

April 19, 2024

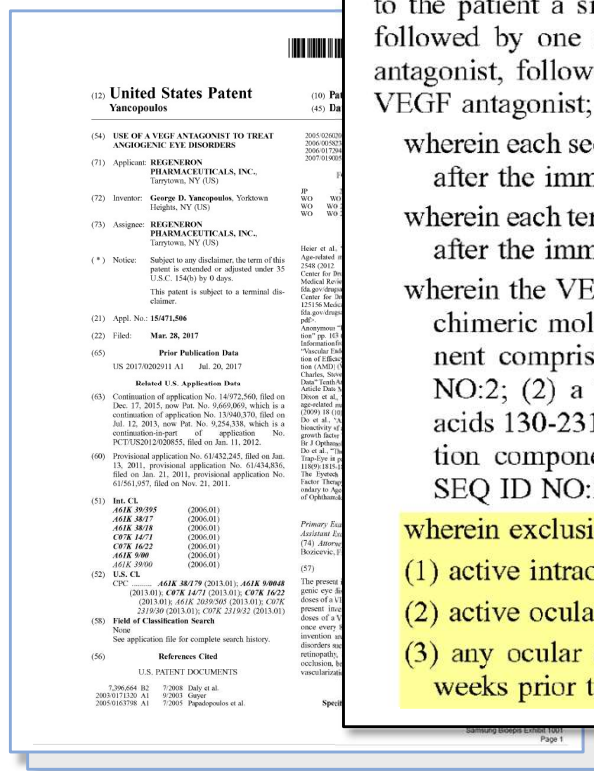
IPR2023-00442

U.S. Patent No. 10,130,681 B2

REGENERON[®]

Mylan v. Regeneron
IPR2023-00442
U.S. Pat. 10,130,681
Demonstrative Exhibit 2388

U.S. Patent No. 10,130,681: The Challenged Claims



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;

wherein the VEGF antagonist is a VEGF receptor-based chimeric molecule comprising (1) a VEGFR1 component comprising amino acids 27 to 129 of SEQ ID NO:2; (2) a VEGFR2 component comprising amino acids 130-231 of SEQ ID NO:2; and (3) a multimerization component comprising amino acids 232-457 of SEQ ID NO:2;

wherein exclusion criteria for the patient include all of:

- (1) active intraocular inflammation;
- (2) active ocular or periocular infection;
- (3) any ocular or periocular infection within the last 2 weeks prior to treatment.

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

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

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

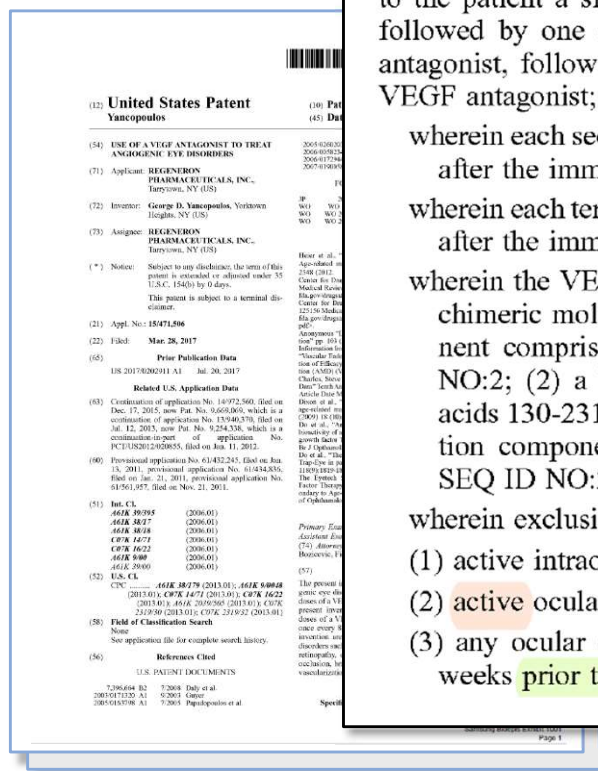
wherein the VEGF antagonist is a VEGF receptor-based chimeric molecule comprising VEGFR1R2-FcAC1(a) encoded by the nucleic acid sequence of SEQ ID NO:1;

wherein exclusion criteria for the patient include all of:

- (1) active intraocular inflammation;
- (2) active ocular or periocular infection;
- (3) any ocular or periocular infection within the last 2 weeks prior to treatment.

Exclusion Criterion 2 and Exclusion Criterion 3 Are Separate and Distinct Claim Limitations

Exclusion Criterion 2 (EC2) and Exclusion Criterion 3 (EC3)



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;

wherein the VEGF antagonist is a VEGF receptor-based chimeric molecule comprising (1) a VEGFR1 component comprising amino acids 27 to 129 of SEQ ID NO:2; (2) a VEGFR2 component comprising amino acids 130-231 of SEQ ID NO:2; and (3) a multimerization component comprising amino acids 232-457 of SEQ ID NO:2;

wherein exclusion criteria for the patient include all of:

- (1) active intraocular inflammation;
- (2) active ocular or periocular infection; ← EC2
- (3) any ocular or periocular infection within the last 2 weeks prior to treatment. ← EC3

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

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

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

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

- (1) active intraocular inflammation;
- (2) active ocular or periocular infection; ← EC2
- (3) any ocular or periocular infection within the last 2 weeks prior to treatment. ← EC3

Petitioner's Original Construction for EC2 and EC3

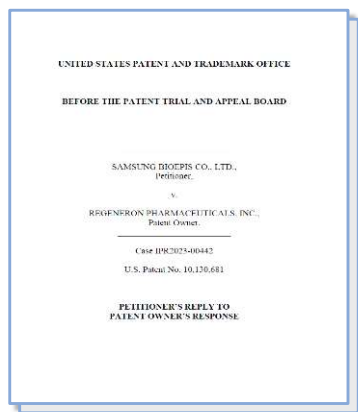
Petitioner construed EC2 and EC3 as separate and distinct limitations

Recited Condition	Plain and Ordinary Meaning
Active intraocular inflammation	Active, on-going inflammation in the interior of the eye, including the uvea
Active ocular or periocular infection	Active, on-going infection in or on the eye (including the anterior and posterior sections) (“ocular”) or in the area surrounding the eye and within its orbit (i.e. the conjunctiva or muscles controlling the eye, etc.) (“periocular”)
Any ocular or periocular infection within the last two weeks	Recent infection within the prior two weeks in or on the eye or in the area surrounding the eye and within its orbit

Ex.1002 at ¶ 92; IPR Petition for '681 Patent, Paper 2 at 2

Petitioner's Change in Position

Petitioner now conflates EC2 and EC3



Dr. Edward Chaum

Petitioner's Expert

Patent Owner's construction also unnecessarily interjects an artificial distinction between "active" and "resolved" into the claims.

Petitioner's Reply, Paper 40 at 7

Q. ...So you don't view exclusion criteria number two and exclusion criteria number three to be different?

...

A. I think they're substantially the same from the perspective of the practitioner.

Ex.2384 at 122:18-24 (objections omitted); see also PO's Response, Paper 26 at 3, 18-19

Petitioner's Proposed Construction Renders EC2 Superfluous

 US01013081B2	
(15) United States Patent Yancopoulos	(10) Patent No.: US 10,130,681 B2 (45) Date of Patent: *Nov. 20, 2018
(54) USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS (71) Applicant: REGENERON PHARMACEUTICALS, INC. , Tarrytown, NY (US) (72) Inventor: George D. Yancopoulos , Yorktown Heights, NY (US) (73) Assignee: REGENERON PHARMACEUTICALS, INC. , Tarrytown, NY (US)	
(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days. This patent is subject to a terminal disclaimer.	
(21) Appl. No.: 15/071,596 (22) Filed: Mar. 28, 2017 (65) Prior Publication Data US 2017/082091 A1 Jul. 20, 2017 Related U.S. Application Data (63) Continuation of application No. 14/972,560, filed on Dec. 17, 2015, now Pat. No. 9,669,007, which is a continuation of application No. 13,940,370, filed on Jul. 12, 2013, now Pat. No. 9,254,338, which is a continuation-in-part of application No. PCT/US2012/028555, filed on Jun. 11, 2012. (60) Provisional application No. 61/432,245, filed on Jun. 13, 2011; provisional application No. 61/434,836, filed on Jun. 21, 2011; provisional application No. 61/561,657, filed on Nov. 21, 2011.	
Int. Cl. A61K 39/395 (2006.01) A61K 38/27 (2006.01) A61K 38/18 (2006.01) C07K 14/71 (2006.01) C07K 16/22 (2006.01) A61K 9/00 (2006.01) A61K 39/00 (2006.01) U.S. Cl. C07C (2013.01); A61K 39/00 (2013.01); C07K 14/71 (2013.01); C07K 16/22 (2013.01); A61K 30/30 (2013.01); C07K 23/39 (2013.01); C07K 23/32 (2013.01)	
Field of Classification Search None See application file for complete search history.	
References Cited U.S. PATENT DOCUMENTS 7,396,664 B2 *2008 Daly et al. 2003/0171328 A1 *2003 Corser 2003/0167709 A1 *2003 Papanicolaou et al.	
26 Claims, 1 Drawing Sheet Specification Includes a Sequence Listing.	
Samsung Bioeip Exhibit 1001 Page 1	

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;

wherein the VEGF antagonist is a VEGF receptor-based chimeric molecule comprising (1) a VEGFR1 component comprising amino acids 27 to 129 of SEQ ID NO:2; (2) a VEGFR2 component comprising amino acids 130-231 of SEQ ID NO:2; and (3) a multimerization component comprising amino acids 232-457 of SEQ ID NO:2;

wherein exclusion criteria for the patient include all of:

(1) active intraocular inflammation;

(2) ~~active ocular or periorbital infection~~; ← **EC2**

(3) any ocular or periorbital infection within the last 2 weeks prior to treatment. ← **EC3**

Petitioner's Proposed Construction Ignores the Express Temporal Language of the Claims

 US010130681B2	
(12) United States Patent Yancopoulos	(10) Patent No.: US 10,130,681 B2 (45) Date of Patent: *Nov. 20, 2018
(54) USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS	
(71) Applicant: REGENERON PHARMACEUTICALS, INC., Tarrytown, NY (US)	
(72) Inventor: George D. Yancopoulos, Yorktown Heights, NY (US)	
(73) Assignee: REGENERON PHARMACEUTICALS, INC., Tarrytown, NY (US)	
(**) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days. This patent is subject to a terminal disclaimer.	
(21) Appl. No.: 15/471,546	
(22) Filed: Mar. 28, 2017	
(65) US 2017/0200311 A1 Jul. 20, 2017 Related U.S. Application Data	
(63) Continuation of application No. 14/972,560 , filed on Dec. 17, 2015, now Pat. No. 9,669,069, which is a continuation of application No. 13/940,370, filed on Jul. 12, 2013, now Pat. No. 9,254,338, which is a continuation-in-part of application No. PCT/US2012/020555, filed on Jun. 11, 2012.	
(60) Provisional application No. 61/432,245 , filed on Jan. 13, 2011, provisional application No. 61/434,886, filed on Jan. 21, 2011, provisional application No. 61/561,957, filed on Nov. 21, 2011.	
(51) Int. Cl. A61K 39/395 (2006.01) A61K 38/37 (2006.01) A61K 38/38 (2006.01) C07K 16/71 (2006.01) C07K 16/22 (2006.01) A61K 39/00 (2006.01)	
(52) U.S. Cl. CPC: A61K 38/37 (2013.01), A61K 39/395 (2013.01), C07K 16/71 (2013.01), C07K 16/22 (2013.01), A61K 2029/503 (2013.01), C07K 231/93 (2013.01), C07K 231/932 (2013.01)	
(58) Field of Classification Search None See application file for complete search history.	
(56) References Cited U.S. PATENT DOCUMENTS 7,396,664 B2 7/2008 Daly et al. 2003/0171330 A1 9/2003 Cyster 2005/0161708 A1 7/2005 Yancopoulos et al.	
FOREIGN PATENT DOCUMENTS JP 2010-091949 3/2010 WO 2006/072319 12/2006 WO 2007/021101 A2 2/2007 WO 2008/063032 5/2008	
OTHER PUBLICATIONS Huter et al., "Intravitreal Anti-VEGF (VEGF Trap-Eye) in Wet Age-Related Macular Degeneration," Ophthalmology, 119:2157-2168 (2012). Center for Drug Evaluation and Research Application No. 21-756 Medical Review(Doc. 17, 2004)-CER, http://www.accessdata.fda.gov/drugsatfda_docs/nda/2004/21-756_Matrgn_mol.pdf . Center for Drug Evaluation and Research H.U.A. Application No. 125156 Medical Review (Jun. 2006)-CER, http://www.accessdata.fda.gov/drugsatfda_docs/nda/2006/125156s01_Lucanta_Moltr.pdf . Anonymous "Lucanta (macular injections) Intravitreal Injection" pp. 10 (Jan. 2009). Information from ClinicalTrials.gov archive View of NCT00673737 "Intravitreal Injections of VEGF Trap-Eye (Eylea) for the Treatment of Efficacy and Safety in Wet Age-Related Macular Degeneration (AMD) (Vinc 27) ClinicalTrials.gov Web Site, 10, 2010. Charles, Steve (Genentech) "VEGF Trap Has Positive DME Data" Genentech Annual Report Form Jan. 29 and 30, 2010. Article Date Mar. 1, 2010. Dione et al., "VEGF Trap-Eye for the treatment of neovascular age-related macular degeneration" Expert Opin. Invest. Drugs (2009) 19:1019-1024. De et al., "An exploratory study of the safety, tolerability and bioactivity of a single intravitreal injection of vascular endothelial growth factor trap-eye in patients with diabetic macular oedema" Br J Ophthalmol, 95(7):841-849 (Feb. 2009). De et al., "The De Vinci Study: phase 2 primary results of VEGF Trap-Eye in patients with diabetic macular oedema" Ophthalmology 118(9):1819-1826 (Sep. 2011). The French Study Group, "Anti-Vascular Endothelial Growth Factor Therapy for Intraocular Chorioidal Neovascularization Secondary to Age-Related Macular Degeneration," American Academy of Ophthalmology, 110(5):979-986 (May 2005). (Continued)	
Primary Examiner — Christine J. Saeed Assistant Examiner — Jon M. Lockard (74) Attorney, Agent, or Firm — Karl Boesche, Boesche, Field & Francis LLP	
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 central seroid chorioretinopathy.	
28 Claims, 1 Drawing Sheet Specification includes a Sequence Listing.	
Samsung Bioepis Exhibit 1001 Page 1	

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;

wherein the VEGF antagonist is a VEGF receptor-based chimeric molecule comprising (1) a VEGFR1 component comprising amino acids 27 to 129 of SEQ ID NO:2; (2) a VEGFR2 component comprising amino acids 130-231 of SEQ ID NO:2; and (3) a multimerization component comprising amino acids 232-457 of SEQ ID NO:2;

wherein exclusion criteria for the patient include all of:

- (1) active intraocular inflammation;
- (2) ~~active~~ ocular or periocular infection; ← **EC2**
- (3) any ocular or periocular infection within the last 2 weeks ~~prior to treatment~~. ← **EC3**

Petitioner's Proposed Construction Has No Support in the Intrinsic Evidence



Dr. Edward Chaum

Petitioner's Expert

"I don't have any direct experience in the design and language of clinical trials."

Ex.2384 at 297:25-298:1

Q. ...So you don't view exclusion criteria number two and exclusion criteria number three to be different?

...

A. I think they're substantially the same from the perspective of the practitioner.

Ex.2384 at 122:18-24 (objections omitted)

Q. And to arrive at your interpretation of what each of these exclusion criteria limitations mean, you did not consult the specification of the 681 patent, correct? . . .

A. Correct.

Q. Okay. And also, in arriving at your plain and ordinary meaning of these exclusion criteria limitations of the challenged claim, you did not consult or rely on the prosecution history of the 681 patent, correct?

A. I did not.

Ex.2384 at 263:12-264:3 (objections omitted)

Petitioner's Proposed Construction Is Contrary to the Intrinsic Evidence

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

Exclusion criteria for both studies were as follows:

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.

(12) United States Patent Yancopoulos

(54) USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS

(71) Applicant: REGENERON PHARMACEUTICALS, INC., Tarrytown, NY (US)

(72) Inventor: George D. Yancopoulos, Yorktown Heights, NY (US)

(73) Assignee: REGENERON PHARMACEUTICALS, INC., Tarrytown, NY (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days. This patent is subject to a terminal disclaimer.

(21) Appl. No.: 15/071,566

(22) Filed: Mar. 26, 2017

(65) Prior Publication Data

US 2017/0020911 A1 Jul. 20, 2017

(65) Related U.S. Application Data

Continuation of application No. 14/972,560, filed on Dec. 17, 2015, now Pat. No. 9,669,069, which is a continuation of application No. 13/940,370, filed on Jul. 12, 2015, now Pat. No. 9,254,338, which is a continuation-in-part of application No. PCT/US2012/020655, filed on Jan. 11, 2012.

(66) Provisional application No. 61/432,245, filed on Jun. 13, 2011, provisional application No. 61/434,836, filed on Jun. 21, 2011, provisional application No. 61/561,957, filed on Nov. 21, 2011.

(51) Int. Cl.

A61K 39/095 (2006.01)

A61K 38/17 (2006.01)

A61K 38/18 (2006.01)

C07K 14/71 (2006.01)

C07K 16/22 (2006.01)

A61K 38/00 (2006.01)

A61K 39/00 (2006.01)

(52) U.S. Cl.

CPC — A61K 38/17 (2013.01); A61K 38/00 (2013.01); C07K 14/71 (2013.01); C07K 16/22 (2013.01); A61K 20/30 (2013.01); C07K 21/93 (2013.01)

(53) Field of Classification Search

None

See application file for complete search history.

(56) References Cited

U.S. PATENT DOCUMENTS

7,398,664 B2 7/2008 Daly et al.

2003/0171320 A1 9/2003 Orger

2005/0183798 A1 7/2005 Papapanagos et al.

US 10,130,681 B2

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cizumab) 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 (refractive 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 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 intravitreal or periorbital 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 intravitreal 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 uveitis or uveitis in either eye. 23. Previous history of scleromalacia in either eye. 24. Aphakia or pseudophakia with absence of posterior capsule (unless it occurred as a result of cataract surgery). 25. Previous history of scleromalacia in either eye. 26. Previous therapeutic radiation in the region of the study eye. 27. History of corneal transplant or corneal dystrophy in the study eye. 28. Significant media opacities, including cataract, in the study eye which might interfere with visual acuity, assessment of safety, or fundus photography. 29. Any concurrent intravitreal 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. 30. 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 intravitreal injection, or which otherwise may interfere with the injection procedure or with evaluation of efficacy or safety. 31. History of any 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. 32. Participation as a subject in any clinical study within the 12 weeks prior to

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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 intravitreally, 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. 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, intrascleral or periorbital routes), as well as those administered systemically with the intent of treating the study eye and/or fellow eye. The study procedures are summarized as follows: 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. 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. OCT images 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. Fundus Photography and Fluorescein Angiography (FA): The anatomical state of the retinal vasculature of the study eye was evaluated by funduscopy examination, fundus photography and FA. At the Screen Visit (Visit 1) funduscopy examination, fundus photography and FA were captured and transmitted for both eyes. Fundus photography 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 FA 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. 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 screen-

Patent Owner's Construction for EC2 and EC3

EC2 and EC3 are distinct limitations, with express temporal language

Claim term	PO's Proposed Construction
"(2) active ocular or periocular infection"	active, ongoing ocular or periocular infection
"(3) any ocular or periocular infection within the last 2 weeks prior to treatment"	any ocular or periocular infection within the last 2 weeks prior to treatment, which is no longer active at the time of treatment

PO's Response, Paper 26 at 19; Ex.2056 at ¶ 120

Proposed Constructions for EC2 and EC3

	PO's Proposed Construction	Petitioner's Proposed Construction
Honors the temporal language of the claims	✓	✗
Is supported by the intrinsic evidence	✓	✗
Avoids rendering EC2 superfluous	✓	✗

The Word “Any” Refers to Disease Type, Not Timing

(12) **United States Patent**
Yancopoulos

(10) Patent
(45) Date

(71) Applicant: **REGENERON PHARMACEUTICALS, INC.**, Tarrytown, NY (US)

(72) Inventor: **George D. Yancopoulos**, Yorktown Heights, NY (US)

(73) Assignee: **REGENERON PHARMACEUTICALS, INC.**, Tarrytown, NY (US)

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(21) Appl. No.: 13/471,566

(22) Filed: Mar. 28, 2017

(65) Prior Publication Data
US 2017/0202911 A1 Jul. 20, 2017

Related U.S. Application Data:
(63) Continuation of application No. 14/972,560, filed on Dec. 17, 2015, now Pat. No. 9,669,069, which is a continuation of application No. 13/940,370, filed on Jul. 12, 2015, now Pat. No. 9,254,338, which is a continuation-in-part of application No. PCT/US2012/020085, filed on Jan. 11, 2012.

(60) Provisional application No. 61/432,245, filed on Jan. 13, 2011, provisional application No. 61/434,836, filed on Jan. 21, 2011, provisional application No. 61/561,957, filed on Nov. 21, 2011.

(51) Int. Cl.
A61K 39/395 (2006.01)
A61K 38/17 (2006.01)
A61K 30/18 (2006.01)
C07K 16/11 (2006.01)
C07K 16/22 (2006.01)
A61K 39/00 (2006.01)
A61K 39/00 (2006.01)

(52) U.S. Cl.
CPC — *A61K 38/17* (2013.01), *A61K 39/00* (2013.01), *C07K 16/11* (2013.01), *C07K 16/22* (2013.01), *A61K 30/18* (2013.01), *C07K 231/39* (2013.01), *C07K 231/92* (2013.01)

(58) Field of Classification Search
None
See application file for complete search history.

(56) References Cited
U.S. PATENT DOCUMENTS
7,396,661 B2 7/2004 Daly et al.
2003/0171330 A1 9/2003 Goner
2005/0163798 A1 7/2005 Papadopoulos et al.

US 10,130,681 B2

1
USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. patent application Ser. No. 14/972,560, filed Dec. 17, 2015, now U.S. Pat. No. 9,669,069 issued Jun. 6, 2017 which is a continuation of U.S. patent application Ser. No. 13/940,370 filed Jul. 12, 2015, now U.S. Pat. No. 9,254,338 issued Feb. 9, 2016 which is a continuation-in-part of International Patent Application No. PCT/US2012/020085, filed on Jan. 11, 2012, which claims the benefit of US Provisional Application Nos. 61/432,245, filed on Jan. 13, 2011, 61/434,836, filed on Jan. 21, 2011, and 61/561,957, filed on Nov. 21, 2011, the contents of which are hereby incorporated by reference in their entirety.

FIELD OF THE INVENTION

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

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.

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.

Methods for treating eye disorders using VEGF antagonists are mentioned in, e.g., U.S. Pat. Nos. 7,303,746; 7,306,799; 7,300,563; 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

The present invention provides methods for treating angiogenic eye disorders. The methods of the invention

2

comprise sequentially administering multiple doses of a VEGF antagonist to a patient over time. In particular, the methods of the invention comprise sequentially administering a VEGF antagonist to a patient at a frequency of once every 8 or more weeks, especially when such doses are preceded by about three doses administered to the patient at a frequency of about 2 to 4 weeks. Thus, according to the methods of the present invention, each secondary dose of VEGF antagonist is administered 2 to 4 weeks after the immediately preceding dose, and each tertiary dose is administered at least 8 weeks after the immediately preceding dose. An example of a dosing regimen of the present invention is shown in the FIGURE. One advantage of such a dosing regimen is that, for most of the course of treatment (i.e., the tertiary dose), it allows for less frequent dosing (e.g., once every 8 weeks) compared to prior administration regimens for angiogenic eye disorders which require multiple administrations throughout the entire course of treatment. (See, e.g., prescribing information for Lucentis®, Genentech, Inc.)

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.

The methods of the present invention comprise administering any VEGF antagonist to a patient. In one embodiment, the VEGF antagonist comprises a recombinant VEGF receptor-based chimeric molecule(s), (also referred to herein as a “VEGF-Trp” 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 “VEGFR2-FcAC10” or “nilvatercept.”

Various administration routes are contemplated for use in the methods of the present invention, including, e.g., topical administration or intracocular administration (e.g., intravitreal administration).

Alibioncept (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.

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

BRIEF DESCRIPTION OF THE FIGURE

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

DETAILED DESCRIPTION

Before the present invention is described, it is to be understood that this invention is not limited to particular

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.

Ground 1: Petitioner's References Do Not Render All Exclusion Criteria Obvious

Ground 1: Petitioner's References for EC3

CATT Ex.1031

MACTEL Exs.1032-33

Expert Opinion

- 1. Introduction
- 2. Background
- 3. Conclusion
- 4. Expert opinion

VEGF Trap-Eye for the treatment of neovascular age-related macular degeneration

James A Olson, Susan CMA O'Neil¹, Jeffrey J Olson² & Niyoshi Mandelkern³
*University of Colorado Health Science Center, Denver, Colorado, Department of Ophthalmology,
¹Department of Neurology, ²Department of Ophthalmology, ³Department of Chemistry, University of Colorado, Denver, Colorado, USA*

Background: Age-related macular degeneration (AMD) affects ~14 million individuals worldwide. Although 90% of patients with AMD have the dry form, neovascular AMD accounts for the vast majority of patients who develop legal blindness. Until recently, few treatment options existed for treatment of neovascular AMD. The advent of anti-VEGF therapy has significantly improved the safety and effectiveness of treatment of neovascular AMD, in addition to the fact anti-VEGF drug classes are in widespread use, combination and monotherapy, a number of indications that interest ophthalmologists are currently under investigation. One promising new drug is aflibercept (VEGF Trap-Eye), a fusion protein that blocks all isoforms of VEGF-A and partially growth factors b and c. Objective: To review the current literature and initial trial data regarding VEGF Trap-Eye for the treatment of neovascular AMD. Methods: Literature reviews of neovascular AMD, VEGF Trap-Eye, a novel anti-VEGF therapy with Phase I and II trial data indicating safety, tolerability and efficacy for the treatment of neovascular AMD. We reviewed the clinical trial VISION I and VISION II comparing VEGF Trap-Eye to ranibizumab are currently continuing and will provide new insight into the clinical applicability of the drug.

Keywords: aflibercept, AMD, neovascularization, VEGF, VEGF inhibition, VEGF Trap

Expert Opin. Invest. Drugs (2009) 19(10), 1033-1035 (Review)

1. Introduction

Age-related macular degeneration (AMD) affects ~17 million individuals in the US and it is estimated that by 2030 this number will increase to about 3 million in the US alone. Worldwide, AMD is reported to affect 14 million people [1]. While the true number of patients suffering from AMD has not been ascertained, it is likely that patients develop severe vision loss due to the disease or fear loss of their vision [2]. Until recently, little therapeutic had been proven other than to inhibit smoking, exercise AMD. In more recent, published literature, ranibizumab (CNV) was treated with eyes have therapy resulting in the best results [3]. While the results of the VISION I and II trials, in the setting of subfoveal disease, are encouraging for a number of reasons, including the higher benefits to visual acuity and the high rate of treatment, certain additional issues [4]. Treatment responses improved with combination of photodynamic therapy (PDT) which yielded a permanent reduction in the need for treatment [5]. While more efficacious than previous treatments, patients receiving VEGF Trap-Eye in phase I and II clinical studies had a decrease in the need to visit and the treatment was of generally not associated with adverse events [6].

The latest human development of agents that inhibit VEGF has largely superseded these previous treatments. The pathogenesis of CNV is the tearing of

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healthcare

1033

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http://www.informahc.com

CATT PATIENT ELIGIBILITY CRITERIA

Inclusion Criteria

All patients must meet the following criteria for entry into the CATT: Lucentis-Avastin Trial:

- Signed informed consent form.
- Age ≥ 50 years of either gender
- Women must be postmenopausal for at least 12 months prior to trial entry, or surgically sterile. If of child bearing potential, a serum pregnancy test with a negative result must be obtained within 14 days prior to the first treatment.
- Women of child bearing potential must be practicing effective contraception implemented during the trial and for at least 60 days following the last dose of study medication.
- No condition that precludes follow-up for 2 years.
- No contraindication to intravitreal injection of Lucentis® or Avastin®, as specified in the exclusion criteria below.

Eligibility criteria for study eyes

Study eyes must meet the following criteria for entry into the CATT: Lucentis-Avastin Trial:

- Newly diagnosed, angiographically documented, previously untreated, active CNV lesion (i.e., leakage on fluorescein angiography AND subretinal, intravitreal, or sub-RPE fluid on OCT) secondary to age-related macular degeneration.
- Best corrected visual acuity in the study eye, using e-ETDRS testing, between 20/25 and 20/50 (Snellen equivalent), inclusive.

Only one eye will be enrolled in the Study. If both eyes are eligible, the patient and study ophthalmologist will select the eye for entry.

- The CNV or vessels of the CNV (i.e., pigment epithelium detachment, subretinal or sub-RPE hemorrhage, masked choroidal, macular edema, or subretinal or sub-RPE or intraretinal fluid) must involve the center of the fovea
- The total area of fibrosis must comprise less than 50% of the total lesion.
- ≥ 1 lesion (≥ 63 microns) in either eye OR late AMD in both eyes
- No previous treatment in the study eye
- Clear ocular media and adequate pupillary dilation to permit good quality fundus imaging.
- Disc and macula color stereoscopic photographs and fluorescein angiogram within 7 days of randomization.
- OCT of the macula within 7 days of randomization.

Document ID: 624646-775 | V15-0468-002 (05/19/01)
unpublished



Page 50
Santavya Biotech Clinical 1011
Page 5

10/2/25, 5:15 AM

History of Changes for Study: NCT00685654

U.S. National Library of Medicine

ClinicalTrials.gov archive

History of Changes for Study: NCT00685654

Pilot Study of Intravitreal Injection of Ranibizumab for Macular Telangiectasia With Neovascularization (MACTEL 2)

[View Full Report](#) | [Download PDF](#)

- Activity timeline representing a view of the study.
- Open periods indicate recruitment, open enrollment and/or follow-up.
- Click either the "target" or "study completion" label on the activity timeline as they are displayed. The target date typically refers to the primary endpoint of the study.
- Click "Close" on the left sidebar to close the activity timeline.
- Select a version. Current data will have a red marking on the study for analysis.
- The green add icon in the table indicates that additional comparison completed data updates have been added to the study system requiring being saved.
- Hover over the "Detailed Description" tab to view the study's detailed description.
- Study dates or intervals are indicated by [REDACTED].
- Study address or location is [REDACTED].

The Wayback Machine - <https://web.archive.org/web/20100710T042431/http://clinicaltrials.gov/ct2/show/NCT00685654>

ClinicalTrials.gov

Home Search Study Types History

Full Text View

Tabular View

Contacts and Locations

No Study Results Posted

Related Studies

Ranibizumab Injections to Treat Macular Telangiectasia Without New Blood Vessel Growth

This study is currently recruiting participants.
Verified by National Institutes of Health Clinical Center (CC), April 2008

Sponsored by:	National Eye Institute (NEI)
Information provided by:	National Institutes of Health Clinical Center (CC)
ClinicalTrials.gov Identifier:	NCT00685654

Purpose

This study will examine whether the drug ranibizumab (Lucentis) can help prevent vision loss in people with macular telangiectasia, a condition in which new blood vessels grow in the retina at the back of the eye and can leak. Such changes in blood vessels are seen in other diseases associated with changes in a body chemical called vascular endothelial growth factor (VEGF). Ranibizumab is an anti-VEGF drug that is effective in treating another eye disease, age-related macular degeneration, with similar changes in eye blood vessels.

People 18 years of age and older with macular telangiectasia in both eyes with no new blood vessel growth in either eye may be eligible for this study. They must have vision better than 20/50 in the study eye.

Participants undergo the following procedures:

- Ranibizumab injections in the study eye are given at least four times over 12 weeks. Depending on the response to treatment and the side effects, additional injections may be given every 4 weeks for up to 1 year. The eye is numbed before the injection and the eye area is cleaned with an antiseptic. Antibiotic drops are used for 3 days following the injection to prevent infection.
- Evaluations before starting treatment, at the time of each injection, and 4 weeks after the last treatment include:
 - History and physical examination.
 - Eye examination with dilation, ophthalmometry and photography. The eye examination measures visually evoked potentials and visual fields. For ophthalmometry test, subjects sit in front of a computer screen and press a button when they see a light on the screen. Measurements and photographs of the retina are also taken.
 - Fluorescein and indocyanine green angiography to examine the blood vessels in the eye. A dye called fluorescein or indocyanine green is injected into a vein in the arm. The dye travels through the veins to the blood vessels in the eye. A camera takes pictures of the eye as it flows through the blood vessels.
- Pregnancy test. Women who are able to become pregnant have a urine pregnancy test before each ranibizumab injection.

Condition	Intervention	Phase
Macular Telangiectasia	Drug: Ranibizumab	Phase I

Study information available for: [Ranibizumab](#).

U.S. FDA Approval

Study Type: Interventional
Study Design: Treatment, Non-Randomized, Open Label, Uncontrolled, Single Group Assignment, Safety/Efficacy Study
Official Title: Pilot Study of Intravitreal Injection of Ranibizumab for Macular Telangiectasia Without Neovascularization (MACTEL 2)

Sponsoring Biotech Cluster Page 1

[illegible]

EC3

Petitioner's MACTEL References Are Inconsistent and Unreliable

MACTEL Ex.1032

1/6/23, 5:15 AM History of Changes for Study: NCT00685854
U.S. National Library of Medicine
ClinicalTrials.gov archive

History of Changes for Study: NCT00685854
Intravitreal Injection of Ranibizumab for Macular Telangiectasia With Neovascularization (MACTEL 2)
[View version: NCT00685854 v1 \(1/1/2008\) on ClinicalTrials.gov](#)

... in the table.

- Delete the study version to compare. One each from columns A and B.
- Choose either the "larger" or "smaller" comparison format to specify how the two study versions are to be displayed. The Side-by-Side format only applies to the Protocol section of the study.
- Click "Compare" to see the comparison and view the differences.
- Delete a version's Submitted Date link to see a recording of the study for that version.
- The yellow AB boxes in the table indicate the study versions currently compared below. A yellow table row indicates the study version currently being viewed.
- Hover over the "Recruitment Status" to see how the study's recruitment status changed.
- Study sites or locations are indicated in **blue**.
- Study sites are indicated in **green**.

NCT00685854

Pilot Study of Intravitreal Injection of Ranibizumab for Macular Telangiectasia With Neovascularization (MACTEL 2)

2	☐	July 18, 2008	Study Status
3	☐	July 24, 2008	Study Description, Study Status and Study Identification
4	☐	July 18, 2008	References and Study Status
5	☐	July 18, 2008	Study Status
6	☐	August 18, 2008	Study Status
7	☐	August 9, 2008	Study Status
8	☐	August 24, 2008	Study Status
9	☐	November 20, 2008	Study Design and Study Status
10	☐	January 17, 2009	Study Status
11	☐	July 18, 2008	Study Status
12	☐	July 2, 2008	Study Status
13	☐	August 27, 2008	Study Status
14	☐	August 27, 2008	References and Study Status
15	☐	December 15, 2008	Recruitment Status, Study Status, Contacts/Locations, Study Design and References

EXCLUSION CRITERIA:

... • Participant has neovascularization in either eye. ...

https://clinicaltrials.gov/ct2/history/NCT00685854?_f=ViewStudyPageTop

1/4
Samsung Bioepis Exhibit 1032
Page 1

MACTEL Ex.1033

The Wayback Machine - <https://web.archive.org/web/20081107014243/http://ClinicalTrials.gov>
ClinicalTrials.gov
A service of the U.S. National Institutes of Health

NCT00685854

Ranibizumab Injections to Treat Macular Telangiectasia Without New Blood Vessel Growth

Verified by National Institutes of Health Clinical Center (CC), April 2008

Sponsored by:	National Eye Institute (NEI)
Information provided by:	National Institutes of Health Clinical Center (CC)
ClinicalTrials.gov Identifier:	NCT00685854

Purpose

his study will examine whether the drug ranibizumab (Lucentis) can help prevent vision loss in people with macular telangiectasia, a condition in which new blood vessels grow in the retina at the back of the eye and can leak. Such changes in blood vessels are seen in other diseases associated with changes in a body chemical called vascular endothelial growth factor (VEGF). Ranibizumab is an anti-VEGF drug that is effective in treating another eye disease, age-related macular degeneration, with similar changes in eye blood vessels.

People 18 years of age and older with macular telangiectasia in both eyes with no new blood vessel growth in either eye may be eligible for this study. They must have vision better than 20/400 in the study eye.

Participants undergo the following procedures:

- Ranibizumab injections in the study eye at least four times over 12 weeks. Depending on the response to treatment and the side effects, additional injections may be given every 4 weeks for up to 1 year. The eye is numbed before the injection and the eye area is cleaned with an antiseptic. Antibiotic drops are used for 3 days following the injection to prevent infection.
- Evaluations before starting treatment, at the time of each injection, and 8 weeks after the last treatment:
 - History and physical examination.
 - Eye examination with dilation, micropertimetry and photography. The eye examination measures visual acuity, eye pressure and eye movements. For the micropertimetry test, subjects sit in front of a computer screen and press a button when they see a light on the screen. Measurements and photographs of the retina are also taken.
 - Fluorescein and indocyanine green angiography to examine the blood vessels in the eye. A dye called fluorescein or indocyanine green is injected into a vein in the arm. The dye travels through the veins to the blood vessels in the eyes. A camera takes pictures of the dye as it flows through the blood vessels.

EXCLUSION CRITERIA:

... • Participant has neovascularization in either eye. ...

Official Title: Pilot Study of Intravitreal Injection of Ranibizumab for Macular Telangiectasia Without Neovascularization (MACTEL 2)

Samsung Bioepis Exhibit 1033
Page 1

PO's Response, Paper 26 at 32-33, 34-35

MACTEL Is Not a Reliable Source

Petitioner's expert was unfamiliar with the contents of Exs.1032 and 1033



Dr. Edward Chaum

Petitioner's Expert

- Incorrectly believed Ex.1032 to be directed to a study of a different a patient population than Ex.1033

Ex.2384 at 220:15-221:25

- Relied on an admittedly incorrect heading to conclude that Ex.1032 would treat patients with neovascularization

Ex.2384 at 221:14-222:25

- Did not independently locate Ex.1032 or Ex.1033

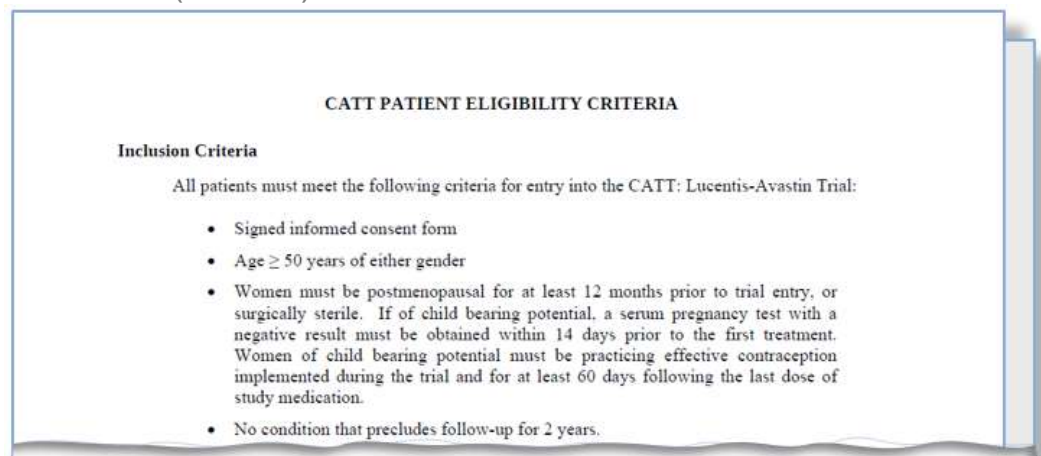
Ex.2384 at 222:25-223:23

- Did not compare Ex.1032 or Ex.1033 with the MACTEL study protocol or MACTEL publication

Ex.2384 at 222:25-223:23

CATT Is Not a Reliable Source

Ex.1031 (“CATT”)



- Unauthenticated excerpt from unknown source document
- Pulled by counsel from UPenn website on the mistaken belief that UPenn was a study sponsor
- Unknown: author, source document, draft or final, complete or incomplete

PO's Response, Paper 26 at 35-38 (citing Ex.2384 at 189:10-190:3, 198:16-199:6, 199:7-14)

CATT Is Not a Reliable Source

Petitioner's expert could not authenticate Ex.1031



Dr. Edward Chaum

Petitioner's Expert

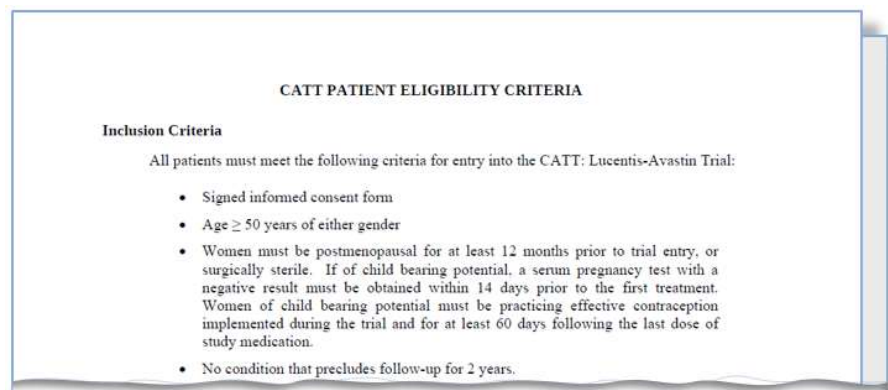
- Testified incorrectly (Ex.1002 at ¶ 101) that University of Pennsylvania—the source of Ex.1031—was the CATT study sponsor
Ex.2384 at 199:7-14
- Did not know who authored or created Ex.1031
Ex.2384 at 189:10-15
- Did not know if Ex.1031 actually came from the CATT study protocol
Ex.2384 at 198:16-199:3
- Did not know whether Ex.1031 was a draft or final version
Ex.2384 at 189:20-22
- Did nothing to verify whether Ex.1031 was a complete listing of CATT exclusion criteria
Ex.2384 at 189:16-190:3;
198:16-199:6

MACTEL and CATT Are Not Sources that the POSA Would Have Consulted

Ex.1032/Ex.1033 (“MACTEL”)



Ex.1031 (“CATT”)



- The Exclusion Criteria of MACTEL and CATT were untested
- MACTEL was a prospective eight-subject study
- MACTEL planned to treat a rare and different (non-angiogenic) ocular condition

MACTEL Does Not Disclose or Teach EC3

EXCLUSION CRITERIA:

...

- History within the past 30 days of a chronic ocular or periocular infection (including any history of ocular herpes zoster).
- Current acute ocular or periocular infection.

Ex.1032, 4 ("MACTEL")

wherein exclusion criteria for the patient include all of:
(1) active intraocular inflammation;
(2) active ocular or periocular infection;
(3) any ocular or periocular infection within the last 2 weeks prior to treatment.

Ex.1001, Claim 1

MACTEL: Chronic Infection Is Different from Non-Chronic Infection



Dr. Diana Do
Patent Owner's Expert

“[T]he POSA would have understood that a recent chronic infection was likely to recur. ... This same concern of recurrence would not be present in the case of an acute infection that had resolved prior to treatment.”

Ex.2056 at ¶ 152;
PO's Response, Paper 26 at 47-48



Dr. Edward Chaum
Petitioner's Expert

Q. ... You can have chronic infection, but you can also have an infection that is not chronic, correct?

A. Correct.

Ex.2384 at 266:19-22

Q. Are there any chronic ocular infections that do not recur?

...

A. I don't know....

Ex.2384 at 251:3-20

MACTEL: Exclusion of Current Acute Infection Does Not Teach Exclusion of Prior Infection

Petitioner's reading of MACTEL conflates current and resolved infection

EXCLUSION CRITERIA:

...

- History within the past 30 days of a chronic ocular or periocular infection (including any history of ocular herpes zoster).
- **Current acute** ocular or periocular infection.

Ex.1032, 4 ("MACTEL")

Additionally excluding "acute" infections would necessarily exclude any other infections that had presented within the weeks immediately before treatment (i.e. generally one to three weeks) **whether resolved or ongoing** through treatment. Pet. 42-47; Ex.1002, ¶¶141-149; Exs.1023-1024.

Petitioner's Reply, Paper 40 at 10-11

MACTEL: Exclusion of Current Acute Infection Does Not Teach Exclusion of Prior Infection

- The POSA can identify active infection on physical exam

Ex.2056 (Do. Decl.) at ¶¶111-112, 146; Ex.2384 (Chaum Tr.) at 125:11-15; see also PO's Response, Paper 26 at 18, 46

- Neither MACTEL nor any other cited reference discloses exclusion of historic infection that is acute (*i.e.*, non-chronic)

PO's Response, Paper 26 at 46-48; PO's Sur-Reply, Paper 45 at 10-11

- Rationale for excluding historic chronic infection does not apply to historic acute infection

PO's Response, Paper 26 at 47-48; PO's Sur-Reply, Paper 45 at 11-12

CATT Does Not Disclose or Teach EC3

Exclusionary Concurrent Ocular Conditions

- ... • Active or recent (within 4 weeks) intraocular inflammation (grade trace or above) in the study eye ...

Ex.1031, 6 ("CATT")

wherein exclusion criteria for the patient include all of:

- (1) active intraocular inflammation;
- (2) active ocular or periocular infection;
- (3) any ocular or periocular infection within the last 2 weeks prior to treatment.

Ex.1001, Claim 1

CATT: “Inflammation” and “Infection” Have Different Meanings in the Art



Dr. Edward Chaum

Petitioner's Expert

Q. [Inflammation and infection] are not synonymous terms, correct?

A. They are not synonymous, no.

Ex.2384 at 215:6-7



Dr. Diana Do

Patent Owner's Expert

- “[T]he rationale for excluding people with historic intraocular inflammation is different than the rationale for excluding ... ocular or periocular infection.”

Ex.2056 at ¶ 157

CATT: Excluding “Intraocular Inflammation” Does Not Inherently Exclude “Ocular or Periocular Infection”



Dr. Edward Chaum

Petitioner's Expert

Q. But there's also inflammation that is not associated with infection, correct?

A. Yes.

Ex.2384 at 215:3-5;
See also, *id.* at 119:18-25



Dr. Diana Do

Patent Owner's Expert

- “Many common ocular infections do not always have intraocular inflammation.”
- “[P]eriocular infection ... does not manifest as intraocular inflammation.”

Ex.1070 at 40:15-17

Ex.2056 at ¶ 158

MACTEL and CATT Each Mandate Exclusion of Their Respective Conditions for One Month

EXCLUSION CRITERIA:

- ...
- History within the past 30 days of a chronic ocular or periocular infection (including any history of ocular herpes zoster).

...

Ex.1032, 4 ("MACTEL")

Exclusionary Concurrent Ocular Conditions

- ...
- Active or recent (within 4 weeks) intraocular inflammation (grade trace or above) in the study eye

...

Ex.1031, 6 ("CATT")

MACTEL and CATT Prohibited Treatment of Patients Eligible for Treatment under the Challenged Claims



Dr. Edward Chaum

Petitioner's Expert

Q. [T]he MacTel exclusion criteria told investigators, do not treat patients having a history within the past 30 days of a chronic ocular/periorcular infection?

A. That's what the criteria says, yes.

Q. And if a MacTel investigator did reduce that 30-day exclusion period, that would be a protocol violation, right?

A. Yes.

Ex.2384 at 253:16-24

Q. [T]he CATT exclusion criteria told investigators, do not treat patients having intraocular inflammation within the past four weeks, right?

A. Within the past four weeks, yes.

Q. And if an investigator reduced that four-week exclusion period of CATT, that would be a protocol violation, correct?

A. Yes.

Ex.2384 at 212:24-213:13



Amneal v. Jazz, IPR2016-00546

No Treatment Under Prior Art

Amneal

All patients taking CNS depressants

Patients taking
valproate (a CNS
depressant)

Present IPR

All patients having had excluded conditions
within the last 4 weeks

Patients with ocular or
periocular infection that
resolved >2 weeks prior

Eligible
Treatment
Population
As Claimed

Amneal Pharms. LLC v. Jazz Pharms. Ireland Ltd., IPR2016-00546,
2016 WL 5222883, *2, *7 (P.T.A.B. July 28, 2016).

Petitioner's "Standard-of-Care" Theory Has No Support



Dr. Edward Chaum

Petitioner's Expert

Q. Do you know if other practitioners exclude from treatment patients who have had recent infections that are not active and ongoing?

A. I don't know how they practice in that regard.

Ex.2384 at 140:2-6

Q. Do you know if your partners, in taking the medical history, ask if their patients have had recent infection?

A. I don't know what their technicians do.

Ex.2384 at 140:14-17

Petitioner's "Standard-of-Care" Theory Has No Support



Dr. Edward Chaum

Petitioner's Expert

Q. ...You've cited a bunch of publications for the proposition that endophthalmitis was the most feared complication of injection?

A. Yes.

Ex.2384 at 142:13-16

Q. None of those publications cite a concern about injecting for a recent as opposed to active infection; is that correct?

* * *

A. I would have to review those.

Ex.2384 at 142:23-143:2 (objection omitted)

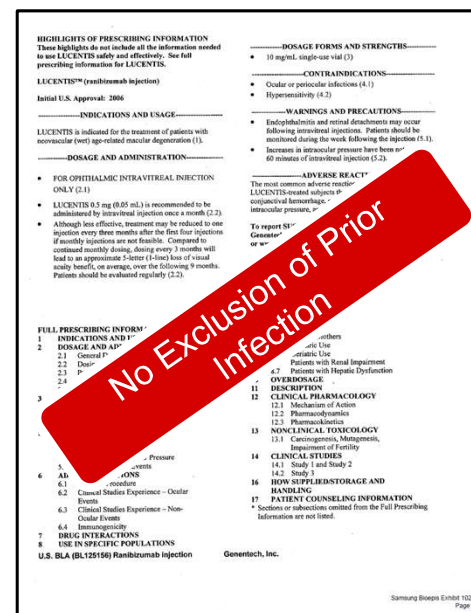
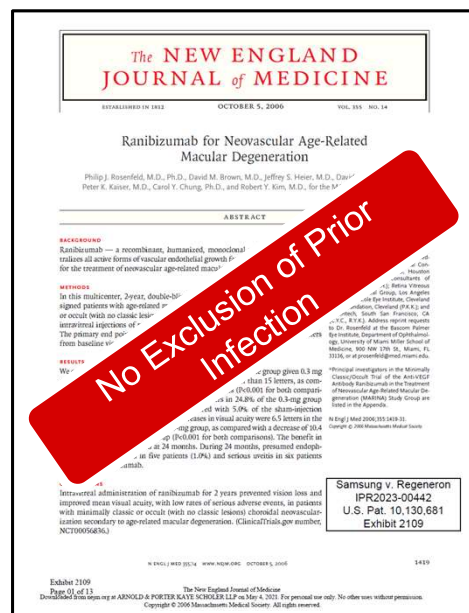
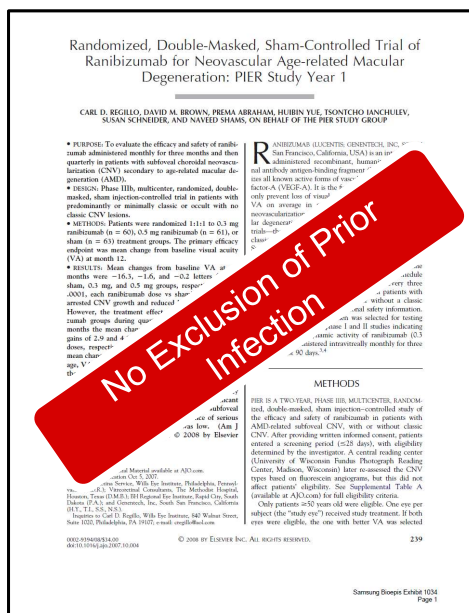
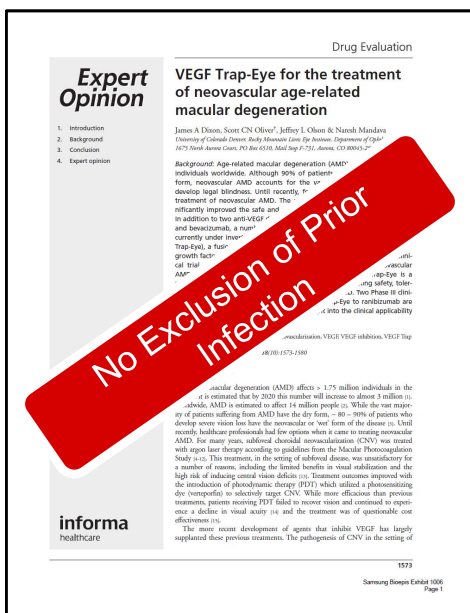
None discloses Petitioner's alleged "standard of care"

Dixon Ex.1006

PIER Ex.1034

Ex.2109

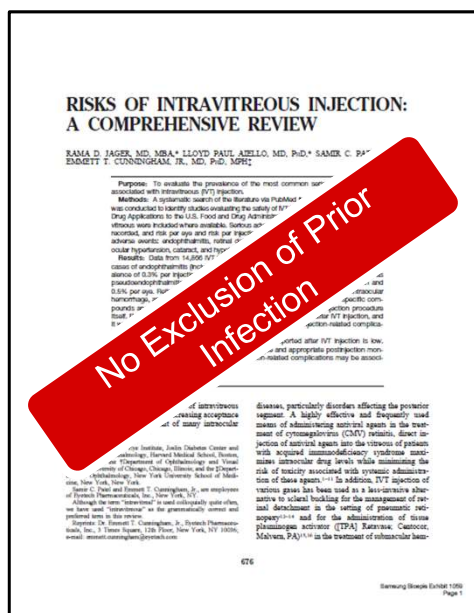
Ex.1026



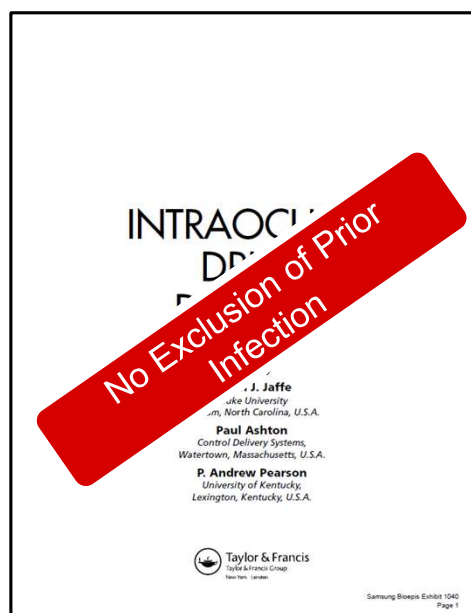
References cited in Petitioner's Reply, Paper 40 at 16; see *also* PO's Sur-reply, Paper 45 at 16-17.

None discloses Petitioner's alleged "standard of care"

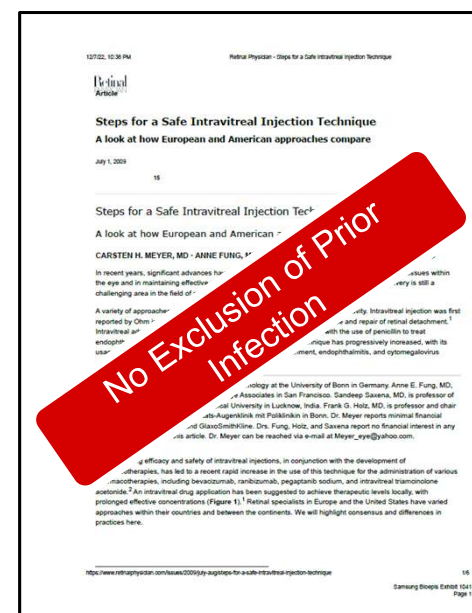
Ex.1059 (Jager)



Ex.1040 (Jaffe)



Ex.1041



References cited in IPR Petition for '681 Patent, Paper 2 at 47; see *also* PO's Sur-reply, Paper 45 at 16-17