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-008CIPCON8
	Confirmation No.	To Be Assigned
	First Named Inventor	YANCOPOULOS, GEORGE D.
	Application Number	To Be Assigned
	Filing Date	December 4, 2020
	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.

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 YANCOPOULOS
Filer:	Karl Bozicevic/Kimberly Zuehlke
Attorney Docket Number:	REGN-008CIPCON8

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	320	320
UTILITY SEARCH FEE	1111	1	700	700
UTILITY EXAMINATION FEE	1311	1	800	800
Pages:				
Claims:				
CLAIMS IN EXCESS OF 20	1202	14	100	1400
Miscellaneous-Filing:				
PUBL. FEE- EARLY, VOLUNTARY, OR NORMAL	1504	1	0	0

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**3220**

Electronic Acknowledgement Receipt

EFS ID:	41300278
Application Number:	17112404
International Application Number:	
Confirmation Number:	6437
Title of Invention:	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS
First Named Inventor/Applicant Name:	George YANCOPOULOS
Customer Number:	96387
Filer:	Karl Bozicevic/Kimberly Zuehlke
Filer Authorized By:	Karl Bozicevic
Attorney Docket Number:	REGN-008CIPCON8
Receipt Date:	04-DEC-2020
Filing Date:	
Time Stamp:	16:31:58
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$3220
RAM confirmation Number	E2020B4G32557926
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	WebADS.pdf	151307 68fd41ad269ca7198435d76f7d15f3b7c3aa6ae3	no	9
Warnings:					
Information:					
2		REGN-008CIPCON8_2020-12-04_Appln_as_fld.pdf	159218 293ce6dfc9eb3761c15971129cabf5f81f086b7c	yes	25

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Abstract	25	25
	Claims	23	24
	Sequence Listing	1	22

Warnings:					
Information:					
3	Drawings-only black and white line drawings	REGN-008CIPCON8_Figure.pdf	105393 2d582f645d0c5d17d717e589b029a39331991bdb	no	1
Warnings:					
The page size in the PDF is too large. The pages should be 8.5 x 11 or A4. If this PDF is submitted, the pages will be resized upon entry into the Image File Wrapper and may affect subsequent processing					
Information:					
4	Oath or Declaration filed	REGN-008CIPCON8_declaration.pdf	173097 6bda7272374e6af80c8c3d8cf30d012e4657b588	no	2
Warnings:					
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Information:					

5	Transmittal Letter	REGN-008CIPCON8_2020-12-04_IDS_Trans.pdf	52869 d285b8c23ecbddbb96ae48c3a860b0219c9a16a6	no	3
Warnings:					
Information:					
6	Information Disclosure Statement (IDS) Form (SB08)	REGN-008CIPCON8_2020-12-04_IDS_SB08A.pdf	194811 20ad46295cde0a8a3498e3c1afbb6bd480970c99	no	18
Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
7		REGN-008CIPCON8_2020-12-04_Prelim_Amend.pdf	83081 d5d0ea3ad794c66d4a2418ca9352aaecb6a2b70f	yes	9

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Applicant Arguments/Remarks Made in an Amendment	7	9
	Claims	2	6
	Preliminary Amendment	1	1

Warnings:					
Information:					
8	Sequence Listing (Text File)	REGN-008CIPCON8_SeqList.txt	6397	no	-
Warnings:					
Information:					
9	Fee Worksheet (SB06)	fee-info.pdf	38432 7dcfd3752a99e8e79c7866b776e51d5e1702ef19	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	964605		

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.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	REGN-008CIPCON8
	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

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	George		YANCOPOULOS	

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

City	Yorktown Heights	State/Province	NY	Country of Residence i	US

Mailing Address of Inventor:

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

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

Correspondence Information:

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

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

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

Application Information:

Title of the Invention	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS		
Attorney Docket Number	REGN-008CIPCON8	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 (08-15)
Approved for use through 04/30/2017. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	REGN-008CIPCON8
	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		

Prefix	**Given Name**	Middle Name	**Family Name**	Suffix	Remove
Registration Number					
Prefix	**Given Name**	Middle Name	**Family Name**	Suffix	Remove
Registration Number					

Additional Representative Information blocks may be generated within this form by selecting the **Add** button.

PTO/AIA/14 (08-15)
Approved for use through 04/30/2017. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	REGN-008CIPCON8
	Application Number	
Title of Invention	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS	

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	17072417	2020-10-16

Prior Application Status	Patented		Remove		
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
17072417	Continuation of	16055847	2018-08-06	10857205	2020-12-08

Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
17072417	Continuation of	16397267	2019-04-29

Prior Application Status	Patented		Remove		
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
16397267	Continuation of	16159282	2018-10-12	10828345	2020-11-10

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	10130681	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

Prior Application Status	Patented		Remove		
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
14972560	Continuation of	13940370	2013-07-13	9254338	2016-02-09

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	REGN-008CIPCON8
	Application Number	
Title of Invention	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS	

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

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

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

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

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

Foreign Priority Information:

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

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

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

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

PTO/AIA/14 (08-15)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	REGN-008CIPCON8
	Application Number	
Title of Invention	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS	

☐ 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 (08-15)
Approved for use through 04/30/2017. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	REGN-008CIPCON8
	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.

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

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

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

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

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

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	REGN-008CIPCON8
	Application Number	
Title of Invention	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS	

Applicant Information:

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

Applicant 1

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

Clear

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

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

Name of the Deceased or Legally Incapacitated Inventor:	

If the Applicant is an Organization check here. ☒

Organization Name	REGENERON PHARMACEUTICALS, INC.

Mailing Address Information For Applicant:

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

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

PTO/AIA/14 (08-15)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	REGN-008CIPCON8
	Application Number	
Title of Invention	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS	

Assignee Information including Non-Applicant Assignee Information:

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

Assignee 1

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

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

Organization Name	REGENERON PHARMACEUTICALS, INC.

Mailing Address Information For Assignee including Non-Applicant Assignee:

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

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

PTO/AIA/14 (08-15)
Approved for use through 04/30/2017. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	REGN-008CIPCON8
	Application Number	
Title of Invention	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS	

Signature:

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

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

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

Signature	/Karl Bozicevic/			Date (YYYY-MM-DD)	
First Name	Karl	Last Name	Bozicevic	Registration Number	28807

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

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.

What is claimed is:

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

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

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

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

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

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

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

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

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

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

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

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

11. The method of claim 9, wherein the VEGF receptor-based chimeric molecule comprises (1) a VEGFR1 component comprising amino acids 27 to 129 of SEQ ID NO:2; (2) a VEGFR2 component comprising amino acids 130-231 of SEQ ID NO:2; and (3) a multimerization component comprising amino acids 232-457 of SEQ ID NO:2.

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

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

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

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

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

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

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

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

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

USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application is a continuation of 17/072,417 filed October 16, 2020 which is a continuation of 16/055,847 filed August 6, 2018, now U.S. Patent 10,857,205 issued December 8, 2020 and is a continuation of 16/397,267 filed April 29, 2019, which is a continuation of 16/159,282 filed October 12, 2018, now U.S. Patent No. 10,828,345 issued November 10, 2020, which is a continuation of 15/471,506 filed March 28, 2017, now U.S. Patent No. 10,130,681 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.

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

[0005] Methods for treating eye disorders using VEGF antagonists are mentioned in, *e.g.*, US 7,303,746; US 7,306,799; US 7,300,563; US 7,303,748; and US 2007/0190058. Nonetheless, there remains a need in the art for new administration regimens for angiogenic eye disorders, especially those which allow for less frequent dosing while maintaining a high level of efficacy.

BRIEF SUMMARY OF THE INVENTION

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

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

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

protein comprising two or more VEGF receptor-based chimeric molecules referred to herein as "VEGFR1R2-FcΔC1(a)" or "aflibercept."

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

[0010] Aflibercept (EYLEA™, Regeneron Pharmaceuticals, Inc) was approved by the FDA in November 2011, for the treatment of patients with neovascular (wet) age-related macular degeneration, with a recommended dose of 2 mg administered by intravitreal injection every 4 weeks for the first three months, followed by 2 mg administered by intravitreal injection once every 8 weeks.

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

BRIEF DESCRIPTION OF THE FIGURE

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

DETAILED DESCRIPTION

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

[0014] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. As used herein, the term "about," when used in reference to a particular recited numerical value, means that the value may vary from the recited value by no more than 1%. For example, as used herein, the expression "about 100" includes 99 and 101 and all values in between (*e.g.*, 99.1, 99.2, 99.3, 99.4, etc.).

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

DOSING REGIMENS

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

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

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

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

[0020] The methods of the invention may comprise administering to a patient any number of secondary and/or tertiary doses of a VEGF antagonist. For example, in certain embodiments, only

a single secondary dose is administered to the patient. In other embodiments, two or more (*e.g.*, 2, 3, 4, 5, 6, 7, 8, or more) secondary doses are administered to the patient. Likewise, in certain embodiments, only a single tertiary dose is administered to the patient. In other embodiments, two or more (*e.g.*, 2, 3, 4, 5, 6, 7, 8, or more) tertiary doses are administered to the patient.

[0021] In embodiments involving multiple secondary doses, each secondary dose may be administered at the same frequency as the other secondary doses. For example, each secondary dose may be administered to the patient 4 weeks after the immediately preceding dose. Similarly, in embodiments involving multiple tertiary doses, each tertiary dose may be administered at the same frequency as the other tertiary doses. For example, each tertiary dose may be administered to the patient 8 weeks after the immediately preceding dose. Alternatively, the frequency at which the secondary and/or tertiary doses are administered to a patient can vary over the course of the treatment regimen. For example, the present invention includes methods which comprise administering to the patient a single initial dose of a VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by at least 5 tertiary doses of the VEGF antagonist, wherein the first four tertiary doses are administered 8 weeks after the immediately preceding dose, and wherein each subsequent tertiary dose is administered from 8 to 12 (*e.g.*, 8, 8½, 9, 9½, 10, 10½, 11, 11½, 12) weeks after the immediately preceding dose. The frequency of administration may also be adjusted during the course of treatment by a physician depending on the needs of the individual patient following clinical examination.

VEGF ANTAGONISTS

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

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

[0024] VEGF receptor-based chimeric molecules include chimeric polypeptides which comprise two or more immunoglobulin (Ig)-like domains of a VEGF receptor such as VEGFR1 (also referred to as Flt1) and/or VEGFR2 (also referred to as Flk1 or KDR), and may also contain a multimerizing domain (*e.g.*, an Fc domain which facilitates the multimerization [*e.g.*, dimerization] of two or more chimeric polypeptides). An exemplary VEGF receptor-based chimeric molecule is a molecule

referred to as VEGFR1R2-FcΔC1(a) which is encoded by the nucleic acid sequence of SEQ ID NO:1. VEGFR1R2-FcΔC1(a) comprises three components: (1) a VEGFR1 component comprising amino acids 27 to 129 of SEQ ID NO:2; (2) a VEGFR2 component comprising amino acids 130 to 231 of SEQ ID NO:2; and (3) a multimerization component ("FcΔC1(a)") comprising amino acids 232 to 457 of SEQ ID NO:2 (the C-terminal amino acid of SEQ ID NO:2 [*i.e.*, K458] may or may not be included in the VEGF antagonist used in the methods of the invention; *see e.g.*, US Patent 7,396,664). Amino acids 1-26 of SEQ ID NO:2 are the signal sequence.

[0025] The VEGF antagonist used in the Examples set forth herein below is a dimeric molecule comprising two VEGFR1R2-FcΔC1(a) molecules and is referred to herein as "VEGFT." Additional VEGF receptor-based chimeric molecules which can be used in the context of the present invention are disclosed in US 7,396,664, 7,303,746 and WO 00/75319.

ANGIOGENIC EYE DISORDERS

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

PHARMACEUTICAL FORMULATIONS

[0027] The present invention includes methods in which the VEGF antagonist that is administered to the patient is contained within a pharmaceutical formulation. The pharmaceutical formulation may comprise the VEGF antagonist along with at least one inactive ingredient such as, *e.g.*, a pharmaceutically acceptable carrier. Other agents may be incorporated into the pharmaceutical composition to provide improved transfer, delivery, tolerance, and the like. The term "pharmaceutically acceptable" means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly, in humans. The term "carrier" refers to a diluent, adjuvant, excipient, or vehicle with which the antibody is administered. A multitude of appropriate

formulations can be found in the formulary known to all pharmaceutical chemists: Remington's Pharmaceutical Sciences (15th ed, Mack Publishing Company, Easton, Pa., 1975), particularly Chapter 87 by Blaug, Seymour, therein. These formulations include, for example, powders, pastes, ointments, jellies, waxes, oils, lipids, lipid (cationic or anionic) containing vesicles (such as LIPOFECTIN™), DNA conjugates, anhydrous absorption pastes, oil-in-water and water-in-oil emulsions, emulsions carbowax (polyethylene glycols of various molecular weights), semi-solid gels, and semi-solid mixtures containing carbowax. Any of the foregoing mixtures may be appropriate in the context of the methods of the present invention, provided that the VEGF antagonist is not inactivated by the formulation and the formulation is physiologically compatible and tolerable with the route of administration. See also Powell et al. PDA (1998) J Pharm Sci Technol. 52:238-311 and the citations therein for additional information related to excipients and carriers well known to pharmaceutical chemists.

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

MODES OF ADMINISTRATION

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

AMOUNT OF VEGF ANTAGONIST ADMINISTERED

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

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

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

TREATMENT POPULATION AND EFFICACY

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

EXAMPLES

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

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

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

[0036] In this Phase I study, 21 subjects with neovascular AMD received a single intravitreal (IVT) dose of VEGFT. Five groups of three subjects each received either 0.05, 0.15, 0.5, 2 or 4 mg of VEGFT, and a sixth group of six subjects received 1 mg. No serious adverse events related to the study drug, and no identifiable intraocular inflammation was reported. Preliminary results showed that, following injection of VEGFT, a rapid decrease in foveal thickness and macular volume was observed that was maintained through 6 weeks. At Day 43 across all dose groups, mean excess

retinal thickness [excess retinal thickness = (retinal thickness – 179μ)] on optical coherence tomography (OCT) was reduced from 119μ to 27μ as assessed by Fast Macular Scan and from 194μ to 60μ as assessed using a single Posterior Pole scan. The mean increase in best corrected visual acuity (BCVA) was 4.75 letters, and BCVA was stable or improved in 95% of subjects. In the 2 highest dose groups (2 and 4 mg), the mean increase in BCVA was 13.5 letters, with 3 of 6 subjects demonstrating improvement of ≥ 3 lines.

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

[0037] This study was a double-masked, randomized study of 3 doses (0.5, 2, and 4 mg) of VEGFT tested at 4-week and/or 12-week dosing intervals. There were 5 treatment arms in this study, as follows: 1) 0.5 mg every 4 weeks, 2) 0.5 mg every 12 weeks, 3) 2 mg every 4 weeks, 4) 2 mg every 12 weeks and 5) 4 mg every 12 weeks. Subjects were dosed at a fixed interval for the first 12 weeks, after which they were evaluated every 4 weeks for 9 months, during which additional doses were administered based on pre-specified criteria. All subjects were then followed for one year after their last dose of VEGFT. Preliminary data from a pre-planned interim analysis indicated that VEGFT met its primary endpoint of a statistically significant reduction in retinal thickness after 12 weeks compared with baseline (all groups combined, decrease of 135μ, $p < 0.0001$). Mean change from baseline in visual acuity, a key secondary endpoint of the study, also demonstrated statistically significant improvement (all groups combined, increase of 5.9 letters, $p < 0.0001$). Moreover, patients in the dose groups that received only a single dose, on average, demonstrated a decrease in excess retinal thickness ($p < 0.0001$) and an increase in visual acuity ($p = 0.012$) at 12 weeks. There were no drug-related serious adverse events, and treatment with the VEGF antagonists was generally well-tolerated. The most common adverse events were those typically associated with intravitreal injections.

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

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

[0039] Most adverse events that were attributed to VEGFT were mild to moderate in severity, but 2 of 5 subjects treated with 3 mg/kg experienced dose-limiting toxicity (DLT) (one with Grade 4

hypertension and one with Grade 2 proteinuria); therefore, all subjects in the 3 mg/kg dose group did not enter the study. The mean percent changes in excess retinal thickness were: -12%, -10%, -66%, and -60% for the placebo, 0.3, 1, and 3 mg/kg dose groups at day 15 (ANOVA $p< 0.02$), and -5.6%, +47.1%, and -63.3% for the placebo, 0.3, and 1 mg/kg dose groups at day 71 (ANOVA $p< 0.02$). There was a numerical improvement in BCVA in the subjects treated with VEGFT. As would be expected in such a small study, the results were not statistically significant.

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

A. Objectives, Hypotheses and Endpoints

[0040] Two parallel Phase III clinical trials were carried out to investigate the use of VEGFT to treat patients with the neovascular form of age-related macular degeneration (Study 1 and Study 2). The primary objective of these studies was to assess the efficacy of IVT administered VEGFT compared to ranibizumab (Lucentis®, Genentech, Inc.), in a non-inferiority paradigm, in preventing moderate vision loss in subjects with all subtypes of neovascular AMD.

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

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

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

B. Study Design

[0044] For each study, subjects were randomly assigned in a 1:1:1:1 ratio to 1 of 4 dosing regimens: (1) 2 mg VEGFT administered every 4 weeks (2Q4); (2) 0.5 mg VEGFT administered every 4 weeks (0.5Q4); (3) 2 mg VEGFT administered every 4 weeks to week 8 and then every 8 weeks (with sham injection at the interim 4-week visits when study drug was not administered (2Q8); and (4) 0.5 mg ranibizumab administered every 4 weeks (RQ4). Subjects assigned to (2Q8) received the 2 mg injection every 4 weeks to week 8 and then a sham injection at interim 4-week

visits (when study drug is not to be administered) during the first 52 weeks of the studies. (No sham injection were given at Week 52).

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

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

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

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

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

[0050] Inclusion criteria for both studies were as follows: (i) signed Informed consent; (ii) at least 50 years of age; (iii) active primary subfoveal CNV lesions secondary to AMD, including juxtafoveal lesions that affect the fovea as evidenced by FA in the study eye; (iv) CNV at least 50% of total

lesion size; (v) early treatment diabetic retinopathy study (ETDRS) best-corrected visual acuity of: 20/40 to 20/320 (letter score of 73 to 25) in the study eye; (vi) willing, committed, and able to return for all clinic visits and complete all study-related procedures; and (vii) able to read, understand and willing to sign the informed consent form (or, if unable to read due to visual impairment, be read to verbatim by the person administering the informed consent or a family member).

[0051] Exclusion criteria for both studies were as follows: 1. Any prior ocular (in the study eye) or systemic treatment or surgery for neovascular AMD except dietary supplements or vitamins. 2. Any prior or concomitant therapy with another investigational agent to treat neovascular AMD in the study eye, except dietary supplements or vitamins. 3. Prior treatment with anti-VEGF agents as follows: (a) Prior treatment with anti-VEGF therapy in the study eye was not allowed; (b) Prior treatment with anti-VEGF therapy in the fellow eye with an investigational agent (not FDA approved, e.g. bevacizumab) was allowed up to 3 months prior to first dose in the study, and such treatments were not allowed during the study. Prior treatment with an approved anti-VEGF therapy in the fellow eye was allowed; (c) Prior systemic anti-VEGF therapy, investigational or FDA/Health Canada approved, was only allowed up to 3 months prior to first dose, and was not allowed during the study. 4. Total lesion size > 12 disc areas (30.5 mm2, including blood, scars and neovascularization) as assessed by FA in the study eye. 5. Subretinal hemorrhage that is either 50% or more of the total lesion area, or if the blood is under the fovea and is 1 or more disc areas in size in the study eye. (If the blood is under the fovea, then the fovea must be surrounded 270 degrees by visible CNV.) 6. Scar or fibrosis, making up > 50% of total lesion in the study eye. 7. Scar, fibrosis, or atrophy involving the center of the fovea. 8. Presence of retinal pigment epithelial tears or rips involving the macula in the study eye. 9. History of any vitreous hemorrhage within 4 weeks prior to Visit 1 in the study eye. 10. Presence of other causes of CNV, including pathologic myopia (spherical equivalent of –8 diopters or more negative, or axial length of 25 mm or more), ocular histoplasmosis syndrome, angioid streaks, choroidal rupture, or multifocal choroiditis in the study eye. 11. History or clinical evidence of diabetic retinopathy, diabetic macular edema or any other vascular disease affecting the retina, other than AMD, in either eye. 12. Prior vitrectomy in the study eye. 13. History of retinal detachment or treatment or surgery for retinal detachment in the study eye. 14. Any history of macular hole of stage 2 and above in the study eye. 15. Any intraocular or periocular surgery within 3 months of Day 1 on the study eye, except lid surgery, which may not have taken place within 1 month of day 1, as long as it was unlikely to interfere with the injection. 16. Prior trabeculectomy or other filtration surgery in the study eye. 17. Uncontrolled glaucoma (defined as intraocular pressure greater than or equal to 25 mm Hg despite treatment with anti-glaucoma medication) in the study eye. 18. Active intraocular inflammation in either eye. 19. Active ocular or periocular infection in either eye. 20. Any ocular or periocular infection within

the last 2 weeks prior to Screening in either eye. 21. Any history of uveitis in either eye. 22. Active scleritis or episcleritis in either eye. 23. Presence or history of scleromalacia in either eye. 24. Aphakia or pseudophakia with absence of posterior capsule (unless it occurred as a result of a yttrium aluminum garnet [YAG] posterior capsulotomy) in the study eye. 25. Previous therapeutic radiation in the region of the study eye. 26. History of corneal transplant or corneal dystrophy in the study eye. 27. Significant media opacities, including cataract, in the study eye which might interfere with visual acuity, assessment of safety, or fundus photography. 28. Any concurrent intraocular condition in the study eye (e.g. cataract) that, in the opinion of the investigator, could require either medical or surgical intervention during the 96 week study period. 29. Any concurrent ocular condition in the study eye which, in the opinion of the investigator, could either increase the risk to the subject beyond what is to be expected from standard procedures of intraocular injection, or which otherwise may interfere with the injection procedure or with evaluation of efficacy or safety. 30. History of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that might affect interpretation of the results of the study or render the subject at high risk for treatment complications. 31. Participation as a subject in any clinical study within the 12 weeks prior to Day 1. 32. Any systemic or ocular treatment with an investigational agent in the past 3 months prior to Day 1. 33. The use of long acting steroids, either systemically or intraocularly, in the 6 months prior to day 1. 34. Any history of allergy to povidone iodine. 35. Known serious allergy to the fluorescein sodium for injection in angiography. 36. Presence of any contraindications indicated in the FDA Approved label for ranibizumab (Lucentis®). 37. Females who were pregnant, breastfeeding, or of childbearing potential, unwilling to practice adequate contraception throughout the study. Adequate contraceptive measures include oral contraceptives (stable use for 2 or more cycles prior to screening); IUD; Depo-Provera®; Norplant® System implants; bilateral tubal ligation; vasectomy; condom or diaphragm plus either contraceptive sponge, foam or jelly.

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

[0053] The study procedures are summarized as follows:

[0054] Best Corrected Visual Acuity: Visual function of the study eye and the fellow eye were assessed using the ETDRS protocol (The Early Treatment Diabetic Retinopathy Study Group) at 4

meters. Visual Acuity examiners were certified to ensure consistent measurement of BCVA. The VA examiners were required to remain masked to treatment assignment.

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

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

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

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

[0059]

C. Results Summary (52 Week Data)

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

Table 1

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

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

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

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

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

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

Table 2

	n	Mean change in visual acuity at week 24 versus baseline (letters)	Mean change in visual acuity at week 52 versus baseline (letters)
Laser	44	2.5	-1.3
VEGFT 0.5 mg monthly (0.5Q4)	44	8.6**	11.0**
VEGFT 2 mg monthly (2Q4)	44	11.4**	13.1**
VEGFT 2 mg every 8 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 for sham-treated patients. The proportion of patients with ocular neovascularization at Week 24 were 0% for VEGFT-treated patients and 6.8% for sham-treated patients, respectively; at Week 52 after receiving VEGFT PRN, proportions were 0% and 6.8% for VEGFT-treated and sham-treated. At Week 24, the mean change from baseline in the VFQ-25 total score was 7.2 vs 0.7 for the VEGFT-treated and sham-treated groups; at Week 52, the scores were 7.5 vs 5.1 for the VEGFT-treated and sham-treated groups.

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

Example 7: Dosing Regimens

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

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

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

[0072] VEGFT 2 mg (0.5 mL) administered by intravitreal injection once every 4 weeks for the first 8 weeks, followed by 2 mg (0.05 mL) via intravitreal injection on a less frequent basis based on

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

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

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

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

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

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

[0078] VEGFT 2 mg (0.5 mL) administered by intravitreal injection once every 4 weeks for the first 16 weeks, followed by 2 mg (0.05 mL) via intravitreal injection on a less frequent basis based on visual and/or anatomical outcomes (as assessed by a physician or other qualified medical professional).

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

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

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

[0082] VEGFT 2 mg (0.5 mL) administered by intravitreal injection once every 4 weeks for the first 20 weeks, followed by 2 mg (0.05 mL) via intravitreal injection administered *pro re nata* (PRN)

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

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

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

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

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

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

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

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

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

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

proliferative vitreoretinopathy (PVR), optic disc neovascularization, corneal neovascularization, retinal neovascularization, vitreal neovascularization, pannus, pterygium, vascular retinopathy, etc.

SEQUENCES

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

ATGGTCAGCTACTGGGACACCGGGGTCCTGCTGTGCGCGCTGCTCAGCTGTCTGCTTCTCAC
AGGATCTAGTTCCGGAAGTGATACCGGTAGACCTTTCGTAGAGATGTACAGTGAAATCCCCGA
AATTATACACATGACTGAAGGAAGGGAGCTCGTCATTCCCTGCCGGGTTACGTCACCTAACAT
CACTGTTACTTTAAAAAAGTTTCCACTTGACACTTTGATCCCTGATGGAAAACGCATAATCTGG
GACAGTAGAAAGGGCTTCATCATATCAAATGCAACGTACAAAGAAATAGGGCTTCTGACCTGT
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TCATAGATGTGGTTCTGAGTCCGTCTCATGGAATTGAACTATCTGTTGGAGAAAAGCTTGTCTT
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AAGCATCAGCATAAGAAACTTGTAAACCGAGACCTAAAAACCCAGTCTGGGAGTGAGATGAAG
AAATTTTTGAGCACCTTAACTATAGATGGTGTAACCCGGAGTGACCAAGGATTGTACACCTGTG
CAGCATCCAGTGGGCTGATGACCAAGAAGAACAGCACATTTGTCAGGGTCCATGAAAAGGACA
AAACTCACACATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCCTCT
TCCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTG
GTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGT
GCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTCAGCG
TCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAAC
AAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACC
ACAGGTGTACACCCTGCCCCCATCCCGGGATGAGCTGACCAAGAACCAGGTCAGCCTGACCT
GCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCG
GAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGC
AAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCA
TGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAATGA

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

MVSYWDTGVLLCALLSCLLLTGSSSGSDTGRPFVEMYSEIPEIIHMTEGRELVIPCRVTSPNITVTLK
KFPLDTLIPDGKRIIWDSRKGFIISNATYKEIGLLTCEATVNGHLYKTNYLTHRQTNTIIDVVLSPSHGI
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.

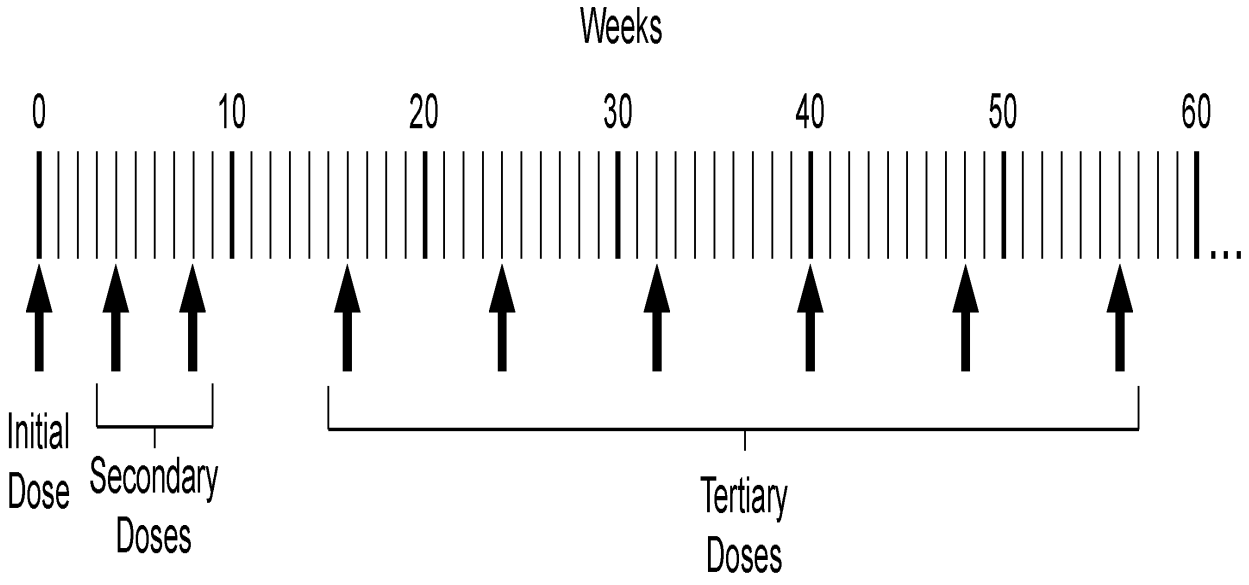
Weeks
0
10
20
30
40
50
60
...
Initial Dose
Secondary Doses
Tertiary Doses

Figure 1

PTO/AIA/01 (06-12)
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DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention	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:

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LEGAL NAME OF INVENTOR

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

Signature: X

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.

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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).
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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 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.

Electronically Filed 12/4/2020

INFORMATION DISCLOSURE STATEMENT	Attorney Docket No.	REGN-008CIPCON8
	Confirmation No.	To Be Assigned
	First Named Inventor	George D. Yancopoulos
	Application Number	To Be Assigned
	Filing Date	December 4, 2020
	Group Art Unit	To Be Assigned
	Examiner Name	To Be Assigned
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:

Applicant submits 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 publications discussed herein are provided to comply with the duty to disclose in accordance with 37 C.F.R. § 1.56. However, nothing herein is to be construed as an admission that the present invention is not entitled to antedate such publication by virtue of prior invention. Further, the dates of publication provided may be different from the actual publication dates which may need to be independently confirmed

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 17/072,417, 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-008CIPCON8.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: December 4, 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, CA 94065
Telephone: (650) 327-3400
Facsimile: (650) 327-3231

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U.S. PATENT DOCUMENTS

Examiner Initial*	Cite No.	Patent Number Number-Kind Code (*if known*)	Issue Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1	7070959	2006-07-04	Papadopoulos	
	2	7303746	2007-12-04	Wiegand	
	3	7303748	2007-12-04	Wiegand	
	4	7306799	2007-12-11	Wiegand	
	5	7396664	2008-07-08	Daly et al.	
	6	8092803	2012-01-10	Furfine et al.	
	7	9254338	2016-02-09	Yancopoulos	
	8	9669069	2017-06-06	Yancopoulos	
	9	10130681	2018-11-20	Yancopoulos	
	10	10406226	2019-09-10	Dix et al.	
	11	10464992	2019-11-05	Furfine et al.	

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	1	2003/0171320	2003-09-11	Guyer	
	2	2005/0163798	2005-07-28	Papadopoulos et al.	
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	4	2006/0058234	2006-03-16	Daly et al.	
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	7	2008/0220004	2008-09-11	Wiegand et al.	
	8	2019/0290725	2019-09-26	Vitti et al.	
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	10	2020/0017572	2020-01-16	Furfine et al.	

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	1	WO 2006/047325	2006-03-04	Genentech, Inc.		
	2	WO 2000/75319	2000-12-14	Regeneron Pharmaceuitcals, Inc.		
	3	WO 2004/106378 A2	2004-12-09	Regeneron Pharmaceuticals, Inc.		
	4	WO 2005/000895 A2	2005-01-05	Regeneron Pharmaceuticals, Inc.		
	5	WO 2007/022101 A2	2007-02-22	Regeneron Pharmaceuticals, Inc.		

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	118	Regeneron SEC Form 10-Q (May 8, 2006)		
	119	Regeneron SEC Form 10-Q (August 8, 2006)		
	120	Regeneron SEC Form 10-Q (November 6, 2006)		
	121	Regeneron SEC Form 10-Q (May 4, 2007)		
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	130	Regeneron SEC Form 10-Q (October 27, 2011)		
	131	Regeneron SEC Form 8-K Exhibit: "Press Release of Regeneron Pharmaceuticals, Inc. dated May 1, 2006" (May 2, 2006)		
	132	Regeneron SEC Form 8-K Exhibit: "Press Release of Regeneron Pharmaceuticals, Inc. dated May 3, 2006" (May 5, 2006)		
	133	Regeneron SEC Form 8-K Exhibit: "Slides presented at the Company's 2006 Annual Meeting of Shareholders held on June 9, 2006" (June 9, 2006)		
	134	Regeneron SEC Form 8-K Exhibit: "Press Release dated May 2, 2007" (May 3, 2007)		
	135	Regeneron SEC Form 8-K Exhibit: "Overheads for presentation at Regeneron's Annual Meeting of Shareholders to be held on June 8, 2007" (June 8, 2007)		
	136	Regeneron SEC Form 8-K Exhibit: "Press Release dated October 1, 2007" (October 1, 2007)		
	137	Regeneron SEC Form 8-K Exhibit: "Press Release dated November 6, 2007" (November 6, 2007)		
	138	Regeneron SEC Form 8-K Exhibit: "Press Release dated May 1, 2008" (May 2, 2008)		
	139	Regeneron SEC Form 8-K Exhibit: "Press Release dated November 4, 2008" (November 4, 2008)		
	140	Regeneron SEC Form 8-K Exhibit: "99(a) Slides that Regeneron Pharmaceuticals, Inc. intends to use in conjunction with meetings with investors at the J.P. Morgan 27th Annual Healthcare Conference in San Francisco on January 12-15, 2009." (January 9, 2009)		
	141	Regeneron SEC Form 8-K Exhibit: "Press Release dated April 30, 2009" (May 1, 2009)		
	142	Regeneron SEC Form 8-K Exhibit: "Press Release dated November 3, 2009." (November 4, 2009)		
	143	Regeneron SEC Form 8-K Exhibit: "Press Release Reporting 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) dated December 20, 2010." (December 20, 2010)		
	144	Regeneron SEC Form 8-K Exhibit: "Press Release dated February 17, 2011" (February 18, 2011)		
	145	Regeneron SEC Form 8-K Exhibit: "Press Release Reporting Positive Results for VEGF Trap-Eye in Second Phase 3 Study in Central Retinal Vein Occlusion, dated April 27, 2011" (April 27, 2011)		
	146	Regeneron SEC Form 8-K Exhibit: "Press Release dated May 3, 2011." (May 3, 2011)		
	147	Regeneron SEC Form 8-K Exhibit: "Press Release, dated June 17, 2011, Announcing that EYLEA™ (aflibercept ophthalmic solution) Received Unanimous Recommendation for Approval for Treatment of Wet AMD from FDA Advisory Committee." (June 21, 2011)		

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	148	Regeneron SEC Form 8-K Exhibit: "Presentation entitled VEGF Trap-Eye in CRVO: 1-year Results of the Phase 3 COPERNICUS Study" (August 22, 2011)		
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	181	Regeneron Press Release "Regeneron Submits Biologics License Application To FDA For VEGF Trap-Eye For Treatment Of Wet Age-Related Macular Degeneration" (February 22, 2011)		
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Examiner Signature		Date Considered	

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				Examiner Name	To Be Assigned
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	NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.		T
	214	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) 38 pages, Latest version submitted October 27, 2014 on ClinicalTrials.gov (NCT01012973_01182013_27424.1)		
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	241	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		
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	243	YANCOPOULOS, "Clinical Application of Therapies Targeting VEGF." Cell 143:13-16 (October 1, 2010)		
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REMARKS UNDER 37 CFR § 1.115

Formal Matters

Claims 21-54 are pending after entry of the amendments set forth herein.

Original claims 1-20 are canceled without prejudice.

Claims 21-54 are added here.

Support for new claims 21-54 can be found in originally pending now canceled claims 1-20, and throughout the specification.

No new matter has been added.

SEQUENCE LISTING

Applicants submit herewith the attached Sequence Listing in .txt format. As set out in MPEP §2422.03(a), the Office has advised that if the sequence listing text file submitted via EFS-Web complies with the requirements of 37 CFR 1.824(a)(2)-(6) and (b) (i.e., is a compliant sequence listing ASCII text file), the text file will serve as both the paper copy required by 37 CFR 1.821(c) and the computer readable form (CRF) required by 37 CFR 1.821(e). Further, per MPEP §2422.03(a), neither (1) a second copy of the sequence listing in a PDF file; nor (2) a statement under 37 CFR 1.821(f) (indicating that the paper copy and CRF copy of the sequence listing are identical) should be submitted.

The Sequence Listing was prepared with the software FASTSEQ for Windows version 4.0, and conforms to the Patent Office guidelines. Applicant respectfully submits that the subject application is in adherence to 37 CFR §§ 1.821-1.825. I hereby certify that the enclosed submission includes no new matter.

Applicants respectfully submit that the present patent application is now in compliance with 37 CFR §§ 1.821-1.825.

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 Applicant wishes 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 Applicant wishes to bring to the Examiner's attention U.S. Patent Application No. 14/972,560, filed December 17, 2015 which issued on June 6, 2017 as U.S. Patent No. 9,669,069.

The Applicant wishes 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. 10,130,681.

The Applicant wishes to bring to the Examiner's attention U.S. Patent Application No. 16/055,847, filed August 6, 2018 which will issue on December 8, 2020 as U.S. Patent No. 10,857,205.

The Applicant wishes to bring to the Examiner's attention U.S. Patent Application No. 16/159,282, filed October 12, 2018 which issued on November 10, 2020 as U.S. Patent No. 10,828,345.

The Applicant wishes to bring to the Examiner's attention co-pending U.S. Patent Application No. 16/397,267, filed April 29, 2019 for which a Notice of Allowance was mailed on November 12, 2020.

The Applicant wishes to bring to the Examiner's attention co-pending U.S. Patent Application No. 17/072,417, filed October 16, 2020 for which no actions have been mailed.

The Applicant wishes to bring to the Examiner's attention co-pending U.S. Patent Application No. 17/112,063, filed December 4, 2020 which was filed concurrently with the above-referenced patent application.

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-008CIPCON8.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: 4 December 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
Telephone: (650) 327-3400
Direct: (650) 833-7735
Facsimile: (650) 327-3231

AMENDMENTS TO THE CLAIMS

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

21. **(New)** A method of treating an angiogenic eye disorder in a patient in need thereof comprising sequentially administering to the patient a single initial dose of 2 mg of aflibercept, followed by two secondary doses of 2 mg of aflibercept followed by one or more tertiary doses of 2 mg of aflibercept;

wherein each secondary dose is administered to the patient by intravitreal injection approximately 4 weeks following 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 anatomic outcomes as assessed by a physician or other qualified medical professional;

wherein the patient achieves a gain in visual acuity within 52 weeks following the initial dose.

22. **(New)** The method of claim 21 wherein the patient gains at least 8 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

23. **(New)** The method of claim 22 wherein said gain in visual acuity is measured using the ETDRS visual acuity chart.

24. **(New)** The method of claim 22 wherein the patient achieves the gain in visual acuity within 24 weeks following the initial dose.

25. **(New)** The method of claim 21 wherein the patient gains at least 9 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

26. **(New)** The method of claim 25 wherein said gain in visual acuity is measured using the ETDRS visual acuity chart.

27. **(New)** The method of claim 25 wherein the patient achieves the gain in visual acuity within 24 weeks following the initial dose.

28. **(New)** The method of claim 21 wherein the patient gains at least 10 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

29. **(New)** The method of claim 28 wherein said gain in visual acuity is measured using the ETDRS visual acuity chart.

30. **(New)** The method of claim 28 wherein the aflibercept is formulated as an isotonic solution.

31. **(New)** The method of claim 30 wherein said isotonic solution contains a sugar.

32. **(New)** The method of claim 28 wherein the aflibercept is formulated with a non-ionic surfactant.

33. **(New)** The method of claim 28 wherein the patient achieves the gain in visual acuity within 24 weeks following the initial dose.

34. **(New)** The method of claim 33 wherein the aflibercept is formulated as an isotonic solution.

35. **(New)** The method of claim 34 wherein said isotonic solution contains a sugar.

36. **(New)** The method of claim 33 wherein the aflibercept is formulated with a non-ionic surfactant.

37. **(New)** A method of treating diabetic macular edema in a patient in need thereof comprising sequentially administering to the patient a single initial dose of 2 mg of aflibercept, followed by one or more secondary doses of 2 mg of aflibercept, followed by one or more tertiary doses of 2 mg of aflibercept;

wherein each secondary dose is administered to the patient by intravitreal injection approximately 4 weeks following 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 anatomic outcomes as assessed by a physician or other qualified medical professional.

38. **(New)** The method of claim 37 wherein the patient gains at least 9 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score within 52 weeks following the initial dose.

39. **(New)** The method of claim 38 wherein said gain in visual acuity is measured using the ETDRS visual acuity chart.

40. **(New)** The method of claim 38 wherein the patient achieves the gain in visual acuity within 24 weeks following the initial dose.

41. **(New)** The method of claim 37 wherein the patient gains at least 10 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score within 52 weeks following the initial dose.

42. **(New)** The method of claim 41 wherein said gain in visual acuity is measured using the ETDRS visual acuity chart.

43. **(New)** The method of claim 41 wherein the aflibercept is formulated as an isotonic solution.

44. **(New)** The method of claim 43 wherein said isotonic solution contains a sugar.

45. **(New)** The method of claim 41 wherein the aflibercept is formulated with a non-ionic surfactant.

46. **(New)** The method of claim 41 wherein the patient achieves the gain in visual acuity within 24 weeks following the initial dose.

47. **(New)** The method of claim 46 wherein the aflibercept is formulated as an isotonic solution.

48. **(New)** The method of claim 47 wherein said isotonic solution contains a sugar.

49. **(New)** The method of claim 46 wherein the aflibercept is formulated with a non-ionic surfactant.

50. **(New)** The method of claim 37 wherein exclusion criteria for the patient include both of:

(1) active ocular inflammation;

(2) active ocular or periocular infection.

51. **(New)** The method of claim 37 wherein four secondary doses are administered to the patient.

52. **(New)** A method of treating age-related macular degeneration in a patient in need thereof comprising sequentially administering to the patient a single initial dose of 2 mg of aflibercept, followed by one or more secondary doses of 2 mg of aflibercept, followed by one or more tertiary doses of 2 mg of aflibercept;

wherein each secondary dose is administered to the patient by intravitreal injection approximately 4 weeks following 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 anatomic outcomes as assessed by a physician or other qualified medical professional;

wherein the method is as effective in achieving a gain in visual acuity as monthly administration of 0.5 mg of ranibizumab by intravitreal injection in human subjects with age-related macular degeneration at 52 weeks following the initial dose.

53. **(New)** The method of claim 52 wherein only two secondary doses are administered to the patient.

54. **(New)** The method of claim 52 wherein the gain in visual acuity is measured by Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

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SEQUENCE LISTING

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

<130> REGN-008CIPCON8

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UNITED STATES PATENT AND TRADEMARK OFFICE

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

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
17/112,404	12/04/2020		3220	REGN-008CIPCON8	34	3

CONFIRMATION NO. 6437

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

FILING RECEIPT

Date Mailed: 12/15/2020

Receipt is acknowledged of this non-provisional utility patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF FIRST INVENTOR, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection.

Please verify the accuracy of the data presented on this receipt. If an error is noted on this Filing Receipt, please submit a written request for a corrected Filing Receipt, including a properly marked-up ADS showing the changes with strike-through for deletions and underlining for additions. If you received a "Notice to File Missing Parts" or other Notice requiring a response for this application, please submit any request for correction to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections provided that the request is grantable.

Inventor(s)

George 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 17/072,417 10/16/2020
which is a CON of 16/055,847 08/06/2018 PAT 10857205
and is a CON of 16/397,267 04/29/2019
which is a CON of 16/159,282 10/12/2018 PAT 10828345
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
(*)Data provided by applicant is not consistent with PTO records.

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

Permission to Access Application via Priority Document Exchange: Yes

Permission to Access Search Results: Yes

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

If Required, Foreign Filing License Granted: 12/14/2020
The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 17/112,404**
Projected Publication Date: 03/25/2021
Non-Publication Request: No
Early Publication Request: No
Title

USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS

Preliminary Class

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

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

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

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

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

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign

patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

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Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

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The United States represents the largest, most dynamic marketplace in the world and is an unparalleled location for business investment, innovation, and commercialization of new technologies. The U.S. offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to promote and facilitate business investment. SelectUSA provides information assistance to the international investor community; serves as an ombudsman for existing and potential investors; advocates on behalf of U.S. cities, states, and regions competing for global investment; and counsels U.S. economic development organizations on investment attraction best practices. To learn more about why the United States is the best country in the world to develop technology, manufacture products, deliver services, and grow your business, visit http://www.SelectUSA.gov or call +1-202-482-6800.

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 17/112,404

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	320
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	700
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	800
TOTAL CLAIMS (37 CFR 1.16(i))	34 minus 20 =	* 14			OR	x 100 =	1400
INDEPENDENT CLAIMS (37 CFR 1.16(h))	3 minus 3 =	*				x 480 =	0.00
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						0.00
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							0.00
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	3220

APPLICATION AS AMENDED - PART II

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

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

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

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Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
17/112,404	12/04/2020	George YANCOPOULOS	REGN-008CIPCON8

CONFIRMATION NO. 6437

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

PUBLICATION NOTICE

OC000000124368548

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

Publication No.US-2021-0085753-A1
Publication Date:03/25/2021

NOTICE OF PUBLICATION OF APPLICATION

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

The publication may be accessed through the USPTO's publically available Searchable Databases via the Internet at www.uspto.gov. The direct link to access the publication is currently http://www.uspto.gov/patft/.

The publication process established by the Office does not provide for mailing a copy of the publication to applicant. A copy of the publication may be obtained from the Office upon payment of the appropriate fee set forth in 37 CFR 1.19(a)(1). Orders for copies of patent application publications are handled by the USPTO's Public Records Division. The Public Records Division can be reached by telephone at (571) 272-3150 or (800) 972-6382, by facsimile at (571) 273-3250, by mail addressed to the United States Patent and Trademark Office, Public Records Division, Alexandria, VA 22313-1450 or via the Internet.

In addition, information on the status of the application, including the mailing date of Office actions and the dates of receipt of correspondence filed in the Office, may also be accessed via the Internet through the Patent Electronic Business Center at www.uspto.gov using the public side of the Patent Application Information and Retrieval (PAIR) system. The direct link to access this status information is currently https://portal.uspto.gov/pair/PublicPair. Prior to publication, such status information is confidential and may only be obtained by applicant using the private side of PAIR.

Further assistance in electronically accessing the publication, or about PAIR, is available by calling the Patent Electronic Business Center at 1-866-217-9197.

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

INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	17/112,404
				Filing Date	2020-12-04
				First Named Inventor	George D. YANCOPOULOS
				Art Unit	To Be Assigned
				Examiner Name	To Be Assigned
Sheet	1	of	1	Attorney Docket Number	REGN-008CIPCON8

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

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

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

	NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.		T
	1	HEIER, J., "Intravitreal VEGF Trap for AMD: An Update, The CLEAR-IT 2 Extension Study" Presented at the annual meeting of the Association for Research in Vision and Ophthalmology, Retina Today (2009) pp. 44-45		

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:	43016561
Application Number:	17112404
International Application Number:	
Confirmation Number:	6437
Title of Invention:	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS
First Named Inventor/Applicant Name:	George YANCOPOULOS
Customer Number:	96387
Filer:	Karl Bozicevic/Kimberly Zuehlke
Filer Authorized By:	Karl Bozicevic
Attorney Docket Number:	REGN-008CIPCON8
Receipt Date:	17-JUN-2021
Filing Date:	04-DEC-2020
Time Stamp:	14:01:11
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-008CIPCON8_2020-06-17_SuppIDS_Trans.pdf	51288 fe69c490bde668cd23cc0ae9f8e62dcac84124be	no	3

Warnings:

Information:					
2	Information Disclosure Statement (IDS) Form (SB08)	REGN-008CIPCON8_2021-06-17_SuppIDS_SB08A.pdf	22841 f6c759e056b197daeccb8037cce53d4c4fc8600a	no	1
Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
3	Non Patent Literature	Heier_10-2009.pdf	73295 7c554f5fad491f0c5d0a6cf8043ea82a80933396	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	147424	

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.

INFORMATION DISCLOSURE STATEMENT	Attorney Docket No.	REGN-008CIPCON8
	Confirmation No.	6437
	First Named Inventor	George D. Yancopoulos
	Application Number	17/112,404
	Filing Date	December 4, 2020
	Group Art Unit	To Be Assigned
Address to: Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Examiner Name	To Be Assigned
	Title: "*Use of a VEGF Antagonist to Treat Angiogenic Eye Disorders*"	

Sir:

Applicant submits 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 publications discussed herein are provided to comply with the duty to disclose in accordance with 37 C.F.R. § 1.56. However, nothing herein is to be construed as an admission that the present invention is not entitled to antedate such publication by virtue of prior invention. Further, the dates of publication provided may be different from the actual publication dates which may need to be independently confirmed

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

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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

☐ **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-008CIPCON8.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: June 17, 2021

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

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

SUBSTITUTE 1449 INFORMATION DISCLOSURE STATEMENT	ATTY. DOCKET NO.	APPLICATION NO.
	REGN-008CIPCON8	17/112,404
	APPLICANT	
	Regeneron Pharmaceuticals, Inc.	
	FILING DATE	GROUP
	December 4, 2020	1647

U.S. PATENT DOCUMENTS					
		DOCUMENT NUMBER	DATE	NAME	REFERENCE PROVIDED*
	1	6,171,586	1/9/2001	Lam *et al.*	not required per 69 Fed. Reg. 56481
	2	7,303,747	12/4/2007	Wiegand *et al.*	not required per 69 Fed. Reg. 56481
	3	7,374,757	5/20/2008	Papadopoulos *et al.*	not required per 69 Fed. Reg. 56481
	4	7,374,758	5/20/2008	Papadopoulos *et al.*	not required per 69 Fed. Reg. 56481
	5	7,378,095	5/27/2008	Cao *et al.*	not required per 69 Fed. Reg. 56481
	6	7,521,049	4/21/2009	Wiegand *et al.*	not required per 69 Fed. Reg. 56481
	7	7,531,173	5/12/2009	Wiegand *et al.*	not required per 69 Fed. Reg. 56481
	8	10,828,345	11/10/2020	Yancopoulos	not required per 69 Fed. Reg. 56481
	9	2003/0113316	6/19/2003	Kaisheva *et al.*	not required per 69 Fed. Reg. 56481
	10	2003/0138417	7/24/2003	Kaisheva *et al.*	not required per 69 Fed. Reg. 56481
	11	2004/0197324	10/7/2004	Liu *et al.*	not required per 69 Fed. Reg. 56481
	12	2006/0217311	9/28/2006	Dix *et al.*	not required per 69 Fed. Reg. 56481
	13	2016/0130337	5/12/2016	Gekkieva *et al.*	not required per 69 Fed. Reg. 56481

FOREIGN PATENT DOCUMENTS						
		DOCUMENT NUMBER	DATE	COUNTRY	TRANSLATION	REFERENCE PROVIDED*
	14	2663325	11/20/2013	EP	n/a	Herewith
	15	97/04801	2/13/1997	WO	n/a	Herewith

NON-PATENT LITERATURE DOCUMENTS			
		DOCUMENT (Including Author, Title, Date, Pertinent Pages, etc.)	REFERENCE PROVIDED*
	16	7,374,758 – Patent Term Extension Application submitted December 22, 2011	Herewith
	17	ADIS R&D Profile "Aflibercept: AVE 0005, AVE 005, AVE0005, VEGF Trap - Regeneron, VEGF Trap (R1R2), VEGF Trap-Eye." Drugs R D, 9(4):261-269 (2008)	Herewith

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	18	Andersen & Krummen, "Recombinant protein expression for therapeutic applications" Current Opinion in Biotechnology 13:117-123 (2002)	Herewith
	19	Anderson *et al.*, "Delivery of Anti-Angiogenic Molecular Therapies for Retinal Disease" Drug Discovery Today 15: 272 (2010)	Herewith
	20	Article in Retinal Physician, "Subspecialty News", available online at http://www.retinalphysician.com/printarticle.aspx?articleID=104007 (March 2010)	Herewith
	21	Ass'n for Res. Vision & Ophthalmology, ARVO® News (Summer 2007)	Herewith
	22	Ass'n for Res. Vision & Ophthalmology, ARVO® News (Winter/Spring 2008)	Herewith
	23	AVASTIN® label	Herewith
	24	Avery, R. L., D. J. Pieramici, M. D. Rabena, A. A. Castellarin, M. A. Nasir and M. J. Giust, "Intravitreal bevacizumab (Avastin) for neovascular age-related macular degeneration" Ophthalmology 113(3): 363-372 e365 (2006)	Herewith
	25	Bashshur *et al.*, "Intravitreal Bevacizumab for the Management of Choroidal Neovascularization in Age-Related Macular Degeneration" Am J. Ophthalmology 142: 1 (2006)	Herewith
	26	Bayer Press Release, "Bayer and Regeneron Dose First Patient in Second Phase 3 Study for VEGF Trap-Eye in Wet Age-Related Macular Degeneration." May 8, 2008	Herewith
	27	Bayer Press Release, "VEGF Trap-Eye Shows Positive Results in Phase II Study in Patients with Diabetic Macular Edema" February 18, 2010	Herewith
	28	Bayer Press Release, "Bayer HealthCare and Regeneron Announce Encouraging 32-Week Follow Up Results From A Phase 2 Study of VEGF Trap-Eye in Age-Related Macular Degeneration" April 28, 2008	Herewith
	29	Bayer Press Release "Bayer HealthCare and Regeneron Announce VEGF Trap-Eye Achieved Durable Improvement in Vision Over 52 Weeks in a Phase 2 Study in Patients with Age-Related Macular Degeneration" August 19, 2008	Herewith

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	30	BMJ Publishing Group Ltd., "Review: Ranibizumab (Lucentis) In Neovascular Age-Related Macular Degeneration: Evidence From Clinical Trials" British J. Ophthalmology (December 2020), https://bjo.bmj.com/content/94/1/2.altmetrics	Herewith
	31	Bontempo, "Preformulation Development of Parenteral Biopharmaceuticals" Drugs and the Pharmaceutical Sciences 85:91-108 (1997)	Herewith
	32	Bressler, N. M. and G. Treatment of Age-Related Macular Degeneration with Photodynamic Therapy Study, "Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin: two-year results of 2 randomized clinical trials-tap report 2." Arch Ophthalmol 119(2): 198-207 (2001)	Herewith
	33	Brown & Regillo, "Anti-VEGF Agents in the Treatment of Neovascular Age-Related Macular Degeneration: Applying Clinical Trial Results to the Treatment of Everyday Patients" Am J. Ophthalmology 144: 627 (2007)	Herewith
	34	Chi *et al.*, "Physical Stability of Proteins in Aqueous Solution: Mechanism and Driving Forces in Nonnative Protein Aggregation" Pharmaceutical Research Vol. 20, No. 9, 1325-1336 (September 2003)	Herewith
	35	Ciulla & Rosenfeld, "Antivascular Endothelial Growth Factor Therapy For Neovascular Age-Related Macular Degeneration" Current Opinion Ophthalmology 20: 158 (2009)	Herewith
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	37	CMS, Local Coverage Determination (LCD) for Ranibizumab (Lucentis) (L29266, First Coast Service Options, Inc June 14, 2011)	Herewith
	38	Controls in SCI experiments, RegenBase. Retrieved January 6, 2021, from http://regenbase.org/control-groups.html	Herewith
	39	Department of Health and Human Services, Office of Inspector General, "Questionable Billing for Medicare Ophthalmology Services" September 2015 OEI-04-12-00280	Herewith
	40	Drug Vehicle (Code C927), National Cancer Institute (NCI). Retrieved January 6, 2021, from https://ncithesaurus.nci.nih.gov/ncitbrowser/ConceptReport.jsp?dictionary =NCI_Thesaurus&code=C927&ns=ncit	Herewith

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NON-PATENT LITERATURE DOCUMENTS			
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	41	EP 2 663 325 File History	Herewith
	42	Eylea® Prescribing Information, Revised 05/2019	Herewith
	43	Ferrara, N. & Kerbel, R., "Angiogenesis as a Therapeutic Target" Nature 438: 967 (2005)	Herewith
	44	Fraser *et al.*, "Single Injections of Vascular Endothelial Growth Factor Trap Block Ovulation in the Macaque and Produce a Prolonged, Dose-Related Suppression of Ovarian Function." J. Clin. Endocrinol & Metab. 90(2): 1114-1122 (February 2005)	Herewith
	45	Genentech, "FDA Approves Lucentis for the Treatment of Wet Age-Related Macular Degeneration," News Release dated June 30, 2006 (June 30, 2006)	Herewith
	46	Gupta, O. P., G. Shienbaum, A. H. Patel, C. Fecarotta, R. S. Kaiser and C. D. Regillo, "A treat and extend regimen using ranibizumab for neovascular age-related macular degeneration clinical and economic impact" Ophthalmology 117(11): 2134-2140 (2010)	Herewith
	47	Heier, "Intravitreal VEGF Trap for AMD: An Update" Retina Today 44 (October 2009)	Herewith
	48	Heier, J. S., P. A. Campochiaro, L. Yau, Z. Li, N. Saroj, R. G. Rubio and P. Lai "Ranibizumab for macular edema due to retinal vein occlusions: long-term follow-up in the HORIZON trial" Ophthalmology 119(4): 802-809 (2012)	Herewith
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	51	Ip, M. S., I. U. Scott, P. C. VanVeldhuisen, N. L. Oden, B. A. Blodi, M. Fisher, L. J. Singerman, M. Tolentino, C. K. Chan, V. H. Gonzalez and S. S. R. Group "A randomized trial comparing the efficacy and safety of intravitreal triamcinolone with observation to treat vision loss associated with macular edema secondary to central retinal vein occlusion: the Standard Care vs Corticosteroid for Retinal Vein Occlusion (SCORE) study report 5" Arch Ophthalmol 127(9): 1101-1114 (2009)	Herewith
	52	Janeway *et al.*, "The structure of a typical antibody molecule" Immunobiology: The Immune System in Health and Disease. 5th edition. New York: Garland Science (2001)	Herewith
	53	Keane *et al.*, "Effect of Ranibizumab Retreatment Frequency on Neurosensory Retinal Volume in Neovascular AMD" Retina 29: 592 (2009)	Herewith
	54	Kim *et al.*, "Potent VEGF Blockade Causes Regression of Coopted Vessels in a Model of Neuroblastoma" Proc. Nat'l Acad. Sci. 99: 11399 (2002)	Herewith
	55	LUCENTIS Approval (2006)	Herewith
	56	LUCENTIS® Label (14 pages)	Herewith
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	58	Macular Photocoagulation Study, G., "Laser photocoagulation of subfoveal neovascular lesions in age-related macular degeneration. Results of a randomized clinical trial. Macular Photocoagulation Study Group" Arch Ophthalmol 109(9): 1220-1231 (1991)	Herewith
	59	Massin, "Anti-VEGF Therapy for Diabetic Macular Edema: An Update" Retina Today 54 (Sept./Oct. 2008)	Herewith
	60	Michels, S., P. J. Rosenfeld, C. A. Puliafito, E. N. Marcus and A. S. Venkatraman, "Systemic bevacizumab (Avastin) therapy for neovascular age-related macular degeneration twelve-week results of an uncontrolled open-label clinical study" Ophthalmology 112(6): 1035-1047 (2005)	Herewith

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	62	Ni & Hui, "Emerging Pharmacologic Therapies for Wet Age-Related Macular Degeneration" Ophthalmologica 223: 401 (2009)	Herewith
	63	Parkins & Lashmar, "The formulation of biopharmaceutical products" Pharmaceutical Science & Technology Today Vol. 3, No. 4: 129-137 (April 4, 2000)	Herewith
	64	Phosphate buffer. Cold Spring Harbor Protocols 2006: pdb.rec8543 (2006)	Herewith
	65	Randolph & Jones, "Surfactant-Protein Interactions" Rational Design of Stable Protein Formulations pp. 159-175, Springer, Boston, MA (2002)	Herewith
	66	RAPTIVA® label	Herewith
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	68	Regeneron Pharmaceuticals Inc. Regeneron Reports Fourth Quarter and Full Year 2004 Financial and Operating Results. Media Release: 22 Feb 2005. Available from URL: http://www.regeneron.com	Herewith
	69	Regeneron Pharmaceuticals Inc. Regeneron Reports Fourth Quarter and Full Year 2005 Financial and Operating Results. Media Release: 24 Feb 2006. Available from URL: http://regeneron.com	Herewith
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	85	The Central Vein Occlusion Study, G., "Evaluation of grid pattern photocoagulation for macular edema in central vein occlusion. The Central Vein Occlusion Study Group M report" Ophthalmology 102(10): 1425-1433 (1995)	Herewith
	86	U.S. DEP'T HEALTH & HUMAN SERVS., NAT'L INST. HEALTH, NAT'L EYE INST., "Age-Related Macular Degeneration: What You Should Know" (Sept. 2015) https://www.nei.nih.gov/sites/default/files/healthpdfs/WYSK_AMD_English_Sept2015_PRINT.pdf	Herewith
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	90	Wall Street Journal, "Genentech's Big Drug for Eyes Faces a Rival" (2007)	Herewith
	91	Wulff *et al.,* "Prevention of Thecal Angiogenesis, Antral Follicular Growth, and Ovulation in the Primate by Treatment with Vascular Endothelial Growth Factor Trap R1R2" Endocrinology 143(7): 2797-2807 (July 2002)	Herewith
	92	XOLAIR® label	Herewith
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Electronic Acknowledgement Receipt

EFS ID:	43207807
Application Number:	17112404
International Application Number:	
Confirmation Number:	6437
Title of Invention:	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS
First Named Inventor/Applicant Name:	George YANCOPOULOS
Customer Number:	96387
Filer:	Karl Bozicevic/Kimberly Zuehlke
Filer Authorized By:	Karl Bozicevic
Attorney Docket Number:	REGN-008CIPCON8
Receipt Date:	09-JUL-2021
Filing Date:	04-DEC-2020
Time Stamp:	11:30:41
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	REGN-008CIPCON8_2021-07-09_SuppIDS_Trans.pdf	53568 49003d1460aa22a0828f0d8ea4e7c81bec2c7969	no	3

Warnings:

Information:					
2	Information Disclosure Statement (IDS) Form (SB08)	Substitute_1449_17112404_2021-07-09_REGN-008CIPCON8.pdf	78557 62ef8fa057728e8d40897fb454c73c132de81e97	no	8
Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
			Total Files Size (in bytes):	132125	

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

New Applications Under 35 U.S.C. 111

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

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

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

New International Application Filed with the USPTO as a Receiving Office

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

Electronically Filed 7/9/2021

INFORMATION DISCLOSURE STATEMENT	Attorney Docket No.	REGN-008CIPCON8
	Confirmation No.	6437
	First Named Inventor	George D. Yancopoulos
	Application Number	17/112,404
	Filing Date	December 4, 2020
	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:

Applicant submits 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 publications discussed herein are provided to comply with the duty to disclose in accordance with 37 C.F.R. § 1.56. However, nothing herein is to be construed as an admission that the present invention is not entitled to antedate such publication by virtue of prior invention. Further, the dates of publication provided may be different from the actual publication dates which may need to be independently confirmed.

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 17/072,417, 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-008CIPCON8.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: July 9, 2021

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

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

INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	17/112,404
				Filing Date	2020-12-04
				First Named Inventor	George D. YANCOPOULOS
				Art Unit	To Be Assigned
				Examiner Name	To Be Assigned
Sheet	1	of	2	Attorney Docket Number	REGN-008CIPCON8

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

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

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

	NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.		T
	1	Eylea®, Highlights of Prescribing Information, Revised 11/2011		
	2	IPR2021-00880, Paper 1, Petition for IPR (May 5, 2021)		
	3	IPR2021-00880, Exhibit 1002, Albini Declaration (May 4, 2021)		
	4	IPR2021-00880, Exhibit 1003, Gerritsen Declaration (April 30, 2021)		
	5	IPR2021-00880, Paper 10, Preliminary Response of Patent Owner (August 16, 2021)		
	6	IPR2021-00881, Paper 1, Petition for IPR (May 5, 2021)		
	7	IPR2021-00881, Exhibit 1002, Albini Declaration (May 4, 2021)		
	8	IPR2021-00881, Exhibit 1003, Gerritsen Declaration (April 26, 2021)		
	9	IPR2021-00881, Paper 10, Preliminary Response of Patent Owner (August 16, 2021)		
	10	IPR2021-00881, Exhibit 2001, Do Declaration (August 13, 2021)		
	11	Mitchell *et al.*, "Evaluating the Impact of Intravitreal Aflibercept on Diabetic Retinopathy Progression in the VIVID-DME and VISTA-DME Studies" Ophthalmol Retina 2(10):988-96 (2018)		
	12	PGR2021-00035, Paper 2, Petition for PGR (January 7, 2021)		
	13	PGR2021-00035, Paper 6, Preliminary Response of Patent Owner (April 15, 2021)		
	14	PGR2021-00035, Exhibit 1003 Wu Declaration (January 7, 2021)		
	15	PGR2021-00035, Exhibit 2001 Do Declaration (April 14, 2021)		
	16	PGR2021-00035, Exhibit 2002 D. Brown Declaration (April 14, 2021)		
	17	CAO, J. R., R.; Wang, Q.; Yancopoulos, G.D.; Wiegand, S.J. (2002). Inhibition of Corneal Neovascularization and Inflammation by VEGF Trap. In "ARVO", Invest. Ophthalmol. Vis. Sci. Vol. 43. E-Abstract 1863		

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	17/112,404
				Filing Date	2020-12-04
				First Named Inventor	George D. YANCOPOULOS
				Art Unit	To Be Assigned
				Examiner Name	To Be Assigned
Sheet	2	of	2	Attorney Docket Number	REGN-008CIPCON8

	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
	18	WANG, Q. R., R.; Cao, J.; Yancopoulos, G.D.; and Wiegand, S.J. (2002). Anti-Angiogenic Properties of a New VEGF Antagonist, VEGF Trap, in a Mouse Model of Retinal Neovascularization. In "ARVO", Invest. Ophthalmol. Vis. Sci., Vol. 43. E-Abstract. 3714		
	19	SAISHIN, Y., Saishin, Y., Takahashi, K., Lima e Silva, R., *et al.* (2003). VEGF-TRAP(R1R2) suppresses choroidal neovascularization and VEGF-induced breakdown of the blood-retinal barrier. J Cell Physiol 195:241-48		
	20	CURSIEFEN, C., Cao, J., Chen, L., Liu, Y., Maruyama, K., *et al.* (2004). Inhibition of hemangiogenesis and lymphangiogenesis after normal-risk corneal transplantation by neutralizing VEGF promotes graft survival. Invest Ophthalmol Vis Sci 45(8):2666-73		
	21	CURSIEFEN, C., Chen, L., Borges, L. P., Jackson, D., Cao, J., *et al.* (2004). VEGF-A stimulates lymphangiogenesis and hemangiogenesis in inflammatory neovascularization via macrophage recruitment. J Clin Invest 113(7):1040-50		
	22	CAO, J.; Song, H.; Renard, R.A.; Liu, Y.; Yancopolous, G.D.; Wiegand, S.J. (2005). Systemic Administration of VEGF Trap Suppresses Vascular Leak and Leukostasis in the Retinas of Diabetic Rats. In "ARVO", Vol. 46. Invest. Ophthalmol. Vis. Sci. E-Abstract 446		
	23	NORK, T. M., Dubielzig, R. R., Christian, B. J., Miller, P. E., Miller, J. M., *et al.* (2011). Prevention of experimental choroidal neovascularization and resolution of active lesions by VEGF trap in nonhuman primates. Arch Ophthalmol 129(8):1042-52		

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:	43680069
Application Number:	17112404
International Application Number:	
Confirmation Number:	6437
Title of Invention:	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS
First Named Inventor/Applicant Name:	George YANCOPOULOS
Customer Number:	96387
Filer:	Karl Bozicevic/Kimberly Zuehlke
Filer Authorized By:	Karl Bozicevic
Attorney Docket Number:	REGN-008CIPCON8
Receipt Date:	03-SEP-2021
Filing Date:	04-DEC-2020
Time Stamp:	11:12:30
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-008CIPCON8_2021-09-03_SuppIDS_Trans.pdf	51621 77b3c91766010dc2ffc03b119f98b2d106053e82	no	2

Warnings:

Information:					
2	Information Disclosure Statement (IDS) Form (SB08)	REGN-008CIPCON8_2021-09-03_SuppIDS_SB08A.pdf	36153 015fbce2447be0e6d1f96efcb82dfca2843ba6f1	no	2
Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
3	Non Patent Literature	125387lbl-20111118.pdf	793050 5c03734e77f1148b0d55d3ab6349462c3e7a5b62	no	15
Warnings:					
Information:					
4	Non Patent Literature	Cao_2002.pdf	36299 e693fe75b60971f6ca8e1d8e35b729fc75be93b8	no	2
Warnings:					
Information:					
5	Non Patent Literature	Cao_2005.pdf	43551 eb7955ce21b031deb532a5f38d0a738efc0b1925	no	2
Warnings:					
Information:					
6	Non Patent Literature	Cursiefen_2004_Inhibition_of_hema.pdf	1178915 c20e10253dcf5992806ef217c653c91af9a56cfd	no	8
Warnings:					
Information:					
7	Non Patent Literature	Cursiefen_2004_VEGF-A_stimulates_lymphangiogenesis.pdf	4515931 d5cb6606895155d33ba1c3d3c5de79049047e84c	no	12
Warnings:					
Information:					
8	Non Patent Literature	IPR2021-00880-2021-05-05_01_Petition_for_Review_of_US9669069_880.pdf	1454636 3eb7d60c61a299ac49257bbaa2f37a6efb840229	no	91
Warnings:					
Information:					

9	Non Patent Literature	IPR2021-00880-2021-08-16_10_POPR_Mylan_069_Patent.pdf	767215 62b60957cb794ccdcc7ab77457f5d4c185c699af	no	70
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Information:					
10	Non Patent Literature	IPR2021-00880-Ex_1002_Albini_Decl_880.pdf	1100357 4c924cf26f34134fb38f62959de15dc3aff6a641	no	119
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Information:					
11	Non Patent Literature	IPR2021-00880-Ex_1003_Gerritsen_Decl_880.pdf	6081340 ae519137a3b230b16a8818485f1e3c6284ce8a00	no	59
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12	Non Patent Literature	IPR2021-00881-2021-05-05_01_Petition_for_IPR_of_9254338_881.pdf	1239630 6977365612a1c5c91994d47caf135b1152338c64	no	89
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13	Non Patent Literature	IPR2021-00881-2021-08-16_10_POPR_Mylan_338_Patent.pdf	801029 3c8b306e28ac79c6dc86d9d327013014abfa8136	no	76
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Information:					
14	Non Patent Literature	IPR2021-00881-Ex_1002_Albini_Decl_881.pdf	23233259 309bc9a75b5ef775299bfa0ff7de17df378af1a3	no	152
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Information:					
15	Non Patent Literature	IPR2021-00881-Ex_1003_Gerritsen_Decl_881.pdf	5491742 61cd4ed4ce04aa2bf5a9e9147c0ffeee6a69585d	no	53
Warnings:					
Information:					

16	Non Patent Literature	IPR2021-00881-Ex2001_Do_Declaration.pdf	306073 9f39940c757a122c755015fb7978e3caf54af627	no	19
Warnings:					
Information:					
17	Non Patent Literature	Mitchell_2018.pdf	6781952 dbf07aca9b56716a91c66dedab29d1b8e2b03cde	no	9
Warnings:					
Information:					
18	Non Patent Literature	Nork_2011.pdf	2073112 0422baa35069c8a843f2285a00830fdd74646fe9	no	11
Warnings:					
Information:					
19	Non Patent Literature	PGR2021-00035-2021-01-07_02_Petition_for_PGR_of_US10828345.pdf	2787300 723df9b9c0e3571dc24ad99e395633fee94380c5	no	92
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Information:					
20	Non Patent Literature	PGR2021-00035-2021-04-15_06_POPR.pdf	726423 3e0210cd63d3078dd2aa8dfc142c599d4e8222b6	no	96
Warnings:					
Information:					
21	Non Patent Literature	PGR2021-00035-Ex_1003_Wu_Declaration.pdf	2852812 674123a21173ad450aac4a919ea02c7fdc99587d	no	81
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Information:					
22	Non Patent Literature	PGR2021-00035-Ex_2001_Do_Declaration.pdf	389537 aa9eefe29251b69326733d5b6e23289687d9eddd	no	35
Warnings:					
Information:					

23	Non Patent Literature	PGR2021-00035-Ex_2002_D_Brown_Declaration.pdf	2704458 ffb2b452babea1bd305e93c4d4257b7124a4c2dd	no	22
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Information:					
24	Non Patent Literature	Saishin_2003.pdf	582298 2194d1ea1d4df56a20264398ec00939c017df130	no	8
Warnings:					
Information:					
25	Non Patent Literature	Wang_2002.pdf	41117 ba3f92115f8ff1f74d748cf92929101bf40fc9bc	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	66069810	

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

New Applications Under 35 U.S.C. 111

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

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

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

New International Application Filed with the USPTO as a Receiving Office

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

Electronically Filed

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT	Attorney Docket No.	REGN-008CIPCON8
	Confirmation No.	6437
	First Named Inventor	George D. Yancopoulos
	Application Number	17/112,404
	Filing Date	December 4, 2020
	Group Art Unit	To Be Assigned
Address to: Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Examiner Name	To Be Assigned
	Title: "*Use of a VEGF Antagonist to Treat Angiogenic Eye Disorders*"	

Sir:

Applicant submits 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 publications discussed herein are provided to comply with the duty to disclose in accordance with 37 C.F.R. § 1.56. However, nothing herein is to be construed as an admission that the present invention is not entitled to antedate such publication by virtue of prior invention. Further, the dates of publication provided may be different from the actual publication dates which may need to be independently confirmed.

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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☐ **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-008CIPCON8.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: 3 September 2021

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

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

SUBSTITUTE 1449 INFORMATION DISCLOSURE STATEMENT	ATTY. DOCKET NO.	APPLICATION NO.
	REGN-008CIPCON8	17/112,404
	APPLICANT	
	REGENERON PHARMACEUTICALS, INC.	
	FILING DATE	GROUP
	December 4, 2020	To be assigned

U.S. PATENT DOCUMENTS					
		DOCUMENT NUMBER	DATE	NAME	REFERENCE PROVIDED*
	1.	US 2004/0213787 A1	2004-10-28	Sleeman *et al.*	not required per 69 Fed. Reg. 56481
	2.	US 6,833,349 B2	2004-12-21	Xia *et al.*	not required per 69 Fed. Reg. 56481
	3.	US 2004/0266688 A1	2004-12-30	Nayak	not required per 69 Fed. Reg. 56481
	4.	US 2005/0032699 A1	2005-02-10	Holash *et al.*	not required per 69 Fed. Reg. 56481
	5.	US 6,879,294 B2	2005-05-24	Davis-Smyth *et al.*	not required per 69 Fed. Reg. 56481
	6.	US 2005/0281822 A1	2005-12-22	Cedarbaum *et al.*	not required per 69 Fed. Reg. 56481
	7.	US 2006/0030000 A1	2006-02-09	Alitalo *et al.*	not required per 69 Fed. Reg. 56481
	8.	US 7,378,095 B2	2008-05-27	Cao *et al.*	not required per 69 Fed. Reg. 56481
	9.	US 7,482,002 B2	2009-01-27	Cedarbaum	not required per 69 Fed. Reg. 56481
	10.	US 2009/0264358 A1	2009-10-22	Yu	not required per 69 Fed. Reg. 56481
	11.	US 7,750,138 B2	2010-07-06	Fang *et al.*	not required per 69 Fed. Reg. 56481
	12.	US 7,951,585 B2	2011-05-31	Ke	not required per 69 Fed. Reg. 56481
	13.	US 8,216,575 B2	2012-07-10	Yu	not required per 69 Fed. Reg. 56481
	14.	US 2013/0295094 A1	2013-11-07	Yancopoulos	not required per 69 Fed. Reg. 56481
	15.	US 9,657,084 B2	2017-05-23	Ke *et al.*	not required per 69 Fed. Reg. 56481

FOREIGN PATENT DOCUMENTS						
		DOCUMENT NUMBER	DATE	COUNTRY	TRANSLATION	REFERENCE PROVIDED*
	16.	CN 1304427C	2007-03-14	China	Machine translation	Previously in US Application 17/072,417
	17.	CN 100502945C	2009-06-24	China	Corresponds to US 2009/0264358 A1	Previously in US Application 17/072,417
	18.	CN 100567325C	2009-12-09	China	Machine translation	Previously in US Application 17/072,417
	19.	WO 2012/097019	2012-07-19	WIPO	N/A	Previously in US Application 17/072,417
	20.	CN 102233132 B	2013-10-23	China	Machine translation	Previously in US Application 17/072,417

EXAMINER	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.

*Copies of the listed references are either submitted herewith or were previously cited by or submitted to, the Office in a prior application. Pursuant to 37 C.F.R. § 1.97(d) and MPEP §609, the indicated reference may have been previously cited by or submitted to, the Office in a prior application, where the prior application is identified by its U.S. Application Number in this Information Disclosure Statement.

SUBSTITUTE 1449 INFORMATION DISCLOSURE STATEMENT	ATTY. DOCKET NO.	APPLICATION NO.
	REGN-008CIPCON8	17/112,404
	APPLICANT	
	REGENERON PHARMACEUTICALS, INC.	
	FILING DATE	GROUP
	December 4, 2020	To be assigned

FOREIGN PATENT DOCUMENTS						
		DOCUMENT NUMBER	DATE	COUNTRY	TRANSLATION	REFERENCE PROVIDED*
	21.	CN 102380096 B	2014-04-30	China	Machine translation	Previously in US Application 17/072,417
	22.	CN 103212075 B	2017-06-27	China	Machine translation	Previously in US Application 17/072,417
	23.	CN 107115294 A	2017-09-01	China	Machine translation	Previously in US Application 17/072,417

NON-PATENT LITERATURE DOCUMENTS			
		DOCUMENT (Including Author, Title, Date, Pertinent Pages, etc.)	REFERENCE PROVIDED*
	24.	Anonymous, Meeting Archive Titled "PA003 Eighteen-Month Results From an Extension Study of a Phase 2, Dose- and Interval-Ranging Study of VEGF Trap-Eye in Wet AMD," presented by David S Boyer, MD at Moscone Center (October 2009)	Previously in US Application 17/072,417
	25.	Anonymous, Meeting Archive Titled "PA040 One-Year Results of the DA VINCI Study of VEGF Trap-Eye in Diabetic Macular Edema," presented by Diana V Do, MD at Orange County Convention Center (October 2011)	Previously in US Application 17/072,417
	26.	Anonymous, Meeting Archive Titled "PA080 One-Year Results of a Phase 2 Study of Intravitreal VEGF Trap-Eye in Patients with Neovascular Age-Related Macular Degeneration," presented by David S Boyer, MD at Georgia World Congress Center (November 2008)	Previously in US Application 17/072,417
	27.	Anonymous, Meeting Archive Titled "PO259 OCT and Fluorescein Angiography Outcomes Through 1 Year for a Phase 2 Study of Intravitreal VEGF Trap-Eye in Neovascular AMD," presented by Peter K Kaiser, MD at Moscone Center (October 2009)	Previously in US Application 17/072,417
	28.	Anonymous, Meeting Archive Titled "PO260 VEGF Trap-Eye Vision-Specific Quality of Life Through 52 Weeks in Patients with Neovascular AMD in CLEAR-IT 2: A Phase 2 Clinical Trial," presented by Allen C Ho, MD at Moscone Center (October 2009)	Previously in US Application 17/072,417
	29.	Anonymous, Meeting Archive Titled "PO492 One-Year Results of the VIEW 1 and VIEW 2 Studies: VEGF Trap-Eye in Wet AMD," presented by David M Brown MD at Orange County Center (October 2011)	Previously in US Application 17/072,417
	30.	Anonymous, Meeting Archive Titled "PO549 The 6-Month (Primary Endpoint) Results of the Phase 3 GALILEO Study: VEGF Trap-Eye in Central Retinal Vein Occlusion," presented by Jean-Francois Korobelnik, MD at Orange County Convention Center (October 2011)	Previously in US Application 17/072,417

EXAMINER	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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SUBSTITUTE 1449 INFORMATION DISCLOSURE STATEMENT	ATTY. DOCKET NO.	APPLICATION NO.
	REGN-008CIPCON8	17/112,404
	APPLICANT	
	REGENERON PHARMACEUTICALS, INC.	
	FILING DATE	GROUP
	December 4, 2020	To be assigned

NON-PATENT LITERATURE DOCUMENTS			
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	32.	Bontempo, "Preformulation Development of Parenteral Biopharmaceuticals," *Drugs and the Pharmaceutical Sciences*, 85:91-108 (1997)	Previously in US Application 17/072,417
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	37.	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>	Previously in US Application 17/072,417
	38.	Center for Drug Evaluation and Research BLA Application Number: 125156 Medical Review, (June 2006) <URL:https://www.accessdata.fda.gov/drugsatfda_docs/nda/2006/125156s0000_Lucentis_MedR.pdf>	Previously in US Application 17/072,417
	39.	Cheung *et al.*, "Combined anti-PIGF and anti-VEGF Therapy Ameliorates Pathological Neovascularization and Improves Retinal Revascularization in the Murine Model of Oxygen Induced Ischemic Retinopathy," ARVO Annual Meeting Abstract, *Investigative Ophthalmology & Visual Science*, 52:6064 (April 2011)	Previously in US Application 17/072,417
	40.	Dixon *et al.*, "VEGF Trap-Eye for the treatment of neovascular age-related macular degeneration," *Expert Opin. Investig. Drugs*, 18(10):1573-1580 (2009)	Previously in US Application 17/072,417

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	47.	Kaiser, "Vascular endothelial growth factor Trap-Eye for diabetic macular oedema," *Br. J. Ophthalmol.*, 93(2):135-36 (February 2009)	Previously in US Application 17/072,417
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	50.	Lalwani, "All About PrONTO: Study Yielded Good Results in AMD With Treatment Guided by OCT," *Retina Today* (May 2007)	Previously in US Application 17/072,417
	51.	Lobov *et al.*, "VEGF Trap Treatment Regresses Pathological Neovessels, Improves Revascularization and Reduces Retinal Ischemia in the Murine Oxygen-Induced Retinopathy (OIR) Model," ARVO Annual Meeting Abstract, *Investigative Ophthalmology & Visual Science*, 52:3128 (April 2011)	Previously in US Application 17/072,417
	52.	Lucentis Approval (June 30, 2006)	Previously in US Application 17/072,417
	53.	Lucentis Label Title, 7 pages, 06/2010 [Cited in Third Party Observations filed in parent application USSN 16/055,847 for which a copy is unavailable on PAIR]	Previously in US Application 17/072,417
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	62.	Regeneron Pharmaceuticals Inc., "Optical Coherence Tomography Outcomes of a Phase 1, Dose-Escalation, Safety, Tolerability, and Bioactivity Study of Intravitreal VEGF Trap in Patients with Neovascular Age-Related Macular Degeneration: The CLEAR-IT 1 Study," poster presented at the 2007 Association for Research in Vision and Ophthalmology meeting in Ft. Lauderdale, Florida (May 2007)	Previously in US Application 17/072,417
	63.	Regeneron Pharmaceuticals Inc., "Regeneron Reports First Quarter 2008 Financial and Operating Results," Press release May 1, 2008.	Previously in US Application 17/072,417
	64.	Regeneron Pharmaceuticals Inc., Form 10-Q, published November 7, 2007, for the period ending September 30, 2007.	Previously in US Application 17/072,417

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	66.	Rosenfeld *et al.*, "Optical coherence tomography findings after an intravitreal injection of bevacizumab (avastin) for neovascular age-related macular degeneration," *Ophthalmic. Surg. Lasers Imaging*, 36(4):331-335 (2005)	Previously in US Application 17/072,417
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	68.	Simo and Hernandez, "Advances in Medical Treatment of Diabetic Retinopathy," *Diabetes Care*, 32(8):1556-1562 (August 2009)	Previously in US Application 17/072,417
	69.	Slides for the 2008 Retina Society Meeting "VEGF Trap-Eye in Wet AMD CLEAR-IT 2: Summary of One-Year Key Results," September 28, 2008.	Previously in US Application 17/072,417
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	73.	IPR2021-00880 dated November 10, 2021, for US 9,669,069 B2	Previously in US Application 17/072,417
	74.	IPR2021-00881 dated November 10, 2021, for US 9,254,338 B2	Previously in US Application 17/072,417

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	86.	Bashshur *et al.*, "Intravitreal Bevacizumab for the Management of Choroidal Neovascularization in Age-Related Macular Degeneration," *Am. J. Ophthalmology*, 142(1):1-9 (2006)	Previously in US Application 17/072,417
	87.	Bayer Press Release, "Bayer and Regeneron Dose First Patient in Second Phase 3 Study for VEGF Trap-Eye in Wet Age-Related Macular Degeneration," May 8, 2008	Previously in US Application 17/072,417
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	100.	Eylea Prescribing Information, Revised 05/2019	Previously in US Application 17/072,417
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	104.	Gupta, O. P., G. Shienbaum, A. H. Patel, C. Fecarotta, R. S. Kaiser and C. D. Regillo, "A treat and extend regimen using ranibizumab for neovascular age-related macular degeneration clinical and economic impact," *Ophthalmology*, 117(11): 2134-2140 (2010)	Previously in US Application 17/072,417
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	108.	Information from ClinicalTrials.gov archive on the VIEW 1 study (NCT00509795) "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Wet Age-Related Macular Degeneration (AMD) (VIEW1)," changes from v8 (March 3, 2009) to v9 (April 28, 2009)	Previously in US Application 17/072,417
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	114.	Massin, "Anti-VEGF Therapy for Diabetic Macular Edema: An Update," Retina Today 54 (Sept./Oct. 2008)	Previously in US Application 17/072,417
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	116.	Ni & Hui, "Emerging Pharmacologic Therapies for Wet Age-Related Macular Degeneration," *Ophthalmologica*, 223:401-410 (Published Online First 20 May 2009)	Previously in US Application 17/072,417
	117.	Parkins & Lashmar, "The formulation of biopharmaceutical products," *Pharmaceutical Science & Technology Today*, 3(4):129-137 (April 4, 2000)	Previously in US Application 17/072,417

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	120.	Raptiva Label (Final Labelling 03-13-2009)	Previously in US Application 17/072,417
	121.	Regeneron Pharmaceuticals Inc., Regeneron Reports Fourth Quarter and Full Year 2004 Financial and Operating Results. Media Release: 22 Feb 2005.	Previously in US Application 17/072,417
	122.	Regeneron Pharmaceuticals Inc., Regeneron Reports Fourth Quarter and Full Year 2005 Financial and Operating Results. Media Release: 24 Feb 2006.	Previously in US Application 17/072,417
	123.	Regeneron Pharmaceuticals Inc., Regeneron Reports Positive Phase 1 Data for the VEGF Trap in Age-Related Macular Degeneration; Preliminary Results Show Improvements in Vision and Reginal Swelling; VEGF Trap Was Well Tolerated at All Dose Levels. Media Release: 1 May 2006.	Previously in US Application 17/072,417
	124.	Regeneron SEC Form 10-Q (September 30, 2009)	Previously in US Application 17/072,417
	125.	Reichert, "Antibody-Based Therapeutics To Watch In 2011," *MABS*, 3(1):76-99 (2011)	Previously in US Application 17/072,417
	126.	Remicade Label (Revised November 2013)	Previously in US Application 17/072,417
	127.	Retina Coding Q & A, Retinal Physician, 16: 18, 54 (July/August 2019)	Previously in US Application 17/072,417
	128.	Rogers *et al.*, "The prevalence of retinal vein occlusion: pooled data from population studies from the United States, Europe, Asia, and Australia," *Ophthalmology*, 117(2):313-319e1 (2010)	Previously in US Application 17/072,417
	129.	Rudge *et al.*, "VEGF Trap as a Novel Antiangiogenic Treatment Currently in Clinical Trials for Cancer and Eye Diseases, and VelociGene-based Discovery of the Next Generation of Angiogenesis Targets," *Cold Spring Harbor Symposia on Quantitative Biology*, 70:411-418 (2005)	Previously in US Application 17/072,417
	130.	Schmidt-Erfurth, "Current Concepts in the Management of Diabetic Macular Edema," *Johns Hopkins Advanced Studies in Ophthalmology*, 7(2):52-59 (2010)	Previously in US Application 17/072,417
	131.	Simulect Label (May 1998)	Previously in US Application 17/072,417
	132.	Spaide *et al.*, "Prospective Study of Intravitreal Ranibizumab as a Treatment for Decreased Visual Acuity Secondary to Central Retinal Vein Occlusion," *Am. J. Ophthalmology*, 147(2):298-306 (2009)	Previously in US Application 17/072,417
	133.	Spielberg, L. & Leys, A., "Intravitreal Bevacizumab for Myopic Choroidal Neovascularization: Short-Term and 1-Year Results," *Bulletin Societe Belge D'Ophtalmologie*, 312:17-27 (2009)	Previously in US Application 17/072,417

EXAMINER	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.

*Copies of the listed references are either submitted herewith or were previously cited by or submitted to, the Office in a prior application. Pursuant to 37 C.F.R. § 1.97(d) and MPEP §609, the indicated reference may have been previously cited by or submitted to, the Office in a prior application, where the prior application is identified by its U.S. Application Number in this Information Disclosure Statement.

SUBSTITUTE 1449 INFORMATION DISCLOSURE STATEMENT	ATTY. DOCKET NO.	APPLICATION NO.
	REGN-008CIPCON8	17/112,404
	APPLICANT	
	REGENERON PHARMACEUTICALS, INC.	
	FILING DATE	GROUP
	December 4, 2020	To be assigned

NON-PATENT LITERATURE DOCUMENTS - UPDATES TO PREVIOUS IDS CITATIONS			
		DOCUMENT (Including Author, Title, Date, Pertinent Pages, etc.)	REFERENCE PROVIDED*
	134.	Steinbrook, "The Price of Sight — Ranibizumab, Bevacizumab, and the Treatment of Macular Degeneration," *N. Eng. J. Med.*, 355(14):1409-1412 (2006)	Previously in US Application 17/072,417
	135.	The Branch Vein Occlusion Study, G., "Argon laser photocoagulation for macular edema in branch vein occlusion," *Am. J. Ophthalmology*, 98(3):271-282 (1984)	Previously in US Application 17/072,417
	136.	The Central Vein Occlusion Study, G., "Evaluation of grid pattern photocoagulation for macular edema in central vein occlusion. The Central Vein Occlusion Study Group M report," *Ophthalmology*, 102(10):1425-1433 (1995)	Previously in US Application 17/072,417
	137.	U.S. Department of Health and Human Services, Food and Drug Administration, "Guidance for industry Q1A(R2) stability testing of new drug substances and products," Rockville, MD (November 2003)	Previously in US Application 17/072,417
	138.	U.S. Department of Health and Human Services, National Institute of Health, National Eye Institute, "Age-Related Macular Degeneration: What You Should Know," (Sept. 2015) https://www.nei.nih.gov/sites/default/files/healthpdfs/WYSK_AMD_English_Sept2015_PRINT.pdf	Previously in US Application 17/072,417
	139.	U.S. Department of Health and Human Services, National Institute of Health, National Eye Institute, "Diabetic Retinopathy: What You Should Know," (Sept. 2015) https://www.nei.nih.gov/sites/default/files/2019-06/Diabetic-Retinopathy-What-You-Should-Know-508.pdf	Previously in US Application 17/072,417
	140.	U.S. Department of Health and Human Services, Office of Inspector General, "Questionable Billing for Medicare Ophthalmology Services" September 2015 OEI-04-12-00280	Previously in US Application 17/072,417
	141.	Wall Street Journal, "Genentech's Big Drug for Eyes Faces a Rival" (2007)	Previously in US Application 17/072,417
	142.	Wulff *et al.*, "Prevention of Thecal Angiogenesis, Antral Follicular Growth, and Ovulation in the Primate by Treatment with Vascular Endothelial Growth Factor Trap R1R2" Endocrinology 143(7): 2797-2807 (July 2002)	Previously in US Application 17/072,417
	143.	Xolair Label (2003)	Previously in US Application 17/072,417
	144.	Zarbin & Rosenfeld, "Pathway-Based Therapies for Age-Related Macular Degeneration: An Integrated Survey of Emerging Treatment Alternatives" Retina 30: 1350 (2010)	Previously in US Application 17/072,417

EXAMINER	DATE CONSIDERED

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Electronic Acknowledgement Receipt

EFS ID:	44366424
Application Number:	17112404
International Application Number:	
Confirmation Number:	6437
Title of Invention:	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS
First Named Inventor/Applicant Name:	George YANCOPOULOS
Customer Number:	96387
Filer:	Karl Bozicevic/Kimberly Zuehlke
Filer Authorized By:	Karl Bozicevic
Attorney Docket Number:	REGN-008CIPCON8
Receipt Date:	24-NOV-2021
Filing Date:	04-DEC-2020
Time Stamp:	14:49:27
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-008CIPCON8_2021-11-24_SuppIDS_Trans.pdf	53506 2165c114c7c840fc9a45a62ca47ca8e116025324	no	3

Warnings:

Information:					
2	Information Disclosure Statement (IDS) Form (SB08)	REGN-008CIPCON8_2021-11-24_SupplDS_1449.pdf	127069 aab13c7d82bde29e690cec51831680d2295235c0	no	12
Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
			Total Files Size (in bytes):	180575	

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

New Applications Under 35 U.S.C. 111

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

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

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

New International Application Filed with the USPTO as a Receiving Office

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

Electronically Filed

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT	Attorney Docket No.	REGN-008CIPCON8
	Confirmation No.	6437
	First Named Inventor	George D. Yancopoulos
	Application Number	17/112,404
	Filing Date	December 4, 2020
	Group Art Unit	To Be Assigned
Address to: Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Examiner Name	To Be Assigned
	Title: "*Use of a VEGF Antagonist to Treat Angiogenic Eye Disorders*"	

Sir:

The attention of the Examiner is invited to the documents listed on the attached Substitute 1449.

Copies of the U.S. patents and published applications listed on the attached Substitute 1449 are not submitted herewith, in accordance with the Strategic Plan Final Rule, 69 Fed. Reg. 56481-56547 (September 21, 2004), effective October 21, 2004.

Copies of the foreign publications and non-patent literature documents listed on the attached Substitute 1449 are submitted in parent U.S. Application No. 17/072,417. Applicant respectfully submits that a subset of references submitted herein were previously submitted in this or a priority application. Nonetheless, Applicant is submitting these previously submitted references to provide an accurate reference citation or to provide a clearer copy of the reference.

Applicant notes that the substitute 1449 accompanying the Information Disclosure Statement submitted for this application on July 9, 2021, inadvertently provided in the "Reference Provided" box that each of the Foreign Patent Documents and Non-Patent Literature Documents were "[h]erewith." Accordingly, the citations previously submitted in the July 9, 2021 Information Disclosure Statement are resubmitted here as Ref. Nos. 75 to 143 in order to clarify the record. Applicant notes that this group of resubmitted citations accounts for part of the citations provided herein.

Applicant would also like to bring to the Examiner's attention that the PTAB has instituted *inter partes* reviews for related U.S. Patent Nos. 9,254,338 and 9,669,069.

It is respectfully requested that the information above be expressly considered during the prosecution of this application, and that the documents be made of record therein and appear among the "References Cited" on any patent to issue therefrom.

No aspect of these submissions constitute admission of prior art status or a disclaimer of claim scope.

Statements

☒ **No statement.** Because this Information Disclosure Statement is being submitted prior to issuance of the first action on the merits of the above-captioned application, no certification or fee is required.

☐ **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-008CIPCON8.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: 24 November 2021

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

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

INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	17/112,404
				Filing Date	December 4, 2020
				First Named Inventor	George D. YANCOPOULOS
				Art Unit	To Be Assigned
				Examiner Name	To Be Assigned
Sheet	1	of	1	Attorney Docket Number	REGN-008CIPCON8

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	6897294	2005-05-24	Davis-Smyth 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				

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

	NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.		T
	1			

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:	44539997
Application Number:	17112404
International Application Number:	
Confirmation Number:	6437
Title of Invention:	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS
First Named Inventor/Applicant Name:	George YANCOPOULOS
Customer Number:	96387
Filer:	Karl Bozicevic/Kimberly Zuehlke
Filer Authorized By:	Karl Bozicevic
Attorney Docket Number:	REGN-008CIPCON8
Receipt Date:	16-DEC-2021
Filing Date:	04-DEC-2020
Time Stamp:	17:19:15
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	REGN-008CIPCON8_2021-12-16_SuppIDS_Trans.pdf	51465 e59d20d2072413618bffb78cf72a53c377e86f89	no	2

Warnings:

Information:					
2	Information Disclosure Statement (IDS) Form (SB08)	REGN-008CIPCON8_2021-12-16_SuppIDS_SB08A.pdf	22107 5513d80fd6c22504463d26bab94490854fb15f86	no	1

Warnings:
Information:
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Total Files Size (in bytes):	73572

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

New Applications Under 35 U.S.C. 111

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

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

New International Application Filed with the USPTO as a Receiving Office

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Electronically Filed

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT		
	Attorney Docket No.	REGN-008CIPCON8
	Confirmation No.	6437
	First Named Inventor	George D. Yancopoulos
	Application Number	17/112,404
	Filing Date	December 4, 2020
	Group Art Unit	To Be Assigned
	Examiner Name	To Be Assigned
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:

Applicant submits 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 publications discussed herein are provided to comply with the duty to disclose in accordance with 37 C.F.R. § 1.56. However, nothing herein is to be construed as an admission that the present invention is not entitled to antedate such publication by virtue of prior invention. Further, the dates of publication provided may be different from the actual publication dates which may need to be independently confirmed

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-008CIPCON8.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: 16 December 2021

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

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

SUBSTITUTE 1449 INFORMATION DISCLOSURE STATEMENT	ATTY. DOCKET NO.	APPLICATION NO.
	REGN-008CIPCON8	17/112,404
	APPLICANT	
	REGENERON PHARMACEUTICALS, INC.	
	FILING DATE	GROUP
	December 4, 2020	To be assigned

U.S. PATENT DOCUMENTS					
		DOCUMENT NUMBER	DATE	NAME	REFERENCE PROVIDED*
	1.	US 7,300,563 B2	2007-11-27	Diaddario, Jr.	not required per 69 Fed. Reg. 56481
	2.	US 7,300,653 B2	2007-11-27	Wiegand *et al.*	not required per 69 Fed. Reg. 56481
	3.	US 7,608,261 B2	2009-10-27	Furfine *et al.*	not required per 69 Fed. Reg. 56481
	4.	US 2010/0160,233 A1	2010-06-24	Bissery *et al.*	not required per 69 Fed. Reg. 56481
	5.	US 7,972,598 B2	2011-07-05	Daly *et al.*	not required per 69 Fed. Reg. 56481
	6.	US 8,029,791 B2	2011-10-04	Papadopoulos *et al.*	not required per 69 Fed. Reg. 56481
	7.	US 8,343,737 B2	2013-01-01	Papadopoulos *et al.*	not required per 69 Fed. Reg. 56481
	8.	US 8,647,842 B2	2014-02-11	Papadopoulos *et al.*	not required per 69 Fed. Reg. 56481
	9.	US 10,857,205 B2	2020-12-08	Yancopoulos	not required per 69 Fed. Reg. 56481
	10.	US 10,888,601 B2	2021-01-12	Yancopoulos	not required per 69 Fed. Reg. 56481
	11.	US 11,066,458 B2	2021-07-20	Furfine *et al.*	not required per 69 Fed. Reg. 56481
	12.	US 11,084,865 B2	2021-08-10	Furfine *et al.*	not required per 69 Fed. Reg. 56481
	13.	US 11,253,572 B2	2022-02-22	Yancopoulos	not required per 69 Fed. Reg. 56481

FOREIGN PATENT DOCUMENTS						
		DOCUMENT NUMBER	DATE	COUNTRY	TRANSLATION	REFERENCE PROVIDED*
	14.	EP 3222285 A1	2017-09-27	EPO	N/A	Previously in US Application 17/072,417

NON-PATENT LITERATURE DOCUMENTS			
		DOCUMENT (Including Author, Title, Date, Pertinent Pages, etc.)	REFERENCE PROVIDED*
	15.	Abraham *et al.*, "Randomized, Double-Masked, Sham-Controlled Trial of Ranibizumab for Neovascular Age-Related Macular Degeneration: PIER Study Year 2," *Am. J. Ophthalmology*, 150(3), pp. 315-324.e1 (September 2010)	Previously in US Application 17/072,417
	16.	Adamis, "Ocular Angiogenesis: Vascular Endothelial Growth Factor and Other Factors," in *Retinal Pharmacotherapy 23*, Nguyen *et al.*, eds., (2010)	Previously in US Application 17/072,417
	17.	American Academy of Ophthalmology, "Anti-VEGF Treatments," https://www.aao.org/eye-health/drugs/anti-vegf-treatments (accessed November 8, 2021)	Previously in US Application 17/072,417

EXAMINER	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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SUBSTITUTE 1449 INFORMATION DISCLOSURE STATEMENT	ATTY. DOCKET NO.	APPLICATION NO.
	REGN-008CIPCON8	17/112,404
	APPLICANT	
	REGENERON PHARMACEUTICALS, INC.	
	FILING DATE	GROUP
	December 4, 2020	To be assigned

NON-PATENT LITERATURE DOCUMENTS			
		DOCUMENT (Including Author, Title, Date, Pertinent Pages, etc.)	REFERENCE PROVIDED*
	18.	American Academy of Ophthalmology, "Bevacizumab," https://eyewiki.aao.org/Bevacizumab (accessed November 2, 2021)	Previously in US Application 17/072,417
	19.	American Academy of Ophthalmology, "Ophthalmology Subspecialists," June 6, 2016, https://www.aao.org/eye-health/tips-prevention/ophthalmology-subspecialists (accessed September 26, 2022)	Previously in US Application 17/072,417
	20.	American Academy of Ophthalmology, "Retinal Vasculitis," https://eyewiki.aao.org/Retinal_Vasculitis (accessed January 13, 2022)	Previously in US Application 17/072,417
	21.	American Academy of Ophthalmology, "What is Avastin," https://www.aao.org/eye-health/drugs/avastin (accessed November 9, 2021)	Previously in US Application 17/072,417
	22.	American Academy of Ophthalmology, "What is Eylea," https://www.aao.org/eye-health/drugs/what-is-eylea (accessed November 9, 2021)	Previously in US Application 17/072,417
	23.	American Academy of Ophthalmology, "What is Lucentis," https://www.aao.org/eye-health/drugs/lucentis (accessed November 9, 2021)	Previously in US Application 17/072,417
	24.	American Society of Retina Specialists, "About Us," https://www.asrs.org/about (accessed December 6, 2021)	Previously in US Application 17/072,417
	25.	American Society of Retina Specialists, "Age-Related Macular Degeneration," https://www.asrs.org/patients/retinal-diseases/2/agerelated-macular-degeneration (accessed December 30, 2021)	Previously in US Application 17/072,417
	26.	American Society of Retina Specialists, "Branch Retinal Vein Occlusion," https://www.asrs.org/patients/retinal-diseases/24/branch-retinal-vein-occlusion (accessed December 30, 2021)	Previously in US Application 17/072,417
	27.	American Society of Retina Specialists, "Central Retinal Vein Occlusion," https://www.asrs.org/patients/retinal-diseases/22/central-retinal-vein-occlusion (accessed December 30, 2021)	Previously in US Application 17/072,417
	28.	American Society of Retina Specialists, "Diabetic Retinopathy," https://www.asrs.org/patients/retinal-diseases/3/diabetic-retinopathy (accessed December 30, 2021)	Previously in US Application 17/072,417
	29.	American Speech-Language-Hearing Association, "Calculating Medicare Fee Schedule Rates," https://www.asha.org/practice/reimbursement/medicare/calculating-medicare-fee-schedule-rates/ (accessed November 22, 2021)	Previously in US Application 17/072,417
	30.	*Amgen v. F. Hoffman-La Roche, Ltd.*, Case No. 05-cv-12237 (D. Mass.), ECF 610-3, Declaration of Alexander M. Klibanov, Ph.D. in Support of Defendants' Opposition to Amgen's Motion for Summary Judgment of Infringement of '422 Claim 1, '933 Claim 3, and '698 Claim 6 (June 28, 2007), cited in Deposition of Dr. Alexander M. Klibanov, Ph.D., on March 24, 2022	Previously in US Application 17/072,417
	31.	Amgen, "Fusion Protein," https://www.amgen.com/stories/2018/08/the-shape-of-drugs-to-come/fusion-protein (accessed January 7, 2022)	Previously in US Application 17/072,417

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NON-PATENT LITERATURE DOCUMENTS			
		DOCUMENT (Including Author, Title, Date, Pertinent Pages, etc.)	REFERENCE PROVIDED*
	32.	Amino acid sequence alignment of SEQ ID NO:2 of the '338 and '069 patents with aflibercept amino acid sequence from WHO 2006, SEQ ID NO:16 of the '758 patent, and SEQ ID NO:16 of the '959 patent, submitted on May 27, 2022, in IPR2021-00881 as Exhibit 1122	Previously in US Application 17/072,417
	33.	Amino acid sequence alignment of SEQ ID NO:2 of the '338 patent with SEQ ID NO:16 of the '758 patent and SEQ ID NO:4 of Dix, submitted in IPR2022-00881 as Exhibit 1093	Previously in US Application 17/072,417
	34.	Amino acid sequence alignment of SEQ ID NO:2 of the '338 patent, aflibercept amino acid sequence from WHO 2006, and SEQ ID NO:2 of the '173 patent, cited in Deposition of Dr. Alexander M. Klibanov, Ph.D., on March 24, 2022, submitted in IPR2021-00881 as Exhibit 1117	Previously in US Application 17/072,417
	35.	Amino acid sequence alignment of SEQ ID NO:2 of the '681 and '601 patents with aflibercept amino acid sequence from WHO 2006, SEQ ID NO:16 of the '758 patent, and SEQ ID NO:16 of the '959 patent, submitted in IPR2022-01226 as Exhibit 1087	Previously in US Application 17/072,417
	36.	Amino acid sequence alignment of SEQ ID NO:2 of the '681 and '601 patents with SEQ ID NO:16 of the '758 patent and SEQ ID NO:2 of the '173 patent, submitted in IPR2022-01226 as Exhibit 1092	Previously in US Application 17/072,417
	37.	Annotated version of '338 patent claim 1, cited in Deposition of Dr. Diana V. Do, M.D., on April 21, 2022	Previously in US Application 17/072,417
	38.	ASRS Clinical Updates, "ASRS Fights Novitas [sic] Decision to Interpret Eylea Usage More Frequently than q8 as 'Off Label'," (May 24, 2016) (accessed April 7, 2022), cited in Deposition of Dr. David M. Brown, M.D., on April 26, 2022	Previously in US Application 17/072,417
	39.	Avastin Label (revised 2004), https://www.accessdata.fda.gov/drugsatfda_docs/label/2004/125085lbl.pdf (accessed September 26, 2022)	Previously in US Application 17/072,417
	40.	BasePair Biotechnologies, "What is an Aptamer? – Aptamers and SELEX," https://www.basepairbio.com/what-is-an-aptamer/ (accessed December 30, 2021)	Previously in US Application 17/072,417
	41.	Batta *et al.*, "Trends in FDA Drug Approvals Over Last 2 Decades: An Observational Study," *J. FAMILY MEDICINE & PRIMARY CARE*, 9, pp. 105-114 (2020)	Previously in US Application 17/072,417
	42.	Bausch and Lomb, "Help Your Patients Obtain Access to Visudyne," https://www.bauschretinarx.com/visudyne/ecp/ordering/ (accessed January 12, 2022)	Previously in US Application 17/072,417
	43.	Bausch and Lomb, "Visudyne," https://www.bauschretinarx.com/visudyne/ecp/about/ (accessed December 2, 2021)	Previously in US Application 17/072,417
	44.	Bausch Health Companies, Form 10-K, 2020	Previously in US Application 17/072,417

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	45.	BCBS Florida, "Vascular Endothelial Growth Factor Inhibitors for Ocular Neovascularization," revised April 1, 2022	Previously in US Application 17/072,417
	46.	Beovu Label (revised June 2020), https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/761125s004lbl.pdf (accessed September 26, 2022)	Previously in US Application 17/072,417
	47.	Beovu Label (revised October 2019), https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761125s000lbl.pdf (accessed September 26, 2022)	Previously in US Application 17/072,417
	48.	Bhisitkul *et al.*, "Alternative anti-VEGF treatment regimens in exudative age-related macular degeneration," *Expert Rev. Ophthalmol.*, 5(6) (January 2010)	Previously in US Application 17/072,417
	49.	BIOSPACE, "Bayer HealthCare AG and Regeneron Pharmaceuticals, Inc. to Collaborate on VEGF Trap for the Treatment Of Eye Diseases; Regeneron Retains U.S. Commercialization Rights, Receives $75 Million Upfront, and Eligible for up to $245 Million of Milestone Payments," (October 19, 2006), https://www.biospace.com/article/releases/bayer-healthcare-ag-and-regeneron-pharmaceuticals-inc-to-collaborate-on-vegf-trap-for-the-treatment-of-eye-diseases-b-regeneron-b-retains-u-s-c/ (accessed September 26, 2022)	Previously in US Application 17/072,417
	50.	Bork *et al.*, "Increasing the Sialylation of Therapeutic Glycoproteins: The Potential of the Sialic Acid Biosynthetic Pathway," *J. Pharm. Sci.*, 98(10), pp. 3499-3508 (October 2009)	Previously in US Application 17/072,417
	51.	Bright Focus Foundation, "Age-Related Macular Degeneration: Facts & Figures," https://www.brightfocus.org/macular/article/age-related-macular-facts-figures (accessed November 5, 2021)	Previously in US Application 17/072,417
	52.	Brown *et al.*, "Intravitreal Aflibercept Injection for Macular Edema Secondary to Central Retinal Vein Occlusion: 1-Year Results from the Phase 3 COPERNICUS Study", *Am. J. Ophthalmol.*, 155, pp. 329-437 (March 2013)	Previously in US Application 17/072,417
	53.	Brown *et al.*, "Ranibizumab Versus Verteporfin Photodynamic Therapy for Neovascular Age-Related Macular Degeneration: Two-Year Results of the ANCHOR Study," *Ophthalmology*, 116(1), pp. 57-65.e5 (January 2009)	Previously in US Application 17/072,417
	54.	Calculator.net, "Sample Size Calculator," https://www.calculator.net/sample-size-calculator.html?type=2&cl2=95&ss2=200&pc2=50&ps2=3000&x=68&y=18#findci (accessed January 25, 2022)	Previously in US Application 17/072,417
	55.	Campochiaro *et al.*, "Antagonism of Vascular Endothelial Growth Factor for Macular Edema Caused by Retinal Vein Occlusions: Two-Year Outcomes," *Ophthalmology*, 117(12), pp. 2387-2394.e5 (December 2010) (online publication)	Previously in US Application 17/072,417
	56.	Cantu *et al.*, "Thioesterases: A New Perspective Based on Their Primary and Tertiary Structures," *Protein Science*, 19(17), pp. 1281-1295 (July 2010)	Previously in US Application 17/072,417
	57.	CAS registry for No. 862111-32-8, cited in Deposition of Dr. Alexander M. Klibanov, Ph.D., on March 24, 2022	Previously in US Application 17/072,417

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	59.	Center for Drug Evaluation and Research, Medical Review for BLA Application No. 125387 (November 18, 2011)	Previously in US Application 17/072,417
	60.	Center for Drug Evaluation and Research, Statistical Review for BLA Application No. 125387 (November 18, 2011)	Previously in US Application 17/072,417
	61.	Centers for Disease Control and Prevention, "Vision Loss: A Public Health Problem," https://www.cdc.gov/visionhealth/basic_information/vision_loss.htm (accessed June 12, 2020)	Previously in US Application 17/072,417
	62.	Centers for Medicare & Medicaid Services, "Medicare Physician & Other Practitioners - by Provider and Service," https://data.cms.gov/provider-summary-by-type-of-service/medicare-physician-other-practitioners/medicare-physician-other-practitioners-by-provider-and-service (accessed November 19, 2021)	Previously in US Application 17/072,417
	63.	Centers for Medicare & Medicaid Services, "Payment Allowance Limits for Medicare Part B Drugs: Effective October 1, 2012, through December 31, 2012," (October 2012), https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Part-B-Drugs/McrPartBDrugAvgSalesPrice/2012ASPFiles (accessed September 26, 2022)	Previously in US Application 17/072,417
	64.	Centers for Medicare & Medicaid Services, "Payment Allowance Limits for Medicare Part B Drugs: Effective October 1, 2013, through December 31, 2013," (October 2013), https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Part-B-Drugs/McrPartBDrugAvgSalesPrice/2013ASPFiles (accessed September 26, 2022)	Previously in US Application 17/072,417
	65.	Centers for Medicare & Medicaid Services, "Payment Allowance Limits for Medicare Part B Drugs: Effective October 1, 2014, through December 31, 2014," (October 2014), https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Part-B-Drugs/McrPartBDrugAvgSalesPrice/2014ASPFiles (accessed September 26, 2022)	Previously in US Application 17/072,417
	66.	Centers for Medicare & Medicaid Services, "Payment Allowance Limits for Medicare Part B Drugs: Effective October 1, 2015, through December 31, 2015," (October 2015), https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Part-B-Drugs/McrPartBDrugAvgSalesPrice/2015ASPFiles (accessed September 26, 2022)	Previously in US Application 17/072,417
	67.	Centers for Medicare & Medicaid Services, "Payment Allowance Limits for Medicare Part B Drugs: Effective October 1, 2016, through December 31, 2016," (October 2016), https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Part-B-Drugs/McrPartBDrugAvgSalesPrice/2016ASPFiles (accessed September 26, 2022)	Previously in US Application 17/072,417

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	68.	Centers for Medicare & Medicaid Services, "Payment Allowance Limits for Medicare Part B Drugs: Effective October 1, 2017, through December 31, 2017," (October 2017), https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Part-B-Drugs/McrPartBDrugAvgSalesPrice/2017ASPFiles (accessed September 26, 2022)	Previously in US Application 17/072,417
	69.	Centers for Medicare & Medicaid Services, "Payment Allowance Limits for Medicare Part B Drugs: Effective October 1, 2018, through December 31, 2018," (October 2018), https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Part-B-Drugs/McrPartBDrugAvgSalesPrice/2018ASPFiles (accessed September 26, 2022)	Previously in US Application 17/072,417
	70.	Centers for Medicare & Medicaid Services, "Payment Allowance Limits for Medicare Part B Drugs: Effective October 1, 2019, through December 31, 2019," (October 2019), https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Part-B-Drugs/McrPartBDrugAvgSalesPrice/2019ASPFiles (accessed September 26, 2022)	Previously in US Application 17/072,417
	71.	Centers for Medicare & Medicaid Services, "Payment Allowance Limits for Medicare Part B Drugs: Effective October 1, 2020, through December 31, 2020," (October 2020), https://www.cms.gov/medicare/medicare-part-b-drug-average-sales-price/2020-asp-drug-pricing-files (accessed September 26, 2022)	Previously in US Application 17/072,417
	72.	Centers for Medicare & Medicaid Services, "Payment Allowance Limits for Medicare Part B Drugs: Effective October 1, 2021, through December 31, 2021," (October 2021), https://www.cms.gov/medicare/medicare-part-b-drug-average-sales-price/2021-asp-drug-pricing-files (accessed September 26, 2022)	Previously in US Application 17/072,417
	73.	Centers for Medicare & Medicaid Services, "Physician Fee Schedule," https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/PhysicianFeeSched (accessed November 22, 2021)	Previously in US Application 17/072,417
	74.	Centers for Medicare & Medicare Services, "2021 ASP Drug Pricing Files," https://www.cms.gov/medicare/medicare-part-b-drug-average-sales-price/2021-asp-drug-pricing-files (accessed November 22, 2021)	Previously in US Application 17/072,417
	75.	Centers for Medicare & Medicare Services, "Medicare Part B Drug Average Sales Price," https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Part-B-Drugs/McrPartBDrugAvgSalesPrice (accessed December 8, 2021)	Previously in US Application 17/072,417
	76.	Chen *et al.*, "Carboxylic ester hydrolases: Classification and database derived from their primary, secondary, and tertiary structures," *Protein Science*, 25(11), pp. 1942-1953 (November 2016)	Previously in US Application 17/072,417
	77.	Christensen, "Methodology of Superiority vs. Equivalence Trials and Non-Inferiority Trials," *J. HEPATOLOGY*, 46(5), pp. 947-954 (May 2007) (online publication)	Previously in US Application 17/072,417

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	78.	Clark *et al.*, "Treatment Paradigms in AMD Management: Assessing Consistent Long-Term Dosing," *RETINA TODAY SUPP.*, pp. 1-16 (September 2017), cited in Deposition of Dr. David M. Brown, M.D., on April 26, 2022	Previously in US Application 17/072,417
	79.	ClinicalTrials.gov Archive, History of Changes for Study: NCT00473330, "A Study of Ranibizumab Injection in Subjects With Clinically Significant Macular Edema (ME) With Center Involvement Secondary to Diabetes Mellitus (RISE)," Version 13, dated March 21, 2017, submitted in IPR2021-00881 as Exhibit 2122	Previously in US Application 17/072,417
	80.	ClinicalTrials.gov Archive, History of Changes for Study: NCT00473382, "A Study of Ranibizumab Injection in Subjects With Clinically Significant Macular Edema (ME) With Center Involvement Secondary to Diabetes Mellitus (RIDE)," Version 13, dated March 21, 2017, submitted in IPR2021-00881 as Exhibit 2123	Previously in US Application 17/072,417
	81.	ClinicalTrials.gov Archive, History of Changes for Study: NCT00485836, "A Study of the Efficacy and Safety of Ranibizumab Injection in Patients With Macular Edema Secondary to Central Retinal Vein Occlusion (CRUISE)," Version 10, dated June 29, 2017, submitted in IPR2021-00881 as Exhibit 2125	Previously in US Application 17/072,417
	82.	ClinicalTrials.gov Archive, History of Changes for Study: NCT00486018, "A Study of the Efficacy and Safety of Ranibizumab Injection in Patients With Macular Edema Secondary to Branch Retinal Vein Occlusion (BRAVO)," Version 12, dated April 4, 2017, submitted in IPR2021-00881 as Exhibit 2124	Previously in US Application 17/072,417
	83.	ClinicalTrials.gov Archive, History of Changes for Study: NCT00519285, "Aflibercept in Combination With Docetaxel in Metastatic Androgen Independent Prostate Cancer (VENICE)," Version 01, dated August 21, 2007, submitted in IPR2021-00881 as Exhibit 2078	Previously in US Application 17/072,417
	84.	ClinicalTrials.gov Archive, History of Changes for Study: NCT00644124, "Aflibercept and Standard Chemotherapy (R-CHOP) in First Line of Non Hodgkin B-Cell Lymphoma," Version 01, dated March 21, 2008, submitted in IPR2021-00881 as Exhibit 2079	Previously in US Application 17/072,417
	85.	ClinicalTrials.gov Archive, History of Changes for Study: NCT00794417, "A Study of Aflibercept Administered in Combination With Pemetrexed and Cisplatin in Patients With Advanced Carcinoma," Version 01, dated November 19, 2008, submitted in IPR2021-00881 as Exhibit 2053	Previously in US Application 17/072,417
	86.	ClinicalTrials.gov Archive, History of Changes for Study: NCT01148615, "A Study of Intravenous Aflibercept With Docetaxel in Chinese Patients With Solid Tumors," Version 01, dated June 21, 2010, submitted in IPR2021-00881 as Exhibit 2054	Previously in US Application 17/072,417

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	87.	ClinicalTrials.gov Archive, History of Changes for Study: NCT01486771, "Macugen for Proliferative Diabetic Retinopathy Study With Extended Dosing (M-PDRS ED)," Version 01, dated December 5, 2011, submitted in IPR2021-00881 as Exhibit 2109	Previously in US Application 17/072,417
	88.	ClinicalTrials.gov Archive, History of Changes for Study: NCT01940900, "A Phase 3 Safety and Efficacy Study of Fovista (E10030) Intravitreous Administration in Combination With Lucentis Compared to Lucentis Monotherapy," Version 21, dated August 13, 2018, submitted in IPR2021-00881 as Exhibit 2025	Previously in US Application 17/072,417
	89.	ClinicalTrials.gov Archive, History of Changes for Study: NCT01944839, "A Phase 3 Safety and Efficacy Study of Fovista (E10030) Intravitreous Administration in Combination With Lucentis Compared to Lucentis Monotherapy," Version 27, dated August 8, 2018, submitted in IPR2021-00881 as Exhibit 2024	Previously in US Application 17/072,417
	90.	ClinicalTrials.gov Archive, History of Changes for Study: NCT02247479, "A Study Investigating the Efficacy and Safety of Lampalizumab Intravitreal Injections in Participants With Geographic Atrophy Secondary to Age-Related Macular Degeneration (CHROMA)," Version 60, dated June 17, 2019, submitted in IPR2021-00881 as Exhibit 2021	Previously in US Application 17/072,417
	91.	ClinicalTrials.gov Archive, History of Changes for Study: NCT02247531, "A Study Investigating the Safety and Efficacy of Lampalizumab Intravitreal Injections in Participants With Geographic Atrophy Secondary to Age-Related Macular Degeneration (SPECTRI)," Version 60, dated October 14, 2019, submitted in IPR2021-00881 as Exhibit 2020	Previously in US Application 17/072,417
	92.	ClinicalTrials.gov Archive, History of Changes for Study: NCT03577899, "Efficacy and Safety Trial of Conbercept Intravitreal Injection for Neovascular AMD(PANDA-1)," Version 06, dated June 23, 2021, submitted in IPR2021-00881 as Exhibit 2023	Previously in US Application 17/072,417
	93.	ClinicalTrials.gov Archive, History of Changes for Study: NCT03630952, "Efficacy and Safety Trial of Conbercept Intravitreal Injection for Neovascular AMD(PANDA-2)," Version 07, dated June 22, 2021, submitted in IPR2021-00881 as Exhibit 2022	Previously in US Application 17/072,417
	94.	ClinicalTrials.gov, "1997: Congress Passes Law (FDAMA) Requiring Trial Registration," https://clinicaltrials.gov/ct2/about-site/history (accessed April 26, 2021)	Previously in US Application 17/072,417
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	96.	CloudResearch, "Determining Sample Size: How Many Survey Participants Do You Need?" https://www.cloudresearch.com/resources/guides/statistical-significance/determine-sample-size/ (accessed January 25, 2022)	Previously in US Application 17/072,417
	97.	CMS.gov Medicare Coverage Database, "Billing and Coding: Aflibercept (Eylea)," https://www.cms.gov/medicare-coverage-database/view/article.aspx?articleid=53387&ver=28&keyword=&keywordType=starts&areaId=all&docType=6,3,5,1,F,P&contractOption=all&hcpcsOption=code&hcpcsStartCode=J0178&hcpcsEndCode=J0178&sortBy=title&bc=1 (accessed April 22, 2021)	Previously in US Application 17/072,417
	98.	Cobo *et al.*, "The Clearance of Intravitreal Gentamicin," *Am. J. Ophthalmology*, 92(1), pp. 59-62 (1981)	Previously in US Application 17/072,417
	99.	Complaint, *Horizon Healthcare Servs., Inc. v. Regeneron Pharms., Inc.*, No. 1:22-cv-10493-FDS (D. Mass. April 4, 2022), ECF Nos. 1 – 1-18	Previously in US Application 17/072,417
	100.	Complaint, *United States v. Regeneron Pharms., Inc.,* No. 1:20-cv-11217-FDS (D. Mass. June 24, 2020), ECF Nos. 1 — 1-39	Previously in US Application 17/072,417
	101.	Corporate Finance Institute, "SEC Filings - Requirements for Public Companies & Where to Find Them," https://corporatefinanceinstitute.com/resources/data/public-filings/sec-filings/ (accessed January 20, 2021)	Previously in US Application 17/072,417
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	127.	Expert Declaration of Ivan T. Hofmann Support of Petitioner's Reply, dated May 27, 2022, in IPR2021-00881 - [[REDACTED]]	Previously in US Application 17/072,417
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	232.	Nucleotide sequence alignment of SEQ ID NO:1 of the '338 patent with SEQ ID NO:15 of the '758 patent and SEQ ID NO:3 of Dix, submitted in IPR2022-00881 as Exhibit 1094	Previously in US Application 17/072,417

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	248.	Regeneron Pharmaceuticals, Inc., "Eylea Injection Receives FDA Approval for Macular Edema Following Retinal Vein Occlusion (RVO)," Press Release, (October 6, 2014) https://investor.regeneron.com/news-releases/news-release-details/eylear-aflibercept-injection-receives-fda-approval-macular-edema (accessed September 26, 2022)	Previously in US Application 17/072,417

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	December 4, 2020	To be assigned

NON-PATENT LITERATURE DOCUMENTS			
		DOCUMENT (Including Author, Title, Date, Pertinent Pages, etc.)	REFERENCE PROVIDED*
	288.	Stefanini *et al.*, "Increase of Plasma VEGF after Intravenous Administration of Bevacizumab Is Predicted by a Pharmacokinetic Model," *CANCER RESEARCH*, 70(23), pp. 9886-9894 (December 2010), cited in Deposition of Dr. Alexander M. Klibanov, Ph.D., on March 24, 2022	Previously in US Application 17/072,417
	289.	Thomas *et al.*, "Comparative Effectiveness of Aflibercept for the Treatment of Patients with Neovascular Age-related Macular Degeneration," *Clinical Ophthalmology*, 7, pp. 495-501 (March 2013)	Previously in US Application 17/072,417
	290.	Thomson Reuters, "Thomson Reuters Links Discovery and Literature Citation Databases," Press Release (January 4, 2010)	Previously in US Application 17/072,417
	291.	Transcript of Deposition of Doris Weber dated May 13, 2022, in IPR2021-00881	Previously in US Application 17/072,417
	292.	Transcript of Deposition of Dr. Alexander M. Klibanov, Ph.D., dated March 24, 2022, in IPR2021-00880 and IPR2021-00881 - [[REDACTED]]	Previously in US Application 17/072,417
	293.	Transcript of Deposition of Dr. David M. Brown, M.D., dated April 26, 2022, in IPR2021-00880 and IPR2021-00881	Previously in US Application 17/072,417
	294.	Transcript of Deposition of Dr. Diana V. Do, M.D., dated April 21, 2022, in IPR2021-00881	Previously in US Application 17/072,417
	295.	Transcript of Deposition of Dr. Lucian V. Del Priore, M.D., dated April 29, 2022, in IPR2021-00881 - [[REDACTED]]	Previously in US Application 17/072,417
	296.	Transcript of Deposition of Dr. Richard Manning, Ph.D., dated May 4, 2022, in IPR2021-00881 - [[REDACTED]]	Previously in US Application 17/072,417
	297.	Transcript of Deposition of Ivan Hofmann dated June 23, 2022, in IPR2021-00880 and IPR2021-00881 - [[REDACTED]]	Previously in US Application 17/072,417
	298.	Transcript of Deposition of Mary Gerritsen, Ph.D., dated June 17, 2022, in IPR2021-00880 and IPR2021-00881	Previously in US Application 17/072,417
	299.	Transcript of Deposition of Thomas Albini, M.D., dated June 22, 2022, in IPR2021-00880 and IPR2021-00881	Previously in US Application 17/072,417
	300.	Transcript of the Teleconference before the United States Patent Trial and Appeal Board dated February 23, 2022, in IPR2021-00881	Previously in US Application 17/072,417
	301.	Transcript of the Teleconference before the United States Patent Trial and Appeal Board dated May 19, 2022, in IPR2021-00880 and IPR2021-00881	Previously in US Application 17/072,417
	302.	Transcript of the Teleconference before the United States Patent Trial and Appeal Board dated September 8, 2021, in IPR2021-00881	Previously in US Application 17/072,417
	303.	U.S. Department of Health and Human Services (ASPE), "Medicare Part B Reimbursement of Prescription Drugs," 6/2014, available at: https://aspe.hhs.gov/sites/default/files/private/pdf/106966/ib_mprpd.pdf (accessed September 26, 2022)	Previously in US Application 17/072,417
	304.	United Healthcare, "Ophthalmologic Policy: VEGF Inhibitors," effective January 1, 2022, submitted in IPR2021-00881 as Exhibit 1167	Previously in US Application 17/072,417

EXAMINER	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.

*Copies of the listed references are either submitted herewith or were previously cited by or submitted to, the Office in a prior application. Pursuant to 37 C.F.R. § 1.97(d) and MPEP §609, the indicated reference may have been previously cited by or submitted to, the Office in a prior application, where the prior application is identified by its U.S. Application Number in this Information Disclosure Statement.

SUBSTITUTE 1449 INFORMATION DISCLOSURE STATEMENT	ATTY. DOCKET NO.	APPLICATION NO.
	REGN-008CIPCON8	17/112,404
	APPLICANT	
	REGENERON PHARMACEUTICALS, INC.	
	FILING DATE	GROUP
	December 4, 2020	To be assigned

NON-PATENT LITERATURE DOCUMENTS			
		DOCUMENT (Including Author, Title, Date, Pertinent Pages, etc.)	REFERENCE PROVIDED*
	305.	USC-Brookings, "Medicare Payment for Physician-Administered (Part B) Drugs: The Interim Final Rule and a Better Way Forward," https://www.brookings.edu/blog/usc-brookings-schaeffer-on-health-policy/2021/02/10/medicare-payment-for-physician-administered-part-b-drugs/ (accessed September 26, 2022)	Previously in US Application 17/072,417
	306.	Vanderkam, "George Yancopoulos: Doing Well by Trying to Do Good," *SCIENTIFIC AMERICAN*, https://www.scientificamerican.com/article/george-yancopoulos-westinghouse/ (accessed April 14, 2022), cited in Deposition of Dr. Diana V. Do, M.D., on April 21, 2022	Previously in US Application 17/072,417
	307.	Verywell Health, "Macular Degeneration: Timeline of Vision Loss Progression," https://www.verywellhealth.com/macular-degeneration-timeline-5069947 (accessed March 21, 2021)	Previously in US Application 17/072,417
	308.	Vestrum Health, "Pharmaceutical Companies," https://www.vestrumhealth.com/pharma.php (accessed January 3, 2022)	Previously in US Application 17/072,417
	309.	Vestum Health, "Homepage," https://www.vestrumhealth.com/index.php (accessed January 3, 2022)	Previously in US Application 17/072,417
	310.	Visudyne Label (revised April 2016), https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/021119s027lbl.pdf (accessed September 26, 2022)	Previously in US Application 17/072,417
	311.	Volkin *et al.*, "Alterations in the Structure of Proteins that Cause Their Irreversible Inactivation," *Developments in Biological Standardization*, 74, pp. 73-81 (1992) (Basel, SI)	Previously in US Application 17/072,417
	312.	Weidner *et al.*, "Observations Regarding the Average Sales Price Reimbursement Methodology," *Evidence-Based Oncology*, 27(4), pp. 156-160 (2021)	Previously in US Application 17/072,417
	313.	Wells *et al.*, "Aflibercept, Bevacizumab, or Ranibizumab for Diabetic Macular Edema," *The New England Journal of Medicine*, 372(13), pp. 1193-1203 (2015)	Previously in US Application 17/072,417
	314.	Wilhelmus, "The Red Eye, Infectious Conjunctivitis, Keratitis, Endophthalmitis, and Periocular Cellulitis," *INFECTIOUS DISEASE CLINICS N. AM.*, 2(1), pp. 99-116 (March 1988) (Philadelphia, PA)	Previously in US Application 17/072,417
	315.	Wirbelauer, "Management of the Red Eye for the Primary Care Physician," *AM. J. MED.*, 119(4), pp. 302-306 (April 2006) (online publication)	Previously in US Application 17/072,417
	316.	World Health Organization, "Blindness and Vision Impairment Fact Sheet," Press Release, (October 14, 2021) https://www.who.int/news-room/fact-sheets/detail/blindness-and-visual-impairment (accessed September 26, 2022)	Previously in US Application 17/072,417
	317.	World Health Organization, "International Nonproprietary Names for Pharmaceutical Substances (INN)," *WHO Drug Information*, 20, pp. 118-119 (2006), cited in Deposition of Dr. Alexander M. Klibanov, Ph.D., on March 24, 2022	Previously in US Application 17/072,417

EXAMINER	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.

*Copies of the listed references are either submitted herewith or were previously cited by or submitted to, the Office in a prior application. Pursuant to 37 C.F.R. § 1.97(d) and MPEP §609, the indicated reference may have been previously cited by or submitted to, the Office in a prior application, where the prior application is identified by its U.S. Application Number in this Information Disclosure Statement.

SUBSTITUTE 1449 INFORMATION DISCLOSURE STATEMENT	ATTY. DOCKET NO.	APPLICATION NO.
	REGN-008CIPCON8	17/112,404
	APPLICANT	
	REGENERON PHARMACEUTICALS, INC.	
	FILING DATE	GROUP
	December 4, 2020	To be assigned

NON-PATENT LITERATURE DOCUMENTS			
		DOCUMENT (Including Author, Title, Date, Pertinent Pages, etc.)	REFERENCE PROVIDED*
	318.	Yahoo Finance, "Beovu Now Publicly Reimbursed in Ontario and New Brunswick for the Treatment of Neovascular Wet AMD," Press Release, (December 17, 2021) https://finance.yahoo.com/news/beovu-brolucizumab-injection-now-publicly-120000109.html (accessed December 30, 2021)	Previously in US Application 17/072,417
	319.	Yang, "Comparison of Binding Characteristics and *in vitro* Activities of Three Inhibitors of Vascular Endothelial Growth Factor A," *Molecular Pharmaceutics*, 11(10), pp. 3421-3429 (October 2014), cited in Deposition of Dr. Alexander M. Klibanov, Ph.D., on March 24, 2022	Previously in US Application 17/072,417
	320.	Yorston, "Anti-VEGF Drugs in the Prevention of Blindness," *Community Eye Health Journal*, 27(87), pp. 44-46 (2014)	Previously in US Application 17/072,417
	321.	Zucchi, "EDGAR: Investors' One-Stop-Shop For Company Filings," *YAHOO!LIFE*, https://www.yahoo.com/lifestyle/tagged/health/edgar-investors-one-stop-shop-170000800.html (accessed January 20, 2021)	Previously in US Application 17/072,417

EXAMINER	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.

*Copies of the listed references are either submitted herewith or were previously cited by or submitted to, the Office in a prior application. Pursuant to 37 C.F.R. § 1.97(d) and MPEP §609, the indicated reference may have been previously cited by or submitted to, the Office in a prior application, where the prior application is identified by its U.S. Application Number in this Information Disclosure Statement.

Electronically Filed

INFORMATION DISCLOSURE STATEMENT	Attorney Docket No.	REGN-008CIPCON8
	Confirmation No.	6437
	First Named Inventor	George D. Yancopoulos
	Application Number	17/112,404
	Filing Date	December 4, 2020
	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:

The attention of the Examiner is invited to the documents listed on the attached Substitute 1449.

Copies of the U.S. patents and published applications listed on the attached Substitute 1449 are not submitted herewith, in accordance with the Strategic Plan Final Rule, 69 Fed. Reg. 56481-56547 (September 21, 2004), effective October 21, 2004.

Copies of the foreign publication and non-patent literature documents listed on the attached Substitute 1449 are submitted in parent U.S. Application No. 17/072,417.

It is respectfully requested that the information above be expressly considered during the prosecution of this application, and that the documents be made of record therein and appear among the "References Cited" on any patent to issue therefrom.

No aspect of these submissions constitute admission of prior art status or a disclaimer of claim scope.

Statement under 37 C.F.R. §§1.56 and 1.2

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

With respect to this statement under *McKesson*, Applicants wishes to bring to the Examiner's attention U.S. Patent Application No. 13/940,370, filed July 12, 2013, which issued as U.S. Patent No. 9,254,338 on February 9, 2016.

With respect to this statement under *McKesson*, Applicants wishes to bring to the Examiner's attention U.S. Patent Application No. 14/972,560, filed December 17, 2015, which issued as U.S. Patent No. 9,669,069 on June 6, 2017.

With respect to this statement under *McKesson*, Applicants wishes to bring to the Examiner's attention U.S. Patent Application No. 15/471,506, filed March 28, 2017, which issued as U.S. Patent No. 10,130,681 on November 20, 2018.

With respect to this statement under *McKesson*, Applicants wishes to bring to the Examiner's attention U.S. Patent Application No. 16/055,847, filed August 6, 2018, which issued as U.S. Patent No. 10,857,205 on December 8, 2020.

With respect to this statement under *McKesson*, Applicants wishes to bring to the Examiner's attention U.S. Patent Application No. 16/159,282, filed October 12, 2018, which issued as U.S. Patent No. 10,828,345 on November 10, 2020.

With respect to this statement under *McKesson*, Applicants wishes to bring to the Examiner's attention U.S. Patent Application No. 16/397,267, filed April 29, 2019, which issued as U.S. Patent No. 10,888,601 on January 12, 2021.

With respect to this statement under *McKesson*, Applicants wishes to bring to the Examiner's attention U.S. Patent Application No. 17/352,892, filed June 21, 2021, which issued as U.S. Patent No. 11,253,572 on February 22, 2022.

With respect to this statement under *McKesson*, Applicant wishes to bring to the Examiner's attention U.S. Patent Application No. 17/072,417, filed October 16, 2020. No actions have been mailed to date.

With respect to this statement under *McKesson*, Applicant wishes to bring to the Examiner's attention U.S. Patent Application No. 17/112,063, filed December 4, 2020. No actions have been mailed to date.

With respect to this statement under *McKesson*, Applicant wishes to bring to the Examiner's attention U.S. Patent Application No. 17/350,958, filed June 17, 2021. No actions have been mailed to date.

With respect to this statement under *McKesson*, Applicant wishes to bring to the Examiner's attention U.S. Patent Application No. 17/740,744, filed May 10, 2022. A Non-Final Office Action was mailed on July 20, 2022.

With respect to this statement under *McKesson*, Applicant wishes to bring to the Examiner's attention *Inter Partes* Review No. IPR2021-00880 of U.S. Patent No. 9,669,069, filed on May 5, 2021; and IPR2021-00881 of U.S. Patent No. 9,254,338, filed on May 5, 2021. Both of which are currently awaiting final decision from PTAB.

With respect to this statement under *McKesson*, Applicant wishes to bring to the Examiner's attention *Inter Partes* Review No. IPR2022-01225 of U.S. Patent No. 10,130,681, filed on July 1, 2022; and IPR2022-01226 of U.S. Patent No. 10,888,601, filed on July 1, 2022.

With respect to this statement under *McKesson*, Applicant wishes to bring to the Examiner's attention *Inter Partes* Review No. IPR2022-01524 of U.S. Patent No. 11,253,572, filed on September 9, 2022.

These documents and the corresponding file wrappers are available on PAIR or PTAB E2E, and thus are not provided with this communication. Please inform the undersigned if there is any difficulty in obtaining the documents from PAIR or PTAB E2E.

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-008CIPCON8.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: October 25, 2022

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

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

Electronic Acknowledgement Receipt

EFS ID:	46891699
Application Number:	17112404
International Application Number:	
Confirmation Number:	6437
Title of Invention:	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS
First Named Inventor/Applicant Name:	George YANCOPOULOS
Customer Number:	96387
Filer:	Karl Bozicevic/Kimberly Zuehlke
Filer Authorized By:	Karl Bozicevic
Attorney Docket Number:	REGN-008CIPCON8
Receipt Date:	25-OCT-2022
Filing Date:	04-DEC-2020
Time Stamp:	19:50:11
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	Information Disclosure Statement (IDS) Form (SB08)	REGN-008CIPCON8_2022-10-25_sup_IDS_1449.pdf	261328 c1bb1a2c3e139dc11f3d220d3d2d93fbd04d17a6	no	25

Warnings:

Information:					
This is not an USPTO supplied IDS fillable form					
2	Transmittal Letter	REGN-008CIPCON8_2022-10-25_sup_IDS_trans.pdf	58282 3dde0766505a347a7801e32ee921667bc81cccdc	no	5
Warnings:					
Information:					
			Total Files Size (in bytes):	319610	

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.

UNITED STATES PATENT AND TRADEMARK OFFICE

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

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/112,404	12/04/2020	George YANCOPOULOS	REGN-008CIPCON8	6437

96387 7590 10/27/2022

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
10/27/2022	ELECTRONIC

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

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

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

docket@bozpat.com

Office Action Summary	Application No. 17/112,404	Applicant(s) YANCOPOULOS, George	
	Examiner JON M LOCKARD	Art Unit 1647	AIA (FITF) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 04 December 2020.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL.** 2b) ☑ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☑ Claim(s) 21-54 is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 21-54 is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☑ The drawing(s) filed on 04 December 2020 is/are: a)☑ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☑ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

Notice of Pre-AIA or AIA Status

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

DETAILED ACTION

Status of Application, Amendments, and/or Claims

2. The Preliminary Amendment filed on 04 December 2020 has been entered in full. Claims 1-20 have been cancelled, and claims 21-54 have been added. Therefore, claims 21-54 are pending and the subject of this Office Action.

Information Disclosure Statement

3. The information disclosure statements (IDS) filed 04 December 2020, 17 June 2021, 09 July 2021, 03 September 2021, 24 November 2021 and 16 December 2021 have been considered by the examiner.

Claim Rejections - 35 USC § 112

4. The following is a quotation of 35 U.S.C. 112(d):

> (d) REFERENCE IN DEPENDENT FORMS.—Subject to subsection (e), a claim in dependent form shall contain a reference to a claim previously set forth and then specify a further limitation of the subject matter claimed. A claim in dependent form shall be construed to incorporate by reference all the limitations of the claim to which it refers.

The following is a quotation of pre-AIA 35 U.S.C. 112, fourth paragraph:

> Subject to the following paragraph [i.e., the fifth paragraph of pre-AIA 35 U.S.C. 112], a claim in dependent form shall contain a reference to a claim previously set forth and then specify a further limitation of the subject matter claimed. A claim in dependent form shall be construed to incorporate by reference all the limitations of the claim to which it refers.

5. Claims 23 and 42 are rejected under 35 U.S.C. 112, fourth paragraph, as being of improper dependent form for failing to further limit the subject matter of the claim upon which it depends,

or for failing to include all the limitations of the claim upon which it depends. Each of the claims recites "wherein said gain in visual acuity is measured using the ETDRS visual acuity chart." However, the claims from which these claims depend, 22 and 41, respectively, already recite that the gain is measured "according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score." Therefore, claims 23 and 42 fail to further limit the claims from which they depend. Applicant may cancel the claim(s), amend the claim(s) to place the claim(s) in proper dependent form, rewrite the claim(s) in independent form, or present a sufficient showing that the dependent claim(s) complies with the statutory requirements. See the "Supplementary Examination Guidelines for Determining Compliance With 35 U.S.C. 112 and for Treatment of Related Issues in Patent Applications" (Federal Register, Vol. 76, No. 27, Wednesday, February 9, 2011), pg. 7166, section "5. Dependent Claims", which states that "If the dependent claim does not comply the with the requirements of § 112, ¶4, the examiner should reject the dependent claim under § 112, ¶4 as unpatentable rather than objecting to the claim" and "a dependent claim must be rejected under § 112, ¶4 if it omits an element from the claim upon which it depends or it fails to add a limitation to the claim upon which it depends".

Double Patenting

6. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the claims at issue are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either

anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

7. A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the reference application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

8. The USPTO internet Web site contains terminal disclaimer forms which may be used. Please visit http://www.uspto.gov/forms/. The filing date of the application will determine what form should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to http://www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

9. Claims 21-54 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-26 of U.S. Patent No. 9,254,338. Although the conflicting claims are not identical, as they recite different dosing schedules, they are not patentably distinct from each other because claims 1-26 of the '338 patent are drawn to a method for treating an angiogenic eye disorder, including age-related macular degeneration, diabetic retinopathy, choroidal neovascularization, vascular leak, and/or retinal edema, comprising administering a fusion

polypeptide having the amino acid sequence set forth in SEQ ID NO:2, which comprises an immunoglobin-like (Ig) domain 2 of a first VEGF receptor (VEGFR1) and Ig domain 3 of a second VEGF receptor (VEGFR2) and a multimerizing component, which is what aflibercept comprises. While the '338 patent does not disclose the dosing schedules set forth in the instant claims, it is routine experimentation to optimize dosages and dosage schedules. The courts have determined that:

> "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller,* 220 F.2d 454, 454, 105 USPQ 223,235, (CCPA 1955).

Therefore, the claims are overlapping in scope.

10. Claims 21-54 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-12 of U.S. Patent No. 9,669,069. Although the conflicting claims are not identical, as they recite different dosing schedules, they are not patentably distinct from each other because claims 1-12 of the '069 patent are drawn to a method for treating an angiogenic eye disorder, including age-related macular degeneration, diabetic retinopathy, diabetic macular edema, central retinal vein occlusion, branch retinal vein occlusion, and corneal neovascularization, comprising administering a fusion polypeptide having the amino acid sequence set forth in SEQ ID NO:2, which comprises an immunoglobin-like (Ig) domain 2 of a first VEGF receptor (VEGFR1) and Ig domain 3 of a second VEGF receptor (VEGFR2) and a multimerizing component, which is what aflibercept comprises. While the '069 patent does not disclose the dosing schedules set forth in the instant claims, it is routine experimentation to optimize dosages and dosage schedules. The courts have determined that:

> "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller,* 220 F.2d 454, 454, 105 USPQ 223,235, (CCPA 1955).

Therefore, the claims are overlapping in scope.

11. Claims 21-54 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-12 of U.S. Patent No. 10,130,681. Although the conflicting claims are not identical, as they recite different dosing schedules, they are not patentably distinct from each other because claims 1-12 of the '681 patent are drawn to a method for treating an angiogenic eye disorder, including age-related macular degeneration, diabetic retinopathy, diabetic macular edema, central retinal vein occlusion, branch retinal vein occlusion, and corneal neovascularization, comprising administering a fusion polypeptide having the amino acid sequence set forth in SEQ ID NO:2, which comprises an immunoglobin-like (Ig) domain 2 of a first VEGF receptor (VEGFR1) and Ig domain 3 of a second VEGF receptor (VEGFR2) and a multimerizing component, which is what aflibercept comprises. While the '681 patent does not disclose the dosing schedules set forth in the instant claims, it is routine experimentation to optimize dosages and dosage schedules. The courts have determined that:

> "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller,* 220 F.2d 454, 454, 105 USPQ 223,235, (CCPA 1955).

Therefore, the claims are overlapping in scope.

12. Claims 21-54 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-11 of U.S. Patent No. 10,828,345. Although the conflicting claims are not identical, as they recite different dosing schedules, they are not patentably distinct from each

other because claims 1-11 of the '345 patent are drawn to a method for treating an angiogenic eye disorder, including age-related macular degeneration, diabetic retinopathy, diabetic macular edema, central retinal vein occlusion, branch retinal vein occlusion, and corneal neovascularization, comprising administering a VEGF antagonist, wherein the VEGF comprises an immunoglobin-like (Ig) domain 2 of Flt1 and Ig domain 3 of Flk1 and a multimerizing component, or aflibercept. While the '345 patent does not disclose the dosing schedules set forth in the instant claims, it is routine experimentation to optimize dosages and dosage schedules. The courts have determined that:

> "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller,* 220 F.2d 454, 454, 105 USPQ 223,235, (CCPA 1955).

Therefore, the claims are overlapping in scope.

13. Claims 21-54 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-47 of U.S. Patent No. 10,888,601. Although the conflicting claims are not identical, as they recite different dosing schedules, they are not patentably distinct from each other because claims 1-47 of the '601 patent are drawn to a method for treating an angiogenic eye disorder, including age-related macular degeneration, diabetic retinopathy, diabetic macular edema, central retinal vein occlusion, branch retinal vein occlusion, and corneal neovascularization, comprising administering aflibercept. While the '601 patent does not disclose the dosing schedules set forth in the instant claims, it is routine experimentation to optimize dosages and dosage schedules. The courts have determined that:

> "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller,* 220 F.2d 454, 454, 105 USPQ 223,235, (CCPA 1955).

Therefore, the claims are overlapping in scope.

14. Claims 21-54 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-30 of U.S. Patent No. 11,203,572. Although the conflicting claims are not identical, as they recite different dosing schedules, they are not patentably distinct from each other because claims 1-30 of the '572 patent are drawn to a method for treating an angiogenic eye disorder, including age-related macular degeneration and macular edema, comprising administering 2 mg of aflibercept, including secondary doses administered every 4 weeks, and tertiary doses administered every 8 weeks. While the '572 patent does not disclose the exact dosing schedules set forth in the instant claims, it is routine experimentation to optimize dosages and dosage schedules. The courts have determined that:

> "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller,* 220 F.2d 454, 454, 105 USPQ 223,235, (CCPA 1955).

Therefore, the claims are overlapping in scope.

15. Claims 21-30, 32-34, 36-43, 45-47 and 49-54 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-30 of U.S. Patent No. 11,253,572. Although the conflicting claims are not identical, as they recite different dosing schedules, they are not patentably distinct from each other because claims 1-30 of the '572 patent are drawn to a method for treating an angiogenic eye disorder, including age-related macular degeneration and macular edema, comprising administering 2 mg of aflibercept, including secondary doses administered every 4 weeks, and tertiary doses administered every 8 weeks. While the '572 patent does not

disclose the exact dosing schedules set forth in the instant claims, it is routine experimentation to optimize dosages and dosage schedules. The courts have determined that:

> "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller,* 220 F.2d 454, 454, 105 USPQ 223,235, (CCPA 1955).

Therefore, the claims are overlapping in scope.

16. Claims 21-54 provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 21-57 of copending Application No. 17/112,063 (reference application). Although the claims at issue are not identical, as they recite different dosing schedules, they are not patentably distinct from each other because claims 21-57 of the '063 application are drawn to a method for treating an angiogenic eye disorder, including age-related macular degeneration and diabetic macular edema, comprising administering 2 mg of aflibercept, including secondary doses administered every 4 weeks, and tertiary doses administered every 8 weeks. While the '063 application does not disclose the exact dosing schedules set forth in the instant claims, it is routine experimentation to optimize dosages and dosage schedules. The courts have determined that:

> "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller,* 220 F.2d 454, 454, 105 USPQ 223,235, (CCPA 1955).

Therefore, the claims are overlapping in scope..

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

17. Claims 21-54 provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 102-130 of copending Application No. 17/072,417 (reference application). Although the claims at issue are not identical, as they recite different dosing schedules, they are not patentably distinct from each other because claims 102-130 of the '417 application are drawn to a method for treating an angiogenic eye disorder, including age-related macular degeneration and macular edema, comprising administering 2 mg of aflibercept every 8 weeks, wherein the patient had received initial and secondary 2 mg doses of aflibercept every 2-4 weeks. While the '417 application does not disclose the exact dosing schedules set forth in the instant claims, it is routine experimentation to optimize dosages and dosage schedules. The courts have determined that:

> "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller,* 220 F.2d 454, 454, 105 USPQ 223,235, (CCPA 1955).

Therefore, the claims are overlapping in scope..

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

Summary

18. No claim is allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon M. Lockard whose telephone number is (571) 272-2717. The examiner can normally be reached on Monday through Friday, 8:00 AM to 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joanne Hama, can be reached on (571) 272-2911. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at **866-217-9197** (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/JON M LOCKARD/
Examiner, Art Unit 1647
October 22, 2022

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/112,404	YANCOPOULOS, George
	Examiner	Art Unit
	JON M LOCKARD	1647

CPC - Searched*		
Symbol	Date	Examiner

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner
NONE		10/22/2022	JML

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

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/112,404	YANCOPOULOS, George
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	JON M LOCKARD	1647

Search Notes		
Search Notes	**Date**	**Examiner**
PE2E Search (USPAT, US-PGPUB, EPO, DERWENT): See attached search history.	10/22/2022	JML
STN (MEDLINE, SCISEARCH, EMBASE, BIOSIS): See attached search history.	10/22/2022	JML
PALM: Inventor search.	10/22/2022	JML
IPR2021-00880 Reviewed Inter Partes Review of U.S. Pat. No. 9,669,069.	10/22/2022	JML
IPR2021-00881 Reviewed Inter Partes Review of U.S. Pat. No. 9,254,338.	10/22/2022	JML
IPR2021-00257 Reviewed Inter Partes Review of U.S. Pat. No. 9,669,069.	10/22/2022	JML
IPR2021-00258 Reviewed Inter Partes Review of U.S. Pat. No. 9,254,338.	10/22/2022	JML
IPR2021-00298 Reviewed Inter Partes Review of U.S. Pat. No. 9,254,338.	10/22/2022	JML
IPR2021-00301 Reviewed Inter Partes Review of U.S. Pat. No. 9,669,069.	10/22/2022	JML
IPR2021-01225 Reviewed Inter Partes Review of U.S. Pat. No. 10,130,681.	10/22/2022	JML
IPR2021-01226 Reviewed Inter Partes Review of U.S. Pat. No. 10,888,601.	10/22/2022	JML
PGR2021-00035 Reviewed Post Grant Review of U.S. Pat. No. 10,828,345.	10/22/2022	JML

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

INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	17/112,404
				Filing Date	2020-12-04
				First Named Inventor	George D. YANCOPOULOS
				Art Unit	~~To Be Assigned~~ 1647
				Examiner Name	~~To Be Assigned~~ Jon Lockard
Sheet	1	of	2	Attorney Docket Number	REGN-008CIPCON8

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				

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NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.		T
	1	Eylea®, Highlights of Prescribing Information, Revised 11/2011		
	2	IPR2021-00880, Paper 1, Petition for IPR (May 5, 2021)		
	3	IPR2021-00880, Exhibit 1002, Albini Declaration (May 4, 2021)		
	4	IPR2021-00880, Exhibit 1003, Gerritsen Declaration (April 30, 2021)		
	5	IPR2021-00880, Paper 10, Preliminary Response of Patent Owner (August 16, 2021)		
	6	IPR2021-00881, Paper 1, Petition for IPR (May 5, 2021)		
	7	IPR2021-00881, Exhibit 1002, Albini Declaration (May 4, 2021)		
	8	IPR2021-00881, Exhibit 1003, Gerritsen Declaration (April 26, 2021)		
	9	IPR2021-00881, Paper 10, Preliminary Response of Patent Owner (August 16, 2021)		
	10	IPR2021-00881, Exhibit 2001, Do Declaration (August 13, 2021)		
	11	Mitchell *et al.*, "Evaluating the Impact of Intravitreal Aflibercept on Diabetic Retinopathy Progression in the VIVID-DME and VISTA-DME Studies" Ophthalmol Retina 2(10):988-96 (2018)		
	12	PGR2021-00035, Paper 2, Petition for PGR (January 7, 2021)		
	13	PGR2021-00035, Paper 6, Preliminary Response of Patent Owner (April 15, 2021)		
	14	PGR2021-00035, Exhibit 1003 Wu Declaration (January 7, 2021)		
	15	PGR2021-00035, Exhibit 2001 Do Declaration (April 14, 2021)		
	16	PGR2021-00035, Exhibit 2002 D. Brown Declaration (April 14, 2021)		
	17	CAO, J. R., R.; Wang, Q.; Yancopoulos, G.D.; Wiegand, S.J. (2002). Inhibition of Corneal Neovascularization and Inflammation by VEGF Trap. In "ARVO", Invest. Ophthalmol. Vis. Sci. Vol. 43. E-Abstract 1863		

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.

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

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	18	WANG, Q. R., R.; Cao, J.; Yancopoulos, G.D.; and Wiegand, S.J. (2002). Anti-Angiogenic Properties of a New VEGF Antagonist, VEGF Trap, in a Mouse Model of Retinal Neovascularization. In "ARVO", Invest. Ophthalmol. Vis. Sci., Vol. 43. E-Abstract. 3714		
	19	SAISHIN, Y., Saishin, Y., Takahashi, K., Lima e Silva, R., *et al.* (2003). VEGF-TRAP(R1R2) suppresses choroidal neovascularization and VEGF-induced breakdown of the blood-retinal barrier. J Cell Physiol 195:241-48		
	20	CURSIEFEN, C., Cao, J., Chen, L., Liu, Y., Maruyama, K., *et al.* (2004). Inhibition of hemangiogenesis and lymphangiogenesis after normal-risk corneal transplantation by neutralizing VEGF promotes graft survival. Invest Ophthalmol Vis Sci 45(8):2666-73		
	21	CURSIEFEN, C., Chen, L., Borges, L. P., Jackson, D., Cao, J., *et al.* (2004). VEGF-A stimulates lymphangiogenesis and hemangiogenesis in inflammatory neovascularization via macrophage recruitment. J Clin Invest 113(7):1040-50		
	22	CAO, J.; Song, H.; Renard, R.A.; Liu, Y.; Yancopolous, G.D.; Wiegand, S.J. (2005). Systemic Administration of VEGF Trap Suppresses Vascular Leak and Leukostasis in the Retinas of Diabetic Rats. In "ARVO", Vol. 46. Invest. Ophthalmol. Vis. Sci. E-Abstract 446		
	23	NORK, T. M., Dubielzig, R. R., Christian, B. J., Miller, P. E., Miller, J. M., *et al.* (2011). Prevention of experimental choroidal neovascularization and resolution of active lesions by VEGF trap in nonhuman primates. Arch Ophthalmol 129(8):1042-52		

Examiner Signature	/JON M LOCKARD/	Date Considered	10/21/2022

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	1	7070959	2006-07-04	Papadopoulos	
	2	7303746	2007-12-04	Wiegand	
	3	7303748	2007-12-04	Wiegand	
	4	7306799	2007-12-11	Wiegand	
	5	7396664	2008-07-08	Daly et al.	
	6	8092803	2012-01-10	Furfine et al.	
	7	9254338	2016-02-09	Yancopoulos	
	8	9669069	2017-06-06	Yancopoulos	
	9	10130681	2018-11-20	Yancopoulos	
	10	10406226	2019-09-10	Dix et al.	
	11	10464992	2019-11-05	Furfine et al.	

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	1	2003/0171320	2003-09-11	Guyer	
	2	2005/0163798	2005-07-28	Papadopoulos et al.	
	3	2005/0260203	2005-11-24	Wiegand et al.	
	4	2006/0058234	2006-03-16	Daly et al.	
	5	2006/0172944	2006-08-03	Wiegand et al.	
	6	2007/0190058	2007-08-16	Shams	
	7	2008/0220004	2008-09-11	Wiegand et al.	
	8	2019/0290725	2019-09-26	Vitti et al.	
	9	2019/0388539	2019-12-26	Dix et al.	
	10	2020/0017572	2020-01-16	Furfine et al.	

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	1	WO 2006/047325	2006-03-04	Genentech, Inc.		
	2	WO 2000/75319	2000-12-14	Regeneron Pharmaceuitcals, Inc.		
	3	WO 2004/106378 A2	2004-12-09	Regeneron Pharmaceuticals, Inc.		
	4	WO 2005/000895 A2	2005-01-05	Regeneron Pharmaceuticals, Inc.		
	5	WO 2007/022101 A2	2007-02-22	Regeneron Pharmaceuticals, Inc.		

Examiner Signature		Date Considered	

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	6	WO 2008/063932	2008-05-29	Genentech, Inc.		
	7	JP 2010-509369	2010-03-25	Genentech, Inc.	See WO 2008/063932 for English Equivalent	
	8	WO 2012/097019	2012-07-19	Regeneron Pharmaceuticals, Inc.		

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Examiner Initials*	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, 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	ADSIS R&D Profile "Aflibercept: AVE 0005, AVE 005, AVE0005, VEGF Trap - Regeneron, VEGF Trap (R1R2), VEGF Trap-Eye." Drugs R D, 9(4):261-269 (2008)		
	4	ANONYMOUS "Lucentis (rangibizymab injection) Intravitreal Injection" pp. 103 (June 2006)		
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	6	BARBAZETTO, "Dosing Regimen And The Frequency Of Macular Hemorrhages In Neovascular Age-Related Macular Degeneration Treated With Ranibizumab." Retina, 30(9):1376-85 (2010)		
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	10	BOYER, "A Phase IIIb Study to Evaluate the Safety of Ranibizumab in Subjects with Neovascular Age-related Macular Degeneration." Ophthalmology, 116(9):1731-39 (September 2009)		
	11	BROWN, "Ranibizumab versus Verteporfin for Neovascular Age-Related Macular Degeneration." N Engl J Med, 355(14):1432-44 (October 5, 2006)		
	12	BROWN, "Primary Endpoint Results of a Phase II Study of Vascular Endothelial Growth Factor Trap-Eye in Wet Age-related Macular Degeneration." Ophthalmology, 118(6):1089-97 (June 2011)		
	13	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)		
	14	BROWNING et al. "Aflibercept for age-related macular degeneration: a game-changer or quiet addition?" American Journal of Ophthalmology, 154(2):222-226 (August 2012)		

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	124	Regeneron SEC Form 10-Q (November 3, 2009)		
	125	Regeneron SEC Form 10-Q (April 29, 2010)		
	126	Regeneron SEC Form 10-Q (July 28, 2010)		
	127	Regeneron SEC Form 10-Q (October 28, 2010)		

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	130	Regeneron SEC Form 10-Q (October 27, 2011)		
	131	Regeneron SEC Form 8-K Exhibit: "Press Release of Regeneron Pharmaceuticals, Inc. dated May 1, 2006" (May 2, 2006)		
	132	Regeneron SEC Form 8-K Exhibit: "Press Release of Regeneron Pharmaceuticals, Inc. dated May 3, 2006" (May 5, 2006)		
	133	Regeneron SEC Form 8-K Exhibit: "Slides presented at the Company's 2006 Annual Meeting of Shareholders held on June 9, 2006" (June 9, 2006)		
	134	Regeneron SEC Form 8-K Exhibit: "Press Release dated May 2, 2007" (May 3, 2007)		
	135	Regeneron SEC Form 8-K Exhibit: "Overheads for presentation at Regeneron's Annual Meeting of Shareholders to be held on June 8, 2007" (June 8, 2007)		
	136	Regeneron SEC Form 8-K Exhibit: "Press Release dated October 1, 2007" (October 1, 2007)		
	137	Regeneron SEC Form 8-K Exhibit: "Press Release dated November 6, 2007" (November 6, 2007)		
	138	Regeneron SEC Form 8-K Exhibit: "Press Release dated May 1, 2008" (May 2, 2008)		
	139	Regeneron SEC Form 8-K Exhibit: "Press Release dated November 4, 2008" (November 4, 2008)		
	140	Regeneron SEC Form 8-K Exhibit: "99(a) Slides that Regeneron Pharmaceuticals, Inc. intends to use in conjunction with meetings with investors at the J.P. Morgan 27th Annual Healthcare Conference in San Francisco on January 12-15, 2009." (January 9, 2009)		
	141	Regeneron SEC Form 8-K Exhibit: "Press Release dated April 30, 2009" (May 1, 2009)		
	142	Regeneron SEC Form 8-K Exhibit: "Press Release dated November 3, 2009." (November 4, 2009)		
	143	Regeneron SEC Form 8-K Exhibit: "Press Release Reporting 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) dated December 20, 2010." (December 20, 2010)		
	144	Regeneron SEC Form 8-K Exhibit: "Press Release dated February 17, 2011" (February 18, 2011)		
	145	Regeneron SEC Form 8-K Exhibit: "Press Release Reporting Positive Results for VEGF Trap-Eye in Second Phase 3 Study in Central Retinal Vein Occlusion, dated April 27, 2011" (April 27, 2011)		
	146	Regeneron SEC Form 8-K Exhibit: "Press Release dated May 3, 2011." (May 3, 2011)		
	147	Regeneron SEC Form 8-K Exhibit: "Press Release, dated June 17, 2011, Announcing that EYLEA™ (aflibercept ophthalmic solution) Received Unanimous Recommendation for Approval for Treatment of Wet AMD from FDA Advisory Committee." (June 21, 2011)		

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	148	Regeneron SEC Form 8-K Exhibit: "Presentation entitled VEGF Trap-Eye in CRVO: 1-year Results of the Phase 3 COPERNICUS Study" (August 22, 2011)		
	149	Regeneron SEC Form 8-K Exhibit: "Press Release Announcing FDA Approval of EYLEA™ (aflibercept) Injection for the Treatment of Wet Age-Related Macular Degeneration, dated November 18, 2011" (November 21, 2011)		
	150	Regeneron Press Release "Positive Interim Phase 2 Data Reported For VEGF Trap-Eye In Age-Related Macular Degeneration" (March 27, 2007)		
	151	Regeneron Press Release "VEGF TRAP-Eye Phase 2 Wet AMD Results Reported At Arvo Annual Meeting" (May 9, 2007)		
	152	Regeneron Press Release "Regeneron Reports Second Quarter Financial And Operating Results" (August 1, 2007)		
	153	Regeneron Pharmaceuticals, Inc., "Regeneron and Bayer Healthcare Initiate Phase 3 Global Development Program for VEGF Trap-Eye In Wet Age-Related Macular Degeneration (AMD)" (August 2, 2007)		
	154	Regeneron Pharmaceuticals, Inc. FORM 10-Q, published on 7 November 2007 for the period ending 30 September 2007		
	155	Regeneron Press Release "Regeneron Announces Positive Primary Endpoint Results From A Phase 2 Study Of VEGF Trap-Eye In Age-Related Macular Degeneration" (October 1, 2007)		
	156	Regeneron Press Release "Regeneron Reports Fourth Quarter And Full Year 2007 Financial And Operating Results" (February 27, 2008)		
	157	Regeneron Pharmaceuticals, Inc., "Regeneron and Bayer HealthCare Announce Encouraging 32-Week Follow-up Results from a Phase 2 Study of VEGF Trap-Eye in Age-Related Macular Degeneration" (April 28, 2008)		
	158	Regeneron, Press release "Regeneron Reports First Quarter 2008 Financial and Operating Results", May 1, 2008.		
	159	Regeneron Press Release, "Bayer and Regeneron Dose First Patient in Second Phase 3 Study for VEGF Trap-Eye in Wet Age-Related Macular Degeneration." May 8, 2008		
	160	Regeneron Pharmaceuticals Inc., "CLEAR-IT-2: Interim Results Of The Phase II, Randomized, Controlled Dose-and Interval-ranging Study Of Repeated Intravitreal VEGF Trap Administration In Patients With Neovascular Age-related Macular Degeneration (AMD)" poster presented at the 2007 Association for Research in Vision and Ophthalmology meeting in Ft. Lauderdale, Florida (May 2007)		
	161	Regeneron Pharmaceuticals Inc., "An Exploratory Study of the Safety, Tolerability and Biological Effect of a Single Intravitreal Administration of VEGF Trap in Patients with Diabetic Macular Edema" poster presented at the 2007 Association for Research in Vision and Ophthalmology meeting in Ft. Lauderdale, Florida (May 2007)		
	162	Regeneron Pharmaceuticals Inc., "Optical Coherence Tomography Outcomes of a Phase 1, Dose-Escalation, Safety, Tolerability, and Bioactivity Study of Intravitreal VEGF Trap in Patients with Neovascular Age-Related Macular Degeneration: The CLEAR-IT 1 Study" poster presented at the 2007 Association for Research in Vision and Ophthalmology meeting in Ft. Lauderdale, Florida (May 2007)		

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	163	Regeneron Pharmaceuticals, Inc., "Regeneron and Bayer HealthCare Announce VEGF Trap-Eye Achieved Durable Improvement in Vision over 52 Weeks in a Phase 2 Study in Patients with Age-related Macular Degeneration" (August 19, 2008)		
	164	Regeneron Pharmaceuticals Inc., " VIEW 1 Vascular Endothelial Growth Factor (VEGF) Trap-Eye 1-Year Results: Investigation of Efficacy and Safety in Wet Age-Related Macular Degeneration (AMD) " presented at Bascom Palmer Eye Institute's Angiogenesis, Exudation and Degeneration 2011 meeting in Miami, Florida (February 12, 2011)		
	165	Regeneron Pharmaceuticals Inc., " VIEW 2 Vascular Endothelial Growth Factor (VEGF) Trap-Eye 1-Year Results: Investigation of Efficacy and Safety in Wet Age-Related Macular Degeneration (AMD) " presented at Bascom Palmer Eye Institute's Angiogenesis, Exudation and Degeneration 2011 meeting in Miami, Florida (February 12, 2011)		
	166	Regeneron Pharmaceuticals Inc., "VEGF Trap-Eye CLEAR-IT 2 Final Primary Endpoint Results" presented at the 2007 Retina Society Conference in Boston, Massachusetts (September 30, 2007)		
	167	Regeneron Pharmaceuticals Inc., "VEGF Trap-Eye Final Phase 2 Results in Age-related Macular Degeneration Presented at 2008 Retina Society Meeting" (September 28, 2008) (XP-002770952)		
	168	Regeneron 2008 Annual Report		
	169	Regeneron Pharmaceuticals, Inc. "Regeneron Reports Full Year and Fourth Quarter 2008 Financial and Operating Results" (February 26, 2009)		
	170	Regeneron Pharmaceuticals, Inc. "Bayer and Regeneron Extend Development Program for VEGF Trap-Eye to Include Central Retinal Vein Occlusion" (April 30, 2009)		
	171	Regeneron Press Release "First Patient Enrolled In Regeneron And Bayer Healthcare VEGF Trap-Eye Phase 3 Program In Central Retinal Vein Occlusion" (July 23, 2009)		
	172	Regeneron Press Release "Enrollment Completed in Regeneron and Bayer HealthCare Phase 3 Studies of VEGF Trap-Eye in Neovascular Age-Related Macular Degeneration (Wet AMD)" September 14, 2009		
	173	Regeneron 2009 Annual Report and 10-K		
	174	Regeneron Press Release, "VEGF Trap-Eye Shows Positive Results in a Phase 2 Study in Patients With Diabetic Macular Edema." February 18, 2010		
	175	Regeneron Press Release "Regeneron Schedules November 22, 2010 Teleconference And Webcast To Discuss Results Of Two Phase 3 Studies With VEGF Trap-Eye In Wet Age-Related Macular Degeneration" (November 19, 2010)		
	176	Regeneron Press Release "Bayer and Regeneron Report Positive Top-Line Results of Two Phase 3 Studies with VEGF Trap-Eye in Wet Age-related Macular Degeneration" November 22, 2010		
	177	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		
	178	Regeneron 2010 Annual Report and 10-K		
	179	Regeneron Press Release "Regeneron And Bayer Start Phase 3 Trial To Extend Ophthalmology Research & Development Program For VEGF Trap-Eye In Asia" (January 18, 2011)		

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	180	Regeneron Press Release "Regeneron To Webcast Investor Briefing On VEGF Trap-Eye Clinical Program On Sunday, February 13th At 9 Am Et" (February 9, 2011)		
	181	Regeneron Press Release "Regeneron Submits Biologics License Application To FDA For VEGF Trap-Eye For Treatment Of Wet Age-Related Macular Degeneration" (February 22, 2011)		
	182	Regeneron Press Release "Regeneron And Bayer Announce Start Of Phase 3 Clinical Program In Diabetic Macular Edema" (April 8, 2011)		
	183	Regeneron Pharmaceuticals, Inc., "FDA Grants Priority Review for VEGF Trap-Eye for the Treatment of Wet Age-Related Macular Degeneration" (April 18, 2011)		
	184	Regeneron Press Release "VEGF Trap-Eye Submitted for EU Marketing Authorization for Treatment of Wet Age-Related Macular Degeneration (June 7, 2011)		
	185	Regeneron Pharmaceuticals, Inc., "Regeneron Announces EYLEA™ (aflibercept ophthalmic solution) Receives Unanimous Recommendation for Approval for Treatment of Wet AMD from FDA Advisory Committee" (June 17, 2011)		
	186	Regeneron Press Release "Regeneron Announces Clinical Presentations at ASRS 2011 Annual Meeting" (August 17, 2011)		
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	193	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		
	194	RUDGE et al. "Clinical Development of VEGF Trap" In: Figg W.D., Folkman J. (eds) Angiogenesis (2008)		
	195	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)		

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	196	SCHMIDT-ERFURTH et al. "Primary Results of an International Phase III Study Using Intravitreal VEGF Trap-Eye Compared to Ranibizumab in Patients with Wet AMD (VIEW 2)" ARVO Annual Meeting Abstract (April 2011)		
	197	SCHMIDT-ERFURTH, "Three-Year Outcomes of Individualized Ranibizumab Treatment in Patients with Diabetic Macular Edema." Ophthalmology, 121(5):1045-53,(May 2014)		
	198	SCHMIDT-ERFURTH et al., "Intravitreal Aflibercept Injection for Neovascular Age-related Macular Degeneration" Ophthalmology (2014) 121:193-201		
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	202	SIMO AND HERNANDEZ, "Advances in Medical Treatment of Diabetic Retinopathy" Diabetes Care, 32(8):1556-1562 (August 2009)		
	203	SLAKTER et al., "Influence of Baseline Angiographic Classification on Outcomes in the CLEAR-IT 2 Phase 2 Study of Intravitreal VEGF Trap-Eye in Neovascular Age-Related Macular Degeneration" ARVO Annual Meeting Abstract (April 2010)		
	204	SLAKTER et al., "A Phase 2, Randomized, Controlled Dose-and Interval-Ranging Study of Intravitreal VEGF Trap-Eye in Patients with Neovascular Age-Related Macular Degeneration: Optical Coherence Tomography (OCT) and Fluorescein Angiography (FA) Outcomes at 1 Year" ARVO Annual Meeting Abstract (April 2009)		
	205	Slides for the 2008 Retina Society Meeting "VEGF Trap-Eye in Wet AMD CLEAR-IT 2: Summary of One-Year Key Results", September 28, 2008.		
	206	SPAIDE, "Ranibizumab According to Need: A Treatment for Age-related Macular Degeneration." Am J Ophthalmology, 143(4):679-680 (April 2007)		
	207	STEWART, "The expanding role of vascular endothelial growth factor inhibitors in opthamology" Mayo Clin Proc. 87(1):77-88 (January 2012)		
	208	STEWART et al., "Predicted biological activity of intravitreal VEGF Trap" British Journal of Ophthalmology, 92(5):667-668 (2008)		
	209	STEWART, "Aflibercept" Nature Reviews: Drug Discovery 11:269-270 (04/01/2012)		
	210	TANNOCK et al., "Aflibercept versus placebo in combination with docetaxel and prednisone for treatment of men with metastatic castration-resistant prostate cancer (VENICE): a phase 3, double-blind randomized trial" Lancet Oncol (2013) 14:760-768		
	211	THOMAS REUTERS INTEGRITY "VEGF Trap-Eye final phase II results in age-related macular degeneration presented at 2008 Retina Society Meeting" (September 28, 2008)		
	212	THURSTON, Gavin "Complementary actions of VEGF and Angiopoietin-1 on blood vessel growth and leakage" J. Anat. (2002) 200:575-580		
	213	THURSTON, "Vascular endothelial growth factor and other signaling pathways in developmental and pathologic angiogenesis." International Journal of Hematology, 80:7-20 (2004)		

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	214	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) 38 pages, Latest version submitted October 27, 2014 on ClinicalTrials.gov (NCT01012973_01182013_27424.1)		
	215	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) 10 pages, Latest version submitted October 27, 2014 on ClinicalTrials.gov (NCT01012973_01252011_27433.1)		
	216	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) 11 pages, Latest version submitted October 27, 2014 on ClinicalTrials.gov (NCT01012973_01262012_27428.1)		
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Examiner Initials*	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.		T
	232	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) 10 pages, Latest version submitted October 27, 2014 on ClinicalTrials.gov (NCT01012973_11012010_27434.1)		
	233	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_11132009_27444.1)		
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Examiner Signature		Date Considered	

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	To Be Assigned
				Filing Date	2020-12-04
				First Named Inventor	George D. YANCOPOULOS
				Art Unit	To Be Assigned
				Examiner Name	To Be Assigned
Sheet	18	of	18	Attorney Docket Number	REGN-008CIPCON8

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Examiner Signature	/JON M LOCKARD/	Date Considered	10/21/2022

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	17/112,404
				Filing Date	December 4, 2020
				First Named Inventor	George D. YANCOPOULOS
				Art Unit	~~To Be Assigned~~ 1647
				Examiner Name	~~To Be Assigned~~ Jon Lockard
Sheet	1	of	1	Attorney Docket Number	REGN-008CIPCON8

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
/J.L/	1	6897294	2005-05-24	Davis-Smyth et al.	

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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				

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	1					

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	REGN-008CIPCON8	17/112,404
	APPLICANT	
	Regeneron Pharmaceuticals, Inc.	
	FILING DATE	GROUP
	December 4, 2020	1647

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	5	7,378,095	5/27/2008	Cao *et al.*	not required per 69 Fed. Reg. 56481
	6	7,521,049	4/21/2009	Wiegand *et al.*	not required per 69 Fed. Reg. 56481
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	11	2004/0197324	10/7/2004	Liu *et al.*	not required per 69 Fed. Reg. 56481
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		DOCUMENT NUMBER	DATE	COUNTRY	TRANSLATION	REFERENCE PROVIDED*
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	15	97/04801	2/13/1997	WO	n/a	Herewith

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	FILING DATE	GROUP
	December 4, 2020	1647

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	19	Anderson *et al.*, "Delivery of Anti-Angiogenic Molecular Therapies for Retinal Disease" Drug Discovery Today 15: 272 (2010)	Herewith
	20	Article in Retinal Physician, "Subspecialty News", available online at http://www.retinalphysician.com/printarticle.aspx?articleID=104007 (March 2010)	Herewith
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	23	AVASTIN® label	Herewith
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SUBSTITUTE 1449 INFORMATION DISCLOSURE STATEMENT	ATTY. DOCKET NO.	APPLICATION NO.
	REGN-008CIPCON8	17/112,404
	APPLICANT	
	Regeneron Pharmaceuticals, Inc.	
	FILING DATE	GROUP
	December 4, 2020	1647

NON-PATENT LITERATURE DOCUMENTS			
		DOCUMENT (Including Author, Title, Date, Pertinent Pages, etc.)	REFERENCE PROVIDED*
	84	The Branch Vein Occlusion Study, G., "Argon laser photocoagulation for macular edema in branch vein occlusion" Am J Ophthalmol 98(3): 271-282 (1984)	Herewith
	85	The Central Vein Occlusion Study, G., "Evaluation of grid pattern photocoagulation for macular edema in central vein occlusion. The Central Vein Occlusion Study Group M report" Ophthalmology 102(10): 1425-1433 (1995)	Herewith
	86	U.S. DEP'T HEALTH & HUMAN SERVS., NAT'L INST. HEALTH, NAT'L EYE INST., "Age-Related Macular Degeneration: What You Should Know" (Sept. 2015) https://www.nei.nih.gov/sites/default/files/healthpdfs/WYSK_AMD_English_Sept2015_PRINT.pdf	Herewith
	87	U.S. DEP'T HEALTH & HUMAN SERVS., NAT'L INST. HEALTH, NAT'L EYE INST., "Diabetic Retinopathy: What You Should Know" (Sept. 2015), https://www.nei.nih.gov/sites/default/files/2019-06/Diabetic-Retinopathy-What-You-Should-Know-508.pdf	Herewith
	88	U.S. Department of Health and Human Services Food and Drug Administration, "Guidance for industry Q1A(R2) stability testing of new drug substances and products" Rockville, MD (November 2003)	Herewith
	89	Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Wet Age-Related Macular Degeneration (AMD) (VIEW1), NCT00509795, ClinicalTrials.gov (Apr. 28, 2009), https://clinicaltrials.gov/ct2/show/NCT00509795 ("NCT-795")	Herewith
	90	Wall Street Journal, "Genentech's Big Drug for Eyes Faces a Rival" (2007)	Herewith
	91	Wulff *et al.,* "Prevention of Thecal Angiogenesis, Antral Follicular Growth, and Ovulation in the Primate by Treatment with Vascular Endothelial Growth Factor Trap R1R2" Endocrinology 143(7): 2797-2807 (July 2002)	Herewith
	92	XOLAIR® label	Herewith
	93	Zarbin & Rosenfeld, "Pathway-Based Therapies for Age-Related Macular Degeneration: An Integrated Survey of Emerging Treatment Alternatives" Retina 30: 1350 (2010)	Herewith

EXAMINER	DATE CONSIDERED
/JON M LOCKARD/	10/21/2022

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BIB DATA SHEET

CONFIRMATION NO. 6437

SERIAL NUMBER	FILING or 371(c) DATE RULE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
17/112,404	12/04/2020	424	1647	REGN-008CIPCON8

APPLICANTS

REGENERON PHARMACEUTICALS, INC., Tarrytown, NY

INVENTORS

George YANCOPOULOS, Yorktown Heights, NY;

**** CONTINUING DATA ***************************

This application is a CON of 17/072,417 10/16/2020
which is a CON of 16/055,847 08/06/2018 PAT 10857205
and is a CON of 16/397,267 04/29/2019 PAT 10888601
which is a CON of 16/159,282 10/12/2018 PAT 10828345
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
(*)Data provided by applicant is not consistent with PTO records.

**** FOREIGN APPLICATIONS ***************************

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED ****

12/14/2020

Foreign Priority claimed ☐ Yes ☑ No 35 USC 119(a-d) conditions met ☐ Yes ☐ No Verified and Acknowledged /JON MCCLELLAND LOCKARD/ Examiner's Signature	☐ Met after Allowance Initials	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
		NY	1	34	3

ADDRESS

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

TITLE

USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS

FILING FEE RECEIVED		
3220	FEES: Authority has been given in Paper No._____ to charge/credit DEPOSIT ACCOUNT No._____ for following:	☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue) ☐ Other _____

BIB (Rev. 05/07).

		❑ Credit

PE2E SEARCH - Search History (Prior Art)

/J.L./

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	British Equivalents	Time Stamp
L1	9876	(flt1 OR vegfr1 OR (vegf ADJ r1)) SAME (flk1 OR kdr OR vegfr2 OR (vegf ADJ r2))	(US-PGPUB; USPAT; EPO; DERWENT)	OR	ON	ON	2022/10/22 02:11 PM
L2	1310	L1 SAME ((chimer$ OR fusion) SAME vegf)	(US-PGPUB; USPAT; EPO; DERWENT)	OR	ON	ON	2022/10/22 02:11 PM
L3	12949	aflibercept zaltrap eylea "vegf trap"	(US-PGPUB; USPAT; EPO; DERWENT)	OR	ON	ON	2022/10/22 02:12 PM
L4	418	(L2 L3) SAME ((eye OR ocular OR retina$ OR macular) WITH disorder)	(US-PGPUB; USPAT; EPO; DERWENT)	OR	ON	ON	2022/10/22 02:13 PM
L5	26	L4 AND @py<="2011"	(US-PGPUB; USPAT; EPO; DERWENT)	OR	ON	ON	2022/10/22 02:14 PM
L6	286	(L2 L3) WITH ((eye OR ocular OR retina$ OR macular) WITH disorder)	(US-PGPUB; USPAT; EPO; DERWENT)	OR	ON	ON	2022/10/22 02:15 PM
L7	11	L6 AND @py<="2011"	(US-PGPUB; USPAT; EPO; DERWENT)	OR	ON	ON	2022/10/22 02:15 PM
L8	543	yancopoulos-g$.in.	(US-PGPUB; USPAT; EPO; DERWENT)	OR	ON	ON	2022/10/22 02:16 PM
L9	94	(L2 L3) AND L8	(US-PGPUB; USPAT; EPO; DERWENT)	OR	ON	ON	2022/10/22 02:16 PM
L10	43	L9 AND treat$.clm.	(US-PGPUB; USPAT; EPO; DERWENT)	OR	ON	ON	2022/10/22 02:17 PM
L11	12	L10 AND aflibercept.clm.	(US-PGPUB; USPAT; EPO; DERWENT)	OR	ON	ON	2022/10/22 02:17 PM

PE2E SEARCH - Search History (Interference)

There are no Interference searches to show.

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U.S. PATENT DOCUMENTS					
		DOCUMENT NUMBER	DATE	NAME	REFERENCE PROVIDED*
	1.	US 2004/0213787 A1	2004-10-28	Sleeman *et al.*	not required per 69 Fed. Reg. 56481
	2.	US 6,833,349 B2	2004-12-21	Xia *et al.*	not required per 69 Fed. Reg. 56481
	3.	US 2004/0266688 A1	2004-12-30	Nayak	not required per 69 Fed. Reg. 56481
	4.	US 2005/0032699 A1	2005-02-10	Holash *et al.*	not required per 69 Fed. Reg. 56481
	5.	US 6,879,294 B2	2005-05-24	Davis-Smyth *et al.*	not required per 69 Fed. Reg. 56481
	6.	US 2005/0281822 A1	2005-12-22	Cedarbaum *et al.*	not required per 69 Fed. Reg. 56481
	7.	US 2006/0030000 A1	2006-02-09	Alitalo *et al.*	not required per 69 Fed. Reg. 56481
	8.	US 7,378,095 B2	2008-05-27	Cao *et al.*	not required per 69 Fed. Reg. 56481
	9.	US 7,482,002 B2	2009-01-27	Cedarbaum	not required per 69 Fed. Reg. 56481
	10.	US 2009/0264358 A1	2009-10-22	Yu	not required per 69 Fed. Reg. 56481
	11.	US 7,750,138 B2	2010-07-06	Fang *et al.*	not required per 69 Fed. Reg. 56481
	12.	US 7,951,585 B2	2011-05-31	Ke	not required per 69 Fed. Reg. 56481
	13.	US 8,216,575 B2	2012-07-10	Yu	not required per 69 Fed. Reg. 56481
	14.	US 2013/0295094 A1	2013-11-07	Yancopoulos	not required per 69 Fed. Reg. 56481
	15.	US 9,657,084 B2	2017-05-23	Ke *et al.*	not required per 69 Fed. Reg. 56481

FOREIGN PATENT DOCUMENTS						
		DOCUMENT NUMBER	DATE	COUNTRY	TRANSLATION	REFERENCE PROVIDED*
	16.	CN 1304427C	2007-03-14	China	Machine translation	Previously in US Application 17/072,417
	17.	CN 100502945C	2009-06-24	China	Corresponds to US 2009/0264358 A1	Previously in US Application 17/072,417
	18.	CN 100567325C	2009-12-09	China	Machine translation	Previously in US Application 17/072,417
	19.	WO 2012/097019	2012-07-19	WIPO	N/A	Previously in US Application 17/072,417
	20.	CN 102233132 B	2013-10-23	China	Machine translation	Previously in US Application 17/072,417

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	21.	CN 102380096 B	2014-04-30	China	Machine translation	Previously in US Application 17/072,417
	22.	CN 103212075 B	2017-06-27	China	Machine translation	Previously in US Application 17/072,417
	23.	CN 107115294 A	2017-09-01	China	Machine translation	Previously in US Application 17/072,417

NON-PATENT LITERATURE DOCUMENTS			
		DOCUMENT (Including Author, Title, Date, Pertinent Pages, etc.)	REFERENCE PROVIDED*
	24.	Anonymous, Meeting Archive Titled "PA003 Eighteen-Month Results From an Extension Study of a Phase 2, Dose- and Interval-Ranging Study of VEGF Trap-Eye in Wet AMD," presented by David S Boyer, MD at Moscone Center (October 2009)	Previously in US Application 17/072,417
	25.	Anonymous, Meeting Archive Titled "PA040 One-Year Results of the DA VINCI Study of VEGF Trap-Eye in Diabetic Macular Edema," presented by Diana V Do, MD at Orange County Convention Center (October 2011)	Previously in US Application 17/072,417
	26.	Anonymous, Meeting Archive Titled "PA080 One-Year Results of a Phase 2 Study of Intravitreal VEGF Trap-Eye in Patients with Neovascular Age-Related Macular Degeneration," presented by David S Boyer, MD at Georgia World Congress Center (November 2008)	Previously in US Application 17/072,417
	27.	Anonymous, Meeting Archive Titled "PO259 OCT and Fluorescein Angiography Outcomes Through 1 Year for a Phase 2 Study of Intravitreal VEGF Trap-Eye in Neovascular AMD," presented by Peter K Kaiser, MD at Moscone Center (October 2009)	Previously in US Application 17/072,417
	28.	Anonymous, Meeting Archive Titled "PO260 VEGF Trap-Eye Vision-Specific Quality of Life Through 52 Weeks in Patients with Neovascular AMD in CLEAR-IT 2: A Phase 2 Clinical Trial," presented by Allen C Ho, MD at Moscone Center (October 2009)	Previously in US Application 17/072,417
	29.	Anonymous, Meeting Archive Titled "PO492 One-Year Results of the VIEW 1 and VIEW 2 Studies: VEGF Trap-Eye in Wet AMD," presented by David M Brown MD at Orange County Center (October 2011)	Previously in US Application 17/072,417
	30.	Anonymous, Meeting Archive Titled "PO549 The 6-Month (Primary Endpoint) Results of the Phase 3 GALILEO Study: VEGF Trap-Eye in Central Retinal Vein Occlusion," presented by Jean-Francois Korobelnik, MD at Orange County Convention Center (October 2011)	Previously in US Application 17/072,417

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	31.	Anonymous, Meeting Archive Titled "PO571 OCT and Fluorescein Angiographic Outcomes Through 1 Year for the Phase 2 Study of Intravitreal VEGF Trap-Eye in Neovascular AMD," presented by Quan Dong Nguyen, MD at Georgia World Congress Center (November 2008)	Previously in US Application 17/072,417
	32.	Bontempo, "Preformulation Development of Parenteral Biopharmaceuticals," *Drugs and the Pharmaceutical Sciences*, 85:91-108 (1997)	Previously in US Application 17/072,417
	33.	Bressler, N. M. Treatment of Age-Related Macular Degeneration with Photodynamic Therapy Study Group, "Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin: two-year results of 2 randomized clinical trials-tap report 2," *Arch. Ophthalmol.,* 119(2):198-207 (2001)	Previously in US Application 17/072,417
	34.	Brown *et al.*, "Ranibizumab for Diabetic Macular Edema (DME): 24-Month Efficacy and Safety Results of RISE - a Phase 3 Randomized Controlled Trial," ARVO Annual Meeting Abstract, *Investigative Ophthalmology & Visual Science*, 52:6647 *(April 2011)*	Previously in US Application 17/072,417
	35.	Brown *et al.*, "Sustained benefits from ranibizumab for macular edema following branch retinal vein occlusion: 12-month outcomes of a phase III study," *Ophthalmology,* 118(8):1594-2049 (2011)	Previously in US Application 17/072,417
	36.	Cao *et al.*, "VEGF Trap Promotes Regression of Choroidal Neovascularization (CNV) and Inhibits Fibrosis and Inflammation in the Subretinal Matrigel CNV Model," ARVO Annual Meeting Abstract, *Investigative Ophthalmology & Visual Science,* 50:2979 (April 2009)	Previously in US Application 17/072,417
	37.	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>	Previously in US Application 17/072,417
	38.	Center for Drug Evaluation and Research BLA Application Number: 125156 Medical Review, (June 2006) <URL:https://www.accessdata.fda.gov/drugsatfda_docs/nda/2006/125156s0000_Lucentis_MedR.pdf>	Previously in US Application 17/072,417
	39.	Cheung *et al.*, "Combined anti-PIGF and anti-VEGF Therapy Ameliorates Pathological Neovascularization and Improves Retinal Revascularization in the Murine Model of Oxygen Induced Ischemic Retinopathy," ARVO Annual Meeting Abstract, *Investigative Ophthalmology & Visual Science*, 52:6064 (April 2011)	Previously in US Application 17/072,417
	40.	Dixon *et al.*, "VEGF Trap-Eye for the treatment of neovascular age-related macular degeneration," *Expert Opin. Investig. Drugs*, 18(10):1573-1580 (2009)	Previously in US Application 17/072,417

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NON-PATENT LITERATURE DOCUMENTS			
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	41.	The Eyetech Study Group, "Anti-Vascular Endothelial Growth Factor Therapy for Subfoveal Choroidal Neovascularization Secondary to Age-related Macular Degeneration," *Ophthalmology*, 110(5):979-986 (May 2003)	Previously in US Application 17/072,417
	42.	Heier *et al.*, "Ranibizumab for Choroidal Neovascularization Secondary to Causes Other Than Age-Related Macular Degeneration: A Phase I Clinical Trial," *Ophthalmology*, 118(1):111-118 (January 2011)	Previously in US Application 17/072,417
	43.	Heier, "Intravitreal Aflibercept for Diabetic Macular Edema: 148-Week Results from the VISTA and VIVID Studies," *Ophthalmology*, 123(11):2376-2385 (2016)	Previously in US Application 17/072,417
	44.	Herceptin label, September 1998	Previously in US Application 17/072,417
	45.	Information from ClinicalTrials.gov archive on the VIEW 2 study (NCT00637377) "VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD (VIEW 2)," v1 (March 17, 2008)	Previously in US Application 17/072,417
	46.	Ip *et al.*, "A randomized trial comparing the efficacy and safety of intravitreal triamcinolone with observation to treat vision loss associated with macular edema secondary to central retinal vein occlusion: the Standard Care vs Corticosteroid for Retinal Vein Occlusion (SCORE) study report 5," *Arch. Ophthalmol.,* 127(9):1101-1114 (2009)	Previously in US Application 17/072,417
	47.	Kaiser, "Vascular endothelial growth factor Trap-Eye for diabetic macular oedema," *Br. J. Ophthalmol.*, 93(2):135-36 (February 2009)	Previously in US Application 17/072,417
	48.	Korobelnik *et al.*, "Intravitreal Aflibercept Injection for Macular Edema Resulting from Central Retinal Vein Occlusion," *Ophthalmology,* 121(1):202-208 (2014)	Previously in US Application 17/072,417
	49.	Krzystolik *et al.*, "Prevention of Experimental Choroidal Neovascularization With Intravitreal Anti-Vascular Endothelial Growth Factor Antibody Fragment," *Arch. Ophthalmol.*, 120(3):338-346 (Mar. 2002)	Previously in US Application 17/072,417
	50.	Lalwani, "All About PrONTO: Study Yielded Good Results in AMD With Treatment Guided by OCT," *Retina Today* (May 2007)	Previously in US Application 17/072,417
	51.	Lobov *et al.*, "VEGF Trap Treatment Regresses Pathological Neovessels, Improves Revascularization and Reduces Retinal Ischemia in the Murine Oxygen-Induced Retinopathy (OIR) Model," ARVO Annual Meeting Abstract, *Investigative Ophthalmology & Visual Science*, 52:3128 (April 2011)	Previously in US Application 17/072,417
	52.	Lucentis Approval (June 30, 2006)	Previously in US Application 17/072,417
	53.	Lucentis Label Title, 7 pages, 06/2010 [Cited in Third Party Observations filed in parent application USSN 16/055,847 for which a copy is unavailable on PAIR]	Previously in US Application 17/072,417
	54.	Macular Photocoagulation Study Group, "Laser photocoagulation of subfoveal neovascular lesions in age-related macular degeneration. Results of a randomized clinical trial," *Arch. Ophthalmol.,* 109(9):1220-1231 (1991)	Previously in US Application 17/072,417

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	55.	Mitchell *et al.*, "Ranibizumab (Lucentis) in Neovascular Age-Related Macular Degeneration: Evidence from Clinical Trials," *Brit. J. Ophthalmology,* 94:2-13 (2010) (first online publication on May 20, 2009)	Previously in US Application 17/072,417
	56.	Mitra *et al.*, "Review of anti-vascular endothelial growth factor therapy in macular edema secondary to central retinal vein occlusions," *Expert Review in Ophthalmol.*, Taylor & Francis, GB 6(6):623-629 (January 2011)	Previously in US Application 17/072,417
	57.	Mousa and Mousa, "Current Status of Vascular Endothelial Growth Factor Inhibition in Age-Related Macular Degeneration," *Biodrugs*, 24(3):183-194 (2010)	Previously in US Application 17/072,417
	58.	Nguyen *et al.*, "A phase I trial of an IV-administered vascular endothelial growth factor trap for treatment in patients with choroidal neovascularization due to age-related macular degeneration," *Ophthalmology*, 113(9):1522e1-1522e14 (Sept 2006) (epub July 28, 2006)	Previously in US Application 17/072,417
	59.	Regeneron Pharmaceuticals Inc., "Regeneron Receives $20 Million Milestone Payment for Initiation of Phase 3 Study of VEGF Trap-Eye in Wet AMD," Media Release: 13 Aug 2007. Available from URL: http://www.regeneron.com	Previously in US Application 17/072,417
	60.	Regeneron Pharmaceuticals Inc., "An Exploratory Study of the Safety, Tolerability and Biological Effect of a Single Intravitreal Administration of VEGF Trap in Patients with Diabetic Macular Edema," poster presented at the 2007 Association for Research in Vision and Ophthalmology meeting in Ft. Lauderdale, Florida (May 2007)	Previously in US Application 17/072,417
	61.	Regeneron Pharmaceuticals Inc., "CLEAR-IT-2: Interim Results Of The Phase II, Randomized, Controlled Dose-and Interval-ranging Study Of Repeated Intravitreal VEGF Trap Administration In Patients With Neovascular Age-related Macular Degeneration (AMD)," poster presented at the 2007 Association for Research in Vision and Ophthalmology meeting in Ft. Lauderdale, Florida (May 2007)	Previously in US Application 17/072,417
	62.	Regeneron Pharmaceuticals Inc., "Optical Coherence Tomography Outcomes of a Phase 1, Dose-Escalation, Safety, Tolerability, and Bioactivity Study of Intravitreal VEGF Trap in Patients with Neovascular Age-Related Macular Degeneration: The CLEAR-IT 1 Study," poster presented at the 2007 Association for Research in Vision and Ophthalmology meeting in Ft. Lauderdale, Florida (May 2007)	Previously in US Application 17/072,417
	63.	Regeneron Pharmaceuticals Inc., "Regeneron Reports First Quarter 2008 Financial and Operating Results," Press release May 1, 2008.	Previously in US Application 17/072,417
	64.	Regeneron Pharmaceuticals Inc., Form 10-Q, published November 7, 2007, for the period ending September 30, 2007.	Previously in US Application 17/072,417

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	68.	Simo and Hernandez, "Advances in Medical Treatment of Diabetic Retinopathy," *Diabetes Care*, 32(8):1556-1562 (August 2009)	Previously in US Application 17/072,417
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	72.	WHO Drug Information, "International Nonproprietary Names for Pharmaceutical Substances (INN)," 20(2):115-119 (2006)	Previously in US Application 17/072,417

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SUBSTITUTE 1449 INFORMATION DISCLOSURE STATEMENT	ATTY. DOCKET NO.	APPLICATION NO.
	REGN-008CIPCON8	17/112,404
	APPLICANT	
	REGENERON PHARMACEUTICALS, INC.	
	FILING DATE	GROUP
	December 4, 2020	To be assigned

NON-PATENT LITERATURE DOCUMENTS - INSTITUTION DECISIONS			
		DOCUMENT (Including Author, Title, Date, Pertinent Pages, etc.)	REFERENCE PROVIDED*
	73.	IPR2021-00880 dated November 10, 2021, for US 9,669,069 B2	Previously in US Application 17/072,417
	74.	IPR2021-00881 dated November 10, 2021, for US 9,254,338 B2	Previously in US Application 17/072,417

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		DOCUMENT NUMBER	DATE	COUNTRY	TRANSLATION	REFERENCE PROVIDED*
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	86.	Bashshur *et al.*, "Intravitreal Bevacizumab for the Management of Choroidal Neovascularization in Age-Related Macular Degeneration," *Am. J. Ophthalmology*, 142(1):1-9 (2006)	Previously in US Application 17/072,417
	87.	Bayer Press Release, "Bayer and Regeneron Dose First Patient in Second Phase 3 Study for VEGF Trap-Eye in Wet Age-Related Macular Degeneration," May 8, 2008	Previously in US Application 17/072,417
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	17/112,404
				Filing Date	2020-12-04
				First Named Inventor	George D. YANCOPOULOS
				Art Unit	To Be Assigned 1647
				Examiner Name	To Be Assigned Jon Lockard
Sheet	1	of	1	Attorney Docket Number	REGN-008CIPCON8

U.S. PATENT DOCUMENTS

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

U.S. PATENT APPLICATION PUBLICATIONS

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NON PATENT LITERATURE DOCUMENTS

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/J.L/	1	HEIER, J., "Intravitreal VEGF Trap for AMD: An Update, The CLEAR-IT 2 Extension Study" Presented at the annual meeting of the Association for Research in Vision and Ophthalmology, Retina Today (2009) pp. 44-45		

Examiner Signature	/JON M LOCKARD/	Date Considered	10/21/2022

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Inventor Information for 17/112404

/J.L./

Inventor Name	City	State/Country
YANCOPOULOS, GEORGE	YORKTOWN HEIGHTS	NEW YORK

Appln Info | Contents | Petition Info | Atty/Agent Info | Continuity Data | Foreign Data | **Inventors** | Applicants | Address | Fees | Post Info | Pre Gr

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L1 4969 S (FLT1 OR VEGFR1 OR (VEGF (W) R1)) (S) (FLK1 OR KDR OR VEGFR2
L2 108 S L1 (P) (CHIMER? OR FUSION)
L3 18853 S AFLIBERCEPT OR ZALTRAP OR EYLEA OR "VEGF TRAP"
L4 121 S (L2 OR L3) (P) ((EYE OR OCULAR OR RETINA? OR MACULAR) (S) D
L5 68 DUP REM L4 (53 DUPLICATES REMOVED)
L6 0 S L5 AND @PD <=2011
L7 0 S L5 AND @PY <=2011
L8 0 S L5 AND @PD<=2011
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L9 2485 S E3 OR E4 OR E8 OR E9
L10 165 S (L2 OR L3) AND L9
L11 74 DUP REM L10 (91 DUPLICATES REMOVED)

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	1	US 7,087,411 B2	08/08/2006	Daly *et al.*	not required per 69 Fed. Reg. 56481

FOREIGN PATENT DOCUMENTS						
		DOCUMENT NUMBER	DATE	COUNTRY	TRANSLATION	REFERENCE PROVIDED*

NON-PATENT LITERATURE DOCUMENTS			
		DOCUMENT (Including Author, Title, Date, Pertinent Pages, etc.)	REFERENCE PROVIDED*
	2	Berker *et al.*, "Surgical treatment of central retinal vein occlusion," *Acta Ophthalmol.*, 86:245-252 (2008)	Herewith
	3	Byeon *et al.*, "Short-Term Results of Intravitreal Bevacizumab for Macular Edema with Retinal Vein Obstruction and Diabetic Macular Edema, *J. OCULAR PHARMACOLOGY AND THERAPEUTICS*, 23(4):387-394 (November 2007)	Herewith
	4	ClinicalTrials.gov, "1997: Congress Passes Law (FDAMA) Requiring Trial Registration," (1997), https://clinicaltrials.gov/ct2/about-site/history, submitted in IPR2023-00099 as Exhibit 1085 (last updated May 2021)	Herewith
	5	Corrections to Kiire *et al.*, "Managing Retinal Vein Occlusion," *BMJ*, 344(e2110):1 (2012)	Herewith
	6	Expert Declaration of Dr. Jay M. Stewart in Support of Petition for *Inter Partes* Review of U.S. Patent No. 10,857,205 B2, dated October 27, 2022, in IPR2023-00099	Herewith
	7	Expert Declaration of Mary Gerritsen, Ph.D. in Support of Petition for *Inter Partes* Review of U.S. Patent No. 10,857,205 B2, dated October 27, 2022, in IPR2023-00099	Herewith
	8	Gewaily *et al.*, "Intravitreal steroids versus observation for macular edema secondary to central retinal vein occlusion," *Cochrane Database Syst. Rev.*, 1(CD007324):1-31 (2009)	Herewith

EXAMINER	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.

*Copies of the listed references are either submitted herewith or were previously cited by or submitted to, the Office in a prior application. Pursuant to 37 C.F.R. § 1.97(d) and MPEP §609, the indicated reference may have been previously cited by or submitted to, the Office in a prior application, where the prior application is identified by its U.S. Application Number in this Information Disclosure Statement.

SUBSTITUTE 1449 INFORMATION DISCLOSURE STATEMENT	ATTY. DOCKET NO.	APPLICATION NO.
	REGN-008CIPCON8	17/112,404
	APPLICANT	
	REGENERON PHARMACEUTICALS, INC.	
	FILING DATE	GROUP
	December 4, 2020	1647

NON-PATENT LITERATURE DOCUMENTS			
		DOCUMENT (Including Author, Title, Date, Pertinent Pages, etc.)	REFERENCE PROVIDED*
	9	Golan *et al.*, "Current Treatment of Retinal Vein Occlusion," *Eur. Ophthalmic Rev.*, 5:62-68 (2011)	Herewith
	10	Keane *et al.*, "Retinal vein occlusion and macular edema – critical evaluation of the clinical value of ranibizumab," *Clinical Ophthalmology*, 5:771-781 (2011)	Herewith
	11	Kiire *et al.*, "Managing retinal vein occlusion," *BMJ*, 344(e499):1-16 (February 2012)	Herewith
	12	Kinge *et al.*, "Efficacy of Ranibizumab in Patients With Macular Edema Secondary to Central Retinal Vein Occlusion: Results From the Sham-Controlled ROCC Study," *American Journal of Ophthalmology*, 150(3):310-314 (2010)	Herewith
	13	Kreatsoulas, "Expanding Therapeutic Options for Retinal Vein Occlusion," *Retina Today*, pp. 20-21 (July/August 2009)	Herewith
	14	Petition for *Inter Partes* Review of U.S. Patent No. 10,857,205 B2, dated October 28, 2022, in IPR2023-00099	Herewith
	15	Pieramici, "Intravitreal Ranibizumab for Treatment of Macular Edema Secondary to Retinal Vein Occlusion," *Retina Today*, 44-46 (March 2009)	Herewith
	16	Regeneron Pharmaceuticals, Inc., "Bayer and Regeneron Extend Development Program for VEGF Trap-Eye to Include Central Retinal Vein Occlusion," Press Release, (Apr. 30, 2009), https://investor.regeneron.com/news-releases/news-release-details/bayer-and-regeneron-extend-development-program-vegf-trap-eye, submitted in IPR2023-00099 as Exhibit 1028 (last accessed November 4, 2022)	Herewith
	17	Regeneron Pharmaceuticals, Inc., "Regeneron and Bayer HealthCare Announce Encouraging 32-Week Follow Up Results from a Phase 2 Study of VEGF Trap-Eye in Age-Related Macular Degeneration," Press Release, (Apr. 28, 2008), http://newsroom.regeneron.com/releasedetail.cfm?releaseid=394066, submitted in IPR2023-00099 as Exhibit 1012 (last accessed November 11, 2022)	Herewith
	18	Regeneron Pharmaceuticals, Inc., "Regeneron Reports Third Quarter 2010 Financial Results and Business Highlights," Press Release (Oct. 28, 2010) https://investor.regeneron.com/news-releases/news-release-details/regeneron-reports-third-quarter-2010-financial-results-and, submitted in IPR2023-00099 as Exhibit 1058 (last accessed November 4, 2022)	Herewith

EXAMINER	DATE CONSIDERED

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SUBSTITUTE 1449 INFORMATION DISCLOSURE STATEMENT	ATTY. DOCKET NO.	APPLICATION NO.
	REGN-008CIPCON8	17/112,404
	APPLICANT	
	REGENERON PHARMACEUTICALS, INC.	
	FILING DATE	GROUP
	December 4, 2020	1647

NON-PATENT LITERATURE DOCUMENTS			
		DOCUMENT (Including Author, Title, Date, Pertinent Pages, etc.)	REFERENCE PROVIDED*
	19	Regeneron Pharmaceuticals, Inc., Quarterly Report Pursuant to Section 13 or 15(d) of the Securities Exchange Act of 1934 (Form 10-Q) , submitted in IPR2023-00099 as Exhibit 1021 (Sept. 30, 2009)	Herewith
	20	Regeneron Pharmaceuticals, Inc., Quarterly Report Pursuant to Section 13 or 15(d) of the Securities Exchange Act of 1934 (Form 10-Q) , submitted in IPR2023-00099 as Exhibit 1022 (Sept. 30, 2010)	Herewith
	21	Shahid *et al.*, "The Management of Retinal Vein Occlusion: is Interventional Ophthalmology the Way Forward?," *Br. J. Ophthalmology*, 90:627-639 (2006)	Herewith
	22	Sophie *et al.*, "Aflibercept: a Potent Vascular Endothelial Growth Factor Antagonist for Neovascular Age-Related Macular Degeneration and Other Retinal Vascular Diseases," *Biol. Ther.*, 2(3):1-22 (2012)	Herewith
	23	Wu *et al.*, "Comparison Of Two Doses Of Intravitreal Bevacizumab (Avastin) For Treatment Of Macular Edema Secondary To Branch Retinal Vein Occlusion," *Retina*, 28:212-219 (2008)	Herewith

EXAMINER	DATE CONSIDERED

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SUBSTITUTE 1449 INFORMATION DISCLOSURE STATEMENT	ATTY. DOCKET NO.	APPLICATION NO.
	REGN-008CIPCON8	17/112,404
	APPLICANT	
	REGENERON PHARMACEUTICALS, INC.	
	FILING DATE	GROUP
	December 4, 2020	1647

NON-PATENT LITERATURE DOCUMENTS - FINAL WRITTEN DECISIONS			
		DOCUMENT (Including Author, Title, Date, Pertinent Pages, etc.)	REFERENCE PROVIDED*
	24	Final Written Decision Determining All Challenged Claims Unpatentable Denying Petitioner's Motion to Exclude Evidence Denying in part and Dismissing in Part Patent Owner's Motion to Exclude Evidence dated November 9, 2022, in IPR2021-00880 dated November 9, 2022, for US 9,669,069 B2	Herewith
	25	Final Written Decision Determining All Challenged Claims Unpatentable Denying in part and Dismissing in part Petitioners' Motion to Exclude Denying in part and Dismissing in part Denying Patent Owner's Motion to Exclude dated November 9, 2022, in IPR2021-00881 dated November 9, 2022, for US 9,254,338 B2	Herewith

EXAMINER	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.

*Copies of the listed references are either submitted herewith or were previously cited by or submitted to, the Office in a prior application. Pursuant to 37 C.F.R. § 1.97(d) and MPEP §609, the indicated reference may have been previously cited by or submitted to, the Office in a prior application, where the prior application is identified by its U.S. Application Number in this Information Disclosure Statement.

Electronic Patent Application Fee Transmittal

Application Number:	17112404
Filing Date:	04-Dec-2020
Title of Invention:	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS
First Named Inventor/Applicant Name:	George YANCOPOULOS
Filer:	Karl Bozicevic/Kimberly Zuehlke
Attorney Docket Number:	REGN-008CIPCON8

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

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

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
SUBMISSION- INFORMATION DISCLOSURE STMT	1806	1	260	260
		Total in USD ($)		**260**

Electronic Acknowledgement Receipt

EFS ID:	47020321
Application Number:	17112404
International Application Number:	
Confirmation Number:	6437
Title of Invention:	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS
First Named Inventor/Applicant Name:	George YANCOPOULOS
Customer Number:	96387
Filer:	Karl Bozicevic/Kimberly Zuehlke
Filer Authorized By:	Karl Bozicevic
Attorney Docket Number:	REGN-008CIPCON8
Receipt Date:	14-NOV-2022
Filing Date:	04-DEC-2020
Time Stamp:	17:18:20
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$260
RAM confirmation Number	E2022ADH18442593
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	Transmittal Letter	REGN-008CIPCON8_2022-11-14_supp_IDS_trans.pdf	58743 d1c49611fdd16c6d3afd888ed447de39e90b4d27	no	5
Warnings:					
Information:					
2	Information Disclosure Statement (IDS) Form (SB08)	REGN-008CIPCON8_2022-11-14_Substitute_1449.pdf	46366 8052b5765ce30621bb0ea9f9caff55d0fd605409	no	4
Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
3	Fee Worksheet (SB06)	fee-info.pdf	38155 98e0fc182a025cf2bf068c33a62d27dd2f51b021	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	143264		

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

New Applications Under 35 U.S.C. 111

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

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

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

New International Application Filed with the USPTO as a Receiving Office

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

Electronically Filed

INFORMATION DISCLOSURE STATEMENT	Attorney Docket No.	REGN-008CIPCON8
	Confirmation No.	6437
	First Named Inventor	George D. Yancopoulos
	Application Number	17/112,404
	Filing Date	December 4, 2020
	Group Art Unit	1647
	Examiner Name	Jon McClelland Lockard
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:

The attention of the Examiner is invited to the documents listed on the attached Substitute 1449.

A copy of the U.S. patent listed on the attached Substitute 1449 is not submitted herewith, in accordance with the Strategic Plan Final Rule, 69 Fed. Reg. 56481-56547 (September 21, 2004), effective October 21, 2004.

Copies of the foreign publication and non-patent literature documents listed on the attached Substitute 1449 are submitted in parent U.S. Application No. 17/072,417.

It is respectfully requested that the information above be expressly considered during the prosecution of this application, and that the documents be made of record therein and appear among the "References Cited" on any patent to issue therefrom.

No aspect of these submissions constitute admission of prior art status or a disclaimer of claim scope.

Statement under 37 C.F.R. §§1.56 and 1.2

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

With respect to this statement under *McKesson*, Applicants wishes to bring to the Examiner's attention U.S. Patent Application No. 13/940,370, filed July 12, 2013, which issued as U.S. Patent No. 9,254,338 on February 9, 2016.

With respect to this statement under *McKesson*, Applicants wishes to bring to the Examiner's attention U.S. Patent Application No. 14/972,560, filed December 17, 2015, which issued as U.S. Patent No. 9,669,069 on June 6, 2017.

With respect to this statement under *McKesson*, Applicants wishes to bring to the Examiner's attention U.S. Patent Application No. 15/471,506, filed March 28, 2017, which issued as U.S. Patent No. 10,130,681 on November 20, 2018.

With respect to this statement under *McKesson*, Applicants wishes to bring to the Examiner's attention U.S. Patent Application No. 16/055,847, filed August 6, 2018, which issued as U.S. Patent No. 10,857,205 on December 8, 2020.

With respect to this statement under *McKesson*, Applicants wishes to bring to the Examiner's attention U.S. Patent Application No. 16/159,282, filed October 12, 2018, which issued as U.S. Patent No. 10,828,345 on November 10, 2020.

With respect to this statement under *McKesson*, Applicants wishes to bring to the Examiner's attention U.S. Patent Application No. 16/397,267, filed April 29, 2019, which issued as U.S. Patent No. 10,888,601 on January 12, 2021.

With respect to this statement under *McKesson*, Applicants wishes to bring to the Examiner's attention U.S. Patent Application No. 17/352,892, filed June 21, 2021, which issued as U.S. Patent No. 11,253,572 on February 22, 2022.

With respect to this statement under *McKesson*, Applicant wishes to bring to the Examiner's attention U.S. Patent Application No. 17/072,417, filed October 16, 2020. A Non-Final Office Action issued on October 17, 2022. A response thereto has not yet been filed.

With respect to this statement under *McKesson*, Applicant wishes to bring to the Examiner's attention U.S. Patent Application No. 17/112,063, filed December 4, 2020. A Non-Final Office Action issued on October 11, 2022. A response thereto has not yet been filed.

With respect to this statement under *McKesson*, Applicant wishes to bring to the Examiner's attention U.S. Patent Application No. 17/350,958, filed June 17, 2021.

With respect to this statement under *McKesson*, Applicant wishes to bring to the Examiner's attention U.S. Patent Application No. 17/740,744, filed May 10, 2022. A Notice of Allowance issued on November 14, 2022. A response thereto has not yet been filed.

With respect to this statement under *McKesson*, Applicant wishes to bring to the Examiner's attention *Inter Partes* Review Application No. IPR2021-00880 of U.S. Patent No. 9,669,069, filed on May 5, 2021. A Final Written Decision dated November 9, 2022, has been issued by PTAB.

With respect to this statement under *McKesson*, Applicant wishes to bring to the Examiner's attention *Inter Partes* Review Application No. IPR2021-00881 of U.S. Patent No. 9,254,338, filed on May 5, 2021. A Final Written Decision dated November 9, 2022, has been issued by PTAB.

With respect to this statement under *McKesson*, Applicant wishes to bring to the Examiner's attention *Inter Partes* Review Application No. IPR2022-01225 of U.S. Patent No. 10,130,681, filed on July 1, 2022; IPR2022-01226 of U.S. Patent No. 10,888,601, filed on July 1, 2022.

With respect to this statement under *McKesson*, Applicant wishes to bring to the Examiner's attention *Inter Partes* Review Application No. IPR2023-00099 of U.S. Patent No. 10,857,205, filed on October 28, 2022.

These documents and the corresponding file wrappers are available on PAIR or PTAB E2E, and thus are not provided with this communication. Please inform the undersigned if there is any difficulty in obtaining the documents from PAIR or PTAB E2E.

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-008CIPCON8.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: 14 November 2022

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

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