

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MYLAN PHARMACEUTICALS INC.,
Petitioner,

v.

REGENERON PHARMACEUTICALS, INC.,
Patent Owner

Inter Partes Review No.: IPR2022-01225

U.S. Patent No. 10,130,681 B2
Filed: March 28, 2017
Issued: November 20, 2018
Inventor: George D. Yancopoulos

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

**EXPERT DECLARATION OF MARY E. GERRITSEN, PH.D.
IN SUPPORT OF PETITION FOR *INTER PARTES* REVIEW OF
U.S. PATENT NO. 10,130,681 B2**

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I, Mary E. Gerritsen, Ph.D., declare as follows:

I. INTRODUCTION.

1. I submit this declaration on behalf of Mylan Pharmaceuticals Inc. (“Petitioner”). I understand that Petitioner is filing a petition with the United States Patent and Trademark Office (“USPTO”) for *inter partes* review of U.S. Patent No. 10,130,681 B2 (the “’681 patent”) (Ex.1001).

2. I am the same Mary E. Gerritsen, Ph.D. who submitted declarations in support of Mylan in connection with the currently-pending *inter partes* reviews of U.S. Patent Nos. 9,669,069 B2 (“the ’069 patent”) and 9,254,338 B2 (“the ’338 patent”), instituted as IPR2021-00880 and IPR2021-00881, respectively. I understand that the ’069 and ’338 patents are related to the ’681 patent being challenged here.

3. This Declaration contains my qualifications; my opinions based on my expertise and my review of the ’681 patent and other documents cited within this Declaration; the factual basis for those opinions; and data or other information I considered in forming my opinions. The opinions and facts set forth in this Declaration are based upon information and my analysis of documents related to the ’681 patent, as well as my knowledge and experience in the pharmaceutical and biotechnology industries.

II. QUALIFICATIONS.

4. I am a pharmacologist with over thirty years of experience in the pharmaceutical and biotechnology industries.

5. In 2010, I founded Gerritsen Consulting, and I have been a consultant for the biotechnology industry on topics related to biotherapeutics and drug discovery in the therapeutic areas of oncology, immuno-oncology, ophthalmology, autoimmune diseases/inflammation, cardiovascular disease, and angiogenesis-related diseases. Specifically, I have collaborated with companies in numerous areas of product development, including research strategy, target selection and assessment, preclinical pharmacology and mechanism of action studies, preparation of Investigational New Drug applications, procedures for clinical trials, and evaluation of pipeline portfolio strategies.

6. Prior to my consulting work, I was the Vice President of Molecular and Cellular Pharmacology at Exelixis, Inc. from 2004-2010. Exelixis is a biotechnology company focused on the development of small molecular therapeutics for the treatment of oncology and metabolic disease. I supervised many of the processes involved in preclinical to early clinical development, including target identification and validation, early lead discovery and validation, lead optimization, cellular and molecular pharmacology studies, pharmacodynamic assays, and early

translational medicine studies. I also collaborated with the clinical groups in the early stages of Phase I clinical trials.

7. From 2003-2004, I was a consultant with Frazier Health Care Ventures in which I was involved in the founding of MacuSight, Inc., a pharmaceutical company focused on angiogenesis disorders, specifically focused on age-related macular degeneration and diabetic macular edema. I was an inventor on several of the patents that were the basis for the foundation of the company which included U.S. Patent Nos. 8,222,271, 8,486,960, and 9,452,156.

8. From 2002-2003, I was the Senior Director, Vascular Biology with Millennium Pharmaceuticals (formerly COR Therapeutics) where I was responsible for development of the strategic plan for vascular biology and oversaw numerous small molecule development programs in the therapeutic indications of atherosclerosis, peripheral vascular disease, and fibrosis.

9. Prior to the above, I was Associate Director of the Department of Cardiovascular Research at Genentech, Inc. from 1997-2001. Separately, I was a senior investigator in the angiogenesis group whose focus was the identification of novel targets for protein-based therapeutics. Throughout my time at Genentech, I was involved in the drafting and filing of over 1,000 patent applications in which over forty such applications issued as patents.

10. Before joining Genentech, I was a Principal Staff Scientist and Group Leader, Institute for Inflammation and Autoimmunity at Bayer Pharmaceuticals (formerly Miles Pharmaceuticals) from 1990-1997. During this time, I led the screening efforts for small molecule inhibitors of leukocyte adhesion, cyclooxygenase, and cytokine release/action while also supervising six laboratories within the Institute. Additionally, I developed collaborations with other industrial development laboratories as well as academic laboratories in order to promote advances in target discovery and assay development.

11. Prior to my roles in the pharmaceutical and biotechnology industry, I received a Bachelor of Science degree in Zoology and a Ph.D. in Endocrinology and Pharmacology from the University of Calgary. I completed my post-doctoral studies in Pharmacology at the University of California, San Diego. Following my post-doctoral work, I was an Assistant and later an Associate Professor of Physiology at New York Medical College from 1980-1989. During this time, I conducted research in therapeutic areas including stroke, inflammation, ophthalmology, and diabetic vascular disease.

12. Throughout my career, I have more than 100 publications in peer-reviewed journals, written numerous book chapters, and authored three books. I am currently, or have been, a member of numerous professional organizations, and I have been presented with numerous awards and honors throughout my career.

13. Additional information about my professional and educational experience, and other background information, is described in my *curriculum vitae* (Ex.1061).

III. SCOPE OF ENGAGEMENT.

14. I have been retained by Petitioner as a technical expert to offer my analysis and opinions regarding various issues related to certain prior art references as they relate to the '681 patent, discussed in more detail below.

15. My time spent on this project is compensated at \$400 per hour. My compensation does not depend in any way on the outcome of Petitioner's petition for *inter partes* review of the '681 patent. Furthermore, I have no financial interest in this matter.

16. My opinions and views set forth in this Declaration are based on my education and training, my experience in academia and the pharmaceutical and biotechnology industries, and on the materials I have reviewed for this case.

17. I have reviewed the '681 patent and relevant sections of its prosecution history before the USPTO, (*see* Ex.1017, '681 FH). I have also reviewed and considered various other documents in arriving at my opinions, and cite them in this Declaration.

18. I have been asked to consider the level of education, skill set and training possessed by persons of ordinary skill in the field relevant to the '681 patent as of at least January 13, 2011.^{1, 2}

19. I have also been asked to consider, from the perspective of the person of ordinary skill in the art as of at least January 13, 2011, whether certain references or documents were available as printed publications, or in other words, whether certain references or documents would have been publicly accessible to persons interested and ordinarily skilled in the subject matter or art, exercising reasonable diligence, before January 13, 2011.

20. I have formed certain opinions on these issues, which I set forth in greater detail below. In sum, it is my opinion that each of the references I discuss in this declaration are printed publications in that they were publicly accessible to persons interested and ordinarily skilled in the subject matter or art of the '681

¹ I have been asked to assume that the priority date of the '681 patent is January 13, 2011, the date of the earliest filed provisional application that appears on the '681 patent cover page. I have formed no opinion regarding the merit of the '681 patent's claim to any priority date.

² I provide my understanding of the qualifications for a person of ordinary skill in the art relevant to the '681 patent in ¶¶ 22-24, below.

patent, exercising reasonable diligence, before January 13, 2011. Moreover, my opinions in this regard are repeatedly confirmed by other contemporaneous prior art documents, which expressly cite the references I have been asked to evaluate. (See ¶¶ 55, 63, 78, 85-90, 100 below).

IV. THE PERSON OF ORDINARY SKILL IN THE ART.

21. As I mentioned above, it is my understanding that my analysis is to be conducted from the perspective of a person of ordinary skill in the art at the time of the invention.

22. I also understand that in defining a person of ordinary skill in the art, the following factors may be considered: (1) the educational level of the inventor; (2) the type of problems encountered in the art; (3) prior art solutions to those problems; (4) rapidity with which innovations are made; and (5) sophistication of the technology and educational level of active workers in the field.

23. I understand that a person of ordinary skill in the art is a hypothetical person who is presumed to be aware of all pertinent art, thinks along conventional wisdom in the art, and is a person of ordinary creativity at the time of the invention. I further understand that the relevant timeframe for assessing the '681 patent's claims from the perspective of a person of ordinary skill in the art is assumed to be January 13, 2011 (the earliest possible priority date for the '681 patent).

24. With respect to the '681 patent, a person of ordinary skill in the art would have: (1) knowledge regarding the diagnosis and treatment of angiogenic eye disorders, including the administration of therapies to treat said disorders; and (2) the ability to understand results and findings presented or published by others in the field, including the publications discussed herein. Typically, such a person would have an advanced degree, such as an M.D. or Ph.D. (or equivalent, or less education but considerable professional experience in the medical, biotechnological, or pharmaceutical field), with practical academic or medical experience in: (i) developing treatments for angiogenic eye disorders, such as age-related macular degeneration ("AMD"), including through the use of VEGF antagonists, or (ii) treating of same, including through the use of VEGF antagonists.

25. A person of ordinary skill in the art would have been aware of the references and teachings described below, as well as other important information and references relating to angiogenic eye disorders, the causes of said disorders, and useful treatments for said disorders.

V. LEGAL STANDARDS.

26. I am not a lawyer and do not purport to offer any legal opinions. In forming my opinions set forth herein, I have been asked to apply certain standards regarding printed publications.

27. I understand that a reference, publication, document, etc. is a “printed publication” if the document is “publicly accessible.” I also understand that a reference is considered “publicly accessible” if it was disseminated or otherwise made available to the extent that persons interested and ordinarily skilled in the subject matter or art, exercising reasonable diligence, can locate it.

28. Thus, a reference that could be classified as a “printed publication” before the priority date of the ’681 patent would be considered prior art to the ’681 patent.

VI. U.S. PATENT NO. 10,130,681.

29. I understand that the ’681 patent issued on November 20, 2018, to Regeneron Pharmaceuticals, Inc. and is titled “USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS,” with George D. Yancopoulos listed as the sole inventor. (Ex.1001, ’681 patent, cover). I also understand that the ’681 patent issued from U.S. Application No. 15/471,506 (“the ’506 Application”), a continuation of U.S. Application No. 14/972,560, filed on December 17, 2015, which issued as the ’069 patent, which is a continuation of U.S. Application No. 13/940,370 (“the ’370 Application”), filed on July 12, 2013, which issued as the ’338 patent, which is a continuation-in-part of International Application No. PCT/US2012/020855, filed on January 11, 2012, and claims priority to U.S. Provisional Application No. 61/432,245, filed on January 13, 2011, U.S. Provisional

Application No. 61/434,836, filed on January 21, 2011, and U.S. Provisional Application No. 61/561,957, filed on November 21, 2011. (*Id.*).

30. I understand that the '681 patent contains two independent claims and twenty-four dependent claims. Independent claims 1 and 14 are listed below:

1. A method for treating an angiogenic eye disorder in a 40
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 45
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; 50
wherein the VEGF antagonist is a VEGF receptor-based
chimeric molecule comprising (1) a VEGFR1 compo-
nent 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 multimeriza- 55
tion 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; 60
(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 5
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 10
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; 15
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; 20
(2) active ocular or periocular infection;
(3) any ocular or periocular infection within the last 2
weeks prior to treatment.

(Ex.1001, '681 patent, 21:40-63 (claim 1); *id.*, 23:5-23 (claim 14)). I also understand that claims 2-13 depend from claim 1, directly or indirectly, and that claims 15-26 depend from claim 14, directly or indirectly. (*Id.*, 21:64 – 23:4 (claims 2-13); *id.*, 23:24 – 24:30 (claims 15-26)).

VII. PROSECUTION HISTORIES OF THE '681 PATENT AND ITS EUROPEAN EQUIVALENTS.

31. I have reviewed the prosecution history for the '681 patent, which I understand appears at Ex.1001. It is my understanding that the '506 Application was filed on March 28, 2017 (*see* Ex.1017, '681 FH, 3/28/2017 Preliminary Amendment, 1) and included twenty-six claims directed towards a method of treating “an angiogenic eye disorder” with a “VEGF antagonist,” (*id.*, 3-6).

32. I have also reviewed EP 2 663 325 (Ex.1062, EP-325), which appears to be the European equivalent to the '370 Application, that issued as the '338 patent. (*Id.*, cover). EP-325 claims the same priority chain as the '506 Application—specifically, EP-325 claims priority to International Application No. PCT/US2012/020855, filed on January 11, 2012, which claims priority to U.S. Provisional Application No. 61/432,245, filed on January 13, 2011, U.S. Provisional Application No. 61/434,836, filed on January 21, 2011, and U.S. Provisional Application No. 61/561,957, filed on November 21, 2011. (*Id.*).

33. As originally filed, it is my understanding that EP-325 included claims similar to those prosecuted in the '370 Application that issued as the '338 patent and those prosecuted in the '506 Application that issued as the '681 patent. (Ex.1062, EP-325, [0020]-[0024]; Ex.1063, EP-325-FH, 7/5/2013 Amendments, 19-20; Ex.1095, '338 FH, 7/12/2013 '370 Application Original Claims, 22-23; Ex.1017, '681 FH, 3/28/2017 Preliminary Amendment, 3-6). I have prepared the following chart to illustrate the similarities between the '506 Application claims, the '370 Application claims, and the EP-325 claims:

'506 Application Original Claims^{3, 4}	EP-325 Original Claims
21. (New) A method for treating an angiogenic eye disorder in a patient, said method comprising sequentially administering to the patient a single initial dose of a VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonist; wherein each secondary dose is administered 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered at least 8 weeks after the immediately preceding dose;	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.

³ It is my understanding that Claims 1-20 of the '506 Application were initially canceled and Claims 21-46 added as noted in the chart. (*See* Ex.1017, '681 FH, 3/28/2017 Preliminary Amendment, 3-6)

⁴ In order to align the claims by limitation, no equivalents to Claims 9-11 of the '370 Application and EP-325 are included for the '506 Application, but I note that the limitations of Claims 9-11 of the '370 Application and EP-325 are included in Claim 1 the '506 Application.

'506 Application Original Claims^{3, 4}	EP-325 Original Claims
wherein the VEGF antagonist is a receptor-based chimeric molecule comprising (1) a VEGFR1 component comprising amino acids 27 to 129 of SEQ ID NO:2; (2) a VEGFR2 component comprising amino acids 130-231 of SEQ ID NO:2; and (3) a multimerization component comprising amino acids 232-457 of SEQ ID NO:2; wherein exclusion criteria for the patient include all of: (1) active intraocular inflammation; (2) active ocular or periocular infection; (3) any ocular or periocular infection within the last 2 weeks prior to treatment.	
22. (New) The method of claim 21, wherein only a single secondary dose is administered to the patient, and wherein the single secondary dose is administered 4 weeks after the initial dose of the VEGF antagonist.	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.
23. (New) The method of claim 21, wherein only two secondary doses are administered to the patient, and wherein each secondary dose is administered 4 weeks after the immediately preceding dose.	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.
24. (New) The method of claim 23, wherein each tertiary dose is administered 8 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.

'506 Application Original Claims^{3, 4}	EP-325 Original Claims
25. (New) The method of claim 21, wherein at least 5 tertiary doses of the VEGF antagonist are administered to the patient, and wherein the first four tertiary doses are administered 8 weeks after the immediately preceding dose, and wherein each subsequent tertiary dose is administered 8 or 12 weeks after the immediately preceding dose.	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.
26. (New) The method of claim 21, wherein the angiogenic eye disorder is selected from the group consisting of: age related macular degeneration, diabetic retinopathy, diabetic macular edema, central retinal vein occlusion, branch retinal vein occlusion, and corneal neovascularization. 27. (New) The method of claim 26, wherein the angiogenic eye disorder is age related macular degeneration.	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 and corneal neovascularization. 7. The method of claim 6, wherein the angiogenic eye disorder is age related macular degeneration.
28. (New) The method of claim 21, wherein all doses of the VEGF antagonist are administered to the patient by topical administration or by intraocular administration.	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.

'506 Application Original Claims^{3, 4}	EP-325 Original Claims
	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.
29. (New) The method of claim 28, wherein all doses of the VEGF antagonist are administered to the patient by intraocular administration. 30. (New) The method of claim 29, wherein the intraocular administration is intravitreal administration. 31. (New) The method of claim 30, wherein the intraocular administration is intravitreal administration.	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

'506 Application Original Claims^{3, 4}	EP-325 Original Claims
	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.
31. (New) The method of claim 30, wherein all doses of the VEGF antagonist comprise from about 0.5 mg to about 2 mg of the VEGF antagonist. 32. (New) The method of claim 31, wherein all doses of the VEGF antagonist comprise 0.5 mg of the VEGF antagonist. 33. (New) The method of claim 31, wherein all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist.	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.

(Ex.1017, '681 FH, 3/28/2017 Preliminary Amendment, 3-4; Ex.1095, '338 FH, 7/12/2013 '370 Application Original Claims, 22-23; Ex.1063, EP-325-FH, 1/23/2012 Claims, 19-20). As noted above, the original claims of the '506

Application are very similar, if not the same but for a few amendments to the claims, to the original claims of the '370 Application, and the original claims of EP-325. (*Id.*).

34. As I describe in more detail in the following paragraphs, several references were cited as prior art against EP-325, confirming, in my opinion their public availability and relevance to the '681 patent.

35. According to the prosecution history of EP-325, the International Searching Authority identified a September 28, 2008 Regeneron Press Release as a “prior art document” that it “considered” in its May 22, 2012 written opinion (referencing the document as “D13”):

D13: XP002674126

Thomson Reuters Integrity: "VEGF Trap-Eye final phase II results in age-related macular degeneration presented at 2008 Retina Society Meeting",

28 September 2008 (2008-09-28), pages 1-1, XP002674126,

D13 (phase II study) describes the improvement of visual acuity in age-related macular degeneration patients after VEGF Trap-Eye monthly or quarterly administration for 12 weeks followed by an 40 additional weeks-treatment on a PNR (as needed) dosing schedule.

(Ex.1063, EP-325-FH, 5/14/2012 International Searching Authority Written Opinion, 3-4; *id.*, 7/19/2012 International Search Report, 1; *see also id.*, 9/5/2016

Third Party Observations, 2 (D13)). The International Search Authority then continued to discuss “D13” as the “closest prior art”:

7.1 **The closest prior art, D13** (phase II study summary), describes the improvement of visual acuity in age-related macular degeneration patients after VEGF Trap-Eye monthly or quarterly administration for 12 weeks followed by 40 additional weeks treatment on a PNR (as needed) dosing schedule.

(*Id.*, 5/14/2012 International Searching Authority Written Opinion, 5).

36. The European Patent Office cited to this same Regeneron Press Release (as “D13”) in reaching its conclusions in its August 21, 2014 Communication:

7.6 **The problem to be solved** “*provision of improved protocols to treat age related macular degeneration, diabetic retinopathy, diabetic macular edema, central retinal vein occlusion and corneal neovascularization*” has not been shown to be solved by the claimed solutions in the present application. The objective technical problem needs to be reformulated to the less ambitious one “*provision of alternative protocols to treat age related macular degeneration, diabetic retinopathy, diabetic macular edema, central retinal vein occlusion and corneal neovascularization*” for which the claimed solutions are obvious in view of D13.

(*Id.*, 8/21/2014 Communication, 8; *see also id.*, 3-5).

37. Indeed, multiple Third-Party Observations were submitted during prosecution of EP 325. The first Third Party Observation included reference to, *inter alia*, Regeneron Press Releases, a ClinicalTrials.gov record from the VIEW2 study, and Regeneron’s Form 10-Q from November 2007—all submitted as “prior art”:

D13:	XP002674126
OBS1:	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
OBS2:	Information from ClinicalTrials.gov archive on the VIEW 2 study (NCT00637377) version available on 17 March 2008
OBS3:	Regeneron Pharmaceuticals, Inc. FORM 10-Q, published on 7 November 2007 for the period ending 30 September 2007
OBS4:	WHO Drug Information, Vol.20, No. 2, 2006, pages 115-119
OBS5:	Dixon et al., Expert Opin. Investig. Drugs (2009) 18 (10): 1-8
OBS6:	Simó and Hernández, Diabetes Care, Volume 32, Number 8, August 2009
OBS7:	Mousa and Mousa, Biodrugs 2010; 24(3); 183-194
OBS8:	Regeneron, Press release "Regeneron Reports First Quarter 2008 Financial and Operating Results", May 1, 2008

(*Id.*, 9/5/2016 Third Party Observations, 2; *see also id.*, 3-4). The second Third Party Observation additionally identified the following:

Annex 1	Press Release of Regeneron dated 22 November 2010
Annex 2	Press Release of Regeneron dated 20 December 2010
Annex 3	Article in Retinal Physician (March 2010)

(*Id.*, 9/7/2016 Third Party Observations, 2).

38. I have also reviewed EP 3 222 285 (Ex.1066, EP-285), which cites EP-325 as an earlier application and also claims priority to U.S. Provisional Application No. 61/432,245, filed on January 13, 2011, U.S. Provisional Application No. 61/434,836, filed on January 21, 2011, and U.S. Provisional Application No. 61/561,957, filed on November 21, 2011. (*Id.*, cover page).

39. EP-285 also contained claims covering 8-week dosing regimens for angiogenic eye disorders such as age related macular degeneration. (Ex.1066, EP-285, 18; Ex.1067, EP-285-FH, 4/28/2017 New Divisional Application, Claims). As I describe in more detail in the following paragraphs, several references were cited as prior art against EP-285, confirming, in my opinion, their public availability and relevance to the '681 patent.

40. According to the prosecution history of EP-285, the International Searching Authority identified three Regeneron Press Releases as “prior art documents” that it “considered” in its June 27, 2017 written opinion (referencing the documents as “D1”, “D2”, and “D10”)):

Regeneron: "Bayer and Regeneron Report Positive Top-Line Results of Two Phase 3 Studies with VEGF Trap-Eye in Wet Age-related Macular Degeneration", Regeneron.com

22 November 2010 (2010-11-22),
XP002770953,

Retrieved from the Internet:
URL:<http://investor.regeneron.com/releasedetail.cfm?releaseid=532099>
[retrieved on 2017-10-09]
* the whole document *

D1 discloses that VEGF Trap-Eye was administered every two months after three monthly loading doses (second page, third paragraph):

"In each of the studies, VEGF Trap-Eye was evaluated for its effect on maintaining and improving vision when dosed as an intravitreal injection on a schedule of 0.5mg monthly, 2mg monthly, or 2mg every two months (following three monthly loading doses), as compared with intravitreal ranibizumab administered 0.5mg every month during the first year of the studies".

In this context, the 2 mg aflibercept dose administered in the first visit corresponds to the single initial dose of the claimed VEGF antagonist, the 2 mg aflibercept doses administered at weeks 4 and 8 correspond to two secondary doses of the claimed VEGF antagonist, wherein each secondary dose is administered 4 weeks after the immediately preceding dose, and the 2 mg aflibercept doses administered thereafter every 8 weeks correspond to the tertiary doses of the claimed VEGF antagonist, wherein each tertiary dose is administered 8 weeks after the immediately preceding dose.

The treatment lasted 52 weeks, which means that the tertiary dose was administered at least 5 times.

The VEGF Trap-Eye was used to treat wet age-related macular degeneration (see first page, first paragraph and headline).

VEGF Trap-Eye is aflibercept ophthalmic solution (see first page, first paragraph of Annex I). Aflibercept is the same molecule as VEGFR1 R2-FcAC 1 (a) to which claim 1 refers.

According to D1 the results of the VIEW studies show that "all regimens of VEGF Trap-Eye (aflibercept ophthalmic solution), including VEGF Trap-Eye dosed every two months, successfully met the primary endpoint compared to the current standard of care, ranibizumab dosed every month" (cf. first page, first paragraph). This shows that a therapeutic effect is indeed obtained by treatment with a dosage regimen as required by the pending claims.

Further, Table 1 presented in Example 4 of the present application is shown on page 2 of D1.

(Ex.1067, EP-285-FH, 6/27/2017 International Searching Authority Written Opinion, 1, 3-4; *id.*, 6/12/2017 International Search Report, 1).

D2: XP002770954

Regeneron: "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)",
regeneron.com

,
20 December 2010 (2010-12-20),
XP002770954,

Retrieved from the Internet:
URL:<http://investor.regeneron.com/releasedetail.cfm?releaseid=537916>

[retrieved on 2017-06-09]

* the whole document *

D2 describes a phase II study in patients with diabetic macular edema. In this study participants were randomized into one of five groups: one group receiving laser treatment (control group), two groups receiving 0.5 or 2 mg of VEGF Trap-Eye monthly, and two groups receiving three initial monthly doses of 2 mg of VEGF Trap-Eye (at baseline and weeks 4 and 8), followed through week 52 by either every two months dosing (corresponding to the regimen defined in pending claim 1) or as-needed dosing (first page, penultimate paragraph). D2 reports that "the previously reported visual acuity gains achieved with VEGF Trap-Eye treatment over 24 weeks (the primary endpoint of the [DA VINCI] study) were maintained or numerically improved up to completion of the study at week 52 in all VEGF Trap-Eye study groups, including 2ms dosed every other month. " (cf, first page, penultimate paragraph)

The treatment lasted 52 weeks, which means that the tertiary dose was administered at least 5 times.

Furthermore, Table 2 presented in Example 5 of the present application is shown on page 2 of D2.

(Ex.1067, EP-285-FH, 6/27/2017 International Searching Authority Written Opinion, 1, 4; *id.*, 6/12/2017 International Search Report, 1).

D10: XP002770952

Regeneron Pharmaceuticals, Bayer, New York University: "VEGF Trap-Eye Final Phase 2 Results in Age-related Macular Degeneration Presented at 2008 Retina Society Meeting", Evaluate.com

,
28 September 2008 (2008-09-28),
XP002770952,
Retrieved from the Internet:
URL:<http://www.evaluategroup.com/Universal/View.aspx?type=Story&id=165320>
[retrieved on 2017-06-09]
* the whole document *

D10 (phase II study) describes the improvement of visual acuity in age-related macular degeneration patients after VEGF Trap-Eye monthly or quarterly administration for 12 weeks followed by an 40 additional weeks-treatment on a PNR (as needed) dosing schedule (whole docs).

(Ex.1067, EP-285-FH, 6/27/2017 International Searching Authority Written Opinion, 1-2; *id.*, 6/12/2017 International Search Report, 3). The International Search Authority then continued to discuss “D1” as the “closest prior art”:

5.1 **The closest prior art, D1,** describes the successful therapeutic use of the compound and dosage regime as claimed for the treatment of wet age-related macular degeneration.

(Ex.1067, EP-285-FH, 6/27/2017 International Searching Authority Written Opinion, 5).

41. The European Patent Office cited to these same Regeneron Press Releases (the same “D1,” “D2,” and “D10”) in reaching its conclusions in its March 26, 2020 Communication:

The problem "provision of alternative therapeutic use of the claimed dosages of a VEGF antagonist comprises VEGFR1 R2-Fc ACI (a) encoded by the nucleic acid sequence of SEQID NOR "has not been solved. The objective technical problem needs to be reformulated to the less ambitious one "provision of a therapeutic use of the claimed dosages of a VEGF antagonist comprises VEGFR1 R2-Fc ACI (a) encoded by the nucleic acid sequence of SEQID NOR", which solution would be obvious in view of D1.

The same problem-solution approach would apply taking any of D2, D3, D4, D7, D8, D10, D11, D12, and D13 as closest prior art.

(*Id.*, 3/26/2020 Communication, 7; *see also id.*, 4-6).

42. The European Patent Office’s reliance on the above-mentioned documents confirms, in my opinion, that each was publicly accessible to persons interested and ordinarily skilled in the subject matter or art of the ’681 patent, exercising reasonable diligence, before 2011. I further note that, as far as I can tell

from reviewing the EP-325 and EP-285 file histories, Regeneron never contested the public availability of those documents.

43. Separately, I find it important to note that, while prosecuting the '681 patent, the Applicants relied extensively on Heier-2012, a reference that, in my opinion, further confirms the public accessibility of Petitioner's asserted ClinicalTrials.gov reports, e.g., NCT-795 and NCT-377:

Study Design

The "VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD" studies (VIEW 1 and VIEW 2) were similarly designed, prospective, double-masked, multinational, parallel-group, active-controlled, randomized clinical trials. The investigators from the VIEW 1 and VIEW 2 studies are listed in Appendix 1, available at <http://aaojournal.org>. Patients in VIEW 1 (registered at www.clinicaltrials.gov on July 31, 2007; **NCT00509795. Accessed August 8, 2012**) were randomized at 154 sites in the United States and Canada. Patients in VIEW 2 (registered at www.clinicaltrials.gov on March 12, 2008; **NCT00637377. Accessed August 8, 2012**) were randomized at 172 sites in Europe, the Middle East, Asia-Pacific, and Latin America; the last patient in both studies completed 52 weeks in September 2010. The study protocols were

(Ex.1018, Heier-2012, 2539; *see also* Ex.1017, '681 FH, 6/25/2018 Applicant Arguments, 9 ("[t]he attached Heier et al. article is a peer reviewed article published in 'Ophthalmology'")).

VIII. DISCLOSURES, KNOWLEDGE, AND INFORMATION AVAILABLE IN THE ART BEFORE JANUARY 13, 2011.

A. JOURNAL ARTICLES.

44. Journal articles are routinely provided online prior to being made available in the printed journal, and their public availability and dissemination online

would have allowed persons interested and ordinarily skilled in the art exercising reasonable diligence to locate them. Not only would a person of ordinary skill in the art have been interested in, and sought out, the information contained in printed journals, but this person would have been able to easily obtain these articles from the journal's website on the date of, or earlier than, the date of printed publication. In fact, journals routinely publish articles on their website earlier than the printed journal in order to disseminate them to the public more quickly and in an easily accessible manner. Additionally, these articles typically appear in web search results when a person of ordinary skill in the art conducts a search using various search engines (e.g., via Google Scholar, Google, PubMed, etc.).

45. For example, the Mitchell article analyzes data from several ranibizumab clinical trials in an assessment of various dosing schedules. (See Ex.1030, Mitchell, 5-7). Mitchell published in print in the British Journal of Ophthalmology ("BJO") in January 2010, but the article states that it was first published online on May 20, 2009. (*Id.*, 2 ("Published Online First 20 May 2009")). "Online First" was the BJO's advanced online publication of manuscripts in PDF form. (Ex.1064, Wayback-BJO-Online First, 1 (Wayback Machine record from February 12, 2009, describing the BJO's "Online First" advanced publication procedure)). According to the BJO's website from February 12, 2009, the articles published through "Online First" were "indexed by PubMed," and would appear, at

least, in PubMed search results. (*Id.*). Furthermore, the BJO retains online download statistics for all their articles and shows that in the first month that Mitchell was available online, May 2009, the PDF was downloaded 299 times. (Ex.1065, BJO-Article Metrics, 1). As such, as of May 20, 2009, a person of ordinary skill in the art exercising reasonable diligence would have been able to locate the article on, among other things, the BJO's website or PubMed, and easily download an electronic copy.

B. REGENERON PRESS RELEASES.

46. In my experience in the pharmaceutical and biotechnology industries, companies like Regeneron and Bayer routinely issue press releases that include, e.g., information on product development and/or clinical trials. These press releases can include information regarding, among other things, the specific product in development, the study design of a clinical trial, and/or preliminary or final results from a specific clinical trial(s). A person of ordinary skill in the art would be interested in this type of information regarding ongoing product development within the industry, including information regarding the development of products of a direct competitor. For example, this type of information continually updates the competitive landscape for a particular market and would assist the person of ordinary skill in the art in evaluating the same. As these press releases are a rich source of information about the ongoing development for a particular treatment, persons of

ordinary skill in the art routinely review such press releases, whether as a result of exercising diligence, received from email alerts (e.g., via Google Alerts), or website updates (e.g., Seeking Alpha, Evaluate Pharma, and FiercePharma). Indeed, I myself have searched for, reviewed and relied upon such press releases throughout my professional career.

47. Regeneron's and Bayer's press releases regarding VEGF Trap-Eye were no different, and, in my opinion, a person of ordinary skill in the art would have sought out this information. As specifically noted below, the Regeneron and Bayer press releases regarding VEGF Trap-Eye disclosed the ongoing development of VEGF Trap-Eye as a therapy for angiogenic eye disorders, including different treatment regimens using VEGF Trap-Eye.

48. Not only would a person of ordinary skill in the art have been interested in, and sought out, the information contained in the Regeneron and Bayer press releases, but this person would have been able to easily obtain these press releases directly from Regeneron's website on the date of each release. In fact, companies routinely publish press releases and other information on the company website under a "News" menu or something similar (e.g., "Media" menu or "Investors & Media" menu) in order to disseminate them to the public in an easily accessible manner, and press releases are well-known to the community interested in the subject matter of the reference as a source of useful information. Additionally, documents such as

press releases typically appear in web search results (e.g., via Google) when a person of ordinary skill in the art conducts a search using various search engines.

49. Thus, as of the date of each press release, a person of ordinary skill in the art would have been able to locate the specific press release on, among other things, Regeneron's website exercising reasonable diligence, easily access each press release via Regeneron's website, and easily download an electronic copy.

1. May 2008 Press Release.

50. Regeneron and Bayer HealthCare AG issued a press release dated May 8, 2008 (Ex.1013, Regeneron (8-May-2008)), which described the Phase 3 age-related macular degeneration VIEW 2 clinical trial as well as results of a Phase 2 clinical trial. (*Id.*, 1-2; *see also* Ex.1032, Bayer (8-May-2008), 1-3).

51. Specifically, Regeneron (8-May-2008) stated that both the complete VIEW 1 trial and the VIEW 2 trial were "designed to evaluate the efficacy and safety of VEGF Trap-Eye administered by intravitreal injection, at dosing intervals of 4 and 8 weeks." (Ex.1013, Regeneron (8-May-2008), 1; Ex.1032, Bayer (8-May-2008), 1). Moreover, the Phase 2 clinical trial described "met both primary and secondary key endpoints" and that "[f]ollowing the initial 12-week fixed-dosing phase of the trial, patients continued to receive therapy at the same dose on a PRN (as needed) dosing schedule based upon the physician assessment of the need for re-treatment." (Ex.1013, Regeneron (8-May-2008), 1-2).

52. Regeneron (8-May-2008) also described the dosing regimens used in the VIEW 2 clinical trial, including “2.0 mg at an 8-week dosing interval, including one additional 2.0 mg dose at week four,” in which one of the dosing arms included a regimen of 2 mg every 8 weeks, with an additional injection at week 4. (Ex.1013, Regeneron (8-May-2008), 1).

53. Regeneron (8-May-2008) concluded that in the Phase 2 clinical trial, “on average, patients on the PRN dosing schedule maintained the gain in visual acuity and decrease in retinal thickness achieved at week 12 through week 32 of the study.” (Ex.1013, Regeneron (8-May-2008), 2).

54. A person of ordinary skill in the art would have understood that the dosing regimens disclosed in Regeneron (8-May-2008) included the experimental group that received VEGF Trap-Eye 2 mg every other month or on a PRN⁵ dosing schedule following the initial monthly injections over the first twelve weeks. (Ex.1013, Regeneron (8-May-2008), 1).

55. A person of ordinary skill in the art would have been interested in, and sought out, the information disclosed in Regeneron (8-May-2008) because it pertains to ongoing product development within the industry, including dosing regimens of a known therapy (VEGF Trap-Eye or aflibercept) in patients with age-related

⁵ “PRN” (or *pro re nata*) is commonly understood as “as needed” dosing.

macular degeneration. (Ex.1013, Regeneron (8-May-2008), 1). Again, my opinion in this regard is, in fact, confirmed by other contemporaneous prior art to the '681 patent that expressly refers to similar Regeneron and Bayer press releases. For example, Adis (Ex.1007, Adis) provides the following among twenty separate references to online "Media Releases":

12. Bayer HealthCare AG. Bayer and Regeneron start additional Phase 3 Study for VEGF Trap-Eye in Wet Age-related Macular Degeneration. Media Release: 8 May 2008. Available from URL: <http://www.bayerscheringpharma.de>
13. Bayer HealthCare AG, Regeneron Pharmaceuticals Inc. Bayer and Regeneron Dose First Patient in Second Phase 3 Study for VEGF Trap-Eye in Wet Age-Related Macular Degeneration. Media Release: 8 May 2008. Available from URL: <http://www.bayerhealthcare.com>

(*Id.*, 268 (emphasis added); *see also* Ex.1032, Bayer (8-May-2008), 1). Indeed, press releases such as Regeneron (8-May-2008) were well-known—and widely available—to the community interested in the subject matter of the '681 patent. (*See, e.g.,* Ex.1007, Adis, 262-63, 268-69).

56. In my opinion (and as confirmed by, e.g., Adis), a person of ordinary skill in the art would have also been able to locate Regeneron (8-May-2008) exercising reasonable diligence, which would have at least led the person of ordinary skill in the art to Regeneron's website where the document was easily accessible, and recognize and comprehend therefrom the essentials of the subject matter

contained therein without further research or experimentation.⁶ Thus, a person of ordinary skill in the art could have easily accessed Regeneron (8-May-2008) via Regeneron's website and easily downloaded an electronic copy.

57. For at least these reasons, it is my opinion that Regeneron (8-May-2008) was a well-known, printed publication that was publicly accessible to persons interested and ordinarily skilled in the subject matter or art of the '681 patent, exercising reasonable diligence, before 2011.

2. September 2008 Press Release.

58. Regeneron and Bayer HealthCare AG issued a press release dated September 28, 2008 (Ex.1056, Regeneron (28-September-2008)), which described the final results for the same "double-masked, prospective, randomized, multi-center Phase 2 trial" in patients with wet age-related macular degeneration, treated with VEGF Trap-Eye that was described in Regeneron (8-May-2008). (*Id.*, 1).

59. As noted above, the patients in the study were "randomized to five dose groups" as follows:

- (1) monthly dose of 0.5 milligrams (mg) of VEGF Trap-Eye for twelve weeks followed by therapy at the same dose on a PRN dosing schedule;

⁶ Ex.1013, Regeneron (8-May-2008), 1.

- (2) monthly dose of 2.0 mg of VEGF Trap-Eye for twelve weeks followed by therapy at the same dose on a PRN dosing schedule;
- (3) quarterly dose of 0.5 mg of VEGF Trap-Eye (at baseline and week 12) followed by therapy at the same dose on a PRN dosing schedule;
- (4) quarterly dose of 2.0 mg of VEGF Trap-Eye (at baseline and week 12) followed by therapy at the same dose on a PRN dosing schedule; or
- (5) quarterly dose of 4.0 mg of VEGF Trap-Eye (at baseline and week 12) followed by therapy at the same dose on a PRN dosing schedule.

(*Id.*, 1).

60. Regeneron (28-September-2008) stated that “[p]atients receiving monthly doses of VEGF Trap-Eye of either 2.0 or 0.5 milligrams (mg) for 12 weeks followed by PRN dosing achieved mean improvements in visual acuity versus baseline” and “mean decreases in retinal thickness versus baseline.” (*Id.*, 1).

61. Regeneron (28-September-2008) also described the dosing regimens used in the two Phase 3 trials, VIEW1 and VIEW2, including “VEGF Trap-Eye dosed . . . 2 mg every 8 weeks (following three monthly doses).” (*Id.*, 1-2).

62. A person of ordinary skill in the art would have understood the dosing regimens disclosed in Regeneron (28-September-2008) included the experimental groups that were to receive VEGF Trap-Eye 2 mg every eight weeks (following three monthly doses) or “monthly doses of 0.5 or 2.0 milligrams (mg) of VEGF Trap-Eye”

followed by “a PRN dosing schedule based upon the physician assessment of the need for re-treatment.” (*Id.*, 1-2).

63. A person of ordinary skill in the art would have been interested in, and sought out, the information disclosed in Regeneron (28-September-2008) because it pertains to ongoing product development within the industry, including dosing regimens of a known therapy (VEGF Trap-Eye or aflibercept) in patients with wet AMD. (*Id.*, 1). Again, my opinion in this regard is, in fact, confirmed by other contemporaneous prior art to the '681 patent that expressly refers to similar Regeneron and Bayer press releases. For example, Adis provides the following among twenty separate references to online “Media Releases”:

14. Regeneron Pharmaceuticals Inc, Bayer HealthCare AG. 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. Media Release: 29 Apr 2008. Available from URL: <http://www.regeneron.com>

(Ex.1007, Adis, 268 (emphasis added)). Indeed, press releases such as Regeneron (28-September-2008) were well-known—and widely available—to the community interested in the subject matter of the '681 patent. (*See, e.g., id.*, 262-63, 268-69).

64. In my opinion (and as confirmed by, e.g., Adis), a person of ordinary skill in the art would have also been able to locate Regeneron (28-September-2008) exercising reasonable diligence, which would have at least led the person of ordinary skill in the art to Regeneron’s website where the document was easily accessible,

and recognize and comprehend therefrom the essentials of the subject matter contained therein without further research or experimentation.⁷ Thus, a person of ordinary skill in the art could have easily accessed Regeneron (28-September-2008) via Regeneron's website and easily downloaded an electronic copy.

65. For at least these reasons, it is my opinion that Regeneron (28-September-2008) was a well-known, printed publication that was publicly accessible to persons interested and ordinarily skilled in the subject matter or art of the '681 patent, exercising reasonable diligence, before 2011.

3. Additional Regeneron Press Releases.

66. Regeneron and Bayer HealthCare AG issued a press release dated March 27, 2007 (Ex.1053, Regeneron (27-March-2007)), which described the twelve-week data for a "Phase 2 randomized study of their VEGF Trap-Eye in patients with the neovascular form of age-related macular degeneration (wet AMD)." (*Id.*, 1).

67. The patients in the study were "randomized to 5 groups" where "[t]wo groups received either 0.5 or 2.0 mg of VEGF Trap-Eye administered every four weeks, and three groups received a single dose of 0.5, 2.0, or 4.0 mg of VEGF Trap-Eye." (*Id.*, 1). Furthermore, the President of Regeneron Research Laboratories was

⁷ See, e.g., Ex.1056, Regeneron (28-September-2008), 1.

quoted as stating “[o]ur Phase 3 program is being designed to test this possibility and further evaluate the safety and efficacy of various doses and dosing intervals of the VEGF Trap-Eye.” (*Id.*).

68. Regeneron and Bayer HealthCare AG issued a press release dated August 2, 2007 (Ex.1054, Regeneron (2-August-2007)) which described “a Phase 3 study of the VEGF Trap-Eye in the neovascular form of age-related macular degeneration (wet AMD).” (*Id.*, 1). Specifically, Regeneron (2-August-2007) described “VEGF Trap-Eye . . . doses . . . 2.0 mg at an eight-week dosing interval.” (*Id.*).

69. Regeneron and Bayer HealthCare AG issued a press release dated April 28, 2008 (Ex.1012, Regeneron (28-April-2008)) which described the thirty-two-week results from a “double-masked, prospective, randomized, multi-center Phase 2 trial” in patients with the “neovascular form of Age-related Macular Degeneration (wet AMD)” treated with VEGF Trap-Eye. (*Id.*, 1).

70. The patients in the study were “randomized to five dose groups” as follows:

- (1) monthly dose of 0.5 milligrams (mg) of VEGF Trap-Eye for twelve weeks followed by therapy at the same dose on a PRN dosing schedule;
- (2) monthly dose of 2.0 mg of VEGF Trap-Eye for twelve weeks followed by therapy at the same dose on a PRN dosing schedule;

- (3) quarterly dose of 0.5 mg of VEGF Trap-Eye (at baseline and week 12) followed by therapy at the same dose on a PRN dosing schedule;
- (4) quarterly dose of 2.0 mg of VEGF Trap-Eye (at baseline and week 12) followed by therapy at the same dose on a PRN dosing schedule; or
- (5) quarterly dose of 4.0 mg of VEGF Trap-Eye (at baseline and week 12) followed by therapy at the same dose on a PRN dosing schedule.

(Ex.1012, Regeneron (28-April-2008), 1).

71. Regeneron (28-April-2008) added that VEGF Trap-Eye was being evaluated “using a monthly loading dose of . . . 2.0 mg for 12 weeks, followed by a nine-month fixed-dosing regimen of . . . 2.0 mg every eight weeks” or “monthly doses of 0.5 or 2.0 milligrams (mg) of VEGF Trap-Eye for 12 weeks” followed by “therapy at the same dose on a PRN dosing schedule based upon the physician assessment of the need for re-treatment.” (Ex.1012, Regeneron (28-April-2008), 1-2).

72. Regeneron issued a press release dated August 19, 2008 (Ex.1089, Regeneron (19-August-2008)) which announced that “VEGF Trap-Eye Achieved Durable Improvement in Vision over 52 Weeks in a Phase 2 Study in Patients with Age-related Macular Degeneration.” (*Id.*, 1). Specifically, Regeneron (19-August-2008) described “monthly doses of ... 2.0 milligrams (mg) of VEGF Trap-Eye (at weeks 0, 4, 8, and 12)” and “[f]ollowing the initial 12-week fixed-dosing phase of

the trial, patients continued to receive therapy at the same dose on a PRN dosing schedule.” (*Id.*). Regeneron (19-August-2008) described that “[p]atients receiving four monthly doses of VEGF Trap-Eye, either 2.0 or 0.5 mg, for 12 weeks followed by PRN dosing thereafter, achieved mean improvements in visual acuity versus baseline of 9.0 letters ($p<0.0001$) and 5.4 letters ($p=0.085$), respectively, and mean decreases in retinal thickness versus baseline of 143 microns ($p<0.0001$) and 125 microns ($p<0.0001$) at week 52, respectively.” (*Id.*).

73. A person of ordinary skill in the art would have understood that the dosing regimens disclosed in Regeneron (19-August-2008) included experimental groups where patients receiving monthly doses of either 2.0 or 0.5 mg VEGF Trap-Eye for 12 weeks followed by PRN dosing achieved improved visual acuity and decreased retinal thickness after one year. (*Id.*, 1).

74. Regeneron issued a press release dated February 26, 2009 (Ex.1041, Regeneron (26-February-2009) which described current business highlights including the “VIEW 1 and VIEW 2 trials ... evaluating dosing intervals of four and eight weeks for VEGF Trap-Eye.” (*Id.*, 1). Specifically, Regeneron (26-February-2009) describes “VEGF Trap-Eye [as] a specially purified and formulated form of VEGF Trap for use in intraocular applications.” (*Id.*).

75. A person of ordinary skill in the art would have understood that the anti-angiogenesis agents disclosed in Regeneron (26-February-2009) included

Regeneron's public statements representing that VEGF Trap-Eye used in intraocular applications is a specially purified and formulated form of VEGF Trap (Aflibercept) that was being evaluated as a second line treatment for metastatic colorectal cancer. (*Id.*, 1).

76. Regeneron issued a press release dated September 14, 2009 (Ex.1068, Regeneron (14-September-2009)) which described two "Phase 3 clinical trials evaluating VEGF Trap-Eye in the treatment of the neovascular form of age-related macular degeneration (wet AMD)," and a Phase 2 trial "for the treatment of Diabetic Macular Edema (DME)." (*Id.*, 1). Specifically, Regeneron (14-September-2009) described "VEGF Trap-Eye . . . dosed . . . 2.0 mg every eight weeks (following three monthly doses)" in the Phase 3 trials and dosing of "2 mg on an as-needed (PRN) basis after three monthly loading doses," in the Phase 2 trial. (*Id.*).

77. A person of ordinary skill in the art would have understood that the dosing regimens disclosed in Regeneron (14-September-2009) included the experimental groups that were to receive VEGF Trap-Eye "2.0 mg every eight weeks (following three monthly doses)," or "2 mg on an as-needed (PRN) basis after three monthly loading doses." (*Id.*, 1).

78. A person of ordinary skill in the art would have been interested in, and sought out, the information disclosed in the above Press Releases because they pertain to ongoing product development within the industry, including dosing

regimens of a known therapy (VEGF Trap-Eye or aflibercept) in patients with wet AMD. (See ¶¶ 50-54, 59-62, 66-73, 76-77, above). Again, my opinion in this regard is, in fact, confirmed by other contemporaneous prior art to the '681 patent that expressly refers to similar Regeneron and Bayer press releases. For example, Adis provides the following among twenty separate references to online “Media Releases”:

14. Regeneron Pharmaceuticals Inc, Bayer HealthCare AG. 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. Media Release: 29 Apr 2008. Available from URL: <http://www.regeneron.com>

(Ex.1007, Adis, 268 (emphasis added)). Indeed, press releases such as Regeneron’s Press Releases were well-known—and widely available—to the community interested in the subject matter of the '681 patent. (See, e.g., *id.*, 262-63, 268-69).

79. In my opinion (and as confirmed by, e.g., Adis), a person of ordinary skill in the art would have also been able to locate these Regeneron Press Releases exercising reasonable diligence, which would have at least led the person of ordinary skill in the art to Regeneron’s website where these documents were easily accessible, and recognize and comprehend therefrom the essentials of the subject matter

contained therein without further research or experimentation.⁸ Thus, a person of ordinary skill in the art could have easily accessed these Press Releases via Regeneron's website and easily downloaded an electronic copy.

80. For at least these reasons, it is my opinion that Regeneron's Press Releases outlined above were well-known, printed publications that were publicly accessible to persons interested and ordinarily skilled in the subject matter or art of the '681 patent, exercising reasonable diligence, before 2011.

C. CLINICALTRIALS.GOV.

81. ClinicalTrials.gov is an electronic registry and results database of clinical studies supported by the U.S. National Institutes of Health that is open and accessible to the public as a "resource that provides patients, their family members, health care professionals, researchers, and the public with easy access to information on publicly and privately supported clinical studies on a wide range of diseases and conditions."⁹ Each study record includes a summary of the study protocol.

⁸ Ex.1053, Regeneron (27-March-2007), 1; Ex.1054, Regeneron (2-August-2007), 1; Ex.1012, Regeneron (28-April-2008), 1; Ex.1068, Regeneron (14-September-2009), 1.

⁹ Ex.1069, Background-ClinicalTrials.gov, 1-3.

ClinicalTrials.gov includes records for several clinical studies involving aflibercept, including:

- VIEW1 (ClinicalTrials.gov identifier NCT00509795) (Ex.1014, NCT-795);
- VIEW2 (ClinicalTrials.gov identifier NCT00637377) (Ex.1015, NCT-377).

82. NCT-795 (VIEW1) was first available as of at least July 31, 2007, and describes a clinical study titled “A Randomized, Double Masked, Active Controlled Phase III Study of the Efficacy, Safety, and Tolerability of Repeated Doses of Intravitreal VEGF Trap in Subjects With Neovascular Age-Related Macular Degeneration.” (Ex.1014, NCT-795, 3; Ex.1070, Wayback Affidavit-069 (Wayback Machine records showing public availability of NCT-795, describing a clinical study titled “A Randomized, Double Masked, Active Controlled Phase III Study of the Efficacy, Safety, and Tolerability of Repeated Doses of Intravitreal VEGF Trap in Subjects With Neovascular Age-Related Macular Degeneration,” prior to January 13, 2011); Ex.1018, Heier-2012, 2539 (“Patients in VIEW 1 (registered at

www.clinicaltrials.gov on July 31, 2007 . . . “)).¹⁰ NCT-795 lists the following experimental “arms” of the study:

Experimental: Arm 1 VEGF Trap-Eye Intravitreal Injection	Drug: VEGF Trap-Eye 0.5 mg VEGF Trap-Eye administered every 4 weeks during the first year. Thereafter a dose may be administered as frequently as every 4 weeks, but no less frequently than every 12 weeks.
Experimental: Arm 2 VEGF Trap-Eye Intravitreal Injection	Drug: VEGF Trap-Eye 2.0 mg VEGF Trap-Eye administered every 4 weeks during the first year.

¹⁰ See also Ex.1015, NCT-377, 3-4; Ex.1070, Wayback-Affidavit-069 (Wayback Machine records showing public availability of NCT-377, describing a clinical study titled “A Randomized, Double Masked, Active Controlled, Phase 3 Study of the Efficacy, Safety, and Tolerability of Repeated Doses of Intravitreal VEGF Trap in Subjects With Neovascular Age-Related Macular Degeneration (AMD),” prior to January 13, 2011); Ex.1018, Heier-2012, 2539 (“Patients in VIEW 2 (registered at www.clinicaltrials.gov on March 12, 2008 . . . ”))).

	Thereafter a dose may be administered as frequently as every 4 weeks, but no less frequently than every 12 weeks.
Experimental: Arm 3 VEGF Trap-Eye Intravitreal Injection	Drug: VEGF Trap-Eye 2.0 mg VEGF Trap-Eye administered every 8 weeks (including one additional 2.0 mg dose at week 4) during the first year. Thereafter a dose may be administered as frequently as every 4 weeks, but no less frequently than every 12 weeks.
Active Comparator: Arm 4	Drug: ranibizumab 0.5 mg administered every 4 weeks during the first year. Thereafter a dose may be administered as frequently as every 4 weeks, but no less frequently than every 12 weeks.

(Ex.1014, NCT-795, 6-8).¹¹ The experimental arms above included the group which required participants to receive “2.0 mg VEGF Trap-Eye administered every 8 weeks (including one additional 2.0 mg dose at week 4) during the first year.” (*Id.*).¹²

83. A person of ordinary skill in the art would have understood that the dosing regimens disclosed in NCT-795 included the experimental group that received VEGF Trap-Eye every two months “including one additional 2.0 mg dose at week 4.” (Ex.1014, NCT-795, 8).¹³

84. A person of ordinary skill in the art would have been interested in and easily accessed and sought out the information disclosed on the ClinicalTrials.gov website regarding NCT-795 and NCT-377 because they each pertain to ongoing product development within the industry, including dosing regimens of a known therapy (VEGF Trap-Eye or aflibercept) in patients with wet AMD. (Ex.1014, NCT-

¹¹ See also Ex.1015, NCT-377, 6 (Experimental Arms 1-3).

¹² See also Ex.1015, NCT-377, 6 (experimental arms included the group which required participants to receive “2.0 mg VEGF Trap-Eye administered every 8 weeks (including one additional 2,0 mg dose at Week 4) during the first year”).

¹³ See also Ex.1015, NCT-377, 6 (included the experimental group that received VEGF Trap-Eye 2.0 mg every two months “including one additional 2,0 mg dose at Week 4”).

795, 3; Ex.1015, NCT-377, 3-4). Thus, in my opinion, NCT-795 and NCT-377 were all “publicly accessible” as they were disseminated or otherwise made available to the extent that persons interested and ordinarily skilled in the subject matter or art of the ’681 patent, exercising reasonable diligence, could locate them.

85. My opinion in this regard is, in fact, confirmed by other contemporaneous prior art to the ’681 patent that expressly cited to clinical trial records from ClinicalTrials.gov, including NCT-795 and NCT-377. For example, Reichert (Ex.1072, Reichert)¹⁴ provides the following disclosures of NCT-795 and NCT-377:

(Lucentis®, Genentech). In the 4 arm VIEW 1 study [NCT00509795], adult patients (50 years and older) in arms 1 and 2 are administered either 0.5 or 2.0 mg aflibercept every four weeks for 1 year, then the same dose is administered as frequently as every four weeks but no less frequently than every 12 weeks. Patients

(*Id.*, 94 (emphasis added)); and

¹⁴ Ex.1072, Reichert, 76; *see also id.*, cover (Reichert is a printed publication that was publicly available prior to January 13, 2011, and would be considered prior art to the ’681 patent).

is September 2013. The on-going VIEW 2 [NCT00637377] has the same design as VIEW 1, but is being conducted at sites in Europe, Asia Pacific, Japan and Latin America by Bayer. A total of 1,211 patients were recruited; the estimated study completion date is August 2011.

(*Id.*, 95 (emphasis added); *see also id.*, 96). Moreover, Reichert makes multiple, express references to obtaining information online directly from ClinicalTrials.gov. (*Id.*, 79 (Table 7 (“listed on clinicaltrials.gov”)); *id.*, 99 (Ref. No. 69 (citing ClinicalTrials.gov record and corresponding internet address))).

86. Similarly, Anderson (Ex.1073, Anderson)¹⁵ provides the following disclosures of NCT-795 and NCT-377 online reports:

Two phase III clinical trials are underway (VIEW-1 in the USA and Canada and VIEW-2 in Europe, Asia-Pacific, Japan and Latin America). These non-inferiority studies aim to compare efficacy of VEGF Trap against ranibizimab. Study completion is expected in 2012 and 2011, respectively (<http://clinicaltrials.gov/ct2/show/NCT00509795>; <http://clinicaltrials.gov/ct2/show/NCT00637377>). The effect of VEGF Trap on DMO is in phase II clinical testing (<http://clinicaltrials.gov/ct2/show/NCT00789477>). Table 1 also

¹⁵ Ex.1073, Anderson, 272 (Anderson is a printed publication that was publicly available prior to January 13, 2011, and would be considered prior art to the '681 patent).

(*Id.*, 275 (emphasis added)). Anderson made additional references to obtaining information from ClinicalTrials.gov. (*Id.*, 272-77, 280; *see also id.*, 373 (Figure 1 (“Graph displaying the number of clinical trials registered with the ClinicalTrials.gov registry (<http://clinicaltrials.gov>) each year between 2001 and 2009.”))).

87. Another example, Ciulla (Ex.1074, Ciulla),¹⁶ provides the following:

52 ($P < 0.0001$ for both from baseline). Currently, two randomized, international phase III studies (VIEW-1 and VIEW-2) (<http://www.clinicaltrials.gov>; NCT00509795, NCT00637377) are comparing intravitreal VEGF trap with ranibizumab.

(*Id.*, 162 (emphasis added)). Ciulla also made numerous other references to ClinicalTrials.gov and obtaining information from that database. (*Id.*, 162-63).

88. Ni (Ex.1075, Ni)¹⁷ provided the following:

¹⁶ Ex.1074, Ciulla, 158 (Ciulla is a printed publication that was publicly available prior to January 13, 2011, and would be considered prior art to the '681 patent).

¹⁷ Ex.1075, Ni, 401 (Ni is a printed publication that was publicly available prior to January 13, 2011, and would be considered prior art to the '681 patent).

- 27 Double-Masked Study of Efficacy and Safety of IVT VEGF Trap-Eye in Subjects with Wet AMD (VIEW 1). <http://www.clinicaltrials.gov/ct2/show/NCT00509795?order=1> (accessed July 31, 2007).
- 28 Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Wet Age-Related Macular Degeneration (AMD) (VIEW 2). <http://clinicaltrials.gov/ct2/show/NCT00637377?order=1> (accessed March 12, 2008).

(*Id.*, 409 (emphasis added)). Additionally, Ni references numerous clinical trials with citations to ClinicalTrials.gov as the source of the information. (*See, e.g., id.*, 408-10).

89. Another example, Zarbin (Ex.1076, Zarbin)¹⁸ provided the following:

in a Phase 1 clinical trial.¹⁵⁰ VEGF Trap-Eye (<http://clinicaltrials.gov/ct2/show/NCT00509795?term=VEGF+Trap-Eye&rank=14>) is formulated for intravitreal injection, appears to be effective in a Phase 2 trial (www.bmctoday.net/retinatoday/2009/10/article.asp?f=1009_08.php), and is now being compared with ranibizumab in a Phase 3 clinical trial. AAV2-sFLT01

¹⁸ Ex.1076, Zarbin, 1350 (Zarbin is a printed publication that was publicly available prior to January 13, 2011, and would be considered prior art to the '681 patent).

(*Id.*, 1360 (emphasis added)). Additionally, Zarbin also references numerous clinical trials with citations to ClinicalTrials.gov as the source of the information. (*See id.*, 1351-52, 1356-62).

90. Dixon (Ex.1006, Dixon)¹⁹ provides the following citations, further confirming that both NCT-795 and NCT-377, including the dosing regimens disclosed therein, were publicly available as of at least September 28, 2008:

46. Double-Masked Study of Efficacy and Safety of IVT VEGF Trap-Eye in Subjects With Wet AMD (VIEW 1) [ClinicalTrials.gov identifier: NCT00509795] ClinicalTrials.gov [online]. Available from: <http://clinicaltrials.gov/ct2/show/NCT00509795> Accessed 28 Sep 2008
47. VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD (VIEW 2). [ClinicalTrials.gov identifier: NCT00637377] ClinicalTrials.gov [online]. Available from: <http://clinicaltrials.gov/ct2/show/NCT00637377> Accessed 28 Sep 2008

¹⁹ Ex.1006, Dixon, 1573 (Dixon is a printed publication that was publicly available prior to January 13, 2011, and would be considered prior art to the '681 patent).

(*Id.*, 1579 (emphasis added)). Accordingly, it is my firm opinion that ClinicalTrials.gov records, NCT-795 and NCT-377, were well-known—and widely available—to the community interested in the subject matter of the '681 patent.

91. Prior to 2011, a person of ordinary skill in the art would have also been able to locate NCT-795 and NCT-377 exercising reasonable diligence, which would have at least led the person of ordinary skill in the art to the ClinicalTrials.gov website where the documents were easily accessible, and recognize and comprehend therefrom the essentials of the subject matter contained therein without further research or experimentation.²⁰ Thus, a person of ordinary skill in the art could have easily accessed NCT-795 and NCT-377 via ClinicalTrials.gov and easily downloaded an electronic copy of each.

92. For the reasons outlined above, a person of ordinary skill in the art would have considered the posting dates cited at ClinicalTrials.gov to be trustworthy and authoritative and it is my opinion that NCT-795 and NCT-377 were well-known, printed publications that were publicly accessible to persons interested and ordinarily skilled in the subject matter or art of the '681 patent, exercising reasonable diligence, before 2011.

²⁰ See Ex.1014, NCT-795, 1; Ex.1015, NCT-377, 1.

D. SEC FILINGS.

93. As I note above (*see* ¶¶ 46-49), company press releases were well-known, and widely available, to persons of ordinary skill in the art. This was especially true of persons of ordinary skill in the art of the '681 patent, who expressly cited Bayer and Regeneron press releases. (*See, e.g.*, Ex.1007, Adis, 262-63, 268-69).

94. Moreover, domestic publicly-traded companies are required to file certain forms with the SEC, and this is well-known by those in the pharmaceutical industry and academia. A company's SEC filings provide "reliable information about [the company]" that allows a person in the art to ensure that they are well informed and up-to-date on all of the most important developments. (Ex.1077, Corporate Finance Institute, 1-3; *see also* Ex.1078, Schneider, 258 (noting that "SEC filings . . . have been considered to be among the most accurate and reliable . . . sources of information available"); Ex.1079, Kuepper, 1-4).

95. SEC filings, such as a company's Form 10-Q, are easily accessible via the Electronic Data Gathering, Analysis, and Retrieval system ("EDGAR") or a company's website. (*See, e.g.*, Ex.1080, Zucchi). SEC filings provide, *inter alia*, information regarding the company's finances as well as recent business activity. (*See id.*; Ex.1081, Hayes, 3-4, 8-10).

96. In my experience in the industry, SEC filings for pharmaceutical or biotechnology companies included information regarding ongoing development of different products, including ongoing clinical trials and the results of completed clinical trials. Thus, a person of ordinary skill in the art would utilize the information contained therein, amongst other references, to keep up to date on the development in the field of interest, especially with direct competitors.

97. First, a person of ordinary skill in the art would be interested in such “Financial and Operating Results” as confirmed by the prior art:

8. Regeneron Pharmaceuticals Inc. Regeneron Reports Second Quarter **Financial and Operating Results**; BLA Filing for Auto-Inflammatory Diseases Planned for Early 2007; Two Antibody Candidates from VelocImmune(R) Program to Enter Clinical Trials Each Year Beginning in 2007. **Media Release**; 3 Aug 2006. **Available from** URL: <http://www.regeneron.com>

(Ex.1007, Adis, 268 (emphasis added); *see also id.* (Ref. Nos. 6, 18)).

98. Second, in my opinion, a person of ordinary skill in the art would have been aware of such company filings, such as Regeneron’s September 30, 2009 10-Q (“2009 10-Q”) (Ex.1021, 2009 10-Q), and would routinely look to 10-Q filings to determine what drugs and treatments pharmaceutical companies were working on. Here, Regeneron disclosed information regarding, among other things, its ongoing development of the VEGF Trap-Eye program—specifically focused on the clinical trials for VEGF Trap-Eye—in its September 30, 2009 10-Q. (Ex.1021, 2009 10-Q, 20 (“The VIEW 1 and VIEW 2 trials are both evaluating VEGF Trap-Eye doses of

. . . 2.0 mg at a dosing interval of eight weeks (after three monthly doses).”). 2009 10-Q also disclosed results of the CLEAR-IT trial, which included “monthly doses of VEGF Trap-Eye of . . . 2.0 . . . mg for 12 weeks followed by PRN dosing,” and the DA VINCI trial. (*Id.*, 19-20).

99. A person of ordinary skill in the art would have understood that the dosing regimens disclosed in 2009 10-Q included the experimental groups that received VEGF Trap-Eye 2.0 mg every eight weeks following three monthly “loading dose” injections or “monthly doses of VEGF Trap-Eye of . . . 2.0 . . . mg for 12 weeks followed by PRN dosing.” (Ex.1021, 2009 10-Q, 19-20).

100. Thus, in my opinion, a person of ordinary skill in the art also would have been interested in, and sought out, the information disclosed in 2009 10-Q because it pertains to ongoing product development within the industry, including dosing regimens of a known therapy (VEGF Trap-Eye or aflibercept) in patients with angiogenic eye disorders such as wet AMD. (Ex.1021, 2009 10-Q, 19-20). My opinion in this regard is confirmed by other contemporaneous prior art to the ’681 patent which expressly refers to the Regeneron 2010 Financial Press Release which, in turn, directed a person of ordinary skill in the art to Regeneron’s company filings with the SEC. (*See* Ex.1007, Adis, 268 (Ref. Nos. 6, 18)). Indeed, company filings such as 2009 10-Q were well known—and widely available—to the community

interested in the subject matter of the '681 patent. (*See id.*, 262-63, 268 (Reference Nos. 6, 18)).

101. It is also my opinion that 2009 10-Q would have been routinely available to a person of ordinary skill in the art. Prior to 2011, a person of ordinary skill in the art would have been able to locate 2009 10-Q exercising reasonable diligence, which would have at least led the person of ordinary skill in the art to Regeneron's website where the document was easily accessible, and recognize and comprehend therefrom the essentials of the subject matter contained therein without further research or experimentation.²¹ Thus, a person of ordinary skill in the art could have easily accessed 2009 10-Q via Regeneron's website and easily downloaded an electronic copy.

102. For at least these reasons, it is my opinion that 2009 10-Q was a well-known, printed publication that was publicly accessible to persons interested and ordinarily skilled in the subject matter or art of the '681 patent, exercising reasonable diligence, before 2011.

IX. CONCLUDING STATEMENTS.

103. In signing this declaration, I understand that the declaration will be filed as evidence in a contested case before the USPTO Patent Trial and Appeal Board. I

²¹ *See* Ex.1021, 2009 10-Q.

acknowledge that I may be subject to cross-examination in this case. If cross-examination is required of me, I will appear for cross-examination during the time allotted for such cross-examination.

104. I declare that all statements made herein of my knowledge are true, and that all statements made on information and belief are believed to be true, and that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Dated: June 30, 2022

A handwritten signature in black ink, appearing to be 'Mary E. Gerritsen', written over a horizontal line.

Mary E. Gerritsen, Ph.D.