol/l (specific activity of 2,000 Ci/mmol). Binding of ^{125}I-VEGF was visualized by X-ray film in both control and diabetic rat kidney sections. In both control and diabetic rats, ^{125}I-VEGF binding was observed in the renal cortex, medulla, and papilla (Fig. 8).

Total binding of VEGF in the diabetic rats was increased by ~50% after 3 weeks of diabetes. Competition studies between radiolabeled VEGF and purified unlabeled VEGF were performed. ^{125}I-VEGF binding was inhibited by 10^{-9}mol/l unlabeled VEGF (i.e., NSB). NSB was <10% in all experiments (Fig. 8).

Cortex: short-term diabetes. Both control and diabetic kidneys showed similar ^{125}I-VEGF binding characteristics (Fig. 9*A*) ($-\log IC_{50}$; control, 11.14 ± 0.14 mol/l vs. diabetic, 11.21 ± 0.03 mol/l, n = 4/group). Renal cortical binding was increased in diabetes (control, 484 ± 11 dpm/mm^2; diabetic, 687 ± 18 dpm/mm^2, P = 0.001, n = 4/group).

Medulla. Medullary binding was also increased in the diabetic kidney (control, 368 ± 10 dpm/mm^2 vs. diabetic, 669 ± 18 dpm/mm^2, P < 0.001, n = 4/group). The binding curve, shown in Fig. 9*B*, was analyzed, and it showed that binding characteristics were modestly, yet statistically, different between the control and diabetic kidneys (control, $-\log IC_{50}$; 10.85 ± 0.16 mol/l; diabetic, 11.16 ± 0.08 mol/l, P < 0.001, n = 4/group).

In vivo binding studies. Localization of VEGF binding sites is shown in Fig. 10. There was increased glomerular binding in diabetic rats in comparison with control rats (control, 2,543 ± 53, n = 6 vs. 4,555 ± 134 dpm/mm^2, n = 5, P < 0.001).

DISCUSSION

The present study has documented increased expression of VEGF within the kidney after induction of diabetes. This increase persisted over the 8 months of diabetes. By means of in situ hybridization and immunohistochemical techniques, VEGF gene expression was localized to the epithelial cells of the glomerulus. This localization of VEGF is as pre-

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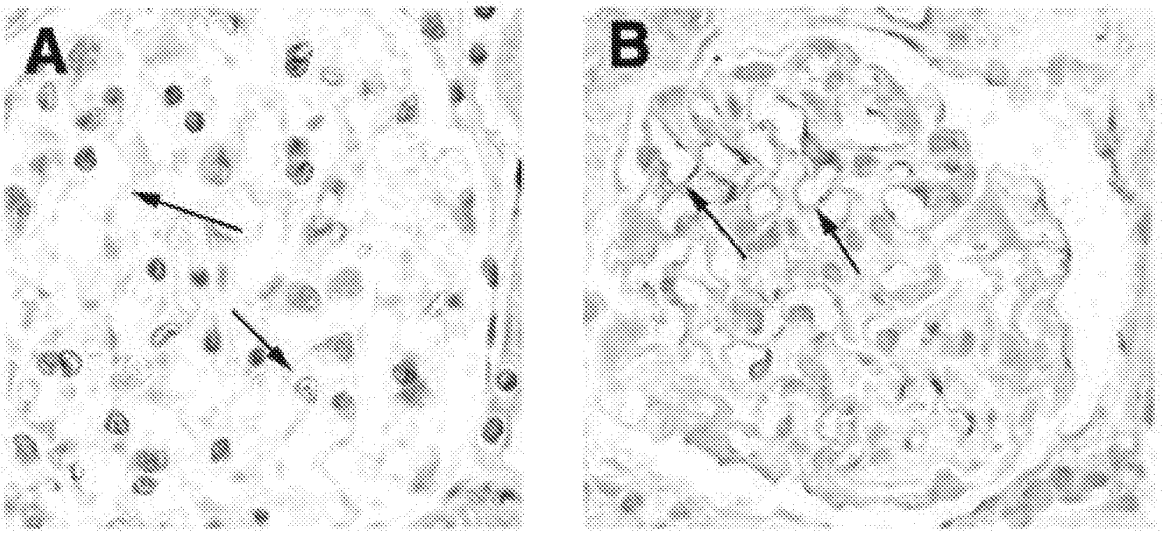


FIG. 7. Paraffin sections (4-μm thick) of control (*A*) and diabetic (*B*) rat kidney were immunostained for VEGFR-2 and counterstained with hematoxylin. Original magnification 380×. The arrows identify immunolabeling to glomerular endothelial cells. There is increased immunostaining in the diabetic kidney.

viously described by other groups and is similar to that reported in human kidney (9). In addition, VEGF was detected in collecting ducts, as has been previously reported (28). Although diabetes was associated with increased VEGF gene expression, as assessed by both Northern analysis and by quantitative evaluation of the in situ hybridization studies, there was no difference in the spatial distribution of glomerular VEGF between control and diabetic rats.

There was also increased gene expression of VEGFR-2 in the kidneys from animals with short-term diabetes. Furthermore, in long-term diabetic rats, VEGFR-2 expression was also noted in the interstitium, including both fibroblasts and peritubular capillaries. This receptor has been shown to mediate the full biological spectrum of actions of VEGF (1). This increase in receptor gene expression was readily observed in short-term diabetes but was not evident in long-term diabetic rats. Although this difference in renal receptor expression between short- and long-term diabetic rats may relate to effects of duration of diabetes, one cannot exclude that other factors, such as the severity of diabetes or low-dose insulin treatment, may also influence VEGF receptor expression.

In situ hybridization studies revealed that VEGFR-2 was expressed in glomeruli, as has been previously reported (28). The endothelial distribution of this VEGF receptor is consistent with the specific mitogenic effect of VEGF on endothelial cells (29). Immunohistochemical studies confirmed that there was translation of the VEGFR-2 mRNA to protein with evidence of receptor protein expression in glomerular endothelial cells, as has been previously reported (9). In the present study, VEGFR-2 was also detected in both control and diabetic rats in cortical fibroblasts and renomedullary interstitial cells. The significance of this finding is as yet unknown, but these cells lie in close proximity to tubular capillaries, and the action of VEGF at these sites may involve effects on vascular integrity. These interstitial cells have been reported to have receptors for many growth factors (30) and vasoactive hormones, such as angiotensin II and endothelin (31).

To complement the studies evaluating VEGFR-2 expression, both in vivo and in vitro autoradiographic techniques were used to assess ^{125}I-VEGF binding in control and diabetic rats. Specific VEGF binding sites were observed in the kidney, including the glomerulus, medullary rays, and papillae of the kidney, as has been previously described by Jakeman et al. (8). Further evaluation of ^{125}I-VEGF binding revealed an increase in specific binding in experimental diabetes consistent with translation of the VEGF receptor mRNA to receptor protein, thereby leading to increased binding of the ligand VEGF. The increase in VEGF binding suggested by in vitro autoradiography is consistent with the increased expression of VEGFR-2 detected in the diabetic kidney using both in situ hybridization and immunohistochemical techniques. These findings using three different methods support the notion that there is upregulation of VEGF receptors in the diabetic kidney.

In vivo autoradiography revealed a similar pattern to the in vitro studies with increased binding, primarily to glomeruli, in diabetes. Although the findings from the in vivo autoradiographic studies could be confounded by renal hemodynamic changes such as diabetes-related renal hyperperfusion-hyperfiltration, this is unlikely to explain the increased renal VEGF binding, since the in vitro autoradiographic studies, which are not confounded by systemic or renal hemodynamic factors, also showed increased binding of the radioligand ^{125}I-VEGF.

Although VEGFR-1 can also bind VEGF with high affinity, recent studies indicate that this protein does not initiate VEGF signal transduction pathways and is not primarily responsible for the biological actions of VEGF in the adult (5,32). This receptor has been previously reported to be present in the kidney (9). However, other groups have suggested that there is minimal or no expression of VEGFR-1 in the kidney (33–35). Indeed, in the present study, VEGFR-1 mRNA

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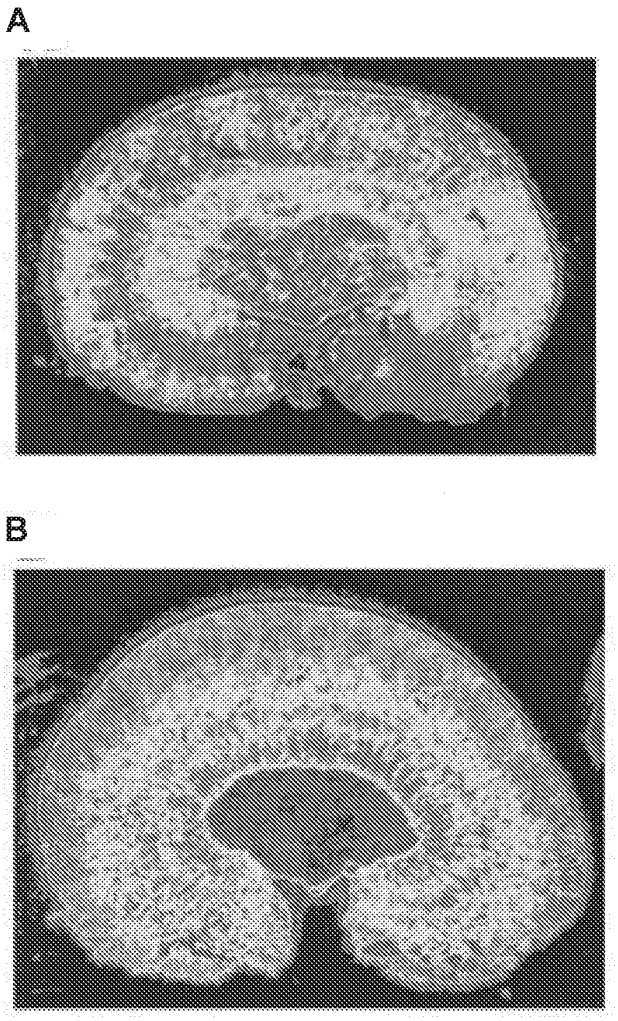


FIG. 8. Magnitude of ^{125}I-VEGF binding in the kidney from control (*A*) and diabetic (*B*) rats is indicated semiquantitatively in pseudocolorized computer images (blue, nil; green, low; yellow, moderate; red, high).

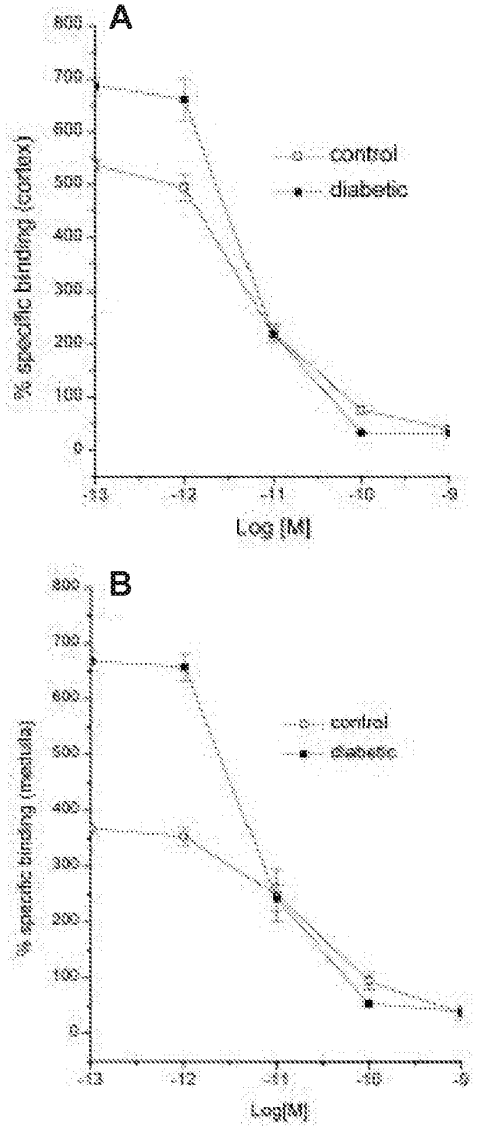


FIG. 9. Binding isotherms for VEGF generated by the incubation of tissue sections in [^{125}I]VEGF with increasing concentrations (10^{-12} to 10^{-9} mol/l) of nonradioactive rat VEGF in control (□, n = 5) and diabetic (■, n = 5) rats in renal cortex (*A*) and medulla (*B*). The y-axis represents percent specific binding.

could not be detected by Northern analysis in either control or diabetic rat kidney. By contrast, abundant VEGFR-1 mRNA expression was observed in rat lung and placenta (data not shown) and in retina, as has been previously reported by our group and others (12,13). It has been suggested that the dominant form of this receptor in the kidney is the soluble form that lacks an intracellular signaling domain (33). Nevertheless, one cannot totally exclude a contribution from this high-affinity receptor in explaining the increase in VEGF binding in the diabetic kidney.

The increase in VEGF in the diabetic kidney is consistent with in vitro studies suggesting that glucose can induce VEGF expression. Williams et al. (36) have reported that acute hyperglycemia induces VEGF gene expression in vascular smooth-muscle cells, via a protein kinase C (PKC)-dependent pathway. A link between PKC and VEGF is further suggested by studies with an orally active PKCβ inhibitor (37). PKCβ_{II} inhibition was associated not only with reduced VEGF-induced retinal permeability (37) but also with retardation of development of albuminuria in streptozotocin-induced diabetic rats (38).

The persistent expression of VEGF in the diabetic kidney may relate not only to the effects of hyperglycemia per se but to the effects of advanced glycated end products (AGEs) that accumulate in diabetic tissues over weeks to months (39). These AGEs have been shown in vitro to activate VEGF expression in retinal Müller cells (40) and in vivo to upregulate VEGF expression in the retina, including cells within the ganglion and inner nuclear layers (41). Various other factors relevant to the pathogenesis of diabetic nephropathy have also been shown to promote VEGF expression, including stretch (42), angiotensin II (43), and a number of

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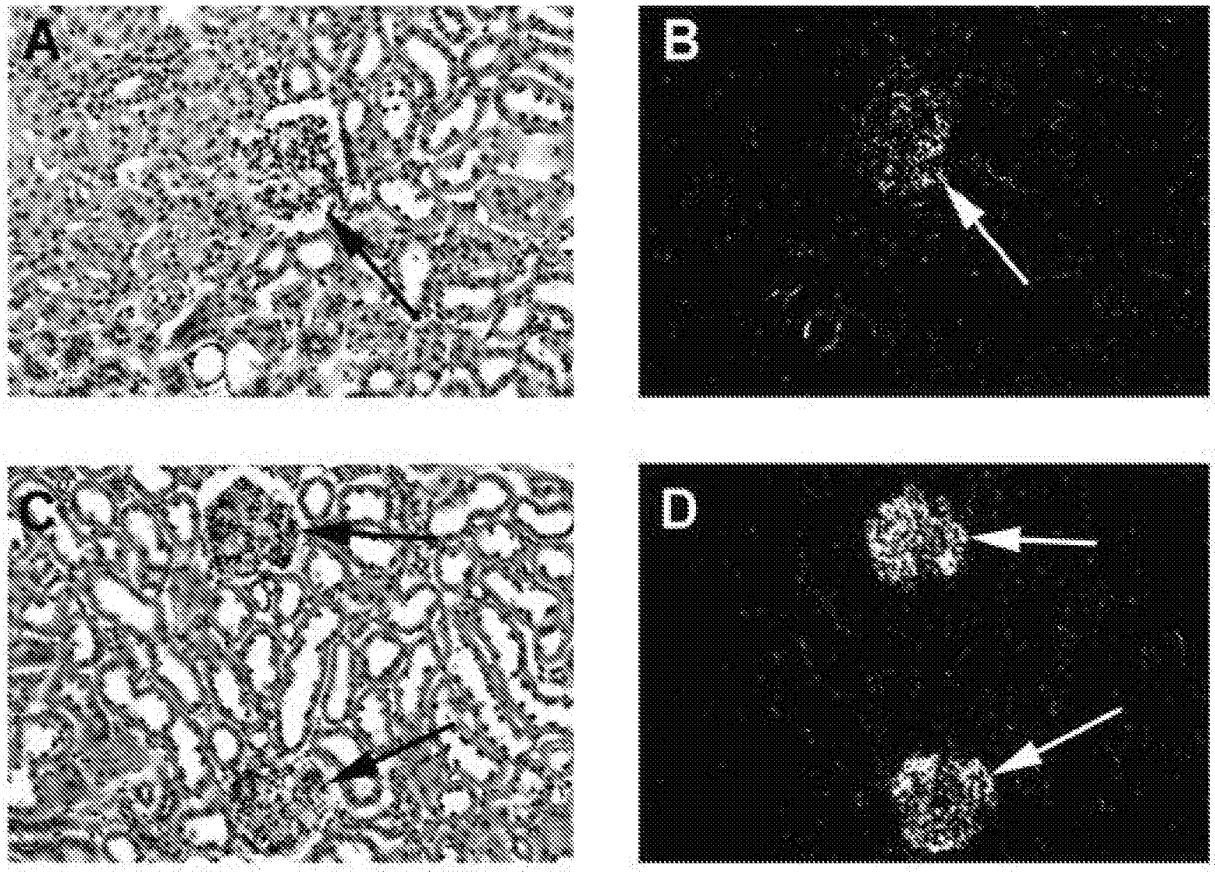


FIG. 10. In vivo binding of ^{125}I-VEGF in the kidney. Light microscopic autoradiographs of kidney cortex from rats administered ^{125}I-VEGF in vivo. Total binding for ^{125}I-VEGF in glomeruli in control (*A*: light field; *B*: dark field) and diabetic (*C*: light field; *D*: dark field) rats. Magnification 200×.

cytokines (44-46). Since it is likely that diabetic nephropathy occurs as a result of an interaction of metabolic factors and hemodynamic factors, it is of particular interest that VEGF expression may be particularly enhanced in the context of angiotensin II and hyperglycemia (47). Transforming growth factor (TGF)-β1 has been reported to downregulate VEGFR-2 expression (48) but to increase gene and protein expression of its ligand, VEGF (49). Since TGF-β1 has been reported to increase in the kidneys from long-term diabetic rats (50,51), it is possible that this cytokine was involved in reducing renal VEGFR-2 overexpression and stimulating VEGF expression in long-term diabetic rats, as was observed in the present study.

The increase in VEGF and VEGFR-2 has been previously reported in the retina in experimental diabetes by several groups (12,13). Hammes et al. (12) reported that there is minimal evidence of expression of VEGF or its receptors in the normal retina with clear evidence of significant synthesis of VEGF and its receptors in the diabetic retina. This was confirmed by Gilbert et al. (13), who also reported that in experimental diabetes there were increased levels of VEGF and VEGFR-2 in the retina. The present study in the kidney provides evidence that the changes observed in the retina are not restricted to one site but also occur in the kidney. From a clinical perspective, a close association has been noted between vision-threatening retinopathy and diabetic renal disease (14,52). This association may be considered to be due to similar pathogenic mechanisms. VEGF must be viewed as a primary candidate for mediating both microvascular complications. The presence of increased ligand as well as increased receptor is suggestive of activation of the VEGF pathway in diabetes. Although it is likely that VEGF plays an important role in ocular neovascularization, its role in the kidney remains to be fully delineated (15). It is clear that VEGF and its receptors are vital for renal development, based on studies in VEGF and VEGF receptor knockout mice (53,54) and on studies involving postnatal administration of neutralizing antibodies to VEGF (55). The localization of VEGF to the glomerular epithelial cell (podocyte) in the current study is similar to the findings of others (56). It has been suggested that VEGF may contribute to the relaxing capacity of the renal vasculature so as to alleviate vascular injury and re-establish vascular integrity (56,57). The importance of this phenomenon in diabetes remains speculative, and, from the present study, it is not possible to determine if overexpression of VEGF in the kidney is deleterious or represents a compensatory mechanism to attenuate renal injury.

The major biological actions of VEGF appear to be the enhancement of vascular permeability and angiogenesis (1). In the retina, these two actions of VEGF are considered rel-

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evant to the development of macular edema and proliferative retinopathy. By contrast, it remains uncertain whether these biological actions of VEGF are relevant to the changes observed in the diabetic kidney. Diabetes is associated with an early increase in albumin permeability, which ultimately leads to the development of albuminuria (58). VEGF is a very potent inducer of permeability (59), and it is possible that this action of VEGF is enhanced in diabetes due to increased synthesis of this peptide within the glomerulus. The importance of VEGF in mediating this effect in diabetes has been suggested by studies in which glucose-induced changes in albumin permeation and blood flow could be prevented by neutralizing antibodies to VEGF (60) or a nonpeptide VEGF antagonist (61).

With respect to VEGF's action as an endothelial mitogen–promoting angiogenesis, the status of the endothelial cell in the diabetic kidney and whether there is associated angiogenesis remains controversial. Østerby et al. (62) have suggested that angiogenesis may occur in human diabetes with duplication of the efferent arteriole. Several other groups have also reported increased blood vessel growth in the diabetic kidney (63–65), but the link of these phenomena to VEGF and VEGF receptor expression remains to be delineated. Indeed, a specific antagonist of VEGF will ultimately be required to determine if VEGF is involved in mediating many of the functional and possibly structural changes observed in diabetic nephropathy.

ACKNOWLEDGMENTS

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VEGF-mediated inflammation precedes angiogenesis in adult brain

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Abstract

Vascular endothelial growth factor (VEGF) has been shown to induce angiogenesis when infused continuously into adult rat brain tissue. In addition, VEGF has been shown to enhance permeability in brain vasculature. Adult rats were continuously infused with mouse VEGF into neocortex for up to 7 days. We studied the development of VEGF-induced vasculature in rat neocortex and evaluated the temporal expression of a wide variety of markers for inflammation and vascular leak in relation to the angiogenic response using immunohistochemistry and Western blot analysis. We report here that VEGF-mediated inflammation in brain is characterized by upregulation of ICAM-1 and the chemokine MIP-1α, as well as a preferential extravasation of monocytes. VEGF causes a dramatic breakdown of the blood–brain barrier, which is characterized by decreased investment of the vasculature with astroglial endfeet. Perivascular cells, in contrast, increase around the newly formed cerebrovasculature. In addition, breakdown of the blood–brain barrier, leukocyte extravasation, and extracellular matrix deposition occur before vascular proliferation. Furthermore, administration of low doses of VEGF induces permeability and inflammation without appreciable vascular proliferation.
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Keywords: Cytokine; Blood–brain barrier; Permeability; Vasculature; Chemokine; VEGF; Inflammation; MIP-1α; Monocytes

Introduction

Vascular endothelial growth factor (VEGF) has been shown to induce vascular proliferation in a variety of tissues (Bauters et al., 1994; Krum et al., 2002; Proescholdt et al., 1999; Rosenstein et al., 1998; Springer et al., 1998; Takeshita et al., 1994), and studies of VEGF null mutant mice have shown that VEGF is necessary for angiogenesis and vasculogenesis in the developing embryo (Ferrara et al., 1996). Consequently, VEGF has been evaluated in clinical trials as a pro-angiogenic factor to treat ischemic conditions (Isner, 1998; Isner et al., 1996; Losordo et al., 1998). Although VEGF's role as an angiogenic factor is well established, it was originally discovered and characterized based on its ability to increase vascular permeability (Senger et al., 1986). VEGF has been shown to increase vascular leak of both proteins and particulates, and it has been proposed that this increase in permeability is a necessary prerequisite for the induction of angiogenesis (for reviews, see Dvorak et al., 1995, 1999).

Many human diseases are characterized by pathological angiogenesis, such as proliferative vascular retinopathies, psoriasis, rheumatoid arthritis, endometriosis, and tumors. In these conditions, VEGF levels are known to be increased before and/or during the angiogenic process (Bhushan et al., 1999; Brown et al., 1993, 1995; Detmar et al., 1994; Harada et al., 1998; Jackson et al., 1997; Kikuchi et al., 1998; Lashkari et al., 2000; Mahnke et al., 2000). In addition, VEGF levels are elevated in many human diseases, or animal models of human disease, which are characterized by inflammation and vascular leak, such as cerebral ischemia, tumor ascites, trauma, early diabetic retinopathy, preeclampsia, ovarian hyperstimulation syndrome, and status epilepticus (Baker et al., 1995; Boulton et al., 1998; Cobbs et al., 1998; Croll et al., 2002; Grad et al., 1998; Hayashi et al., 1997; Issa et al., 1999; Kovacs et al., 1996; Kraft et al.,

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1999; Lee et al., 1999; Lennmyr et al., 1998; Levin et al., 1998; McClure et al., 1994; Neulen et al., 1995; Pichiule et al., 1999; Plate et al., 1999; Slevin et al., 2000; Spirin et al., 1999; Zebrowski et al., 1999). Therefore, a clear understanding of VEGF-mediated angiogenesis and vascular leak is critical if VEGF-related treatments for these pathological conditions are to be evaluated.

We have employed continuous infusion of exogenous VEGF protein into adult rat neocortex as a model for understanding more fully the nature and development of VEGF-induced changes in cerebral blood vessel structure and function. VEGF induces an angiogenic response when infused continuously into adult rat brain via osmotic minipump, or when delivered by way of an adenoviral vector (Proescholdt et al., 1999; Rosenstein et al., 1998). When applied to the brain surface or parenchyma, VEGF induces a rapid and dramatic increase in vascular permeability (Dobrogowska et al., 1998). Our findings show that VEGF acts either directly or indirectly as a potent pro-inflammatory cytokine in adult rat brain, and that increases in vascular permeability and indices of inflammation precede VEGF-induced angiogenesis of brain vasculature.

Materials and methods

Subjects

Adult male Sprague–Dawley rats (300–400 g) from Taconic laboratories (Germantown, NY) were housed two per cage within a temperature and humidity-stabilized animal facility with food and water available ad libitum. Animals were maintained on a 12:12 light–dark cycle (lights on 0600 h) and were allowed to acclimate for at least 1 week before any experimental manipulations. All experiments were conducted under the auspices of protocols approved by the Regeneron Animal Care and Use Committee.

Surgeries

Animals were anesthetized with chloral hydrate (170 mg/kg)–pentobarbital (35.2 mg/kg) ip. Cannulae (2 mm long; Plastics One, Roanoke, VA) were stereotaxically implanted in the right frontoparietal cortex (0.5 mm anterior, 3.2 mm lateral to bregma) as described previously (Croll et al., 1998). Polyvinyl catheters (Bolab, Lake Havasu City, AZ) were attached to the cannulae with cyanoacrylate glue, filled with sterile PBS, and heat-sealed (Loctite 495, Loctite Corp., Newington, CT). One week later (to permit surgical trauma to attenuate), animals were briefly anesthetized with either halothane (5% induction, 1.5% maintenance) in 1:2 oxygen–nitrous oxide or isoflurane (2.5% induction, 2% maintenance) in oxygen. An incision was made in the nape of the neck, the tip of the catheter was cut, and an osmotic minipump (model 2002, 0.5 μl/h, Alza Corporation, Palo Alta, CA) was attached to the catheter using cyanoacrylate glue.

Minipumps containing VEGF were attached to preimplanted PBS-filled catheters on day 0. Because the pumps had to first pump PBS from the catheters into the brains before VEGF protein could reach the brain, VEGF took an average of 21–23 h to reach the brain. Hence, the 1-day time point represents one to several hours of VEGF infusion, rather than a full day of VEGF infusion. Minipumps contained either recombinant mVEGF 164 in PBS, VEGF + Flt-Fc, or PBS (proteins produced at Regeneron). In some experiments, comparison proteins (hFc, hAngiopoietin 1, and hAngiopoietin 2) were infused instead of PBS at concentrations equaling or exceeding the VEGF dose to control for nonspecific protein effects. Angiopoietin 1 and 2 were selected for infusion to control for nonspecific effects of protein growth factors on brain tissue. The hFc protein was selected for infusion both as a general protein control and as a control for the hFc portion of the Flt-Fc. The responses seen in animals infused with control proteins were not different from those observed in animals infused with PBS, except for an occasional tendency toward increased microglial reaction at the infusion site. For dosing experiments, VEGF was given at 30, 60, 120, or 240 ng/day. Flt-Fc, which binds to VEGF with high affinity, was co-infused with either the 120 or 240 ng/day dose of VEGF at 4.8 or 9.6 μg/day (an approximately 10-fold molar excess compared to VEGF). Because Flt-Fc binds to the exogenous VEGF, preventing it from binding to its endogenous receptors, any nonspecific effects of infusion of VEGF protein into brain tissue should be prevented by co-infusion with Flt-Fc. Indeed, nonspecific tissue irritation would be expected to worsen with the addition of increased protein load (i.e., VEGF + Flt-Fc as opposed to just VEGF). Studies of the chronological development of the VEGF-induced vascular responses and detailed analyses of the 7-day neovasculature used 240 ng/day of VEGF. All experiments were repeated at least once, with group sizes of three to six animals in each treatment group in each study, to ensure that the results obtained were consistent.

Immunohistochemistry

After an overdose of chloral hydrate-pentobarbital, animals were exsanguinated and perfused transcardially with heparinized saline (5 IU/l) followed by 4% buffered paraformaldehyde at 4°C. Some animals received a bolus intravenous injection of 0.026-μm-diameter fluorescent microspheres (Duke Scientific, Palo Alto, CA) 30 min before exsanguination and perfusion. Brains were removed and placed in 30% buffered sucrose and later sectioned at 40 μm in the coronal plane. Sections were stored in cryoprotectant (Watson et al., 1986) at −20°C until stained. Brains were immunostained with the antibodies listed in Table 1 using a biotinylated secondary antibody-avidin-peroxidase reaction (Vectastain Elite kit, Vector Laboratories, Burlingame, CA) as described previously (Morse et al., 1993).

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Table 1
Antibodies used for immunostaining

Stains for	Antibody	Species	Dilution	Supplier	City
Vascular endothelial cells	RECA	mouse	1:250	Serotec	Raleigh, NC
Leukocytes	OX-1	mouse	1:10,000	Harlan Bioproducts	Cincinnati, OH
Microglia (macrophage)	OX-42	mouse	1:10,000	Serotec	Raleigh, NC
Astroglia	GFAP	rabbit	1:60,000	Dako	Carpinteris, CA
Immunoglobulin	Rat IgG	rabbit	1:1500	Vector Laboratories	Burlingame, CA
Nitric oxide synthase	eNOS	rabbit	1:250	Transduction Laboratories	Lexington, KT
T cells	R73	mouse	1:5000	Serotec	Raleigh, NC
Monocyte/macrophage	ED-1	mouse	1:15,000	Serotec	Raleigh, NC
ICAM-1	CD-54	mouse	1:10,000	Serotec	Raleigh, NC
Smooth muscle cells/pericytes	α-SMA	mouse	1:500	Dako	Carpinteris, CA
Fibrinogen	Fibrinogen	rabbit	1:20,000	Dako	Carpinteris, CA
VEGF	VEGF	goat	1 μg/ml	R&D Systems	Minneapolis, MN
Proliferating cells	Ki67	mouse	1:100	PharMingen	San Diego, CA
Proliferating cells	BrdU	mouse	1:833	Becton-Dickinson	Franklin Lakes, NJ
Proliferating cells	Histone H3	rabbit	1 μg/ml	Upstate Biotechnology	Lake Placid, NY
Proliferating cells	PCNA	mouse	1:100	Dako	Carpinteris, CA

Quantification

Changes in vascular quality were evaluated quantitatively using stereological techniques. Animals were perfused with 2% paraformaldehyde, the brains were removed, and then frozen in methylbutane on dry ice. Brains were stored at −80 °C until sectioned on a cryostat. Within each group, a third of the brains each were pseudorandomly selected for sectioning at 10 μm in coronal, sagittal, and transverse planes. Stereology was performed on RECA-stained slides after acquisition of images by a DAGE MTI CCD725 video camera (Dage, Michigan City, IN) attached to a Nikon microscope (Morrell Instruments, Melville, NY). Images were analyzed using the NIH Image software (NIH, Bethesda, MD). All vasculature within the approximated field of VEGF diffusion was evaluated (a 3-mm square block of cortex centered on the cannula tip).

Percentage of tissue area containing vessels was determined by point-count stereology. An acetate containing points in a grid pattern were overlaid on the images taken from sections sampled every 200 μm throughout the approximately 1.5 mm extent of VEGF diffusion (for a total of approximately seven to eight sections analyzed per animal). All points (intersections) which laid over a vessel were counted and were represented as a proportion of total points. Points were counted if they either lay on a RECA-positive lumen or lay within a space completely encircled by a circumferential RECA-positive lumen. Spaces in the tissue produced by the cannula track were excluded from analysis. Percentage of vascular area for each brain was expressed as percentage of tissue area occupied by vessels averaged over all of the sections. Percentage of tissue area occupied by vasculature was compared for VEGF ($n = 7$) vs. PBS-infused ($n = 7$) animals using an independent-groups Student's t test with alpha set at 0.05.

Changes in the proportion of tissue area occupied by vasculature can be attributed either to changes in vascular diameter or changes in vessel length. Vessel diameters were also measured using NIH Image on the same sections sampled for vessel density measurements. Vessels were sampled using a pseudorandomly oriented grid. Vessel diameter was taken by measuring the length of the line representing the smallest perpendicular distance across the vessel. Because more of the grid intersections in the VEGF animals than the PBS animals were overlying vasculature, more vessels were sampled for the VEGF than the PBS animals. However, the mean diameter was determined for each section and then for each animal, such that only one value was statistically analyzed per animal. Vascular diameter was compared for VEGF vs. PBS-infused animals using an independent groups Student's t test with alpha set at 0.05.

All stereological analyses and histological analyses were conducted by observers blind to the treatment condition of the animals from which the tissue was taken.

Western blot analysis

After 7 days of infusion with VEGF or PBS, animals were anesthetized with chloral hydrate-pentobarbital and were rapidly decapitated. The brains were removed and placed inside a 1.5-mm brain block (Zivic-Miller, Allentown, PA). The brain was cut coronally through the cannula track, and the 1.5-mm slab on either side of the track was taken and placed on a cold metal block. Using a fine scalpel blade, cuts were made 1.5 mm lateral and medial to the cannula track in the cortex. The tissue between the cuts in each slab was taken through the entire depth of cortex, placed in a vial, and immediately frozen on dry ice. Tissue was also taken from naive rats.

Tissue was homogenized in lysis buffer containing 1.0% NP40, 0.5% deoxycholic acid, 0.1% SDS, and protease inhibitors (1 Complete tablet, Boehringer Mannheim/Roche, Indianapolis, IN). Lysate (10–20 μl), diluted from 1:1 to 1:5 with sample buffer, was loaded onto each lane of a 12% Tri-Glycine pre-cast Western blot gel. A nonreducing gel was run at 150 V using a Novex Minicell

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II gel electrophoresis unit (Novex/Invitrogen, Carlsbad, CA) for 2 h. Protein was transferred to a nitrocellulose membrane (Novex/Invitrogen) for 2–16 h. After transfer, membranes were washed in TBS-T and transferred into a solution containing primary antibody for all Westerns except for the rat IgG Western analysis (rabbit anti-fibrinogen antibody, 1:1000, Dako, Carpinteris, CA; mouse anti-ICAM-1 antibody, 1:1000, Serotec, Raleigh, NC). After an overnight incubation, membranes were washed in TBS-T and transferred to an HRP-conjugated secondary antibody (for rat IgG: goat anti-rat, 1:10,000, Boehringer Mannheim/Roche; for fibrinogen: goat anti-rabbit, 1,10,000, Chemicon, Temecula, CA; for ICAM-1: goat anti-mouse, 1:5000, Boehringer Mannheim/Roche) for 1 h. After washing, membranes were treated with ECL (Amersham Pharmacia Biotech, Piscataway, NJ) and tranferred onto film (Kodak, Rochester, NY). Films were exposed from 0.5 s to 2 min. For all antibodies, secondary-only gels were run to control for nonspecific bands. In addition, positive protein controls were available and run for fibrinogen (Sigma, St. Louis, MO) and rat IgG (IgG1κ, Serotec).

LightCycler PCR

Tissue was collected for RT-PCR analysis of chemokine levels as described for Western blots, except that equivalent tissue was also taken from the contralateral hemisphere of each animal. Tissues were taken after 2, 4, or 7 days of 240 ng/day VEGF. RNA levels were determined for MCP-1, RANTES, MIP-1α, and GRO-α. Lightcycler PCR was performed as previously described (Lie and Petropoulos, 1998; Ransohoff et al., 2002; Schreiber et al., 2001). Data were analyzed using a 2 (treatment) × 3 (time) × 2 (hemisphere) mixed factorial ANOVA, with alpha = 0.05. Tissue was collected from two separate cohorts of animals, and the data were generated by an experimenter blind to the treatment group of the animals. The control group for the first cohort was vehicle (PBS), and the control group for the second cohort was a protein, human Fc, infused at a dose equivalent to that of VEGF. Data from the two control groups were compared using an ANOVA and were combined for the final analysis after confirming statistically that the results from these groups did not differ. In addition, data from the two cohorts were not found to differ from each other overall by ANOVA.

In situ hybridization

Slides were taken for in situ hybridization from those prepared for the quantitative analysis. The MIP-1α riboprobe was prepared as previously described (Glabinski et al., 1997). In situ hybridization was conducted as previously described (Davis et al., 1996), except that slides were exposed to emulsion for 4 weeks before developing. A control slide from each brain was hybridized to the sense probe, and no specific hybridization pattern was detected.

Results

VEGF dose response

PBS or VEGF (30, 60, 120, or 240 ng/day) were infused continuously into the neocortex of adult male Sprague–Dawley rats for 7 days. Tissue was collected and processed histologically for evaluation of vascular changes. Immunostaining for rat endothelial cell antigen (RECA) revealed that there was little obvious change in cerebral vascular density or morphology when VEGF was infused at a dose of 30 ng/day. At 60 ng/day, small increases in vascular density, tortuosity, and vessel diameter became apparent. These changes became progressively more marked when VEGF was infused at 120 and 240 ng/day (Fig. 1). To confirm the effect of VEGF infusion on vascular leak, tissue sections were also stained for rat IgG, which is excluded from the brain parenchyma of normal adult rats. In rats infused with PBS alone, only a very small amount of rat IgG staining was evident immediately adjacent to the cannula track. However, infusion of VEGF produced a marked extravasation of rat IgG within the brain parenchyma. The amount of rat IgG detected in brain increased in a dose-dependent manner (Fig. 1). Additional sections were immunostained with the pan-leukocyte marker OX-1 to assess infiltration of inflammatory cells into the brain. Few, if any, leukocytes were found in brains infused with PBS, but even the lowest dose of VEGF (30 ng/day), which produced no appreciable changes in vascular morphology, led to a marked extravasation of leukocytes (Fig. 1). The magnitude of the inflammatory response was again clearly dose-dependent. In contrast, infusion of comparison proteins such as human recombinant Angiopoietin-1 and human Fc produced no increase in the extravasation of rat IgG or leukocytes compared to PBS alone (Angiopoietin-1 data shown in Fig. 2C). Furthermore, co-infusion of a 10-fold molar excess of Flt-Fc blocked the leak, inflammation, and increased vasculature induced by VEGF administration (data not shown for leak and inflammation; vasculature shown in Fig. 2D).

Characterization of the VEGF-induced Neovasculature

Vascular morphology

An extensive characterization of the VEGF-induced neovasculature was undertaken following 7 days of infusion. Immunostaining for VEGF revealed that detectable levels of infused protein were apparent within a 1.5-mm radius from the cannula tip (Fig. 3A). RECA immunostaining further revealed that alterations in the normal morphology of brain vasculature were confined to the region of VEGF distribution (refer back to Fig. 2B). The central portion of the infused region was characterized by the presence of a tortuous, large-caliber vascular tangle. At the margin of the VEGF infusion, where VEGF immunostaining was lightest, cerebral vessel morphology was relatively normal,

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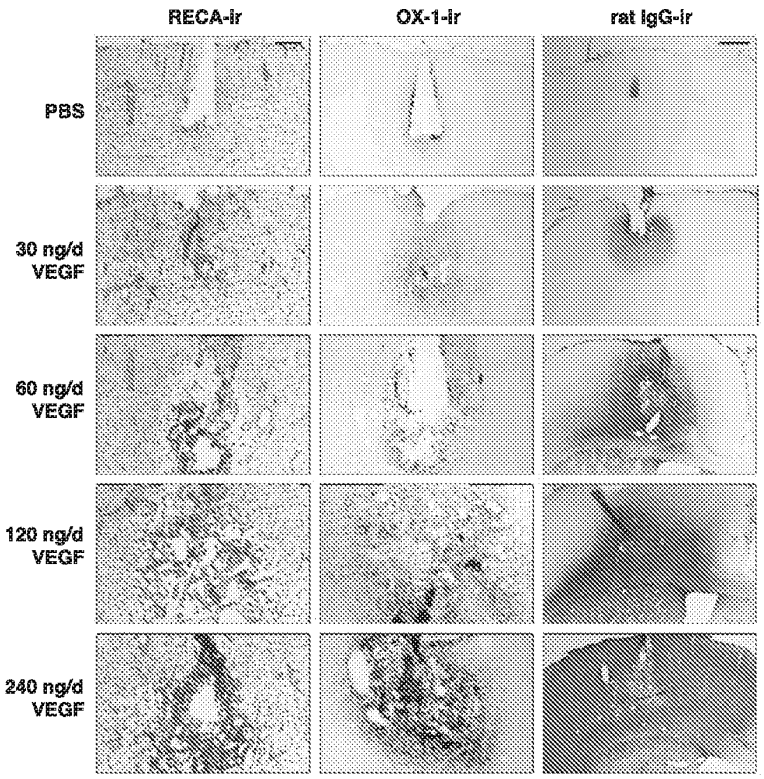


Fig. 1. Immunolocalization of rat endothelial cell antigen (RECA, for visualization of blood vessels), OX-1 (pan-leukocyte), and rat IgG (to visualize extravasated plasma proteins) in brains infused with either PBS or 30, 60, 120, or 240 ng/day of VEGF for 7 days. Angiogenesis, inflammation, and vascular leak were all dose-dependent effects of continuous VEGF infusion. The experiment was conducted twice ($n = 4–6$ per group each time) with comparable results. Scale bar = 300 μm for RECA and OX-1, and 625 μm for rat IgG.

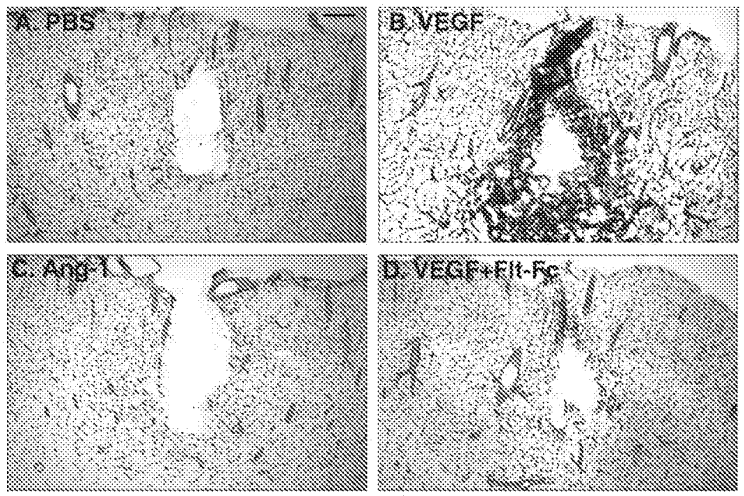


Fig. 2. Immunostaining for RECA after continuous infusion into cortex for 7 days. (A) Infusion of phosphate-buffered saline (PBS) results in minimal vascular change around the cannula track. (B) Infusion of 240 ng/day VEGF induces marked angiogenesis. (C) Infusion of Angiopoietin-1 cannot be differentiated from infusion of PBS. (D) Co-infusion of the receptor body Flt-Fc with VEGF completely prevents VEGF-induced angiogenesis. Each observation was made consistently (in a minimum of two experiments containing four animals per infusion group). Scale bar = 200 μm.

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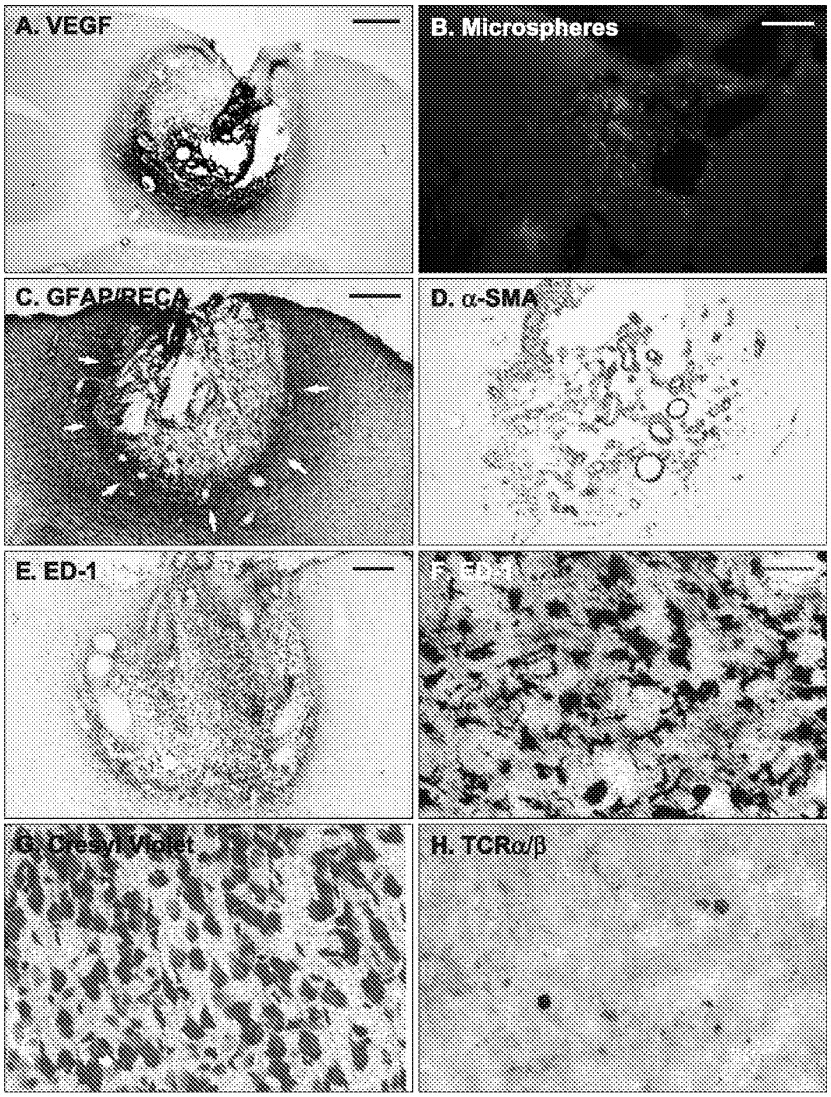


Fig. 3. Cortex infused with 240 ng/day VEGF for 7 days. For panels A–E, the area outside the region of VEGF diffusion displays normal vasculature and can be observed at the edges of the photomicrographs. PBS-infused brains have a similar appearance to the areas outside of the range of VEGF diffusion. (A) VEGF immunostaining shows diffusion of VEGF protein approximately 1.5 mm from the cannula track. (B) Fluorescent microspheres (0.026 μm in diameter) administered intravenously 30 min before sacrifice show that the vasculature within the infused site is acutely leaky at 7 days. (C) A GFAP (dark brown/black) stain shows that there is a dense halo of reactive astroglia located at the peripheral margin of the VEGF-infusion site (approximate boundary with unexposed tissue indicated by the white arrows). In contrast, the center of the VEGF-infusion site is relatively depleted of astrocytes, such that the neovasculature is not well invested with astroglial endfeet. (D) In contrast, α-smooth muscle actin (αSMA) immunostaining illustrates an increased investment of the neovasculature by α-SMA-positive perivascular cells. (E) ED-1, a macrophage/monocyte marker, reveals that most of the inflammatory infiltrate is of monocyte/macrophage origin. (F) A higher magnification view of ED-1-positive cell profiles. (G) Cresyl violet staining after 1 day of VEGF infusion shows the presence of occasional PMNs (example illustrated with an arrow). PMNs are also rarely observed at later time points after VEGF infusions. (H) T cell stain reveals that T cells are not major components of the VEGF-induced immune response. An arrow indicates a TCR-positive cell profile. All findings were confirmed in at least two independent experiments ($n = 4–6$ animals per group per experiment). Scale bars = 500 μm for A, 300 μm for B, 545 μm for C, 340 μm for D and E, and 30 μm for F, G, and H.

though the distance between vascular elements was clearly increased because of local edema. Despite the relative decrease in vascular density at the periphery of the VEGF infusion sites, quantification of vascular density by point-count stereology revealed a significant increase in mean vascular density across the entire field of the infusion in VEGF vs. PBS-treated animals (Table 2). In addition, analysis of vessel diameters revealed a statistically significant increase in mean vessel caliber in the field of VEGF infusion (Table 2).

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Table 2
Quantification of vascular parameters

Measure	Vehicle	VEGF	t test results
Vascular density (%)	15.3	36.9	$t(12) = 4.429$, $P < 0.0008$
Vascular diameter (μm)	7.1	17.1	$t(12) = 4.469$, $P < 0.0008$

Each value represents the mean value obtained after quantification of seven animals in each group after 7 days of infusion with 240 ng/day VEGF.

Vascular leak

VEGF-induced neovasculature was characterized by a markedly abnormal vascular permeability, as evidenced by the extravasation of both endogenous serum proteins to demonstrate chronic leak (rat IgG, Fig. 1) and fluorescent microspheres (0.026 μm in diameter), injected intravenously 30 min before sacrifice, to demonstrate acute leak (Fig. 3B). Both the endogenous serum proteins and the microspheres are normally excluded from the brain parenchyma, and there is no specific biological mechanism by which microspheres could be actively transported into the brain during pathological states. Therefore, leakage of microspheres not only demonstrates acute leak at time of sacrifice, but is also likely to reflect a generalized, nonspecific leak.

Astrocytes and perivascular cells

The leak of proteins and particulate matter into the brain suggested that the blood–brain barrier was compromised in the VEGF-affected neovasculature. One important contributor to the blood–brain barrier is astroglial endfeet. GFAP immunostaining revealed a marked decrease in GFAP immunoreactivity within the field of VEGF infusion and intensified staining of reactive glia along the boundary between the affected and unaffected tissue (Fig. 3C). Where VEGF concentrations were highest, the few remaining astroglial endfeet did not closely invest the blood vessels as they normally do in rat brain. Interestingly, immunostaining for α-smooth muscle actin (SMA) showed that the investment of vasculature with SMA-positive perivascular cells was not decreased but, rather, was dramatically increased by VEGF infusion (Fig. 3D).

Inflammation

As previously noted, VEGF infusion produced a marked local inflammatory response. Therefore, additional immunostaining studies were conducted to determine the identity of the leukocytes at the infusion site. ED-1 immunostaining revealed that the majority of the inflammatory cells located within the region of VEGF infusion were of monocyte/macrophage origin (Figs. 3E and F), although very few cells were polymorphonuclear cells (Fig. 3G) and almost none were lymphocytes (TCRα/β stain, Fig. 3H). Because the extravasation of inflammatory cells is typically accompanied by the upregulation of adhesion molecules, which initiate leukocyte rolling and sticking, we evaluated the expression of the adhesion molecule ICAM-1. ICAM-1 was dramatically upregulated in the brains of the VEGF-infused animals (Fig. 4), coincident with both inflammation and the leak of rat IgG and fibrinogen into brain tissue (Fig. 4).

Development of VEGF-induced neovasculature

Vascular morphology

To evaluate the development of VEGF-induced vascular tangles, brains were taken after 1, 3, 5, or 7 days of VEGF infusion. After 1 day of infusion, there was no evidence of VEGF-induced vascular changes (Fig. 5). At 3 days of infusion, changes in vascular morphology were very subtle and variable (Fig. 5). Consistent changes in vascular morphology, including increased vessel diameter and tortuosity, were not clearly evident until 5 days after initiation of the infusion and were more pronounced at 7 days (Fig. 5).

Cellular proliferation

Immunostaining conducted with the proliferation marker Ki67 revealed that, consistent with the results observed with the RECA stain, there was no apparent proliferation of endothelial or perivascular cells after 1 day of infusion (data not shown). At 3 days, there were many Ki67-positive cells present within the field of VEGF diffusion, but few of these were endothelial cells (Fig. 6). Staining for proliferating cell nuclear antigen (PCNA), phosphorylated histone H3, and BrdU (injected at 50 mg ip daily in one experiment) all stained similar non-endothelial cell populations (data not shown). Most stained cells appeared

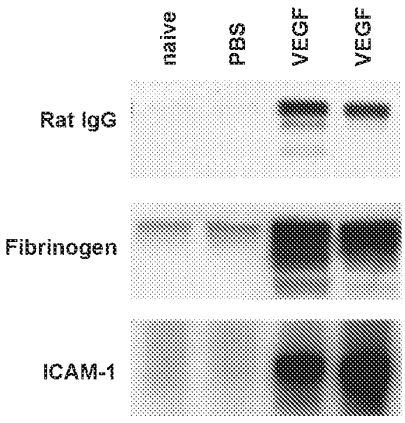


Fig. 4. Unreduced Western blot analyses of rat IgG, fibrinogen, and ICAM-1 found in tissue lysate from rat cortical tissue infused with 240 ng/day VEGF for 7 days. Results obtained from representative unoperated control animals (naive), PBS-infused animals, and two different VEGF-infused animals are illustrated. All Western blot analyses were conducted on two to three different sets of animals at two different protein concentrations (10 and 30 μg). Results were consistent for all proteins analyzed. Results of Westerns were also confirmed by immunostaining tissue sections in separate cohorts of animals (not shown for ICAM-1).

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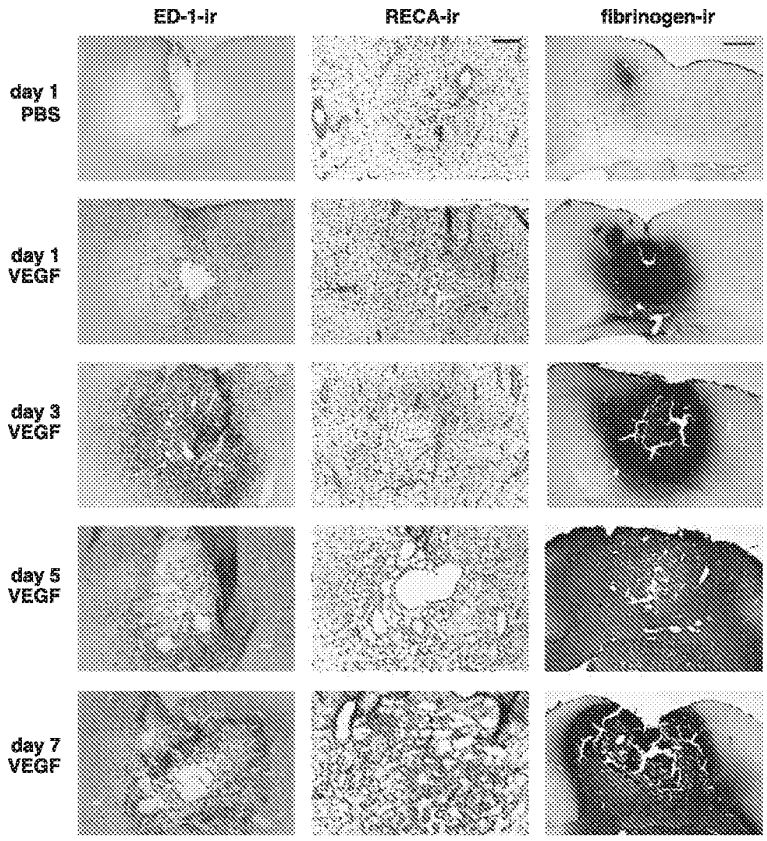


Fig. 5. Immunoreactivity for the monocyte/macrophage marker ED-1, RECA, and fibrinogen are shown for 1, 3, 5, and 7 days after the initiation of 240 ng/day VEGF infusion. Panels in the top row show results after 1 day of PBS infusion. Vascular leak and inflammation are markedly greater after 1 day of VEGF infusions than after 1 day of PBS infusions. Inflammation reaches a plateau by 3–5 days on infusion, and vascular leak plateaus by 5 days of infusions. The experiment was conducted three times ($n = 3–4$ per group per experiment), with each stain completed at least twice. Scale bar = 200 μm for ED-1, 250 μm for RECA, and 625 μm for fibrinogen.

to be of either glial or monocytic morphology (Fig. 6), including dramatic proliferation of both microglia and astroglia at day 7, in agreement with recent findings (astrocytes, Krum et al., 2002). More consistent increases in endothelial cell proliferation were observed at 5 and 7 days of infusion (day 7 shown in Fig. 6). In spite of the dramatic investment of vasculature by smooth muscle cells and pericytes during VEGF infusion, few cells double stained for both Ki67 and α-smooth muscle actin can be observed surrounding the vasculature, suggesting the possibility that these cells were recruited from another site (Fig. 6). Indeed, streams of cells positive for smooth muscle actin, some also positive for Ki67, can be observed in the supracallosal region during VEGF infusion (Fig. 6, 3d Ki67/α-SMA).

Inflammatory cells

In contrast to the delayed effect of VEGF infusion on angiogenesis, OX-1 staining revealed that extravasation of leukocytes began to occur as early as 1 day after the initiation of VEGF infusions (Fig. 5). This inflammation is likely to be a direct consequence of VEGF application because there is no more damage or tissue disruption in VEGF-infused animals than in vehicle or protein-infused animals at early time points (determined by Nissl staining, data not shown). Hematoxylin and eosin staining revealed that polymorphonuclear cells (PMNs) were present, but in very small numbers (refer back to Fig. 3G). T cells, as revealed by TCRα/β immunostaining, were very rarely observed. OX-1 immunostaining revealed, however, that the inflammatory response was marked at day 1, increased dramatically at day 3, and continued at high levels at days 5 and 7 of infusion (Fig. 5). The majority of the inflammatory cells at all time points evaluated were determined to be of monocyte/macrophage lineage based on ED1 immunostaining (compare the monocyte marker ED-1 in Fig. 5 to the pan-leukocyte marker OX-1 in Fig. 1).

Vascular leak

In agreement with the VEGF dose-response results, the temporal development of vascular leak paralleled the time

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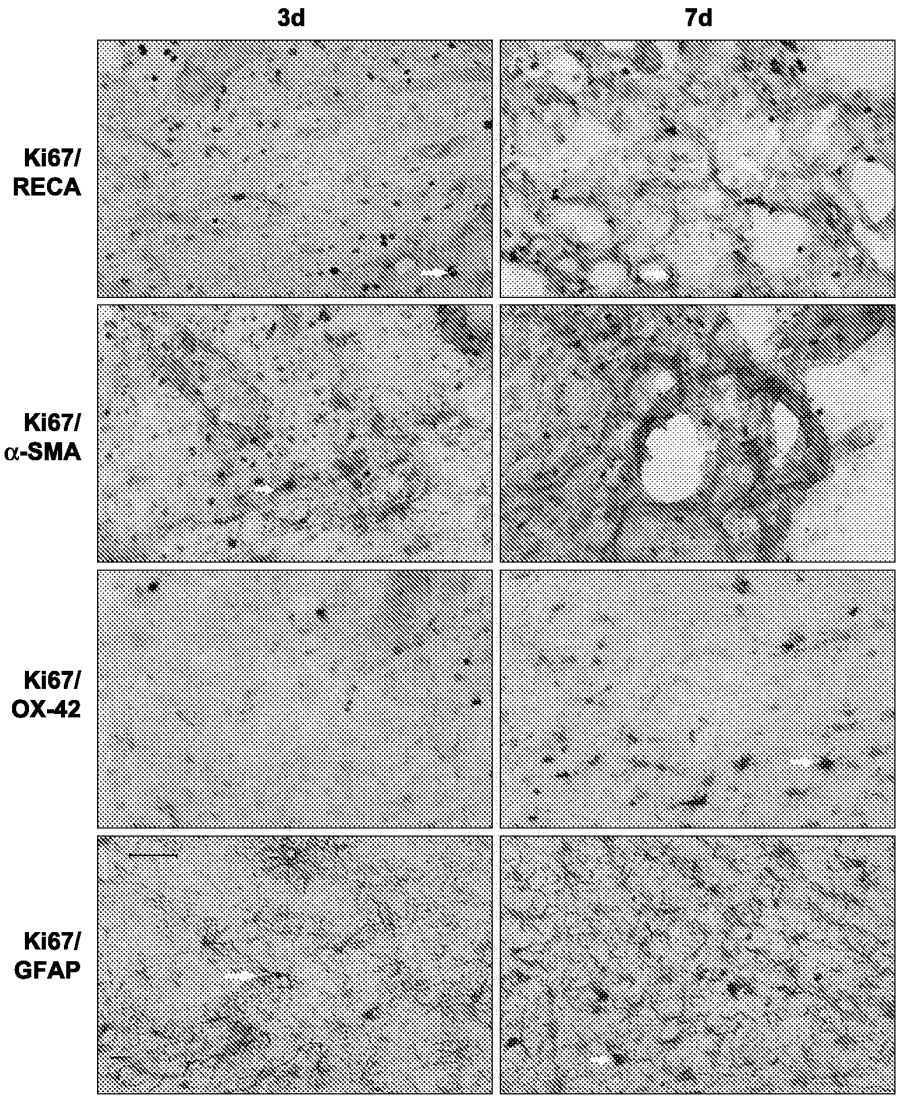


Fig. 6. Double immunoreactivity for Ki67 (a marker of proliferating cells), with RECA, α-SMA, OX-42, and GFAP show that VEGF results, either directly or indirectly, in the proliferation of multiple cell types. Data are shown at 3 and 7 days after the initiation of 240 ng/day VEGF infusion. Ki67 staining was not dramatic at 1 day of VEGF infusions (data not shown). RECA immunostaining reveals that although there are some candidate proliferating endothelial cells (examples shown by arrows), most proliferating cells, especially at 3 days of infusions, are not endothelial cells. In addition, smooth muscle cells did not account for the majority of proliferating cells, although an occasional proliferating smooth muscle actin-positive cell could be identified migrating toward the VEGF infusion site (see arrow). Most proliferating cells were OX-42-positive. Most of these double-positive cells appeared to be monocytic, but at 7 days of infusion, many proliferating cells with a microglial morphology could be identified (see arrow). Large numbers of GFAP-positive cells were double-stained for Ki67. These cells could be first observed at 3 days of VEGF infusions, but were even more numerous at 7 days of VEGF infusions (see arrows). Scale bar = 50 μm.

course of leukocyte extravasation. That is, infusion of VEGF resulted in an influx of plasma proteins and leukocytes into brain parenchyma which preceded its effects on endothelial cell proliferation. A modest extravasation of plasma proteins and leukocytes was already apparent after 1 day of infusion, and dramatic leak and inflammation were consistently evident at 3, 5, and 7 days of infusion (Fig. 5, fibrinogen staining).

Chemokines

Chemokine mRNA levels were evaluated in brains infused for 2, 4, or 7 days with VEGF, PBS, or control protein (human Fc). LightCycler RT-PCR revealed dramatic increases in MCP-1 mRNA [$F(1,94) = 12.116$, $P < 0.0008$] and modest increases in RANTES mRNA [$F(1,94) = 9.049$, $P < 0.004$] in the infused cortices of both control and VEGF-infused brains, but upregulation of

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these chemokines was not significantly associated with infusion of VEGF [$F(1,94) = 1.264$, $P > 0.26$ for MCP-1, $F(1,94) = 2.679$, $P > 0.10$ for RANTES, and additionally, $F(1,44) = 0.529$, $P > 0.47$ for GRO-α, which showed no upregulation in ipsilateral cortex]. In marked contrast, VEGF infusion produced a dramatic and selective upregulation of transcripts for MIP-1α [$F(1,68) = 8.959$, $P < 0.004$; Fig. 7D].

In situ hybridization for MIP-1α mRNA revealed that only a few cells expressing MIP-1α mRNA were evident in PBS-infused brains, and these were located immediately adjacent to the cannula track (data not shown). In marked contrast, in VEGF-treated animals, MIP-1α mRNA was expressed at high levels in many cells located preferentially near the periphery of the field of VEGF infusion (Fig. 7A). In contrast, most extravasated inflammatory cells are located at the core of the infusion (Fig. 7B). The cell bodies of the hybridized cells appeared dark and angular in the thionin counterstain, properties most typically found in microglia, but also sometimes observed in astroglia, pericytes, or other cell types (Fig. 7C).

Discussion

VEGF is a known mediator of angiogenesis and vascular permeability. Our results demonstrate that VEGF also acts, either directly or indirectly, as a potent pro-inflammatory cytokine. In addition, we show that vascular leak and inflammation precede the endothelial cell proliferation that occurs in response to VEGF.

Chronology and dose response of VEGF-induced vascular changes

Vascular changes with VEGF infusion into brain parenchyma occur with a significant delay upon exposure of normal brain tissues to even high levels of exogenous VEGF. This observation also appears to be the case when angiogenesis is initiated by endogenous VEGF. For instance, after cerebral ischemia, VEGF mRNA is increased within hours of the ischemic injury (Cobbs et al., 1998; Hayashi et al., 1997; Issa et al., 1999, Kovacs et al., 1996; Lee et al., 1999; Lennmyr et al., 1998; Pichiule et al., 1999, Plate et al., 1999), but the angiogenic response

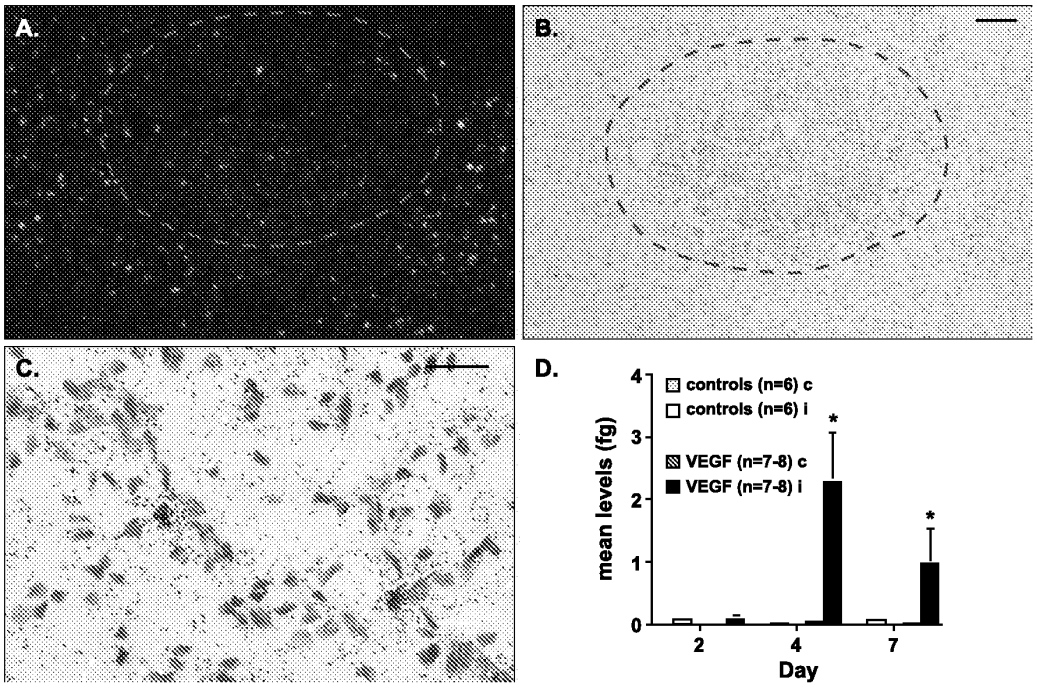


Fig. 7. MIP-1α mRNAs after VEGF infusion. (A) Dark-field photomicrograph of MIP-1α in situ hybridization after 7 days of VEGF infusion. The majority of MIP-1α positive cells lie at the periphery of the infusion site; outlined by the dashed line in panels A and B. Only one or two positive cells were found adjacent to the cannula track in PBS-infused animals. (B) Bright-field photomicrograph from the same section as panel A showing that the majority of the extravasated inflammatory cells were in the core of the VEGF-infused region in which cells hybridized for MIP-1α were sparse. Scale bar for A and B = 200 μm. (C) Higher magnification view of area indicated in panel B showing that MIP-1α positive cells (examples indicated by arrows) have an angular morphology. Scale bar = 50 μm. (D) MIP-1α mRNA levels determined by LightCycler PCR after 2, 4, or 7 days infusion of 240 ng/day VEGF. Results were obtained from two separate cohorts of animals, as described in Materials and methods. c = contralateral side, i = ipsilateral side, $^*P < 0.05$, significantly different from control group.

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is not evident until days later (Beck et al., 2000; Marti et al., 2000). Our observation of delayed angiogenesis was made based on data obtained with RECA immunostaining and proliferation markers. RECA will stain all mature vasculature and most vascular sprouts; however, we cannot rule out the possibility that earlier, RECA-negative basal lamina could have been present before the 3-day time point. Future studies might investigate very early events in the development of vascular sprouts in mature brain vasculature.

In contrast to the apparently delayed angiogenic response, blood–brain barrier compromise occurs very rapidly upon exposure to VEGF. We have observed vascular leak 1 day after VEGF minipump implantation, the earliest time point evaluated, but others have documented vascular permeability within 30 min of acute application (Dobrogowska et al., 1998). In addition, we showed that low doses of VEGF, which did not lead to appreciable angiogenesis within our 7-day infusions, rapidly and substantially increased vascular permeability. VEGF-mediated vascular leak was always accompanied by leukocyte extravasation. Hence, leukocyte extravasation, like vascular leak, occurred at earlier time points and lower doses than angiogenesis.

It has been proposed that VEGF-mediated increases in vascular permeability represent the first step in the angiogenic process (Dvorak et al., 1995, 1999). Vascular leak leads to the deposition of plasma proteins, such as fibrinogen, which can form an extracellular matrix on which endothelial cells can migrate. In this schema, vascular leak facilitates subsequent angiogenesis and may be a necessary pre-requisite for vascular proliferation.

VEGF and inflammation

Although VEGF's roles as a permeability and angiogenic factor are well established, less is understood about VEGF's role in the induction or augmentation of inflammation. We observed a reliable and dramatic induction of a leukocyte infiltrate at early time points of VEGF administration, before the development of obvious angiogenesis. In addition, we observed inflammation at low doses of VEGF insufficient to induce angiogenesis. Using immunostaining, we have shown that the majority of extravasated inflammatory cells are of monocyte/macrophage lineage. VEGF is a monocyte attractant in vitro (Heil et al., 2000; Waltenberger et al., 2000) and stimulates hematopoiesis in vivo (Hattori et al., 2001). The effect of VEGF on monocytes could be direct because monocytes express VEGFR1 (Flt-1) receptors (Sawano et al., 2001).

Consistent with the increased extravasation of leukocytes, we have detected an increase in the adhesion molecule ICAM-1 in the VEGF-infused cortex. VEGF has previously been shown to increase ICAM-1 both in vitro (Kim et al., 2001; Melder et al., 1996) and in vivo (Miyamoto et al., 2000; Proescholdt et al., 1999). ICAM-1 is normally expressed at negligible levels in adult rat brain (refer to naive band in Fig. 4). The increases in this adhesion protein in VEGF-infused brains are consistent with an increased inflammatory response because adhesion molecules encourage leukocyte sticking and rolling in the brain vasculature (for review, see del Zoppo, 1997). VEGF also increases integrin expression on leukocytes (Byzova et al., 2000; Heil et al., 2000). The interaction of leukocyte integrins with ICAM-1 appears necessary for the transendothelial migration of monocytes in response to VEGF (Heil et al., 2000).

Once rolling, leukocytes extravasate into brain in the presence of a leukocyte chemoattractant protein. Among the most common leukocyte attractants are chemokines (for review, see Ransohoff and Tani, 1998). We have discovered that VEGF potently and selectively upregulates the beta chemokine MIP-1α, which attracts or modulates the function of multiple types of inflammatory cells (Alam et al., 1992; Fahey et al., 1992; Schall et al., 1993). VEGF's effect on MIP-1α does not generalize broadly to other chemokines, as VEGF did not significantly upregulate MCP-1, RANTES, or GRO-α. Trauma alone dramatically upregulated MCP-1, as previously reported (McTigue et al., 1998; Sun et al., 2000).

We have yet to determine whether VEGF's effects on the inflammatory chemokine MIP-1α are direct or indirect, although an indirect effect seems likely given the delayed nature of the upregulation. Extravasated monocytes release many cytokines which could act on resident brain cells or newly extravasated immune cells to increase MIP-1α. MIP-1α levels increase in microglia and astrocytes upon exposure to cytokines or ischemia (McManus et al., 1998; Peterson et al., 1997; Takami et al., 1997). The increased expression of MIP-1α in cells surrounding the VEGF infusion site could serve to further propagate the inflammatory response initiated by VEGF infusion.

MIP-1α is increased in neurological disorders associated with vascular permeability and inflammation. For example, MIP-1α is elevated both in human multiple sclerosis lesions (Baranzini et al., 2000; Boven et al., 2000) and in the lesions observed in the animal model, experimental allergic/autoimmune encephalitis (Fischer et al., 2000; Glabinski et al., 1998; Nygardas et al., 2000). In fact, the severity of symptoms in experimental allergic encephalitis is decreased in animals deficient in an MIP-1α receptor, CCR1 (Rottman et al., 2000), although this decreased severity has not yet been observed in MIP-1α deficient animals (Tran et al., 2000). MIP-1α also increases within 4–6 h after cerebral ischemia (Gourmala et al., 1999; Kim et al., 1995; Pang et al., 2002; Spleiss et al., 1998; Takami et al., 1997), concurrent with increased post-ischemic VEGF mRNA levels (Cobbs et al., 1998; Hayashi et al., 1997; Issa et al., 1999; Kovacs et al., 1996;

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Lee et al., 1999; Lennmyr et al., 1998; Pichiule et al., 1999, Plate et al., 1999).

Examples of VEGF-induced inflammation in vivo have been reported previously, albeit sparsely, in the literature. Mice overexpressing endogenous VEGF exhibit marked inflammation in their skins (Detmar et al., 1998; Xia et al., 2003). VEGF delivered via adenovirus induces a monocyte/macrophage infiltrate in brain similar to the inflammatory response which we have observed (Proescholdt et al., 1999). This inflammatory response could not be induced using other adenoviruses, but could be induced using VEGF protein co-infused with viral particles. Here, we demonstrate that administration of VEGF alone is sufficient to induce an inflammatory reaction. Given the complete inhibition of VEGF's actions by Flt-Fc, the potential for this and similar reagents to inhibit not only angiogenesis, but also VEGF-induced inflammation, should be more fully explored.

Our understanding of the role of VEGF-mediated inflammation in the angiogenic process is still developing. However, increasing evidence suggests that, at least in the adult, VEGF-mediated inflammation is inseparable from, and might participate directly in, the initiation of the angiogenic process as has been proposed previously for vascular leak (Dvorak et al., 1995, 1999). Pathological retinal angiogenesis, which can be suppressed by blockade of VEGF-164, has been shown to be inhibited both by monocyte depletion (Ishida et al., 2003) and by deletion of the gene for ICAM-1 (Sakurai et al., 2003). In addition, placental growth factor (PlGF), a VEGF family member which acts at VEGFR1 but not VEGFR2, induces angiogenesis which is blocked after monocyte depletion in animals (Pipp et al., 2003), suggesting the possibility that angiogenesis mediated by VEGFR1 may be critically dependent on monocytes.

Monocytes secrete both degradative enzymes and a variety of trophic and regulatory factors which establish conditions conducive to endothelial cell proliferation and migration (Pakala et al., 2002). Proliferating vasculature expresses high levels of ICAM-1 coincident with increased numbers of adherent monocytes (Scholz et al., 2000). Monocytes, in particular, are frequently associated with proliferating blood vessels (Arras et al., 1998; Schaper and Buschmann, 1999; Scholz et al., 2000) and can open passages in existing vasculature to encourage the development of vascular sprouts (Molodovan et al., 2000). Furthermore, monocytes can differentiate into endothelial-like phenotypes in vitro, especially when treated with VEGF (Fernandez Pujol et al., 2000), raising the possibility that monocytes might contribute directly to angiogenesis as a source of new endothelial cells. Circulating blood cells have been shown previously to integrate into vascular endothelium (Shi et al., 1998). Thus, although the exact role(s) of inflammatory cells in pathological VEGF-mediated angiogenesis remains to be determined, a contributory role seems clear.

Acknowledgments

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Antibodies against Vascular Endothelial Growth Factor Improve Early Renal Dysfunction in Experimental Diabetes

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Abstract. Vascular endothelial growth factor (VEGF) is a cytokine that potently stimulates angiogenesis, microvascular hyperpermeability, and endothelium-dependent vasodilation, effects that are largely mediated by endothelial nitric oxide synthase (eNOS). The expression of VEGF is pronounced in glomerular visceral epithelial cells, but its function in renal physiology and pathophysiology is unknown. VEGF expression is upregulated by high ambient glucose concentrations in several cell types *in vitro* and in glomeruli of diabetic rats. To assess the role of VEGF in the pathophysiology of early renal dysfunction in diabetes, monoclonal anti-VEGF antibodies (Ab) were administered to control and streptozotocin-induced diabetic rats for 6 wk after induction of diabetes. Based on *in vitro* binding studies, an adequate serum VEGF inhibitory activity was achieved during the entire course of anti-VEGF Ab administration. Anti-VEGF Ab treatment but not administration of isotype-matched control Ab decreased hyperfiltration, albuminuria, and glomerular hypertrophy in diabetic rats. VEGF blockade also prevented the upregulation of eNOS expression in glomerular capillary endothelial cells of diabetic rats. Antagonism of VEGF had no effect on GFR and glomerular volume in control rats. These results identify VEGF as a pathogenetic link between hyperglycemia and early renal dysfunction in diabetes. Targeting VEGF may prove useful as a therapeutic strategy for the treatment of early diabetic nephropathy.

It is well established that hyperglycemia is a major risk factor for the development and progression of diabetic nephropathy. Hyperglycemia induces multiple cellular and molecular alterations that presage the development of renal vascular dysfunction. However, the exact sequence of events from exposure to high glucose concentrations to development of renal damage remains equivocal. Early alterations in the diabetic kidney include the development of glomerular hyperfiltration and glomerular hypertrophy, followed by thickening of the glomerular basement membrane, mesangial matrix accumulation, increased urinary albumin excretion rate (UAER), and ultimately progression to glomerular sclerosis. There is compelling evidence for the involvement of various growth factors, including insulin-like growth factor-I (IGF-I) and transforming growth factor-β (TGF-β), in the early renal changes in diabetes (1,2).

Vascular endothelial growth factor (VEGF) is a member of a family of heparin-binding growth factors that very potently stimulate endothelial cell proliferation and play a pivotal role in physiologic and pathologic angiogenesis (3). In addition, VEGF is one of the most potent vascular permeabilizing agents known and has the capacity to induce endothelium-dependent vasodilation. Several lines of evidence indicate that endothelium-derived nitric oxide (NO) acts as a downstream mediator for VEGF (4,5). In cultured endothelial cells, VEGF stimulates endothelial NO synthase (eNOS) expression and activity, resulting in enhanced generation of bioactive NO (6). In the normal kidney, VEGF is strongly expressed in podocytes and its binding sites are localized mainly on glomerular endothelial cells (7–9). Because of this strategic anatomic location, it has been speculated that VEGF may play a role in the regulation of glomerular permeability and glomerular endothelial cell growth (10). Recent studies have demonstrated an upregulation of VEGF and its receptors in kidneys of diabetic rats (11,12). However, whether VEGF plays a causative role in the pathophysiology of diabetic nephropathy remains unknown. Nevertheless, in view of its known biologic properties, its high glomerular expression in physiologic circumstances, and its upregulation in diabetes, VEGF is an ideal candidate to provide a mechanistic link between hyperglycemia and glomerular hypertrophy, glomerular hyperfiltration, and increased glomerular permeability for macromolecules. We therefore investigated the possibility that inhibition of VEGF activity prevents the onset of early renal dysfunction in experimental diabetes. In addition, the effect of VEGF blockade on glomerular eNOS expression was studied.

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Materials and Methods

Laboratory Animals

The studies were performed with female Wistar rats (Iffa Credo, Brussels, Belgium) that received care in accordance with the national

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guidelines for animal protection. Diabetes was induced by intravenous injection of streptozotocin (65 mg/kg; Pfanstiel Europe LTD, Davenham, UK). Slow-release insulin implants (Linshin, Scarborough, Canada), with a release rate of 1 U/24 h, were used to maintain moderate hyperglycemia. Age-matched control rats received an intravenous injection of buffer solution and placebo implants composed of palmitic acid. Final experiments were carried out 6 wk after the induction of diabetes. At the beginning of each experiment, plasma samples were drawn for analysis of glucose, fructosamine, and total protein levels.

Anti-VEGF Antibody Treatment

Monoclonal anti-VEGF antibodies (Ab) and isotype-matched control Ab were prepared as described previously (13). Briefly, female 8-wk-old BALB/c mice (Harlan Sprague Dawley, Inc., Indianapolis, IN) were immunized, then received a booster three times, 21 d apart, by intraperitoneal and subcutaneous injections of 50 μg of rh-$VEGF_{165}$, emulsified with an equal volume of Complete Freund's Adjuvant for the primary immunization and Incomplete Freund's Adjuvant for secondary immunizations. The mouse with the highest serum titer to $rhVEGF_{165}$ as measured by enzyme-linked immunosorbent assay received an intravenous injection of an additional 30 μg of immunogen in phosphate-buffered saline (PBS), 21 d after the last immunization. Three d later, spleen cells were harvested for production of hybridomas to $rhVEGF_{165}$. Two hybridoma cell lines with highest Ab titer and neutralizing Ab activity were cloned three to four times by limiting dilution in 96-well microtiter plates. Ascites fluid was collected from pristane (Sigma Chemical Co., St. Louis, MO) primed BALB/c mice that received intraperitoneal injections of each of the cloned hybridomas (10^7 cells), and purified IgG was prepared by Protein A chromatography (Sigma). The isotype and light chain composition of the Ab and the characterization of neutralizing activity were performed as described previously (13).

Diabetic rats were either untreated (n = 11) or treated with anti-VEGF Ab (n = 12) or with isotype-matched control Ab (n = 9). One mg of the appropriate Ab was injected intraperitoneally three times per week, starting 2 d after the streptozotocin injection until the final experiments. Age-matched control rats were either untreated (n = 12) or treated with anti-VEGF Ab (n = 7) during 6 wk.

VEGF Binding Studies

To determine the efficiency of the anti-VEGF treatment, we obtained serum samples at baseline and after 2, 4, and 6 wk of treatment with anti-VEGF or control Ab. The samples were drawn from the tail vein just before the next Ab administration. Binding studies were performed using a fusion protein composed of the seven loop ectodomain of Flt-1 fused to the heavy chains of a mouse IgG_{2a} Ab. The fusion protein was captured onto Immulon 4 strip wells with IgG_{2a}-specific goat anti-mouse Ab (Sigma). Increasing concentrations of monoclonal anti-VEGF Ab (used as standards) and increasing dilutions of serum (1:50, 1:100, and 1:250) were incubated separately with 4 ng/ml ^{125}I-VEGF (Biomedical Technologies Inc., Stoughton, MA) for 30 min at 37°C before adding to the receptor. Nonspecific binding was defined as the binding measured in the presence of a 100-fold molar excess of unlabeled VEGF. Incubations were terminated after 60 min at 22°C by washing the wells once with 400 μl of ice-cold PBS, then twice more with 200 μl of ice-cold PBS. Bound VEGF was measured in a gamma spectrometer (Life Technologies, Inc., Schaumburg, IL).

Measurement of UAER and GFR

For determination of UAER, rats were housed in metabolic cages two times for 24 h and the urine was collected. Urine samples were stored at −20°C until analysis. Albumin was determined with an enzyme-linked immunosorbent assay kit specific for rat albumin (Nephrat, Exocell, Philadelphia, PA). To obtain an estimate of GFR, we measured inulin clearance. The rats were anesthetized with thiobutabarbital (Inactin, RBI, Natick, MA; 100 mg/kg intraperitoneally). The trachea was intubated, a jugular vein was cannulated for continuous infusion of isotonic saline at a rate matching diuresis, and a carotid artery was cannulated for drawing of blood samples. Inulin clearance was measured using the slope technique, as described previously (14). A single dose of FITC-Inulin (Sigma, 80 mg/kg) was administered intravenously as a bolus, and plasma samples were obtained at t = 3, 30, 120, 140, 160, and 180 min. FITC-inulin plasma levels were measured with a scanning fluorescence detector (Waters 474, Milford, MA). Inulin clearance was calculated as the ratio of administered dose and area under the curve of the inulin plasma levels.

Measurement of Kidney Weight and Estimation of Glomerular Volume

Kidneys of six animals from each experimental group were rinsed with PBS by retrograde aortic perfusion for 1 min. The right kidney was perfusion-fixed with 2% glutaraldehyde in PBS, stored in the same fixative for 24 h, and rinsed in PBS. Kidneys were embedded in paraplast and stained with Masson-Goldner's trichrome technique. Morphometric analysis was carried out with a semiautomatic image analysis system (VIDS IV, AiTectron, Düsseldorf, Germany) connected to a Zeiss photomicroscope. Cross-sectional glomerular tuft area (A_T, minimal convex polygon) was determined from the mean of 80 random glomerular profiles per animal. Mean glomerular tuft volume (V_T) was calculated as $V_T = \beta/k \times (A_T)(3/2)$, with β = 1.38, the shape coefficient for spheres and k = 1.1, a size distribution coefficient (15).

Immunocytochemistry for eNOS

The expression of eNOS in the glomeruli was investigated using indirect immunocytochemistry. After retrograde aortic perfusion with PBS for 1 min, the left kidney of six animals from each experimental group was removed and snap-frozen in melting isopentane cooled by liquid nitrogen. Five-μm frozen sections were prepared with a 2800 Frigocut E cryostat microtome (Reichert-Jung GmbH, Nussloch, Germany) and fixed in acetone for 10 min. Nonspecific Ab staining was blocked by incubation with PBS containing 0.2% cold-water fish gelatin (Sigma), 2% bovine serum albumin (Sigma), and 2% fetal calf serum (Sigma) for 30 min at room temperature. Incubation with a mouse monoclonal Ab against human eNOS isotype IgG1 (Transduction Laboratories, Lexington, KY), diluted 1:1000 in PBS containing fish gelatin, was carried out overnight at 4°C. Ab binding was visualized with Cy3-conjugated goat anti-mouse IgG Ab (Jackson Laboratories, West Grove, PA). Sections were mounted and viewed with a Polyvar fluorescence microscope (Reichert-Jung). The specificity of the immunolabeling was confirmed by incubation without primary Ab and by incubation with nonspecific Ab.

The intensity of the eNOS Ab staining in the kidneys was evaluated by two independent investigators who were unaware of the status of the animals. Because the receptors for VEGF are localized mainly on glomerular capillary endothelial cells (7–9), eNOS staining was assessed semiquantitatively in these cells. For each kidney, 20 glomerular profiles, cut in equatorial section planes and successively appear-

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ing in the visual field of the microscope when moving the section through the entire depth of the cortex, were evaluated. The number of capillary profiles stained by eNOS Ab was determined and normalized for glomerular surface area.

Immunocytochemical Localization of the Anti-VEGF and Control Ab

To exclude the possibility of precipitation of the Ab or Ab-antigen complexes in the glomeruli, we analyzed a separate group of kidneys (3 diabetes + anti-VEGF Ab, 1 control + anti-VEGF Ab, 2 diabetes + control Ab, 2 diabetes, 2 control). Kidneys were rinsed with PBS by retrograde aortic perfusion for 1 min, then perfusion-fixed with 2% paraformaldehyde and stored in the same fixative for 24 h before being washed with PBS and embedded in paraffin. To detect the murine anti-VEGF Ab, we deparaffinized 5-μm kidney sections with xylene followed by 100% ethanol, rehydrated them with graded ethanol (100%, 95%, and 70%) followed by PBS, blocked them for 1 h at room temperature using 2% normal goat serum in PBS (Sigma), then incubated them for 1 h at room temperature with anti-mouse IgG, Cy3 conjugate (Sigma), diluted 1:500 in PBS containing 2% normal goat serum.

Statistical Analyses

The data are presented as mean ± SEM. ANOVA and unpaired *t* tests were used as appropriate to test statistical significance. The significance level was set at $P < 0.05$.

Results

Characteristics of Laboratory Animals

Diabetic animals had significantly higher plasma glucose and fructosamine levels as compared with the age-matched control rats (Table 1). There were no differences in metabolic control between the Ab-treated and the untreated diabetic rats. Body weights were significantly lower in diabetic rats as compared with control rats. There were no significant differences in body weight among the diabetic groups. Kidney weight was significantly higher in all diabetic animals as compared with the control groups. The kidney weight in the diabetic animals that were treated with anti-VEGF Ab tended to be lower than in the other diabetic groups, but the difference was not significant (Table 1). Food consumption was approximately 70% higher in diabetic animals as compared with controls, without significant differences between the diabetic groups (Table 1).

VEGF Binding Studies

VEGF inhibitory activities were measured after dilution of the serum at 1:50, 1:100, and 1:250. The results of the 1:50 dilution are displayed in Figure 1. At baseline, VEGF inhibitory activity was low and not different between experimental groups. A significantly increased serum inhibitory activity was found at 2, 4, and 6 wk of treatment with anti-VEGF Ab in both diabetic and control rats. At 4 wk, inhibitory activity was somewhat lower in anti-VEGF–treated control rats as compared with anti-VEGF–treated diabetic rats. Because the inhibitory activity of undiluted serum of anti-VEGF–treated rats is almost 100%, the clinical relevance of this difference may be minimal. No changes in VEGF inhibitory activity were seen in diabetic rats during treatment with control Ab, except at 6 wk, when a lower inhibitory activity was noted. The inhibitory activities at 1:100 and 1:250 dilution of the serum were lower than those at 1:50 dilution but followed a similar pattern (data not shown).

Measurement of UAER and GFR

Untreated diabetic rats showed a marked elevation of the UAER after 6 wk of diabetes, which was partially reduced by anti-VEGF treatment but not by administration of control Ab (Figure 2). Inulin clearance was elevated in diabetic rats, as compared with control rats (Figure 3). The development of hyperfiltration in the diabetic rats was largely prevented by treatment with anti-VEGF Ab but not by injection of control Ab. The anti-VEGF Ab treatment did not significantly decrease GFR in control rats.

Glomerular Volume

Glomerular volume was significantly higher in diabetic rats as compared with age-matched control rats. Anti-VEGF Ab treatment decreased glomerular volume in diabetic rats but not in control animals (Figure 4). Administration of control Ab did not affect glomerular volume in diabetic rats.

Immunocytochemical Study of eNOS Expression

Positive eNOS staining was detectable in the endothelial cells of preglomerular vessels (arcuate arteries, interlobular arteries, afferent arterioles), of glomerular capillaries, and of postglomerular vessels (efferent arterioles, peritubular capillar-

Table 1. Gravimetric and biochemical characteristics of the experimental groups[a]

	Control (n = 12)	Control + Anti-VEGF Ab (n = 7)	Diabetes (n = 11)	Diabetes + Anti-VEGF Ab (n = 12)	Diabetes + Control Ab (n = 9)
Glycemia (mg/dl)	144 ± 12	117 ± 8	430 ± 36[b]	438 ± 63[b]	459 ± 31[b]
Fructosamine (μmol/g total protein)	1.78 ± 0.04	1.79 ± 0.06	4.00 ± 0.23[b]	4.17 ± 0.31[b]	3.92 ± 0.28[b]
Body weight (g)	285 ± 4	273 ± 5	253 ± 6[b]	259 ± 8[b]	254 ± 7[b]
Kidney weight (g)	0.91 ± 0.03	0.88 ± 0.02	1.20 ± 0.05[b]	1.12 ± 0.03[b]	1.20 ± 0.05[b]
Food consumption (g)	14.0 ± 1.4	14.1 ± 1.3	24.5 ± 1.5[b]	22.5 ± 1.9[b]	23.5 ± 1.4[b]

[a] VEGF, vascular endothelial growth factor; Ab, antibody.
[b] $P < 0.001$ *versus* controls.

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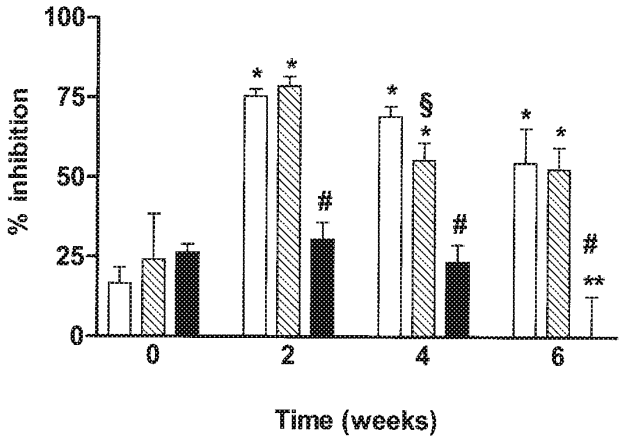


Figure 1. Serum inhibitory activities in diabetic rats + anti-vascular endothelial growth factor (VEGF) antibody (Ab) ($n = 12$, □), control rats + anti-VEGF Ab ($n = 7$, ▨) and diabetic rats + control Ab ($n = 9$, ■) before and 2, 4, and 6 wk after the start of treatment. Inhibitory activities are expressed as percentage of inhibition by 1:50 diluted serum of the binding between ^{125}I-VEGF and Flt-1 *in vitro*. Comparison among time points: *, $P < 0.001$ *versus* 0 wk; **, $P < 0.05$ *versus* 0, 2, and 4 wk. Comparison among groups: #, $P < 0.001$ *versus* diabetic + anti-VEGF Ab and control + anti-VEGF Ab; §, $P < 0.05$ *versus* diabetic + anti-VEGF Ab.

ies, vascular bundles in the outer medulla). In the glomeruli, the number of stained capillary profiles per glomerulus, normalized for glomerular surface area, was significantly higher in diabetic rats compared with control rats (12.6 ± 0.8 *versus* 9.1 ± 0.1; $P < 0.01$). The increased staining for eNOS in the glomerular capillary endothelial cells was also present in diabetic rats that were treated with control Ab (13.1 ± 1.33; $P < 0.05$ *versus* control) but not in anti-VEGF Ab-treated diabetic rats (8.1 ± 0.4; $P < 0.01$ *versus* diabetes and diabetes + control Ab; Figure 5).

Immunocytochemical Localization of the Anti-VEGF and Control Ab

No staining was detected in either glomeruli, tubules, or peritubular spaces, indicating that the anti-VEGF or control Ab did not accumulate in the kidney (data not shown).

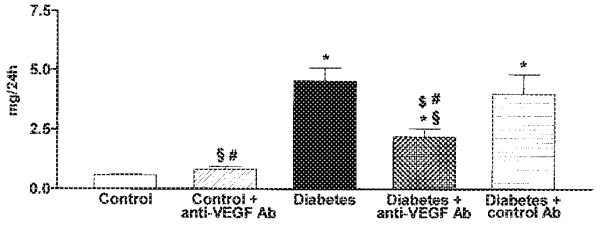


Figure 2. Albuminuria in untreated ($n = 12$) and anti-VEGF Ab-treated ($n = 7$) control rats and in untreated ($n = 11$), anti-VEGF Ab-treated ($n = 12$), and control Ab-treated ($n = 9$) diabetic rats. *, $P < 0.0001$ *versus* control; §, $P < 0.001$ *versus* diabetes; #, $P < 0.02$ *versus* diabetes + control Ab; $, $P < 0.01$ *versus* control + anti-VEGF Ab.

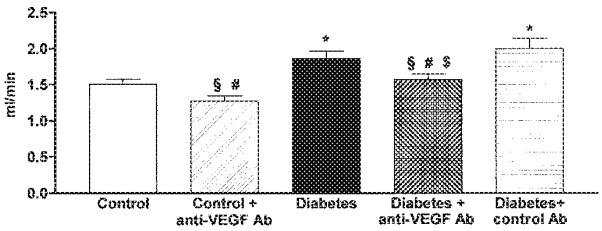


Figure 3. FITC-inulin clearance in untreated ($n = 12$) and anti-VEGF Ab-treated ($n = 7$) control rats and in untreated ($n = 11$), anti-VEGF Ab-treated ($n = 12$), and control Ab-treated ($n = 9$) diabetic rats. *, $P < 0.01$ *versus* control; §, $P < 0.05$ *versus* diabetes; #, $P < 0.01$ *versus* diabetes + control Ab; $, $P < 0.05$ *versus* control + anti-VEGF Ab.

Discussion

A potential role for VEGF in the pathophysiology of early diabetic nephropathy can be reasoned based on several lines of evidence. First, VEGF is constitutively expressed with a distinct glomerular localization, which suggests an important role in the regulation of glomerular permeability, blood flow, and endothelial cell growth (10). In the adult kidney, VEGF mRNA and protein expression is very pronounced in visceral epithelial cells (7–9). VEGF receptor mRNA and protein were detected in endothelial cells of glomerular capillaries (8,9,11) and pre- and postglomerular vessels (8). The finding that glomerular endothelial cells are a major binding site for exogenous ^{125}I-VEGF (9,11) is consistent with these observations. Although it remains unclear how VEGF crosses the glomerular basement membrane, it is reasonable to postulate the existence of a local regulatory mechanism, with generation of the peptide in podocytes, paracrine secretion, and binding on glomerular capillary endothelium.

Second, VEGF expression is increased in several cell types and tissues by high ambient glucose concentrations. High glucose levels in the culture medium upregulate VEGF expression in vascular smooth muscle cells (16), in retinal epithelial cells (17), and in glomerular endothelial cells (18). Upregulation of VEGF has been demonstrated in the retina of diabetic patients (19) and experimental animals (20). An increased renal expression of VEGF mRNA and protein was reported in

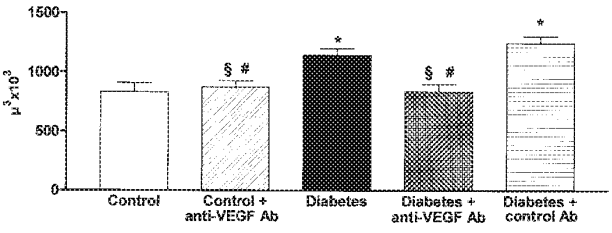


Figure 4. Glomerular volume in untreated ($n = 6$) and anti-VEGF Ab-treated ($n = 6$) control rats and in untreated ($n = 6$), anti-VEGF Ab-treated ($n = 6$), and control Ab-treated ($n = 6$) diabetic rats. *, $P < 0.01$ *versus* control; §, $P < 0.01$ *versus* diabetes; #, $P < 0.001$ *versus* diabetes + control Ab.

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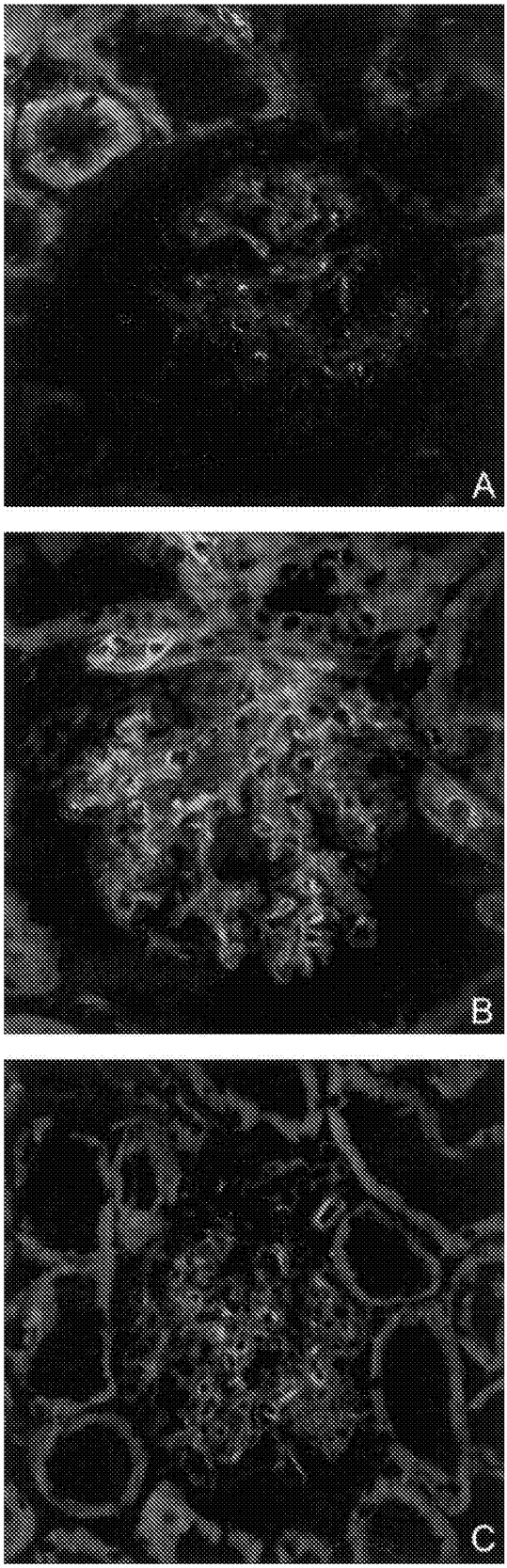


Figure 5. Immunocytochemical staining for endothelial nitric oxide synthase (eNOS) in control (A), control Ab-treated diabetic (B), and anti-VEGF Ab-treated (C) kidneys. Staining is detectable in glomerular capillaries and in afferent and efferent arterioles, visible at the vascular pole of the glomeruli. As compared with control rats, the glomeruli of control Ab-treated diabetic rats are characterized by increased number of eNOS-positive capillary profiles. Treatment of diabetic rats with neutralizing anti-VEGF Ab results in a lower number of stained capillaries, which is not different from controls. Magnification, ×330.

experimental rat models of diabetes type I (11) and type II (12). In addition, the expression of VEGF receptors was found to be upregulated in kidneys of diabetic rats (11).

Finally, interference with the VEGF-NO axis was shown to prevent microvascular dysfunction induced by high glucose levels in the dorsal skinfold chamber of the rat (13).

Although these studies suggest a causal role for VEGF in the pathophysiology of diabetic nephropathy, the evidence remains circumstantial. The present data are the first to support an causative role for VEGF in the early renal changes in diabetes. Streptozotocin-induced diabetic rats and age-matched control rats were treated chronically with murine monoclonal anti-VEGF Ab or with isotype-matched control Ab, the latter to exclude an effect of immunization. Based on *in vitro* binding studies, an adequate serum VEGF inhibitory activity was achieved during the entire course of anti-VEGF Ab administration. In diabetic rats, anti-VEGF treatment partially prevented early renal dysfunction. The decrease in GFR in the anti-VEGF Ab-treated diabetic rats could not merely be attributed to precipitation of antigen-Ab complexes in the glomerular basement membrane, because no extravascular murine Ab was detected at the end of the experiment by immunohistochemical analysis. The effects were specific for diabetes, because the anti-VEGF Ab did not affect filtration rate and glomerular volume in control rats. These findings are consistent with a previous report that a $VEGF_{165}$ aptamer did not affect glomerular morphology in normal rats (21). The present results indicate that the upregulation of VEGF and its receptors in the diabetic kidney, as reported by others (11,12), contributes to the pathophysiology of early renal dysfunction in diabetes. The beneficial effect of VEGF-blockade does not exclude the involvement of other growth factors in the pathogenesis of early diabetic renal dysfunction. Inhibition of TGF-β (22,23) and interference with the growth hormone/IGF-I system (24,25) were shown recently to prevent manifestations of early experimental diabetic nephropathy. Several diabetes-induced mediators interact in their adverse effects on the kidney; therefore, it is not surprising that correction of any of them results in amelioration of diabetic nephropathy. In addition, it should be noted that the deleterious effects of VEGF may be limited to early diabetes. When diabetic vascular disease is full-blown and results in tissue ischemia, VEGF may actually be essential for collateral vessel formation (26).

Several recent studies provided evidence that VEGF exerts its angiogenic, vascular permeability, and hemodynamic ef-

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fects via upregulation of eNOS in endothelial cells (4–6). The action of NO as a downstream mediator of VEGF is commensurate with the upregulation of the NO system in early diabetes and its implication in the pathogenesis of early renal dysfunction. NOS blockade substantially reduces or even completely eliminates the hyperfiltration in experimental diabetes (27–29). Chronic administration of NG-nitro-L-arginine methyl ester to diabetic rats partially prevented the increase in glomerular volume in diabetic rats (30). In the present study, an increased expression of eNOS was documented in glomerular capillary endothelial cells of the diabetic rats, confirming earlier findings (27,30). VEGF blockade prevented the upregulation of eNOS in the diabetic glomeruli, thus supporting the contention that VEGF binds to its receptors on glomerular capillary endothelial cells and increases eNOS expression in these cells.

The mechanism(s) by which VEGF may affect glomerular permeability and filtration rate remains speculative. VEGF is known to induce fenestrations in endothelial cells *in vitro* (31), and it has been hypothesized that VEGF is involved in the induction and maintenance of the fenestrae in the glomerular capillary endothelial cells (9). It is, however, generally acknowledged that the capillary fenestrations do not represent the ultimate barrier for filtration but rather that the glomerular basement membrane and the podocyte foot processes with their interconnecting slit diaphragms restrict the passage of proteins. Alternatively, VEGF could affect the filtration barrier by increasing the production of NO in glomerular endothelial cells, which in turn diffuses to the podocytes and acts on the slit pores. In support of this hypothesis, local NOS blockade is known to reduce glomerular ultrafiltration coefficient (32). In addition, VEGF may increase glomerular filtration surface area by stimulating glomerular capillary endothelial cell growth. Nyengaard and Rasch (33) demonstrated that the increased glomerular filtration surface in diabetes results from a formation of new glomerular capillaries, in addition to a slight elongation of existing capillaries. This phenomenon is analogous to the capillary proliferation observed in diabetic retinas and in other vascular beds and thus may be understood as one expression of a generalized diabetic microangiopathy. Our finding that blockade of VEGF prevented the increase in glomerular tuft volume in diabetic rats supports the contention that VEGF is an essential growth factor for glomerular capillaries in pathophysiologic circumstances. In accordance, administration of a $VEGF_{165}$ aptamer was found to decrease glomerular endothelial cell regeneration in experimental glomerulonephritis (21).

The cause of the upregulation of VEGF in diabetes remains speculative, but multiple factors may be implicated. Several factors relevant to the pathogenesis of diabetic complications have been shown to promote VEGF expression in various cell types and tissues, including advanced glycation end products (34), angiotensin II (35), reductive stress (13), reactive oxygen species (36), TGF-β (37), and IGF-I (38). Importantly, protein kinase C (PKC), which is increasingly recognized as a central mediator of the damaging effects of hyperglycemia, has been shown to upregulate VEGF (16,39). Direct (40) or indirect (41) inhibition of PKC activation in diabetic rats produced similar improvement of glomerular hyperfiltration and albuminuria as in our study, further supporting a link between PKC and VEGF. Taken together, many factors could act independently or in combination to increase VEGF expression in the diabetic kidney. However, the *in vivo* relevance of these pathways remains to be determined. In addition to increased renal expression of VEGF and its receptors (11,12), a disturbed feedback regulation of VEGF could contribute to the pathophysiologic effects of VEGF in the diabetic kidney. Because VEGF is a molecule with very high potency, the existence of powerful defense mechanisms may be assumed. One such mechanism may be the binding of VEGF to the heparin sulfate glycosaminoglycan side chains in the glomerular basement membrane (42). It is tempting to speculate that the reduced heparin content of the glomerular basement membrane in diabetes (43) may contribute to an increased access of VEGF to its receptors.

In conclusion, blockade of VEGF has renoprotective effects in early streptozotocin-induced diabetes in rats. In comparison with untreated diabetic rats, animals that were treated with monoclonal Ab against VEGF exhibited a smaller increase in GFR, glomerular volume, and UAER. The present study demonstrates a new mechanism by which hyperglycemia causes renal dysfunction. Targeting VEGF may prove useful as a therapeutic strategy for the treatment of early diabetic nephropathy.

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