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.: IPR2021-00881

U.S. Patent No. 9,254,338 B2
Filed: July 12, 2013
Issued: February 9, 2016
Inventor: George D. Yancopoulos

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

EXPERT DECLARATION OF DR. THOMAS A. ALBINI IN SUPPORT OF PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 9,254,338 B2

Joining Petitioner: Apotex

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1. My name is Dr. Thomas A. Albini. I have been retained by counsel for Mylan Pharmaceuticals Inc. ("Mylan" or "Petitioner") to provide my opinion regarding U.S. Patent No. 9,254,338 (Ex.1001, the "'338 patent"), which I understand is assigned to Regeneron Pharmaceuticals, Inc. ("Regeneron"). I understand that Petitioner intends to petition for *inter partes* review of the '338 patent, and will request that the United States Patent and Trademark Office cancel certain claims of the '338 patent as unpatentable. My opinions in this expert declaration support Petitioner's request for *inter partes* review of the '338 patent and the cancellation of claims 1, 3-11, 13-14, 16-24, and 26 (the "challenged claims").

I. QUALIFICATIONS AND BACKGROUND.

A. Education and Experience.

2. I received a Bachelor of Arts degree, *Magna Cum Laude*, from Princeton University in 1994. I obtained my M.D. from Johns Hopkins University School of Medicine in 1999. I completed an internal medicine internship at Jackson Memorial Hospital in Miami, Florida, and an ophthalmology residency at the Doheny Eye Institute of the University of Southern California.

3. After my residency, I completed a uveitis and ocular pathology clinical and research fellowship at the Doheny Eye Institute followed by a vitreoretinal surgery fellowship at the Cullen Eye Institute of the Baylor College of Medicine.

4. I was an instructor in ocular inflammation, uveitis, and ophthalmic pathology at the Doheny Eye institute from 2003-2004. I joined the faculty at the Bascom Palmer Eye Institute of the University of Miami Miller School of Medicine as an Assistant Professor of Clinical Ophthalmology in 2006. I held the position of Associate Professor of Clinical Ophthalmology at the Bascom Palmer Eye Institute from 2012 to June 2018. Since July 2016, I have served as co-director of the vitreoretinal surgery fellowship. Since June 2018, I have been a Professor of Clinical Ophthalmology. In my current and prior positions, I have been involved in the teaching and training of medical students, fellows, and residents in the area of ophthalmological surgical techniques, specifically, injection protocols for the administration of therapeutics for the treatment of age-related macular degeneration (AMD) and other vitreoretinal eye disorders. Further, in 2006, I began my current roles as a staff ophthalmologist at both the Anne Bates Leach Eye Hospital of the Bascom Palmer Eye Institute as well as the Jackson Memorial Hospital.

5. I was awarded the American Academy of Ophthalmology Achievement Award in 2011 and Senior Achievement Award in 2019. In 2012, I received the Service Award from the American Society of Retina Specialists for outstanding service to the Society's scientific and educational programs. I also received the Senior Honor Award from the American Society of Retina Specialists in 2012.

6. I have served as an editor, co-editor, or on the editorial board of several publications, including Retina Today, the website for the American Society of Retina Specialists, New Retina MD, and the Journal of VitreoRetinal Diseases.

7. My clinical practice is focused on the diagnosis and treatment of patients suffering from various macular diseases, such as macular degeneration, diabetic retinopathy and related disorders, as well as uveitis. I have experience with surgical interventions as well as the prescription and administration of various intravitreally-administered anti-angiogenesis agents.

8. I was and currently am a member in several Professional and Academic Societies, including American Academy of Ophthalmology, Association for Research in Vision and Ophthalmology, American Society of Retina Specialists, Miami Ophthalmological Society, Vitrectomy Buckle Society, American Uveitis Society, The Macula Society, Pan American Association of Ophthalmology, and The Retina Society, among others.

9. I have authored or co-authored over two hundred and fifty (250) publications, including book chapters, peer-reviewed scientific papers, abstracts, and other published works. Several of these publications pertain to AMD, retinal detachment, retinal and choroidal diseases, or diabetic macular edema (DME), among other disorders of the eye.

10. In all, I have over fifteen (15) years of hands-on clinical and research experience specializing in treating vitreoretinal disorders and the prescription, and intravitreal administration, of VEGF antagonists. I have included a copy of my *curriculum vitae* in support of my opinions. (Ex.1038, Albini CV).

B. Bases for Opinions and Materials Considered.

11. In addition to my education, knowledge of the relevant published art, training, and experience, in forming the opinions I provide in this declaration, I have also considered the exhibits cited herein.

C. Scope of Work.

12. I have been retained by Petitioner as an expert in this matter to provide my various opinions regarding the '338 patent. I receive $500 per hour for my services. No part of my compensation is dependent upon my opinions given or the outcome of this case. I do not have any current or past affiliation with Regeneron, or any of the named inventors on the '338 patent.

II. LEGAL STANDARDS.

13. For my opinions in this declaration, I understand that it requires applying various legal principles. As I am not an attorney, I have been informed about various legal principles that govern my analysis. I have used my understanding of those principles in forming my opinions. I summarize my understanding of those legal principles as follows:

14. **Burden of Proof.** I understand that Petitioner bears the burden of proving unpatentability in this proceeding by a preponderance of the evidence. I am informed that this preponderance of the evidence standard means that Petitioner must show that unpatentability is more probable than not.

15. **Claim Construction.** I have also been told that when I review and consider the claims, the claim term(s) should be analyzed under their ordinary and customary meaning as understood from the perspective of one of ordinary skill in the art, taking into account the claim language itself, specification, and prosecution history pertaining to the patent, as well as relevant extrinsic evidence. I have applied this standard in formulating my opinions, and set forth my understanding of the scope of particular claim terms discussed below.

16. **Anticipation.** I have been asked to consider the question of anticipation, namely, whether the claims cover something that is new, or novel. I am told that the concept of anticipation requires that each and every element of a challenged claim is present in or otherwise taught by a single reference. I also understand that an anticipatory reference does not need to explicitly describe each element because anticipation can occur when a claimed limitation is necessarily inherent or otherwise implicit in the relevant reference.

17. **Obviousness.** I have been asked to consider the question of obviousness/non-obviousness. Again, I am told that this analysis must be from the

perspective of the person of ordinary skill in the art, and whether such person would consider any differences between the prior art and what is claimed to have been obvious. To make this assessment, I have been informed that the concept of patent obviousness involves four factual inquiries:

- the scope and content of the prior art;
- the differences between the claimed invention and the prior art;
- the level of ordinary skill in the art; and
- so-called secondary considerations of non-obviousness.

18. I have further been instructed that one cannot use the challenged patent itself (here, the '338 patent) as a guide from which to select prior art elements, or otherwise engage in hindsight. Rather, the better approach is to consider what the person of ordinary skill in the art knew, and what the art taught; suggested; or motivated the person of ordinary skill in the art to further pursue; and to differentiate between steps that were routinely done (such as in response to known problems, steps, or obstacles), and those which, for example, may have represented a different way of solving existing or known problems.

19. I am also informed that when there is some recognized reason to solve a problem, and there are a finite number of identified, predictable, and known solutions, a person of ordinary skill in the art has good reason to pursue the known options within his or her technical grasp. If such an approach leads to the expected

success, it is likely not the product of innovation but of ordinary skill and common sense. In addition, when a patent simply arranges old elements with each performing its known function and yields no more than what one would expect from such an arrangement, the combination is obvious.

20. I understand that before reaching any final conclusion on obviousness, the obviousness analysis requires consideration of objective indicia of non-obviousness, if offered. These must be considered to ensure that, for example, there were not some unanticipated problems, obstacles, or hurdles that may seem easy to overcome in hindsight, but which were not readily overcome prior to the relevant invention date of the patents/claims at issue here. I understand that these objective indicia are also known as "secondary considerations of non-obviousness," and may include long-felt but unmet need and unexpected results, among others. I also understand, however, that any offered evidence of secondary considerations of non-obviousness must be comparable with the scope of the challenged claims. This means that for any offered evidence of secondary considerations of non-obviousness to be given substantial weight, I understand the proponent of that evidence must establish a "nexus" or a sufficient connection or tie between that evidence and the merits of the claimed invention, which I understand specifically incorporates any novel element(s) of the claimed invention. If the secondary considerations evidence offered actually results from something other than the merits of the claim, then I

understand that there is no nexus or tie to the claimed invention. I also understand it is the patentee that has the burden of proving that a nexus exists.

21. With respect to long-felt need, I understand that the evidence must show that a particular problem existed for a long period of time. More specifically, I understand that for a "need" to be long-felt and unmet, (i) the need must be persistent and recognized by those of ordinary skill in the art; (ii) the need must not be satisfied by another before the alleged invention; and (iii) the claimed invention itself must satisfy the alleged need. I also understand that long-felt need is analyzed as of the date that the problem is identified. Furthermore, I understand that long-felt need should be based upon alleged inadequacies in the technical knowledge of those skilled in the art, not due to business-driven market forces.

22. I further understand that, absent a showing of a long-felt, unmet need, the mere passage of time without the claimed invention is not evidence of non-obviousness.

23. With respect to unexpected results, I understand that any results upon which a patentee wishes to rely as an indicator of non-obviousness must be based on a comparison of the purported inventions with the closest prior art.

24. However, I understand that secondary considerations will not overcome a strong showing of obviousness.

25. **Public Availability.** I have also been asked to consider whether there is a reasonable likelihood that some of the references discussed herein would have been publicly accessible before the priority date of the '338 patent. I have been informed that a reference is "publicly accessible" if the document has been 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.

III. PERSON OF ORDINARY SKILL IN THE ART.

26. As I mentioned above, I have been informed by counsel 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. I also understand that the person of ordinary skill in the art is assumed to know, understand, and be familiar with all of the relevant prior art, and that such person is not an automaton, but rather a person of ordinary creativity.

27. I have also been informed by counsel 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.

28. After considering the above-mentioned factors, it is my opinion that 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 AMD, including through the use of VEGF antagonists, or (ii) treating of same, including through the use of VEGF antagonists.

IV. SUMMARY OF OPINIONS.

29. It is my opinion that Dixon anticipates the challenged claims of the ’338 patent through Dixon’s disclosure of the dosing regimen used by Regeneron in their Phase 3 VIEW1 and VIEW2 AMD trials (3 monthly doses of 2 mg, followed by 2 mg every eight weeks).

30. It is my opinion that Adis anticipates the challenged claims of the ’338 patent through Adis’ disclosure of the dosing regimen used by Regeneron in their Phase 3 VIEW1 and VIEW2 AMD trials (3 monthly doses of 2 mg, followed by 2 mg every eight weeks).

31. It is my opinion that Regeneron's May 2008 Press Release ("Regeneron (8-May-2008)") anticipates the challenged claims of the '338 patent through the disclosure of the dosing regimen used by Regeneron in their Phase 3 VIEW2 AMD trial (3 monthly doses of 2 mg, followed by 2 mg every eight weeks).

32. It is my opinion that Regeneron's publicly accessible clinicaltrials.gov submissions (NCT-795 and NCT-377) also anticipate the challenged claims of the '338 patent through their disclosure of the dosing regimen used by Regeneron in their Phase 3 VIEW1 and VIEW2 AMD trials (3 monthly doses of 2 mg, followed by 2 mg every eight weeks).

33. It is my opinion that the public disclosures of Regeneron's VIEW1/VIEW2 trials make the challenged claims obvious, because they disclose all aspects of the claimed dosing regimen, and because combined with the skilled person's knowledge regarding the VEGF Trap-Eye/aflibercept sequence and structure (as disclosed in the '758 patent and Dix), as well as the motivation in the art to reduce injection frequency, and the positive results observed in the Phase 2 CLEAR-IT clinical trials, persons of ordinary skill in the art would have had a reasonable expectation of success in using the VIEW1/VIEW2 regimens.

34. It is also my opinion that there are no "secondary considerations" that would support the patentability of the claims of the '338 patent. First, it is my understanding that secondary considerations are not relevant in the context of

anticipation and it is my opinion that each of the VIEW1/VIEW2 disclosures mentioned above anticipate the '338 patent claims. Second, in the context of obviousness, it is my opinion that the arguments presented by Regeneron to the U.S. Patent and Trademark Office do not support a finding of surprising or unexpected results, especially given the positive and promising results reported for the Phase 2 trial and public disclosure of the Phase 3 dosing regimen.

V. THE '338 PATENT (Ex.1001).

35. I have read the '338 patent, which is titled "Use of a VEGF Antagonist to Treat Angiogenic Eye Disorders," as well as the issued claims. I am very familiar with the state of the art at the time this patent was first filed, which I have been asked to assume is January 13, 2011.[1] The '338 patent lists George D. Yancopoulos as the sole inventor.

[1] I understand the following from the cover page of the '338 patent: (i) Application No. 13/940,370 ("the '370 application") issued as the '338 patent on or about February 9, 2016; (ii) the '370 application was filed July 12, 2013; (iii) as a "continuation-in-part" of application No. PCT/US2012/020855, which was filed on January 11, 2012; and (iv) the '338 patent lists three "provisional" applications filed, respectively, on (a) January 13, 2011; (b) January 21, 2011; and (c) November 21,

36. I have reviewed the '338 patent claims from the perspective of a person of ordinary skill in the art and applied each claim's ordinary and customary meaning in light of the claims, the specification, and the prosecution history, as well as any relevant extrinsic evidence. I understand that Petitioner is challenging claims 1, 3-11, 13-14, 16-24, and 26.

37. Claims 1 and 14 are the only independent claims and read as follows:

> **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 232-457of SEQ ID NO:2.

2011, as "Related U.S. Application Data." (*See* Ex.1001, '338 patent at Cover). I have been asked to assume that the priority date of the '338 patent is January 13, 2011. I have formed no opinion regarding the merit of the '338 patent's claim to that date.

* * *

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.

(Ex.1001, '338 patent, 23:2-18 (claim 1); *id.*, 24:3-15 (claim 14)).

38. Challenged claims 3-11 and 13 all depend, either directly or indirectly, from claim 1.

39. Challenged claims 16-24 and 26 all depend, either directly or indirectly, from claim 14.

A. Claim Construction.

40. In my opinion, a person of ordinary skill in the art would reach at least the following conclusions regarding the claim language:

41. **First**, although the terms "initial dose," "secondary dose," and "tertiary dose" are not typically used in practice, a person of ordinary skill in the art would understand the terms to have the meaning expressly given to them in the '338 patent specification:

> The terms "initial dose," "secondary doses," and "tertiary doses," refer to the temporal sequence of administration of the VEGF antagonist. Thus, the "initial dose" is the dose which is administered at the beginning of the treatment regimen (also referred to as the "baseline dose"); the "secondary doses" are the doses which are administered after the initial dose; and the "tertiary doses" are the doses which are administered after the secondary doses.

(*See* Ex.1001, '338 patent, 3:31-38). The '338 patent further states that "[t]he initial, secondary, and tertiary doses…will generally differ from one another in terms of frequency of administration." (*Id.*, 3:38-41). For example, the '338 patent states that "each secondary dose 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." (*Id.*, 3:46-51). The '338 patent explains that "the immediately preceding dose" means "in a sequence of multiple administrations, the dose of VEGF antagonist which is administered to a patient prior to the administration of the very next dose in the sequence with no intervening doses." (*Id.*, 3:51-56). These are the meanings I have applied to these terms in formulating my opinions.

42. **Second**, to a person of ordinary skill, the reference to administering at "4 weeks" in the claims is synonymous in the art with treating angiogenic eye disorders with *monthly* administration. Likewise, the reference to "administered at least 8 weeks" is synonymous in the art with treating angiogenic eye disorders with

bi-monthly (or every-other-month) administration. This is also consistent with my own experience treating angiogenic eye disorders—i.e., I consider "4 weeks" to be synonymous (or interchangeable) with "monthly," and "8 weeks" to be synonymous (or interchangeable) with "bi-monthly," (or every-other-month). (*See id.*, 7:54-56).

43. **Third,** although I have been informed that a claim preamble is presumed not to be a claim limitation, I have been asked for my opinion on the scope of the term "method for treating" should the Board wish to construe the term. In my opinion, without any parameters set forth in the claim or any additional guidance from the claim itself, a person of ordinary skill in the art would apply a plain and customary meaning to the term, which would include administering a therapeutic agent to a patient. I have analyzed the specification and have not seen an alternative definition for the term in the specification. I have seen a reference to "efficacy," and if one were to equate a method for treating with a particular efficacy, the definition in the patent provides that the method demonstrate efficacy within 104 weeks from initiation, and that the patients exhibit a loss of 15 or fewer letters on the ETDRS visual acuity chart. (*Id.*, 7:16-31).

44. **Fourth**, with respect to claims 1 and 14 (and the claims that depend therefrom), a person of ordinary skill in the art would understand the "VEGFR1 component," "VEGFR2 component," and the "multimerization component"—all of which refer to separate amino acid domains of "SEQ ID NO:2" and the

corresponding DNA sequence of "SEQ ID NO:1"—as collectively referring to aflibercept (a/k/a VEGF Trap or VEGF Trap-Eye), for at least the following reasons:

- The amino acid sequence provided in the '338 patent specification for "SEQ ID NO:2" is the identical amino acid sequence Regeneron previously submitted to the U.S. Patent and Trademark Office as referring to aflibercept (a/k/a VEGF Trap or VEGF Trap-Eye).[2] (*Compare id.*, SEQ ID NO:2, *with* Ex.1010, '758 patent, Fig.24A-C (disclosing the nucleotide sequence and deduced amino acid sequence, as well as a description of each molecular component therein (i.e., the signal sequence, the FLT1 Ig domain 2, the FLK1 Ig domain 3, and the FcΔC1 domain), 10:15-17 (specifying that this molecule is termed "VEGFR1R2-FcΔC1(a)."); *see also, e.g.*, Ex.1024, '758 FH, 12/22/2011 Patent Term Extension Application, 2, 6-7 ("The name of the active ingredient of EYLEA™ is aflibercept, also known as VEGF trap, VEGF-trap, VEGF Trap-Eye and VEGF-TRAP$_{R1R2}$ . . . [,] a fusion protein consisting of (a) a vascular

[2] In the course of my analysis, I requested that exhibits be created that compare the SEQ ID NO:1 and SEQ ID NO:2 of the '338 patent with sequences disclosed in the prior art references. I have reviewed these exhibits and confirmed that these sequences are the same. (Ex.1093; Ex.1094).

endothelial growth factor (VEGF) receptor component having immunoglobulin-like (Ig) domains consisting of an Ig domain 2 of a first VEGF receptor that is human Fltl and an Ig domain 3 of a second VEGF receptor that is human Flkl; and (b) an Fc portion of human IgG1," and further explaining to the U.S. Patent and Trademark Office that the amino acid sequence of aflibercept is set forth in Figures 24A-24C of the '758 patent));

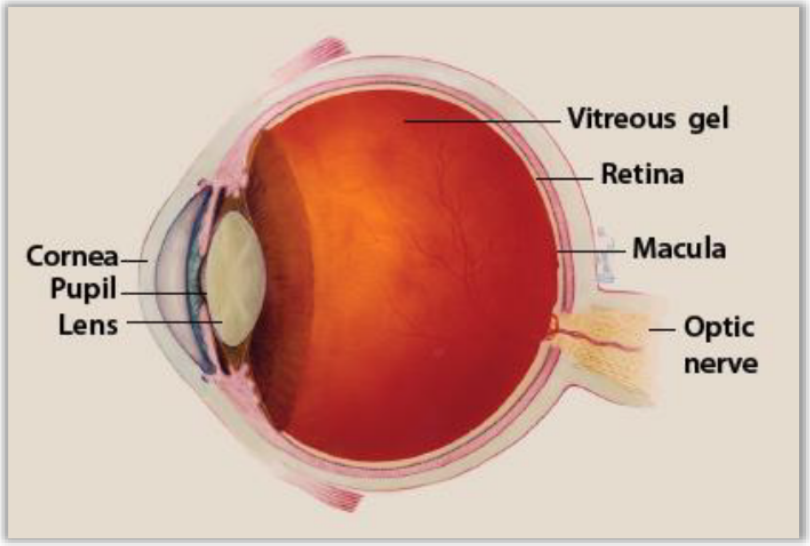
- The '338 patent specification states that "[a]n exemplary VEGF antagonist that can be used in the context of the present invention is a multimeric VEGF-binding protein comprising two or more VEGF receptor-based chimeric molecules referred to herein as 'VEGFR1R2-FcΔC1(a)' or 'aflibercept.'" (Ex.1001, '338 patent, 2:32-37); and
- It was well known in the art that this fusion VEGF antagonist was commonly referred to as "VEGF Trap," and also known as "aflibercept," as well as "VEGF Trap-Eye" when formulated for intraocular delivery. These terms were often used interchangeably by those of ordinary skill in the art. (*See, e.g.*, Ex.1006, Dixon, 1575 ("VEGF Trap-Eye and aflibercept (the oncology product) have the same molecular structure."); Ex.1039, '095 patent, 1:45-54; Ex.1040, WHO Drug Info, 118-19; Ex.1021, 2009 10-Q, 20 (using VEGF Trap and aflibercept

interchangeably and explaining that "VEGF Trap-Eye is a specially purified and formulated form of VEGF Trap for use in intraocular applications"); Ex.1007, Adis, 261 (indicating in the title that aflibercept, VEGF Trap (R1R2), and VEGF Trap-Eye, among other terms, are understood by a person of ordinary skill in the art to refer, interchangeably, to the same drug)).

VI. BACKGROUND.

A. Vitreoretinal Disorders.

45. The following Figure illustrates the normal anatomy of the eye:



(Ex.1042, NIH AMD, 2). Vitreoretinal disorders relate to problems involving the retina, macula, and vitreous fluid (or gel). The retina is the light-sensitive tissue lining the back of the eye, which converts light rays into impulses that travel through

the optic nerve to the brain, where they are interpreted as images. The macula is the small area at the center of the retina, which, because of the high concentration of cones in that region, is responsible for high-acuity color vision, which enables one to distinguish among different colors. The vitreous fluid (or gel) is the clear, jelly-like substance that fills the inside of the eye from the lens to the retina, helping the eye maintain its shape.

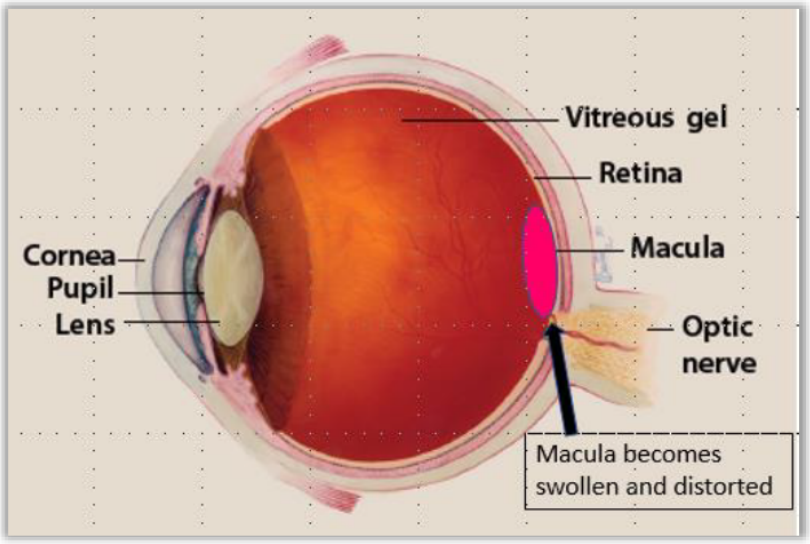
46. Vitreoretinal disorders such as AMD and diabetic retinopathy (DR) are the leading causes of visual impairment in developed countries, and the prevalence of these disorders is expected to rise with the increase in the aged population. (*See* Ex.1006, Dixon, 1573).

1. Age-related macular degeneration (AMD).

47. The NIH's National Eye Institute describes AMD as "a common eye condition and a leading cause of vision loss among people age 60 and older. It causes damage to the macula, a small spot near the center of the retina and the part of the eye needed for sharp, central vision, which lets us see objects that are straight ahead." (Ex.1042, NIH AMD, 1).

48. AMD can be classified as either "dry" (nonexudative) or "wet" (exudative). (*See, e.g.*, Ex.1036, Regeneron (28-April-2008), 2). In wet AMD, new blood vessels grow beneath the retina and leak blood and/or fluid, causing disruption

and dysfunction of the retina, as I have illustrated in the following modification of Figure 1 from NIH AMD:



(Ex.1042, NIH AMD, 2 (modified to illustrate neovascular (wet) AMD); *see also* Ex.1036, Regeneron (28-April-2008), 2). This creates blind spots in central vision and eventual scarring or formation of a disciform that represents the end-stage of AMD and associated vision loss.

49. As of 2009, it was reported that AMD "affects > 1.75 million individuals in the US and it is estimated that by 2020 this number will increase to almost 3 million," and "[w]orldwide, AMD is estimated to affect 14 million people." (Ex.1006, Dixon, 1573).

50. Early treatments for wet AMD were focused on laser and photodynamic therapy, in which portions of the eye were cauterized to prevent the spread of new

blood vessels. However, while this therapy could be effective at controlling vision loss in some patients, the therapy itself could result in vision loss in some portions of the eye. (*See* Ex.1043, Brown, 627; Ex.1006, Dixon, 1573 ("[Patients treated with photodynamic therapy] continued to experience a decline in visual acuity and the treatment was of questionable cost and effectiveness.")).

2. Diabetic retinopathy (DR).

51. DR "occurs when diabetes damages the tiny blood vessels in the retina, which is the light-sensitive tissue at the back of the eye." (Ex.1044, NIH DR, 1). DR "can cause blood vessels in the retina to leak fluid or hemorrhage (bleed), distorting vision." (*Id.*, 1-2). Further, "[i]n its most advanced stage, new abnormal blood vessels proliferate (increase in number) on the surface of the retina which can lead to scarring and cell loss in the retina." (*Id.*, 2). DR is the "leading cause of vision impairment and blindness among working-age adults." (*Id.*, 1).

3. Diabetic macular edema (DME).

52. DME is a consequence of DR. "DME is the build-up of fluid (edema) in a region of the retina called the macula." (Ex.1044, NIH DR, 3). "DME is the most common cause of vision loss among people with diabetic retinopathy." (*Id.*).

B. Angiogenesis and Vascular Endothelial Growth Factor (VEGF).

53. Angiogenesis is a key process necessary for embryonic development of the vascular system; early gene knockout studies revealed that loss of one or more

genes responsible for angiogenesis results in embryonic lethality. (*See* Ex.1045, Ferrara-1999, 1359). However, aberrant angiogenesis has also been identified as a contributor to the development of many tumors and disorders associated with increased vascularization. (*See id.*, 1360). Early on, researchers recognized the potential promise of targeting angiogenesis as a therapeutic strategy for treating diseases and disorders characterized by increased vascularity. (*See id.*, 1359-60).

C. VEGF Antagonists.

54. While VEGF may be "a naturally occurring protein in the body whose normal role is to trigger formation of new blood vessels (angiogenesis) to support the growth of the body's tissues and organs," (Ex.1036, Regeneron (28-April-2008), 2), additional research also identified a role for VEGF in tumor angiogenesis, with studies showing an upregulation of VEGF in various tumor types, (Ex.1046, Ferrara-2005, 968). As a result, anti-angiogenic VEGF inhibitors were identified as potential therapies, and were soon developed and entered clinical testing. (*Id.*, 971).

55. One of the first of these was bevacizumab, a humanized monoclonal antibody approved for the treatment of metastatic colon cancer in combination with 5-fluoruracil (5FU). (*Id.*, 967, 971).

56. VEGF has also been identified as a factor in the abnormal growth and fragility of new blood vessels in the eye, a condition associated with wet AMD. (*See id.*, 971-72; Ex.1012, Regeneron (28-April-2008), 2 ("Blockade of VEGF, which

can prevent abnormal blood vessel formation and vascular leak, has proven beneficial in the treatment of wet AMD and a VEGF inhibitor, ranibizumab, has been approved for treatment of patients with this condition.")). This led some physicians to suggest that bevacizumab and other anti-VEGF factors could be used to treat vitreoretinal diseases. Indeed, since the initial approval of bevacizumab for use in treating cancer, some ophthalmic physicians have used it off-label for the treatment of AMD (via intravitreal injection) with promising results. (*See, e.g.*, Ex.1047, Bashshur, 1).

57. In addition, based on the recognition that neovascularization and vascular leakage are a major cause of vision loss in wet AMD, anti-VEGF agents were also developed for the specific purpose of treating AMD.

58. One of these, ranibizumab, is a humanized monoclonal Fab fragment capable of blocking the activity of VEGF-A, and marketed under the name LUCENTIS®. Approved in 2006, it was originally indicated for the treatment of wet AMD via monthly intravitreal administration of 0.5 mg. The prescribing information available in 2006 also suggested a regimen of less frequent dosing following four monthly intravitreal injections. (Ex.1048, Lucentis PI, 1). Less frequent dosing was a preferred option due to the nature of intravitreal injections.

59. Intravitreal treatment involves administering an injection directly into the vitreous of the eye. Because of this, patients can experience significant pain and

discomfort. Soreness in the injected eye is a frequent side effect. In addition, potential complications that can occur include subconjunctival hemorrhage, infection, and inflammation. While the risk of infection is small, the consequences can be devastating. Lastly, the cost and inconvenience of monthly visits and injections can be a major drawback for patients, many of whom are elderly, cannot drive due to their deteriorating vision, and must rely on family, friends, or public transportation to get to their appointments—which can sometimes take 2-5 hours because of the assessments (OCT scan and visual acuity) that must be done, followed by the actual treatment, if necessary.

60. These drawbacks and risks were a recognized concern in the mid- and late-2000's. As a result, the frequency of injections was the subject of investigation for those of ordinary skill in the art at the time, as well as in the patient community, and the trend in the mid- to late-2000's already was moving away from monthly dosing. This is evident from the LUCENTIS® (ranibizumab) 2006 prescribing information ("treatment may be reduced to one injection every three months after the first four injections"), as well as the ranibizumab trials that post-date the early ANCHOR and MARINA monthly dosing trials, almost all of which were exploring ways to reduce injection frequency, including through *pro re nata*, i.e., as-needed, dosing schedules ("PRN"). (*See, e.g.*, SUSTAIN (PRN dosing after 3 monthly loading doses); EXCITE (quarterly dosing after 3 monthly loading doses); PrONTO

(PRN dosing after three monthly loading doses); SAILOR (PRN dosing after 3 monthly loading doses); and PIER (quarterly dosing after 3 monthly loading doses); Ex.1030, Mitchell, 6-7).

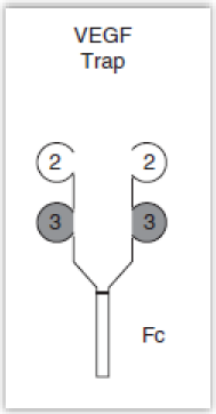
61. Also, in my experience, by 2010/2011 very few physicians were engaging in straight monthly dosing of VEGF antagonists. The typical practice was to either (1) treat with 2 or 3 monthly loading doses, followed by as-needed dosing thereafter, based on OCT and visual acuity assessments; or (2) engage in what has been termed "treat-and-extend," which involves 2 or 3 loading doses, followed by increased spacing between visits, so long as the patient is maintaining gains in visual acuity. (*See, e.g.*, Ex.1027, Spaide, 305; Ex.1049, Spielberg, 24).

62. Thus, those in the medical and research communities were actively investigating, and already incorporating, ways to reduce the time, expense, and patient discomfort associated with monthly intravitreal injections. (*See, e.g.*, Ex.1006, Dixon, 1574; Ex.1036, Regeneron (28-April-2008), 1 (noting that the long residence time of VEGF Trap-Eye in the eye means that the drug may be able to be dosed less frequently than once-monthly); Ex.1050, Schmidt-Erfurth, 1153 ("[The ranibizumab PrONTO study] suggested that flexible OCT-guided retreatment could sustain visual gain with fewer injections, a concept which has since become a popular model in clinical practice, particularly in Europe."); Ex.1051, Keane, 592

("[M]uch effort has focused on the development of alternative treatment regimens, which would reduce the number of injections required . . . .")).

D. VEGF Trap-Eye/Aflibercept.

63. VEGF Trap-Eye is a VEGF blocker developed by Regeneron. Unlike the VEGF blocker ranibizumab, which is a humanized monoclonal antibody, VEGF Trap-Eye is a fusion protein of Ig domain 2 of human VEGFR1 and Ig domain 3 of human VEGFR2 combined with a human IgG Fc fragment, as depicted below:



(Ex.1006, Dixon, 1575-76, Fig.1; *see also* Ex.1036, Regeneron (28-April-2008), 2 ("VEGF Trap-Eye is a fully human, soluble VEGF receptor fusion protein that binds all forms of VEGF-A along with the related Placental Growth Factor (PIGF).")).

64. In 2002, Regeneron published an article detailing its development of VEGF Trap-Eye, a high-affinity VEGF blocker "that has prolonged *in vivo* pharmacokinetics and pharmacodynamics, lacks nonspecific toxicities, and can

effectively suppress the growth and vascularization of a number of different types of tumors *in vivo*," and was intended to treat disorders associated with increased angiogenesis. (Ex.1004, Holash, 11393).

65. From this, the authors concluded that "although the parental VEGF-Trap and its VEGF-Trap$_{R1R2}$ derivative are quite comparable *in vitro* (see above), the VEGF-Trap$_{R1R2}$ performs much better *in vivo*, presumably because of its dramatically enhanced pharmacokinetic profile." (*Id.*, 11395-96).

66. The authors closed with a report of studies comparing VEGF-Trap$_{R1R2}$ with anti-VEGF monoclonal antibodies, and concluded that efficacy of VEGF Trap was equal to or better than anti-VEGF antibodies. This led the authors to conclude that the efficacious dose of the VEGF Trap may be lower than that of a monoclonal anti-VEGF antibody. (*See id.*, 11397).

67. The Holash authors concluded that VEGF Trap may be useful in the treatment of retinopathies, given the contribution of pathological angiogenesis to such disorders. (*See id.*).

68. This is consistent with the understanding of physicians at the time that VEGF Trap-Eye was known to have a high binding affinity to VEGF, which the medical community believed could translate to good clinical efficacy outcomes.

69. Subsequent work by Regeneron reinforced VEGF Trap's potential as a possible antiangiogenic therapy for vascular eye diseases. For example, Rudge

noted that blocking VEGF-A exhibited impressive results in the treatment of wet AMD, suggesting that a VEGF blockade like VEGF Trap could be useful in treating eye disorders characterized by leaky and proliferating vasculature. (Ex.1052, Rudge, 411).

70. Rudge also includes experimental work which indicated a role for VEGF in the pathology of other vascular eye disorders, including diabetic edema, DR, and AMD. (*Id.*, 414). Preclinical studies with VEGF Trap showed that it was able to inhibit choroidal and corneal neovascularization, suppress vascular leak in the retina, and promote the survival of corneal transplants by inhibiting neovascularization. (*Id.*). Following the promising preclinical trials, VEGF Trap entered clinical trials assessing its effectiveness in treating AMD and diabetic edema and retinopathy. The preliminary results showed that "VEGF Trap can rapidly and impressively decrease retinal swelling, and that these changes can be associated with improvement in visual acuity." (*Id.*, 414-15; *see also* Ex.1088, Nguyen-2006, 1522). The authors also noted that the VEGF Trap was in the process of entering even more clinical trials related to vascular eye diseases. (Ex.1052, Rudge, 415).

E. Regeneron's Press Releases and Clinical Trials.

71. In the mid-2000's, Regeneron began reporting on its clinical trials of VEGF Trap-Eye in AMD patients. Provided below is a table summarizing the trials, their nomenclature, exemplary dosing regimens involved, and some of the references

that refer to those studies, which will be discussed in greater detail later in my declaration.

Trial	Name	Reference(s)	Dosing Regimen
Phase 1 (AMD)	CLEAR-IT 1	Dixon; Nguyen-2009	Single intravitreal dose (incl. 0.5, 2, and 4 mg doses)
Phase 2 (AMD)	CLEAR-IT 2	Dixon; Adis	Monthly or quarterly through week 12 followed by PRN (incl. 0.5, 2, and 4 mg doses)
Phase 3 (AMD)	VIEW1; VIEW2	Dixon; Adis; NCT-795; NCT-377; Regeneron (8-May-2008)[3]	Monthly through week 8, followed by every 8 weeks (0.5 and 2 mg doses)

[3] The VIEW1 and VIEW2 trials were discussed in numerous Regeneron press releases between August 2007 and the time the '338 patent priority applications were filed in 2011. Regeneron (8-May-2008) is provided here as an illustrative example.

72. In addition, because some of the AMD clinical trials involving ranibizumab (LUCENTIS®) are discussed throughout my declaration, and the dosing regimens used in those studies are relevant to the dosing regimen used in Regeneron's Phase 3 VIEW1/2 studies of VEGF Trap-Eye, a table summarizing those studies is also provided:

Trial[4]	Dosing Regimen
MARINA (AMD)	Monthly
ANCHOR (AMD)	Monthly
PIER (AMD)	Quarterly after 3 initial monthly injections
EXCITE (AMD)	Quarterly after 3 initial monthly injections
PrONTO (AMD)	PRN after 3 initial monthly injections
SAILOR (AMD)	PRN after 3 initial monthly injections
SUSTAIN (AMD)	PRN after 3 initial monthly injections

73. In connection with Regeneron's VEGF Trap clinical program, Regeneron issued a series of press releases, beginning around 2007, disclosing, in

[4] A summary of these trials also can be found in Ex.1035, Mitchell.

sum, the following information regarding its clinical trials to persons of ordinary skill in the art:

Press Release	Representative Disclosure
27 Mar. 2007 (Ex.1053)	**Phase 2 trial**: 4-week (i.e., monthly) dosing with VEGF Trap-Eye yields "a statistically significant reduction in retinal thickness after 12 weeks." (Ex.1053, Regeneron (27-March-2007), 1).
2 Aug. 2007 (Ex.1054)	**Phase 2 trial**: Results show monthly (i.e., every 4 week) VEGF Trap-Eye dosing yields "a statistically significant reduction in retinal thickness and improvement in visual acuity after 12 weeks." (Ex.1054, Regeneron (2-August-2007), 1). **Phase 3 trial**: VIEW1 trial initiated, testing the safety and efficacy of VEGF Trap-Eye dosed at either 4 week intervals (0.5 and 2.0 mg) or 8 week intervals (2.0 mg). (*Id.*).
28 Apr. 2008 (Ex.1036)	**Phase 2 trial**: Previously reported gains in visual acuity and decreases in retinal thickness for week 12 were maintained out to week 32 when using a PRN (i.e., *pro re nata* or as-needed) dosing schedule after week 12. (Ex.1036, Regeneron (28-April-2008), 1).

Press Release	Representative Disclosure
	Phase 3 trials (VIEW1 & 2): Testing "a monthly loading dose of 0.5 mg or 2.0 mg for 12 weeks, followed by a nine-month fixed-dosing regimen of 0.5 mg monthly, 2.0 mg monthly, or 2.0 mg every eight weeks." (*Id.*, 2).
8 May 2008 (Ex.1013)[5]	**Phase 3 trials (VIEW1 & 2)**: Evaluating "2.0 mg [VEGF Trap-Eye] at an 8-week dosing interval, including one additional 2.0 mg dose at week four," for up to one year—i.e., doses at weeks 0, 4, 8, 16, 24, 32, 40, and 48. (Ex.1013, Regeneron (8-May-2008), 1).
19 Aug. 2008 (Ex.1089)	**Phase 2 trial**: 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. (Ex.1089, Regeneron (19-August-2008), 1). **Phase 3 trials (VIEW1 & 2)**: Studies involve "2.0 mg [VEGF Trap-Eye] every 8 weeks (following three monthly doses)"—

[5] The same information was reported by Regeneron's partner, Bayer, in their own press release, dated the same day. (*See, e.g.*, Ex.1032, Bayer (8-May-2008)).

Press Release	Representative Disclosure
	i.e., doses at weeks 0, 4, and 8, followed by doses at weeks 16, 24, 32, 40, and 48. (*Id.*).
28 Sept. 2008 (Ex.1056)	**Phase 2 trial**: 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.[6] (Ex.1056, Regeneron (28-September-2008), 1). **Phase 3 trials (VIEW1 & 2)**: Studies involve "2.0 mg [VEGF Trap-Eye] every 8 weeks (following three monthly doses)"—i.e., doses at weeks 0, 4, and 8, followed by doses at weeks 16, 24, 32, 40, and 48.[7] (*Id.*, 2).

[6] The September 28, 2008 Press Release also reported that the Phase 2 results were presented earlier that day at the 2008 annual meeting of the Retina Society in Scottsdale, AZ, and that slides, including data reported at the meeting, were available at the Regeneron website.

[7] The Phase 3 VIEW1 and VIEW2 studies reported in the above disclosures appear to correspond to the Phase 3 study reported in the '338 patent at Example 4. (*Compare* Ex.1056, Regeneron (28-September-2008), 2, *with* Ex.1001, '338 patent, 9:10 – 13:48).

Press Release	Representative Disclosure
14 Sep. 2009 (Ex.1068)	**Phase 3 trials (VIEW1 & 2)**: Treatment arms for the first year of the VIEW studies to be (i) 0.5 mg every four weeks; (ii) 2.0 mg every four weeks; and (iii) 2.0 mg every eight weeks following three monthly doses—i.e., doses at weeks 0, 4, and 8, followed by doses at weeks 16, 24, 32, 40, and 48. PRN dosing to be used for the second year of the programs. (Ex.1068, Regeneron (14-September-2009), 1).

VII. SCOPE AND CONTENT OF THE PRIOR ART REFERENCES.

A. Dixon (Ex.1006).

74. Dixon was published in 2009. I understand that because Dixon published before the earliest priority date of the '338 patent,[8] it is prior art. I have reviewed Dixon. Dixon is an article summarizing the current state of AMD therapies

[8] I have been asked by counsel for Mylan to use January 13, 2011, as the priority date of the '338 patent for purposes of my declaration. I understand that counsel for Mylan reserves the right to challenge whether there is sufficient support in the priority document for Regeneron to properly rely on this date.

as of 2009, and profiling in particular, the development and clinical testing of Regeneron's VEGF Trap-Eye, including the details of Regeneron's VIEW Phase 3 dosing regimen. The following paragraphs represent examples of the disclosures in Dixon that, in my opinion, are relevant to the method(s) of treatment claimed in the '338 patent:

75. As an initial matter, Dixon discloses that "[i]n addition to two anti-VEGF drugs currently in widespread use, ranibizumab and bevacizumab, a number of medications that interrupt angiogenesis are currently under investigation." (Ex.1006, Dixon, 1573).

76. To that end, Dixon reports on several ranibizumab studies, including the PIER and PrONTO studies initiated by Genentech in 2004, which, according to Dixon, were intended to study alternative dosing schedules that might reduce the "time and financial burden of monthly injections." (*Id.*, 1574).

- The PIER study assessed patients after receiving 3 monthly (i.e., every 4 week) injections, followed by quarterly (i.e., every 12 week) dosing.
- The PrONTO study assessed patients after receiving 3 monthly (i.e., every 4 week) injections, followed by as needed (p.r.n.) dosing. The PrONTO study reported that "78% of patients had maintained vision and vision had improved by > 3 lines in 43% of patients with an average of five injections a year." (*Id.*).

77. While acknowledging the efficacious outcomes achieved with ranibizumab and bevacizumab, Dixon states that in the development of new drugs for treating AMD, the focus was on improving efficacy and extending the duration of action, and thus, allowing for less frequent dosing.[9] (*Id.*). Regeneron's VEGF Trap-Eye—which, at the time, was well known and in commercial development for the treatment of AMD—was identified by Dixon as "[o]ne promising new drug" that "blocks all isoforms of VEGF-A and placental growth factors-1 and -2." (*Id.*, 1573).

78. Among other VEGF Trap related disclosures,[10] Dixon discusses Regeneron's Phase 2 trial, named CLEAR-IT-2. (*Id.*, 1576). The CLEAR-IT-2 trial included 5 dose groups:

- 0.5 mg monthly for 12 weeks (i.e., doses at weeks 0, 4, 8, and 12);

[9] This was a logical benefit. As I mention elsewhere in this declaration, physicians and patients were interested in reducing the frequency of dosing of anti-VEGF agents given, among other things, the unpleasantness of intravitreal injections.

[10] For example, Dixon discusses (i) Regeneron's CLEAR-IT-1 trial, a two-part, Phase 1 study of intravitreal aflibercept in patients with AMD; and (ii) "a small open-label safety study for the treatment of diabetic macular edema" with a single dose of 4 mg VEGF Trap.

- 2.0 mg monthly for 12 weeks (i.e., doses at weeks 0, 4, 8, and 12);
- 0.5 mg quarterly for 12 weeks (i.e., doses at weeks 0 and 12);
- 2.0 mg quarterly for 12 weeks (i.e., doses at weeks 0 and 12); and
- 4.0 mg quarterly for 12 weeks (i.e., doses at weeks 0 and 12). (*Id.*).

Following each of the above fixed dosing regimens, "patients were treated with the same dose of VEGF Trap-Eye on a p.r.n. [i.e., as needed][11] basis." (*Id.*).

79. Dixon states that in the Phase 2 CLEAR-IT-2 trial, "[p]atients initially treated with 2.0 or 0.5 mg of VEGF Trap-Eye monthly achieved mean improvements of 9.0 ($p < 0.0001$) and 5.4 ($p < 0.085$) ETDRS letters with 29 and 19% gaining, respectively, $\geq$ 15 ETDRS letters at 52 weeks." (*Id.*). Dixon also states that "[d]uring the p.r.n. dosing period, patients initially dosed on a 2.0 mg monthly schedule received an average of 1.6 more injections and those initially dosed on a 0.5 mg monthly schedule received an average of 2.5 injections." (*Id.*).

[11] In my experience, PRN dosing at this stage in any such dosing regimen involves monthly visits wherein each patient is evaluated and a determination is made (on a monthly basis) whether another injection is required. Consequently, in my opinion, the most frequent dosing that would typically occur under such a "p.r.n. basis" is monthly (or every 4 weeks).

80. Dixon also reported on Regeneron's Phase 3 AMD studies, named VIEW1 and VIEW2, which were intended to "evaluate the safety and efficacy of intravitreal VEGF Trap-Eye." (*Id.*). The planned dosing regimens included:

- 0.5 mg every 4 weeks (i.e., doses at weeks 0, 4, 8, 12, . . .);
- 2.0 mg every 4 weeks (i.e., doses at weeks 0, 4, 8, 12, . . .); and
- 2.0 mg every 8 weeks *after 3 initial, monthly doses* (i.e., doses at weeks 0, 4, and 8, followed by doses at weeks 16, 24, 32, 40, 48 . . .). (*Id.*).

Also included as a comparator was 0.5 mg of ranibizumab administered every 4 weeks (i.e., monthly). (*Id.*). Furthermore, "[a]fter the first year of the study, patients will enter a second year of p.r.n. dosing evaluation." (*Id.*). The choice of every eight weeks, or bimonthly dosing, for the VIEW trials is consistent with Dixon's stated concerns among physicians about the time and financial burdens of monthly administration required for existing therapies, like ranibizumab, and the suggestion that "desirable attributes for emerging therapies for neovascular AMD include higher visual improvement rates and *decreased dosing intervals*." (*Id.*, 1577 (emphasis added)).

81. The Dixon authors also noted that "VEGF Trap-Eye is under Phase II investigation in DME and Phase III investigation in central retinal vein occlusion [RVO]" and suggested that "FDA approval of VEGF Trap-Eye for these indications

would significantly add to the ophthalmologists' armamentarium for treatment of retinal vascular disease." (*Id.*, 1577-78).

82. Lastly, I note that much of Dixon's information about Regeneron's Phase 3 VIEW studies was derived from online records from clinicaltrials.gov—the same records that I discuss in this declaration. (*See id.*, 1579, (Ref. Nos. 46-47 (citing NCT00509795, accessed Sep. 28, 2008, and NCT00637377, also accessed Sep. 28, 2008))).

B. Adis (Ex.1007).

83. The Adis reference was published in 2008. I understand because the Adis reference published before January 13, 2011, the earliest priority date of the '338 patent, it is prior art.

84. Adis discloses that "[a]flibercept is a fully human recombinant fusion protein composed of the second Ig domain of VEGFR1 and the third Ig domain of VEGFR2, fused to the Fc region of human IgG_1," and that while Regeneron and Sanofi were developing it for the treatment of cancer, Regeneron and Bayer were developing it for eye disorders. (Ex.1007, Adis, 261). Throughout Adis, the authors use the terms aflibercept and VEGF Trap-Eye interchangeably. (*See, e.g.*, *id.*, Title).

85. Adis states that "Regeneron and Bayer initiated a phase III trial of aflibercept in approximately 1200 patients with the neovascular form of wet AMD in August 2007." (*Id.*, 263).

86. According to Adis, the VIEW1 and VIEW2 trials were initiated to evaluate the safety and efficacy of (1) 0.5 and 2.0 mg doses administered monthly (i.e., at weeks 0, 4, 8, 12, 16 . . .); or (2) 2.0 mg doses administered every 8 weeks following three monthly doses (i.e., at weeks 0, 4, 8, 16, 24, 32, 40, and 48). (*Id.* ("2.0 mg at an 8-week dosing interval, including one additional 2.0 mg dose at week 4.")).[12]

87. Adis also discusses Regeneron disclosures indicating that "Regeneron has completed a 12-week, phase II trial in patients with wet AMD, to evaluate the safety and efficacy of intravitreal aflibercept using different doses and dose regimens." (*Id.*). Adis states that these dosing regimens were:

- 0.5 mg monthly for 12 weeks (i.e., doses at weeks 0, 4, 8 and 12);
- 2.0 mg monthly for 12 weeks (i.e., doses at weeks 0, 4, 8. and 12);
- 0.5 mg quarterly for 12 weeks (i.e., doses at weeks 0 and 12);
- 2.0 mg quarterly for 12 weeks (i.e., doses at weeks 0 and 12); and
- 4.0 mg quarterly for 12 weeks (i.e., doses at weeks 0 and 12). (*Id.*).

[12] Notably, Adis cites Regeneron and Bayer Press Releases retrieved online from the companies' respective websites. (*Id.*, 263, 268, Ref. Nos. 10-13). In my opinion, this confirms that such press releases were well known and widely available to persons of ordinary skill in the art prior to January 2011.

88. Adis also covers the Phase 2 AMD trial results, reporting that at the 32-week point, "157 patients receiving either 0.5 or 2.0 mg followed by as-needed (PRN) dosing achieved mean improvements in visual acuity of 8.0 and 10.1 letters, respectively, and mean decreases in retinal thickness of 141 and 162 microns, respectively." (*Id.*, 267). The authors continue, noting that over the 20 weeks following the 12-week loading dose period, patients only required on average one additional injection "to maintain visual acuity gain achieved," and observing that while PRN dosing following fixed quarterly dosing maintained improvements, it was not as robust as those results achieved with initial fixed monthly dosing. (*Id.*, 268). They also report that Phase I AMD preliminary results "have shown rapid, substantial and prolonged (≥ 4 weeks) reductions in retinal thickness with single-dose intravitreal injections of VEGF Trap." (*Id.*).

89. Lastly, I note that much of Adis' information about Regeneron's Phase 2 CLEAR-IT-2 and Phase 3 VIEW studies was derived from Regeneron and Bayer press releases—some of which are the same press releases that I discuss in this declaration. (*See id.*, Ref. Nos. 10-16).

C. Regeneron (8-May-2008) (Ex.1013).

90. Regeneron (8-May-2008) is dated May 8, 2008. Because Regeneron (8-May-2008) published[13] before January 13, 2011, the earliest priority date of the '338 patent, it is my understanding that Regeneron (8-May-2008) qualifies as prior art to the '338 patent.

[13] I was also asked whether, in my opinion, Regeneron (8-May-2008) was publicly available to persons of ordinary skill in the art prior to January 13, 2011. In my opinion, accessing records such as Regeneron (8-May-2008) is a task consistent with the exercise of reasonable diligence and would have involved little more than calling up Regeneron's website and clicking on the press releases kept therein. Furthermore, in my opinion, Regeneron's press releases at this time were well known and widely available to persons of ordinary skill in the art of treating angiogenic eye disorders. Indeed, I am aware of several colleagues who reviewed such press releases prior to January 2011. For example, Adis (Ex.1007) cited to over 15 Regeneron and Bayer press releases in its 2008 discussion of aflibercept (VEGF Trap-Eye), confirming, in my opinion, the public availability and widespread dissemination of Regeneron (8-May-2008). In sum, it is my opinion that Regeneron (8-May-2008) was unequivocally available publicly to persons of ordinary skill in the art prior to January 13, 2011.

91. Regeneron (8-May-2008) reports on the commencement of the second Phase 3 trial (VIEW2) for evaluating the safety and efficacy of VEGF Trap-Eye in treating AMD. (Ex.1013, Regeneron (8-May-2008), 1). The VIEW2 trial was intended to evaluate patients enrolled from Europe, Asia Pacific, Japan, and Latin America, and was described as a "confirmatory Phase 3 trial" to follow positive Phase 2 results that showed VEGF Trap-Eye was able to reduce retinal thickness and improve visual acuity. (*Id.*). Dr. Yancopoulos, CEO of Regeneron and sole inventor on the '338 patent, was quoted as touting the need to provide "optimal care to those patients with wet AMD" and to evaluate "different dosing regimens." (*Id.*). Those dosing regimens were to include:

- 0.5 mg every 4 weeks (i.e., monthly);
- 2.0 mg every 4 weeks (i.e., monthly); and
- 2.0 mg every eight weeks (i.e., bimonthly) with an additional dose at week 4 (in other words, three monthly doses followed by bimonthly dosing). (*Id.*).

Following the first year of dosing according to the above regimens, the second year will incorporate a "flexible, criteria-based extended regimen with a dose administered at least every 12 weeks, but not more often than every 4 weeks." (*Id.*).

92. Regeneron (8-May-2008) also reports on the results of the Phase 2 trial, disclosing that at 12 weeks "VEGF Trap-Eye met both primary and secondary key

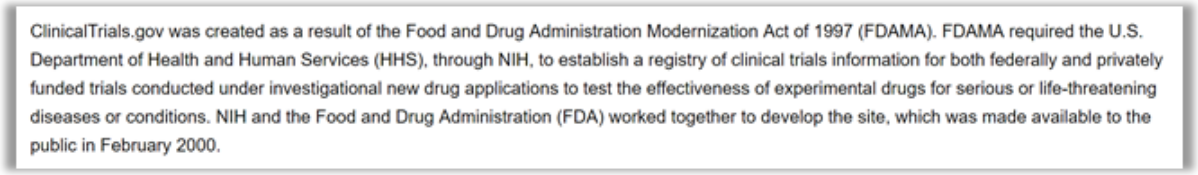
endpoints: a statistically significant reduction in retinal thickness . . . and a statistically significant improvement from baseline in visual acuity." (*Id.*). They further disclosed that following the 12-week fixed dosing loading phase of the trial, patients were treated on a PRN/as-needed basis, and reported that the PRN dosing, through week 32, "maintained the gain in visual acuity and decrease in retinal thickness achieved at week 12." (*Id.*).

D. NCT-795 (Ex.1014).

93. NCT-795 is an online record from the site clinicaltrials.gov, a database of clinical trial information developed by the National Library of Medicine and a service of the U.S. National Institutes of Health.

1. ClinicalTrials.gov.

94. Clinicaltrials.gov is a website publicly accessible to anyone, including physicians, patients, and researchers, interested in viewing information pertaining to clinical trials being conducted in the United States and abroad [available since at least 2000]:


ClinicalTrials.gov was created as a result of the Food and Drug Administration Modernization Act of 1997 (FDAMA). FDAMA required the U.S. Department of Health and Human Services (HHS), through NIH, to establish a registry of clinical trials information for both federally and privately funded trials conducted under investigational new drug applications to test the effectiveness of experimental drugs for serious or life-threatening diseases or conditions. NIH and the Food and Drug Administration (FDA) worked together to develop the site, which was made available to the public in February 2000.

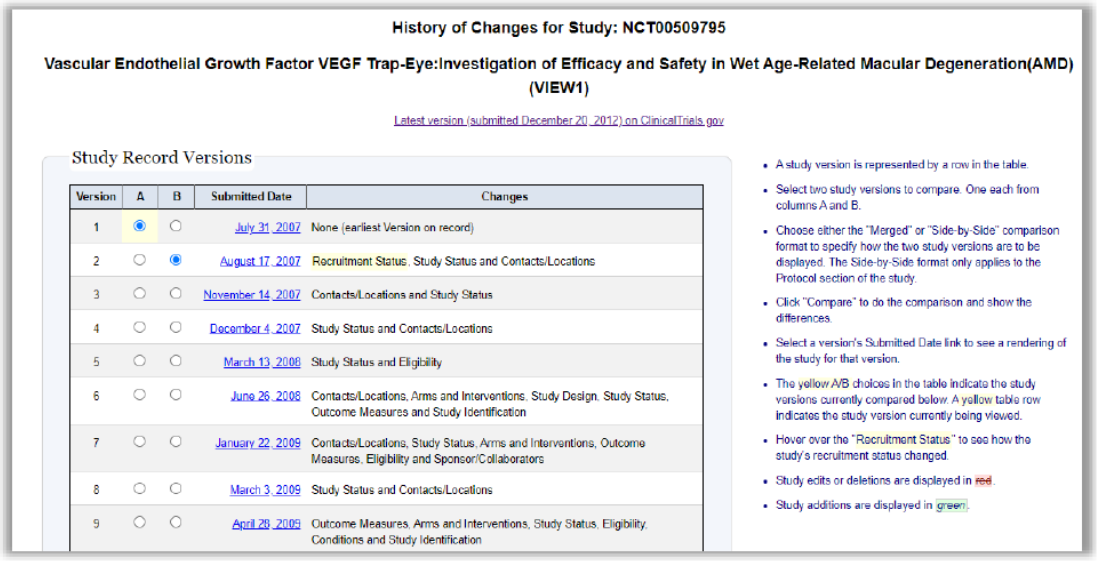
95. I am, and have been throughout the majority of my clinical career, aware of clinicaltrials.gov as a valuable online resource for learning about the latest

clinical trials involving drugs for the treatment of retinovitreal eye disorders. In fact, the first time I posted clinical trial data to clinicaltrials.gov was in 2009.

96. I am also aware that clinicaltrials.gov maintains an archive site, found at the link "History of Changes" in each NCT clinical trial record, e.g.:

Responsible Party:	Regeneron Pharmaceuticals
ClinicalTrials.gov Identifier:	NCT00509795 History of Changes
Other Study ID Numbers:	VGFT-OD-0605
First Posted:	August 1, 2007 Key Record Dates
Results First Posted:	April 16, 2012
Last Update Posted:	December 28, 2012
Last Verified:	December 2012

97. I understand that this "History of Changes" site maintains updates to each clinical trial record, and that these updates can be retrieved from the online archive site with the date on which the update occurred indicated in the file record, along with a comparison showing changes that were made since the previous update. A partial snapshot of this portion of the "History of Changes" page is shown here:



History of Changes for Study: NCT00509795

Vascular Endothelial Growth Factor VEGF Trap-Eye:Investigation of Efficacy and Safety in Wet Age-Related Macular Degeneration(AMD) (VIEW1)

Latest version (submitted December 20, 2012) on ClinicalTrials.gov

Study Record Versions

Version	A	B	Submitted Date	Changes
1	◉	○	July 31, 2007	None (earliest Version on record)
2	○	◉	August 17, 2007	Recruitment Status, Study Status and Contacts/Locations
3	○	○	November 14, 2007	Contacts/Locations and Study Status
4	○	○	December 4, 2007	Study Status and Contacts/Locations
5	○	○	March 13, 2008	Study Status and Eligibility
6	○	○	June 26, 2008	Contacts/Locations, Arms and Interventions, Study Design, Study Status, Outcome Measures and Study Identification
7	○	○	January 22, 2009	Contacts/Locations, Study Status, Arms and Interventions, Outcome Measures, Eligibility and Sponsor/Collaborators
8	○	○	March 3, 2009	Study Status and Contacts/Locations
9	○	○	April 28, 2009	Outcome Measures, Arms and Interventions, Study Status, Eligibility, Conditions and Study Identification

- A study version is represented by a row in the table.
- Select two study versions to compare. One each from columns A and B.
- Choose either the "Merged" or "Side-by-Side" comparison format to specify how the two study versions are to be displayed. The Side-by-Side format only applies to the Protocol section of the study.
- Click "Compare" to do the comparison and show the differences.
- Select a version's Submitted Date link to see a rendering of the study for that version.
- The yellow A/B choices 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 edits or deletions are displayed in ~~red~~.
- Study additions are displayed in green.

98. I further understand that the "Submitted Date" column indicates the date on which the updated information was provided to clinicaltrials.gov and thus the date on or about which the information was publicly accessible from the database.

99. In sum, it is my firm opinion that clinicaltrial.gov records (including archives and updates) were well known and widely available to persons of ordinary skill in the art prior to January 2011. I myself regularly searched for and consulted records in the clincialtrials.gov database before 2011 and continue to do so today. The consultation of clinicaltrials.gov is a regular aspect of the research that I do in assessing the safety and efficacy of new drugs, and in my experience, many of my colleagues who treat angiogenic eye disorders regularly consult the online records

of clinicaltrials.gov as well. My opinion regarding the public availability of NCT-795, specifically, is further confirmed by prior art references to the '338 patent, which cite to NCT-795 (as obtained from clinicaltrials.gov), as well as several other clinicaltrials.gov records. (*See, e.g.*, Ex.1006, Dixon, 1576, 1579).[14]

2. NCT-795 discloses the VIEW1 regimen.

100. NCT-795 was originally submitted on July 31, 2007. (*See, e.g.*, Ex.1014, NCT-795, 1, 3). NCT-795 describes the VIEW1 study as a Phase 3 randomized double-masked safety and efficacy study of intravitreal VEGF Trap-Eye in the treatment of neovascular age-related macular degeneration (wet AMD). (*Id.*, 3-4). The record also states that the primary outcome measure will be visual acuity changes compared to baseline, and that the study is anticipated to involve about 1200 patients in the U.S. and Canada. (*Id.*, 4, 9).

101. I have used the archive document that compares the April 28, 2009 version to the March 3, 2009 version. The description at the top of the page indicates that the April 28, 2009 version is "v9" and the March 3, 2009 version is "v8." The record indicates that changes made from March 3, 2009 to April 28, 2009 are

[14] Citations to the clinicaltrials.gov records for NCT00509795 and/or NCT00637377 can also be found in other publications before 2011. (*See, e.g.*, Ex.1073, Anderson, 275; Ex.1074, Ciulla, 162; Ex.1075, Ni, 403, 409; Ex.1076, Zarbin, 1360).

displayed in a "merged" format, and I understand from the document that additions are indicated in green, while deletions or edits are displayed in red strikethrough. (*Id.*, 1-2).

102. The April 28, 2009 update provides the specific dosing regimens for each VIEW treatment arm. (Ex.1014, NCT-795, 5-8). The April 28, 2009 record states that April 28, 2009 was the date the update was submitted and April 29, 2009 the date it was posted. (*Id.*, 4). From my experience using, and my knowledge of, the site and how it works and archives information, I understand that to mean that the information displayed on that page and the subsequent pages, would have been the information available to researchers on or about April 29, 2009. Therein, the record indicates that patients will be randomly assigned to one of four treatment regimens:

- 2 mg VEGF Trap-Eye every 4 weeks (2Q4);
- 0.5 mg VEGF Trap-Eye every 4 weeks (0.5Q4);
- 2 mg VEGF Trap-Eye every 8 weeks (2Q8); and
- 0.5 mg ranibizumab every 4 weeks (RQ4). (*Id.*, 5-7).

103. The record also states that experimental arm 3 will include "2.0 mg VEGF Trap-Eye administered every 8 weeks (including one additional 2.0 mg dose at week 4) during the first year":

Assigned Interventions
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.*

(*Id.*, 8). In other words, subjects in the 2Q8 treatment arm were to receive 2 mg injections at weeks 0, 4, 8, 16, 24, 32, etc. (i.e., 3 monthly loading doses, followed by every-eight-week dosing). The April 28, 2009 record also states that the primary outcome measure will be "[t]he proportion of subjects who maintain vision at Week 52, where a subject is classified as maintaining vision if the subject has lost fewer than 15 letters on the ETDRS chart compared to baseline (i.e. prevention of moderate vision loss)." (*Id.*, 9). The record also notes that the timeframe for this assessment will be "Week 52." (*Id.*).

E. NCT-377 (Ex.1015).

104. NCT-377 is an online record from the site clinicaltrials.gov, a database of clinical trial information developed by the National Library of Medicine and a service of the U.S. National Institutes of Health. As stated above, clinicaltrials.gov is a website publicly accessible to anyone, including physicians, patients, and researchers, interested in viewing information pertaining to clinical trials being conducted in the United States and abroad. My statements above regarding NCT

records and my opinion regarding their availability to persons of ordinary skill in the art apply equally to this record, NCT-377.

105. My opinion regarding the public availability of NCT-377, specifically, is further confirmed by prior art to the '338 patent, which cite to NCT-377 (as obtained from clinicaltrials.gov) as well as several other clinicaltrials.gov records. (*See, e.g.*, Ex.1006, Dixon, 1576, 1579).[15]

106. NCT-377 indicates that the earliest version of NCT-377 was submitted on March 17, 2008, and first posted March 18, 2008. (Ex.1015, NCT-377, 1, 4). From my experience using, and my knowledge of, the site and how it works and archives information, I understand that to mean that the information displayed on that page and the subsequent pages, would have been the information available to online observers on or about March 17-18, 2008. (*See, e.g.*, *id.* ("First Submitted that Met QC Criteria: March 17, 2008"; "First Posted: March 18, 2008")). The March 17, 2008 record describes the VIEW2 study as a "phase III, double-masked, randomized, study of the efficacy and safety of VEGF Trap-Eye in patients with neovascular age-related macular degeneration" and further states that "[a]pproximately 1200 patients will be randomized in Europe, Asia, Japan, Australia and South America." (*Id.*, 5).

[15] *See supra* note 15.

107. The NCT-377 record also lists 4 treatment arms, or interventions, for the VIEW2 study, including Arm 3:

Arms	Assigned Interventions
Experimental: Arm 3	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.

(*Id.*, 6). The additional 2.0 mg dose at week 4 means that 2.0 mg doses were to be administered at weeks 0, 4, and 8, followed by doses at weeks 16, 24, 32, 40, and 48.

108. Additional treatment arms of the VIEW2 study included:

- **Arm 1:** 0.5 mg every 4 weeks during the first year (i.e., doses at weeks 0, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52). Thereafter doses as frequently as every 4 weeks but no less frequently than every 12 weeks;
- **Arm 2:** 2.0 mg every 4 weeks during the first year (i.e., doses at weeks 0, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52). Thereafter doses as frequently as every 4 weeks but no less frequently than every 12 weeks; and
- **Arm 4:** 0.5 mg ranibizumab every 4 weeks during the first year (i.e., doses at weeks 0, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52). Thereafter

doses as frequently as every 4 weeks but no less frequently than every 12 weeks. (*Id.*, 6).

109. Subsequent updates were made and archived between April 2008 and November 2014. (*Id.*, 1-3). However, the dosing regimens remained unchanged from the original throughout these subsequent updates.

F. ’664 Patent (Ex.1009).

110. U.S. Patent No. 7,396,664 issued July 8, 2008, from Application No. 11/204,709, filed on August 16, 2005, and is assigned, on its face, to Regeneron Pharmaceuticals, Inc. I understand that the ’664 patent qualifies as prior art to the ’338 patent because it issued prior to January 13, 2011, the earliest priority date of the ’338 patent.

111. The ’664 patent is drawn to VEGF Traps that “are therapeutically useful for treating VEGF-associated conditions and diseases,” (Ex.1009, ’664 patent, Abstract), specifically, “eye disorders such as macular degeneration and diabetic retinopathy,” (*id.*, 2:64 – 3:12).

112. The ’664 patent states that the invention includes “a fusion polypeptide comprising receptor components R1-R2-F, wherein R1 is vascular endothelial cell growth factor (VEGF) receptor component Ig domain 2 of Flt-1 (Flt1D2), R2 is VEGF receptor component Ig domain 3 of Flk-1 (Flk1D3) (also known as KDR), and F is a fusion component.” (*Id.*, 1:36-42). Further, “[i]n a preferred embodiment,

R1 and R2 are the only receptor components present. In a specific embodiment, the VEGF-binding fusion polypeptide is amino acids 27-129 (R1) and 130-231 (R2) of SEQ ID NO:8, or a variant thereof." (*Id.*, 1:47-51).

113. Moreover, the '664 patent states that "[t]he fusion component F is selected from the group consisting of a multimerizing component, a serum protein, or a molecule capable of binding a serum protein" and that "[p]referably, the multimerizing component is an immunoglobulin domain." (*Id.*, 1:52-54, 64-65). The '664 patent specifies that one embodiment of "F is a full-length or truncated immunoglobulin domain consisting of amino acids 232-458, 232-457, or 352-458 of SEQ ID NO:8." (*Id.*, 1:65-67). The '664 patent continues, stating that "a signal sequence (S) may be included at the beginning (or N-terminus) of the fusion polypeptide of the invention." (*Id.*, 2:28-30). Further, in a specific embodiment, "the fusion polypeptide of the invention expressed in a mammalian cell line such as a CHO cell comprises amino acids 27-457 of SEQ ID NO:8." (*Id.*, 2:53-55).

G. '758 Patent (Ex.1010).

114. U.S. Patent No. 7,374,758 issued May 20, 2008, from Application No. 11/016,503, filed on December 17, 2004, and is assigned, on its face, to Regeneron Pharmaceuticals, Inc. I understand that the '758 patent qualifies as prior art to the '338 patent because it issued prior to January 13, 2011, the earliest priority date of the '338 patent.

115. The ’758 patent is drawn to “[m]odified chimeric polypeptides with improved pharmacokinetics” and methods of “using the modified polypeptides to decrease or inhibit plasma leakage and/or vascular permeability in a mammal.” (Ex.1010, ’758 patent, Abstract). The ’758 patent discloses the VEGF fusion polypeptide disclosed as preferred embodiments in the ’664 patent discussed above. Specifically, the ’758 patent sets forth in Figure 24A-C the annotated sequence of VEGFR1R2-FcΔC1(a), which includes the signal sequence (aa 1-26); the Flt-1 Ig domain 2 (aa 27-129); the Flk-1 Ig domain 3 (aa 130-231); and the Fc domain (aa 232-458). (*Id.*, Fig.24A-C; *see also id.*, 10:15-17 (“Nucleotide (SEQ ID NO:15) and deduced amino acid sequence (SEQ ID NO:16) of the modified Flt1 receptor termed VEGFR1R2-FcΔC1(a).”)).

H. Dix (Ex.1033).

116. U.S. Publication No. 2006/0217311 (“Dix”) was published September 28, 2006, from Application No. 11/387,256, filed March 22, 2006. Because Dix published before January 13, 2011, the earliest priority date of the ’338 patent, it is my understanding that Dix qualifies as prior art to the ’338 patent.

117. Dix is drawn to “[f]ormulations of a vascular endothelial growth factor (VEGF)-specific fusion protein antagonist” wherein “[p]referably, the fusion protein has the sequence of SEQ ID NO:4.” (Ex.1033, Dix, Abstract). I note that SEQ ID NO:4 of Dix is the same as that of SEQ ID NO:2 of the ’338 patent.

118. Dix discloses that "[a] soluble VEGF-specific fusion protein antagonist, termed a 'VEGF trap' has been described [in Kim (Ex.1090) and Holash (Ex.1004)], which applications are specifically incorporated by reference in their entirety." (*Id.*, [0005]). Dix describes the fusion protein as containing the second Ig domain of Flt1, the third Ig domain of Flk1, and a multimerizing component, and more specifically, where the fusion protein has the amino acid sequence of SEQ ID NO:2 or SEQ ID NO:4. (*Id.*, [0008]). More preferred embodiments consist of formulations containing the fusion protein with the amino acid sequence of SEQ ID NO:4. (*Id.*, [0013]-[0014]). Furthermore, a specific embodiment includes a fusion protein comprising amino acids 27-457 of SEQ ID NO:4. (*Id.*, [0030]).

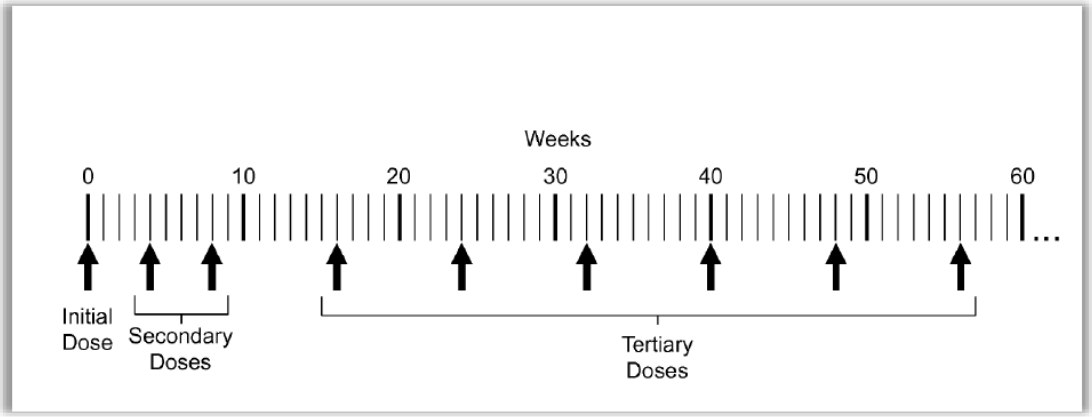
VIII. UNPATENTABILITY OF THE '338 PATENT.

A. Claims 1, 3-11, 13, 14, 16-24, and 26 of the '338 Patent Are Anticipated by Dixon (Ex.1006).

119. I was asked to review the challenged claims of the '338 patent and compare them to the disclosures of Dixon. It is my opinion that Dixon discloses every element of the claimed method(s) and thus anticipates each of the challenged claims of the '338 patent.

120. First, Figure 1 of the '338 patent (as reproduced below) is presented as depicting an "exemplary dosing regimen" of the claimed method where "a single 'initial dose' . . . 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."



(Ex.1001, '338 patent, Fig.1, 2:54-60).

121. Based upon my reading of the patent specification, including Figure 1, and the claims of the '338 patent, it is my opinion that Figure 1 represents a dosing regimen that falls squarely within the scope of the challenged claims, including claim 1. For example, the '338 patent states that "FIG. 1 shows an exemplary dosing regimen of the present invention." In addition, the '338 patent explains that the figure illustrates a dosing regimen in which "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." Because I will be using a modified version of

Figure 1 of the '338 patent below to illustrate how the prior art discloses the claimed dosing regimen, I have prepared a side-by-side table showing how the claimed dosing regimens of the '338 patent correspond to Figure 1 of the '338 patent.

Figure 1	Claim 1[16]
"a single 'initial dose' of VEGF antagonist ('VEGFT') is administered at the beginning of the treatment regimen (i.e. at 'week 0')" (Ex.1001, '338 patent, 2:55-57).	"a single initial dose of a VEGF antagonist"
"two 'secondary doses' are administered at weeks 4 and 8, respectively" (*Id.*, 2:57-58).	"followed by one or more secondary doses of the VEGF antagonist . . . wherein each secondary dose is administered 2 to 4 weeks after the immediately preceding dose"
"and at least six 'tertiary doses' are administered once every 8 weeks thereafter, i.e., at weeks 16, 24, 32, 40, 48, 56, etc." (*Id.*, 2:58-60).	"followed by one or more tertiary doses of the VEGF antagonist . . . wherein each tertiary dose is administered at least 8 weeks after the immediately preceding dose"

122. In addition, I note that dependent claims 3 and 4 offer a narrower version of claim 1, and further specify *exactly* the regimen depicted in Figure 1. For example, claim 3 specifies "wherein only two secondary doses are administered to the patient, and wherein each secondary dose is administered 4 weeks after the

[16] Because the dosing regimen aspects of claim 14 are identical, this analysis would apply equally to that claim.

immediately preceding dose." Compare to the Figure 1 legend: "two 'secondary doses' are administered at weeks 4 and 8, respectively." (*Id.*, 2:57-58).

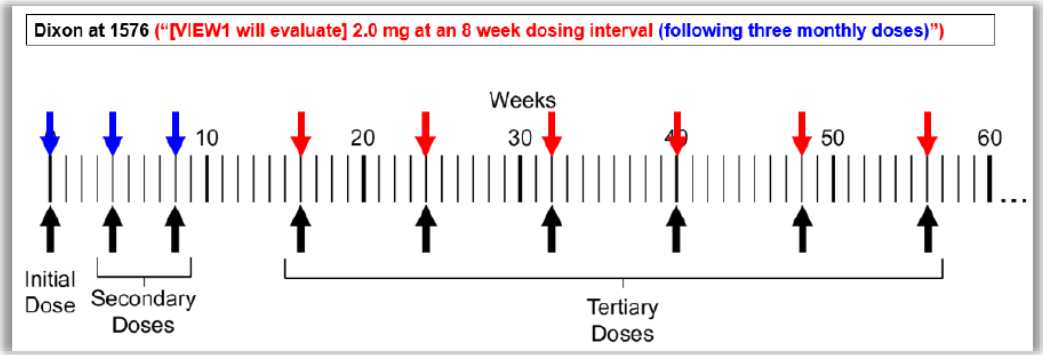
123. Claim 4 is dependent on claim 3, and thus, I have been informed, incorporates all aspects of claim 3, and thus contains the secondary dose information claimed in claim 3. It also specifies that "each tertiary dose is administered 8 weeks after the immediately preceding dose." Compare to the Figure 1 legend: "'tertiary doses' are administered once every 8 weeks thereafter, i.e., at weeks 16, 24, 32, 40, 48, 56, etc." (*Id.*, 2:59-60).

124. Therefore, in my opinion, claim 4 represents the narrowest of the dosing regimen claims, and also corresponds precisely to the dosing regimen portrayed in Figure 1 of the '338 patent, and reproduced above.

125. Because the Figure 1 dosing regimen corresponds to the narrowest dosing regimen claim, it also is representative of claim 1, from which claim 4 depends, as well as each of the other challenged claims directed to dosing regimens (i.e., claims 1, 3, 4, 5, 14, 16, 17, 19). I also note that this regimen comes straight from the VIEW1/VIEW2 Phase 3 studies.

126. To illustrate why Dixon anticipates the challenged claims, I have prepared the following *modified* version of Figure 1 from the '338 patent (set forth below), to show how Dixon discloses the exact dosing regimen set forth in Figure 1

of the '338 patent, as well as that which is claimed in the challenged claims of the '338 patent:



(Ex.1001, '338 patent, Fig.1 (modifications added)). Dixon's disclosure of "2.0 mg at an 8 week dosing interval (following three monthly doses)" aligns precisely with Figure 1. For example, Dixon's disclosure of "three monthly doses" (**blue arrows**), equates to an "initial dose" and two "secondary doses," as those terms are used and defined in the patent. Dixon's disclosure of "an 8 week dosing interval" (**red arrows**) equates to the claimed "tertiary doses." Dixon further states that "[a]fter the first year of the study, patients will enter a second year of p.r.n. [i.e., as needed] dosing evaluation." (Ex.1006, Dixon, 1576).

127. The last element of claim 1—"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"—is merely a recitation of the molecular architecture or structure of the "aflibercept" / "VEGF Trap-Eye" disclosed in Dixon, a fact that was disclosed well before January 2011. (*See, e.g.*, Ex.1006, Dixon, 1575-76, Fig.1; Ex.1010, '758 patent, Fig.24A-C (disclosing the nucleotide sequence and deduced amino acid sequence, as well as a description of each molecular component therein (i.e., the signal sequence, the FLT1 Ig domain 2, the FLK1 Ig domain 3, and the FcΔC1 domain), 10:15-17 (specifying that this molecule is termed "VEGFR1R2-FcΔC1(a).")); Ex.1033, Dix, [0013]-[0014], [0030]; Ex.1039, '095 patent, 1:45-54; Ex.1021, 2009 10-Q, 20 (using VEGF Trap and aflibercept interchangeably and explaining that "VEGF Trap-Eye is a specially purified and formulated form of VEGF Trap for use in intraocular applications"); Ex.1007, Adis, 261 (indicating in the title that aflibercept, VEGF Trap (R1R2), and VEGF Trap-Eye, among other terms, are understood by a person of ordinary skill in the art to refer, interchangeably, to the same drug); Ex.1093). As a result, through Dixon's disclosure of VEGF Trap-Eye/aflibercept, Dixon discloses this aspect of claim 1.

1. Claim 1 of the '338 patent is anticipated by Dixon.

128. Below, I have constructed a chart for the purpose of showing where each and every claim element from claim 1 is found in the Dixon reference:

Claim 1:	Dixon
A method for treating[17] an angiogenic eye disorder in a patient, said method comprising sequentially administering to the patient a single initial dose of a	"Phase III trial of VEGF Trap-Eye" in patients "with neovascular AMD" where VEGF Trap-Eye is administered at "2.0 mg at an 8 week dosing interval

[17] In my opinion, claim 1 does not specify a particular level of treating, in terms of efficacy measures, and I have been informed that claim preambles are presumed to be non-limiting. However, even if the preamble were a limitation, in my experience, any patient involved in a clinical study is, by definition, being treated. Further, the VEGF Trap-Eye Phase 2 data showed effective treatment of AMD, an angiogenic eye disorder, with a regimen that involved even fewer doses, on average, than the VEGF Trap-Eye Phase 3 dosing regimen would require, which is a regimen that falls squarely within the scope of claim 1 of the '338 patent. The Phase 2 results were publicly available well before the filing date of the '338 patent. (*See, e.g.*, Ex.1006, Dixon, 1576; Ex.1007, Adis, 267-68; Ex.1013, Regeneron (8-May-2008), 1-2; Ex.1056, Regeneron (28-September-2008), 1-2). In addition, the VIEW Phase 3 results using the every-8-week dosing regimen confirm that those prior art regimens treated patients with AMD, and that effective treatment of that patient population is an inherent aspect of those regimens. (Ex.1018, Heier-2012, 2541-45). The same would apply if Regeneron were to argue, as I understand they have in another matter, that the term "tertiary dose" carries with it an efficacy requirement.

Claim 1:	Dixon
VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonist;	(following three monthly doses)." (Ex.1006, Dixon, 1576). AMD is well known to be an angiogenic eye disorder, and the dosing sequence disclosed for the VIEW1/VIEW2 trials would have involved sequential administration.
wherein each secondary dose is administered 2 to 4 weeks after the immediately preceding dose; and	"2.0 mg at an 8 week dosing interval (*following three monthly doses*)." (*Id.* (emphasis added)). As I explain above, "three monthly doses" involves a dose at baseline, i.e., day 0, as well as a "secondary dose" one month later (i.e., "4 weeks after the immediately preceding dose"), and another "secondary dose" one month after that (i.e., "4 weeks after the immediately preceding dose").
wherein each tertiary dose is administered at least 8 weeks after the immediately preceding dose;	"2.0 mg *at an 8 week dosing interval* (following three monthly doses)." (*Id.* (emphasis added)). As I explain above, an "8 week dosing interval" involves a regimen in which each 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 232-457of SEQ ID NO:2.	"One promising new drug is aflibercept (VEGF Trap-Eye) . . . ." (*Id.*, 1573). "VEGF Trap-Eye is a fusion protein of key binding domains of human VEGFR-1 and -2 combined with a human IgG Fc fragment . . . . VEGF Trap-Eye and aflibercept . . . have the

Claim 1:	Dixon
	same molecular structure . . . ." (*Id.*, 1575).[18]

As a result, Dixon anticipates claim 1 of the '338 patent.

2. Dependent claims 3 and 4 are anticipated by Dixon.

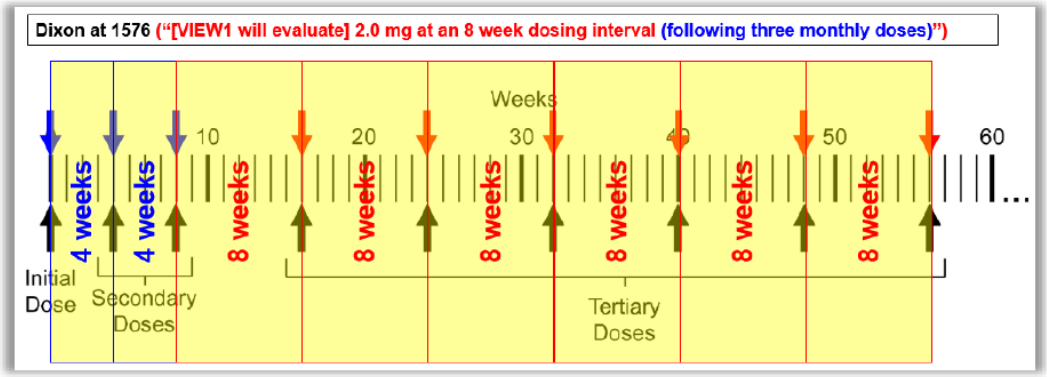
129. I have been informed that claims 3 and 4 can be described as "dependent" on claim 1. It is my understanding that a dependent claim incorporates the elements of the claims from which it depends.

130. Claim 3 limits the method of claim 1 to "wherein only two secondary doses are administered to the patient, and wherein each secondary dose is administered 4 weeks after the immediately preceding dose." And, claim 4 further limits the method of claim 3 to "wherein each tertiary dose is administered 8 weeks after the immediately preceding dose."

131. As illustrated in my modified Figure 1 of the '338 patent as provided below, which exemplifies a regimen falling within the scope of all the challenged claims, Dixon discloses the elements of claim 3 (each secondary dose is

[18] As discussed above, the structure and sequence of VEGF Trap-Eye/aflibercept was well known to those of ordinary skill in the art. (*See, e.g.*, *supra* Sec. VIII(A)).

administered 4 weeks after the immediately preceding dose) and claim 4 (each tertiary dose is administered 8 weeks after the immediately preceding dose):



(Ex.1001, '338 patent, Fig.1 (modifications added)).

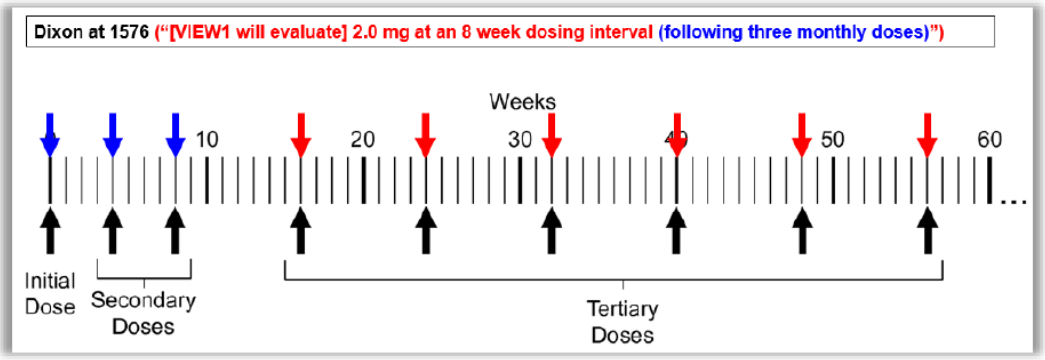
132. Accordingly, for these reasons, as well as the reasons set forth for claim 1 above, it is my opinion that claims 3 and 4 of the '338 patent are anticipated by Dixon.

3. Dependent claim 5 is anticipated by Dixon.

133. Claim 5 claims the method of claim 1, "wherein at least 5 tertiary doses" are administered, and "wherein the first four tertiary does 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."

134. Dixon discloses that the every-8-week aspect of the VIEW1 and VIEW2 clinical trials will last at least a year. (Ex.1006, Dixon, 1576 ("*After the first year* of the study, patients will enter a second year of p.r.n. dosing [T]he primary

outcome will be the proportion of patients who maintain vision *at week 52*." (emphasis added)). As illustrated in my modified Figure 1 below, the "8 week dosing interval" disclosed in Dixon would result in "at least 5 tertiary doses," e.g., administered at weeks 16, 24, 32, 40, and 48 (**red arrows**), each administered 8 weeks after the immediately preceding dose:



(Ex.1001, '338 patent, Fig.1 (modifications added)).

135. Thus, for these reasons, as well as for the reasons discussed above for claim 1, it is my opinion that claim 5 of the '338 patent is anticipated by Dixon.

4. Dependent claims 6 and 7 are anticipated by Dixon.

136. Claim 6 is dependent on claim 1 and recites the method of claim 1, "wherein the angiogenic eye disorder is selected from the group consisting of" several well-known eye disorders, including AMD. Claim 7, which depends from claim 6, recites "wherein the angiogenic eye disorder is age related macular degeneration."

137. The Dixon reference indicates in the title that VEGF Trap-Eye was being studied for the treatment of AMD, which is an angiogenic eye disorder. Likewise, the bulk of the reference discusses VEGF Trap-Eye as it relates to the treatment of AMD, including the discussion of the Phase 1 CLEAR-IT-1 clinical trial in patients with neovascular AMD; the Phase 2 CLEAR-IT-2 clinical trials in wet AMD; and the Phase 3 VIEW1 and VIEW2 clinical trials. It is in the discussion of the VIEW1 and VIEW2 trials for wet AMD that the dosing regimen of 3 monthly doses followed by every 8 week dosing was disclosed, after reporting that the Phase 2 trial results had shown mean improvements in visual acuity and retinal thickness, which are key indicators of success when treating AMD. Thus, Dixon discloses the treatment of AMD, which was known to be an angiogenic eye disorder.

138. Thus, for these reasons, as well as for the reasons discussed above for claim 1, it is my opinion that claims 6 and 7 of the ’338 patent are anticipated by Dixon.

5. Dependent claims 8-10 are anticipated by Dixon.

139. Dependent claim 8 depends from claim 1 and recites “wherein all doses of the VEGF antagonist are administered to the patient by topical administration or by intraocular administration.”

140. Claim 9 depends from claim 8 and specifies intraocular administration.

141. Claim 10 depends from claim 9 and specifies that "the intraocular administration is intravitreal administration."

142. Dixon discloses that the VIEW1 and VIEW2 studies "will evaluate the safety and efficacy of ***intravitreal*** VEGF Trap-Eye." (Ex.1006, Dixon, 1576 (emphasis added)). Intravitreal injection is a type of intraocular administration—more specifically, administration directly into the vitreous of the eye. This element is therefore expressly disclosed and taught by Dixon.

143. Therefore, for these reasons, as well as the reasons set forth for claim 1 above, it is my opinion that claims 8-10 are anticipated by Dixon.

6. Dependent claims 11 and 13 are anticipated by Dixon.

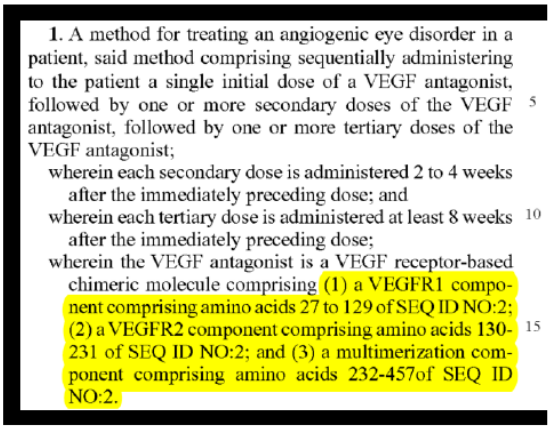
144. Dependent claim 11 depends from claim 10 and recites "wherein all doses of the VEGF antagonist comprise from about 0.5 mg to about 2 mg of the VEGF antagonist." Dependent claim 13 depends from claim 11 and specifies "wherein all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist."

145. Dixon discloses the treatment arms in the VIEW1 and VIEW2 studies which included "intravitreal VEGF Trap-Eye at…2.0 mg at an 8 week dosing interval (following three monthly doses)." (Ex.1006, Dixon, 1576). Dixon therefore expressly discloses the doses of claims 11 and 13.

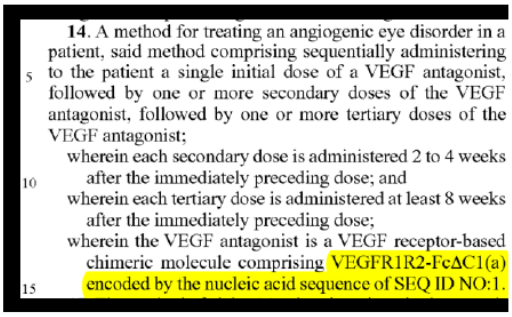
146. Therefore, for these reasons, as well as the reasons set forth above for claim 10 and claim 1, it is my opinion that claims 11 and 13 are anticipated by Dixon.

7. Independent claim 14 is anticipated by Dixon.

147. Claim 14 of the '338 patent is identical to claim 1 with the only exception being in the third "wherein" clause:



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 232-457of SEQ ID NO:2.



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.

148. First, claim 14 recites the same dosing regimen as that recited in claim 1: "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." Thus, for the same reasons discussed above with respect to claim 1, (*see* ¶ 128), it is also my opinion that Dixon discloses these identical elements in claim 14.

149. Second, in my opinion, Dixon also discloses the VEGF antagonist element of claim 14. Just as for claim 1, Dixon expressly discloses VEGF Trap-Eye/aflibercept, and the sequence aspect of claim 14 was widely published in the prior art. (*See, e.g.*, Ex.1006, Dixon, 1575-76, Fig.1; Ex.1010, '758 patent, Fig.24A-

C (disclosing the nucleotide sequence and deduced amino acid sequence, as well as a description of each molecular component therein (i.e., the signal sequence, the FLT1 Ig domain 2, the FLK1 Ig domain 3, and the FcΔC1 domain); *id.*, 10:15-17 (specifying that this molecule is termed "VEGFR1R2-FcΔC1(a).")); Ex.1033, Dix, [0013]-[0014], [0030]; Ex.1039, '095 patent, 1:45-54; Ex.1021, 2009 10-Q, 20 (using VEGF Trap and aflibercept interchangeably and explaining that "VEGF Trap-Eye is a specially purified and formulated form of VEGF Trap for use in intraocular applications"); Ex.1007, Adis, 261 (indicating in the title that aflibercept, VEGF Trap (R1R2) and VEGF Trap-Eye, among other terms, are understood by a person of ordinary skill in the art to refer, interchangeably, to the same drug); Ex.1094).

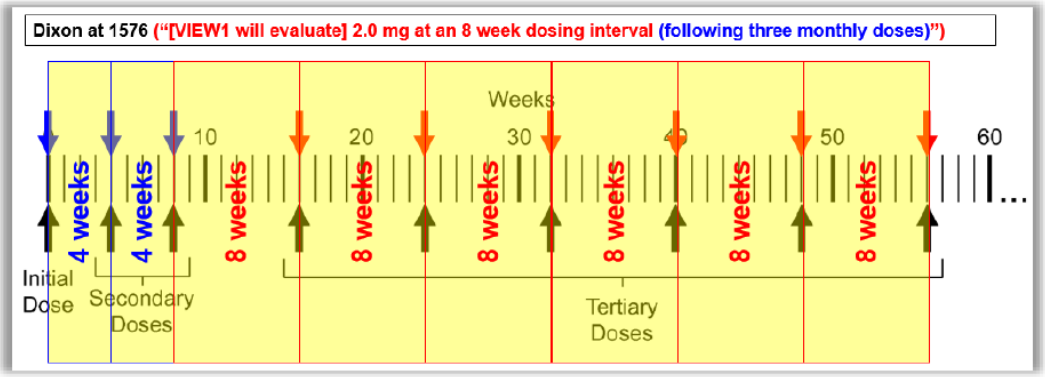
150. Therefore, for these reasons, as well as the reasons set forth above for claim 1, it is my opinion that claim 14 is anticipated by Dixon.

8. Dependent claims 16 and 17 are anticipated by Dixon.

151. Claim 16 limits the method of claim 14 to "wherein only two secondary doses are administered to the patient, and wherein each secondary dose is administered 4 weeks after the immediately preceding dose." Claim 17 further limits the method of claim 16 to "wherein each tertiary dose is administered 8 weeks after the immediately preceding dose."

152. As I explained with respect to claims 3 and 4 above, Dixon discloses the elements of claim 16 (each secondary dose administered 4 weeks after the

immediately preceding dose) and claim 17 (each tertiary dose is administered 8 weeks after the immediately preceding dose), as is illustrated in modified Figure 1 below:



(Ex.1001, '338 patent, Fig.1 (modifications added)).

153. Accordingly, for these reasons, as well as for the reasons discussed above for claim 14, it is my opinion that claims 16 and 17 of the '338 patent are anticipated by Dixon.

9. Dependent claims 18 and 20 are anticipated by Dixon.

154. Claim 18 is dependent on claim 17, which ultimately depends from claim 14, and recites "wherein the angiogenic eye disorder is age related macular degeneration." Claim 20 is dependent on claim 14 and recites "wherein the angiogenic eye disorder is selected from the group consisting of" several well-known eye disorders, including AMD.

155. The Dixon reference indicates in the title that VEGF Trap-Eye was being studied for the treatment of AMD. Likewise, the bulk of the reference discusses VEGF Trap-Eye as it relates to the treatment of AMD, including the discussion of the Phase 1 CLEAR-IT-1 clinical trial in patients with neovascular AMD; the Phase 2 CLEAR-IT-2 clinical trials in wet AMD; and the Phase 3 VIEW1 and VIEW2 clinical trials. It is in the discussion of the VIEW1 and VIEW2 trials for wet AMD that the dosing regimen of 3 monthly doses followed by every 8 week dosing was disclosed, after reporting that the Phase 2 trial results had shown mean improvements in visual acuity and retinal thickness, which are key indicators of success when treating AMD. Dixon therefore expressly discloses treating an angiogenic eye disorder, including AMD, as required by claims 18 and 20.

156. Thus, for these reasons, as well as for the reasons discussed above for claims 14, 16, and 17, it is my opinion that claims 18 and 20 of the ’338 patent are anticipated by Dixon.

10. Dependent claim 19 is anticipated by Dixon.

157. Claim 19 claims the method of claim 14, “wherein at least 5 tertiary doses” are administered, and “wherein the first four tertiary does 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.”

158. Dixon discloses that the VIEW1 and VIEW2 clinical trials will last at least a year. (Ex.1006, Dixon, 1576 ("*After the first year* of the study, patients will enter a second year of p.r.n. dosing . . . . [T]he primary outcome will be the proportion of patients who maintain vision *at week 52*." (emphasis added)).

159. As explained above with respect to claim 5, moreover, one year of dosing on an every-8-week dosing schedule after three monthly doses would result in at least 5 "tertiary" doses (**red arrows** in above figure). For example, after three monthly doses at weeks 0, 4, and 8, the every-8-week dosing regimen disclosed in Dixon for the VIEW1 and VIEW2 studies would result in doses being administered at weeks 16, 24, 32, 40, and 48, meaning that "at least 5 tertiary doses" would be administered at least 8 weeks after the immediately preceding dose, before the end of the one year trial.

160. Thus, for these reasons, as well as for the reasons discussed above for claim 14, it is my opinion that claim 19 of the '338 patent is anticipated by Dixon.

11. Dependent claims 21-23 are anticipated by Dixon.

161. Dependent claim 21 depends from claim 14 and recites "wherein all doses of the VEGF antagonist are administered to the patient by topical administration or by intraocular administration."

162. Claim 22 depends from claim 21 and specifies intraocular administration.

163. Claim 23 depends from claim 22 and specifies that "the intraocular administration is intravitreal administration."

164. To a person of ordinary skill in the art, it is well understood that intravitreal administration is a form of intraocular administration. Intraocular administration refers to administration to the eye generally, while intravitreal administration, a subset of intraocular administration, refers to administration directly into the vitreous of the eye.

165. In Dixon's disclosure of the VIEW1 and VIEW2 studies, Dixon stated that the study "will evaluate the safety and efficacy of intravitreal VEGF Trap-Eye." (Ex.1006, Dixon, 1576). Dixon therefore expressly discloses intravitreal administration.

166. Therefore, for these reasons, as well as for the reasons discussed above for claim 14, it is my opinion that claims 21-23 are anticipated by Dixon.

12. Dependent claims 24 and 26 are anticipated by Dixon.

167. Dependent claim 24 depends from claim 23 and recites "wherein all doses of the VEGF antagonist comprise from about 0.5 mg to about 2 mg of the VEGF antagonist." Dependent claim 26 depends from claim 24 and specifies "wherein all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist."

168. Dixon discloses the VIEW1 and VIEW2 studies in which the treatment arms included "intravitreal VEGF Trap-Eye at . . . 2.0 mg at an 8 week dosing

interval (following three monthly doses)." (Ex.1006, Dixon, 1576). Dixon therefore expressly discloses the doses of claims 24 and 26.

169. Therefore, for these reasons, as well as the reasons set forth above for the claims from which claims 24 and 26 depend, it is my opinion that claims 24 and 26 are anticipated by Dixon.

B. Claims 1, 3-11, 13, 14, 16-24, and 26 of the '338 Patent Are Anticipated by Adis (Ex.1007).

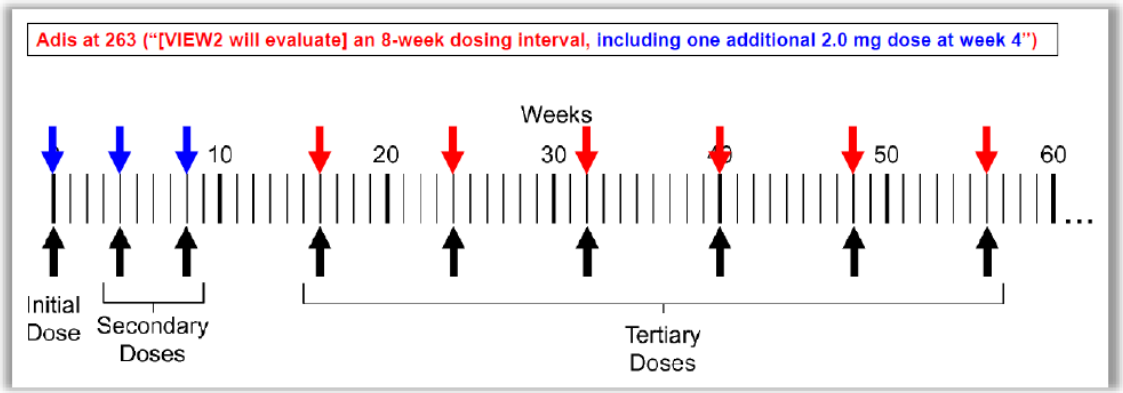
1. Claim 1 of the '338 patent is anticipated by Adis.

170. Claim 1 of the '338 patent has been set forth above.

171. I was asked to review the challenged claims of the '338 patent and compare them to the disclosures of Adis. It is my opinion that Adis discloses every element of the claimed method(s) and thus anticipates each of the challenged claims of the '338 patent.

172. For example, like Dixon above, Adis discloses Regeneron's planned Phase 3 trials being conducted with VEGF Trap-Eye, VIEW1 and VIEW2. Adis discloses the VIEW regimen, i.e., "2.0 mg at an 8-week dosing interval, including one additional 2.0 mg dose at week 4." (Ex.1007, Adis, 263). In other words, one of the dosing regimens being tested in the VIEW trials was every-8-week dosing following three monthly doses. This has been shown using the same overlay presented above, in which I have used Figure 1 of the '338 patent, which shows a

regimen that exemplifies each challenged claim, to illustrate how Adis discloses the exact dosing regimen set forth in Figure 1 of the '338 patent, as well as that which is claimed in the challenged claims of the '338 patent, as depicted here:



(Ex.1001, '338 patent, Fig.1 (modifications added)).

173. While Adis does not use the exact terms "initial," "secondary," and "tertiary," one of ordinary skill in the art readily would have recognized that the "initial dose" would have been the first dose given—in this case the dose given at time zero—and that the "secondary doses . . . wherein each secondary dose is administered 2 to 4 weeks after the immediately preceding dose," could be found in Adis' disclosure of "an 8-week dosing interval, *including one additional 2.0 mg dose at week 4*" (**blue arrows**). (*See, e.g.*, Ex.1007, Adis, 263 (emphasis added)).

174. Similarly, one of ordinary skill in the art would have recognized that the "tertiary doses . . . wherein each tertiary dose is administered at least 8 weeks

after the immediately preceding dose," correspond to the "8-week dosing interval" doses disclosed in Adis (**red arrows**). (*See, e.g., id.*).

175. In my opinion, the VIEW dosing regimen described in Adis is the precise dosing regimen that was described in Figure 1 in the '338 patent and which falls squarely within the scope of claim 1.

176. With respect to the VEGF antagonist element of claim 1, I note that this description is merely a recitation of the molecular architecture of the "aflibercept" and "VEGF Trap-Eye" disclosed in Adis, a fact that was disclosed well before January 2011. (*See, e.g.*, Ex.1006, Dixon, 1575-76, Fig.1; Ex.1010, '758 patent, Fig.24A-C (disclosing the nucleotide sequence and deduced amino acid sequence, as well as a description of each molecular component therein (i.e., the signal sequence, the FLT1 Ig domain 2, the FLK1 Ig domain 3, and the FcΔC1 domain); *id.*, 10:15-17 (specifying that this molecule is termed "VEGFR1R2-FcΔC1(a).")); Ex.1033, Dix, [0013]-[0014], [0030]; Ex.1039, '095 patent, 1:45-54; Ex.1021, 2009 10-Q, 20 (using VEGF Trap and aflibercept interchangeably and explaining that "VEGF Trap-Eye is a specially purified and formulated form of VEGF Trap for use in intraocular applications"); Ex.1007, Adis, 261 (indicating in the title that aflibercept, VEGF Trap (R1R2) and VEGF Trap-Eye, among other terms, are understood by a person of ordinary skill in the art to refer, interchangeably, to the

same drug); Ex.1093). As a result, through Adis' disclosure of VEGF Trap-Eye/aflibercept, Adis discloses this aspect of claim 1.[19]

177. Accordingly, for these reasons, it is my opinion that claim 1 of the '338 patent is anticipated by Adis.

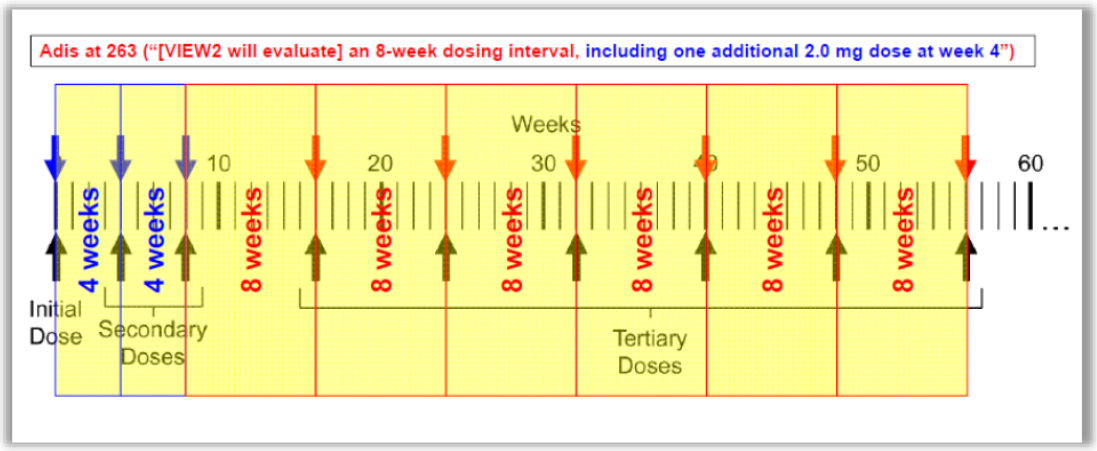
2. Dependent claims 3 and 4 are anticipated by Adis.

178. Dependent claim 3 claims 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."

179. Claim 4 claims the method of claim 3, "wherein each tertiary dose is administered 8 weeks after the immediately preceding dose."

180. As discussed above and illustrated in my modified Figure 1 of the '338 patent, Adis discloses the elements of claim 3 (each secondary dose administered 4 weeks after the immediately preceding dose) and claim 4 (each tertiary dose is administered 8 weeks after the immediately preceding dose):

[19] Regarding the preamble, *see, e.g.*, *supra* note 18; Ex.1007, Adis, 268 ("After the last fixed-dose administration at week 12, patients from all dose groups required on average only one additional injection over the following 20 weeks to maintain visual acuity gain achieved.").



(Ex.1001, '338 patent, Fig.1 (modifications added)).

181. Accordingly, for these reasons, as well as the reasons presented for claim 1, it is my opinion that claims 3 and 4 of the '338 patent are anticipated by Adis.

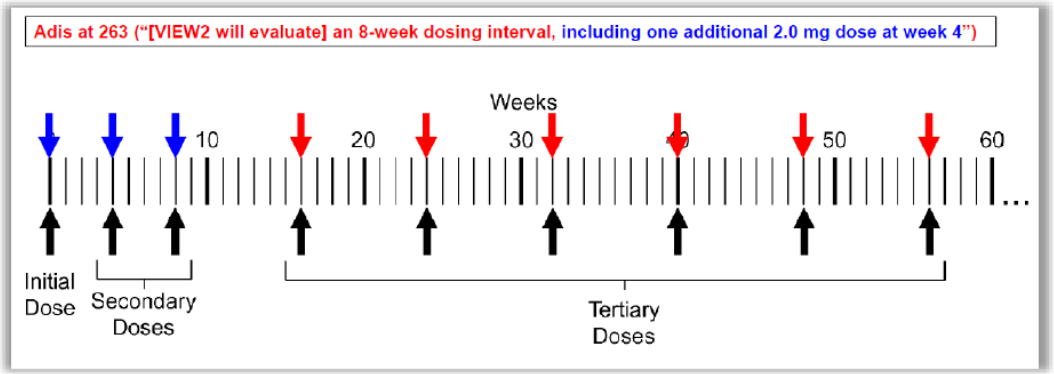
3. Dependent claim 5 is anticipated by Adis.

182. Claim 5 claims the method of claim 1, "wherein at least 5 tertiary doses" are administered, and "wherein the first four tertiary does 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."

183. Adis discloses that the VIEW1 and VIEW2 clinical trials will last at least a year. (Ex.1007, Adis, 263 ("Patients will continue to be treated and followed for an additional year, ***after the first year of treatment***" and "[t]he primary endpoint

will be the proportion of patients treated with aflibercept who maintain vision ***at the end of 1 year*** compared with ranibizumab patients." (emphases added)).

184. One year of dosing on an every-8-week dosing schedule after three monthly doses would result in at least 5 "tertiary" doses administered at least 8 weeks after the immediately preceding dose. Again, a graphic is useful in illustrating this:



(Ex.1001, '338 patent, Fig.1 (modifications added)). Using the modified graphic from the '338 patent, it is apparent that the every-8-week dosing regimen disclosed in Adis for the VIEW1 and VIEW2 studies would result in "tertiary" doses being administered at least at weeks 16, 24, 32, 40, and 48, meaning that "at least 5 tertiary doses" would be administered before the end of the one-year trial.

185. Thus, for these reasons, as well as for the reasons discussed above for claim 1, it is my opinion that claim 5 of the '338 patent is anticipated by Adis.

4. Dependent claims 6 and 7 are anticipated by Adis.

186. Claim 6 is dependent on claim 1 and recites the method of claim 1, "wherein the angiogenic eye disorder is selected from the group consisting of" several well-known eye disorders, including AMD. Claim 7, which depends from claim 6, recites "wherein the angiogenic eye disorder is age related macular degeneration."

187. The Adis reference indicates in the abstract that aflibercept was being developed for eye disorders and that "[b]lockade of VEGF can also prevent blood vessel formation and vasuclar [sic] leakage associated with wet age-related macular degeneration (AMD)." (Ex.1007, Adis, 261). Likewise, Adis discusses Regeneron's disclosures of the VIEW1 and VIEW2 trials, which were intended to study VEGF Trap-Eye/aflibercept in wet AMD. (*Id.*, 263). It is in the discussion of the VIEW1 and VIEW2 trials for wet AMD, which is an angiogenic eye disorder, that the dosing regimen of doses at weeks 0, 4, and 8, followed by every-8-week dosing, was disclosed. Thus, Adis discloses the treatment of AMD, a well-known angiogenic eye disorder.

188. Thus, for these reasons, as well as for the reasons discussed above for claim 1, it is my opinion that claims 6 and 7 of the '338 patent are anticipated by Adis.

5. Dependent claims 8-10 are anticipated by Adis.

189. Dependent claim 8 depends from claim 1 and recites "wherein all doses of the VEGF antagonist are administered to the patient by topical administration or by intraocular administration."

190. Claim 9 depends from claim 8 and specifies intraocular administration.

191. Claim 10 depends from claim 9 and specifies that "the intraocular administration is intravitreal administration."

192. In Adis' disclosure of the VIEW studies, Adis states that the study "will evaluate the safety and efficacy of intravitreal aflibercept." (Ex.1007, Adis, 263). Adis also notes that Regeneron's Phase 2 trial was designed to "evaluate the safety and efficacy of intravitreal aflibercept using different doses and dose regimens." (*Id.*). Intravitreal injection is a type of intraocular administration—more specifically, administration directly into the vitreous of the eye. This element is therefore expressly disclosed and taught by Adis.

193. Thus, for these reasons, as well as for the reasons discussed above for claim 1, it is my opinion that claims 8-10 of the '338 patent are anticipated by Adis.

6. Dependent claims 11 and 13 are anticipated by Adis.

194. Dependent claim 11 depends from claim 10 and recites "wherein all doses of the VEGF antagonist comprise from about 0.5 mg to about 2 mg of the

VEGF antagonist." Dependent claim 13 depends from claim 11 and specifies "wherein all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist."

195. Adis discloses the VIEW1 and VIEW2 studies in which the treatment arms included VEGF Trap-Eye/aflibercept administered at a 2.0 mg dose. (Ex.1007, Adis, 263). Adis therefore expressly discloses the doses of claims 11 and 13.

196. Therefore, for these reasons, as well as the reasons set forth above for claim 10 and claim 1, it is my opinion that claims 11 and 13 are anticipated by Adis.

7. Independent claim 14 is anticipated by Adis.

197. Claim 14 of the '338 patent is identical to claim 1 with the only exception being in the third "wherein" clause.

198. First, claim 14 recites the same dosing regimen as that recited in claim 1: "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." Thus, for the same reasons discussed above with respect to claim 1, (*see* ¶¶ 170-77), it is also my opinion that Adis discloses these identical elements in claim 14.

199. Second, in my opinion, Adis discloses the VEGF antagonist element of claim 14. Adis expressly discloses VEGF Trap-Eye/aflibercept, and the sequence aspect of claim 14 was widely published in the prior art. (*See, e.g.*, Ex.1006, Dixon, 1575-76, Fig.1; Ex.1010, '758 patent, Fig.24A-C (disclosing the nucleotide

sequence and deduced amino acid sequence, as well as a description of each molecular component therein (i.e., the signal sequence, the FLT1 Ig domain 2, the FLK1 Ig domain 3, and the FcΔC1 domain), 10:15-17 (specifying that this molecule is termed "VEGFR1R2-FcΔC1(a).")); Ex.1033, Dix, [0013]-[0014], [0030]; Ex.1039, '095 patent, 1:45-54; Ex.1021, 2009 10-Q, 20 (using VEGF Trap and aflibercept interchangeably and explaining that "VEGF Trap-Eye is a specially purified and formulated form of VEGF Trap for use in intraocular applications"); Ex.1007, Adis, 261 (indicating in the title that aflibercept, VEGF Trap (R1R2) and VEGF Trap-Eye, among other terms, are understood by a person of ordinary skill in the art to refer, interchangeably, to the same drug); Ex.1094).

200. Therefore, for these reasons, as well as the reasons set forth above for claim 1, it is my opinion that claim 14 is anticipated by Adis.

8. Dependent claims 16 and 17 are anticipated by Adis.

201. Claim 16 limits the method of claim 14 to "wherein only two secondary doses are administered to the patient, and wherein each secondary dose is administered 4 weeks after the immediately preceding dose." Claim 17 further limits the method of claim 16 to "wherein each tertiary dose is administered 8 weeks after the immediately preceding dose."

202. These elements are similar in scope to those discussed above with respect to claims 3 and 4, and as I explained with respect to those claims, Adis

discloses the elements of "each secondary dose is administered 4 weeks after the immediately preceding dose" and "each tertiary dose is administered 8 weeks after the immediately preceding dose." (*See, e.g.*, Ex.1007, Adis, 263 ("2.0 mg at an 8-week dosing interval, including one additional 2.0 mg dose at week 4.")).

203. Accordingly, for these reasons, as well as for the reasons discussed above for claims 3, 4, and 14, it is my opinion that claims 16 and 17 of the '338 patent are anticipated by Adis.

9. Dependent claims 18 and 20 are anticipated by Adis.

204. Claim 18 depends from claim 17, which ultimately depends from claim 14, and recites "wherein the angiogenic eye disorder is age related macular degeneration." Claim 20 depends from claim 14 and recites "wherein the angiogenic eye disorder is selected from the group consisting of" several well-known eye disorders, including AMD.

205. These elements are similar in scope to those discussed above with respect to claims 6 and 7, and as I explained with respect to those claims, Adis discloses the VIEW1 and VIEW2 trials, and the treatment arms used therein, which were designed to assess wet AMD. (*See, e.g.*, Ex.1007, Adis, 263 ("Regeneron and Bayer initiated a phase III trial of aflibercept in approximately 1200 patients with the neovascular form of wet AMD . . . .")). Adis therefore expressly discloses treating AMD, an angiogenic eye disorder.

206. Thus, for these reasons, as well as for the reasons discussed above for claims 6, 7, 14, 16, and 17, it is my opinion that claims 18 and 20 of the ’338 patent are anticipated by Adis.

10. Dependent claim 19 is anticipated by Adis.

207. Claim 19 claims the method of claim 14, “wherein at least 5 tertiary doses” are administered, and “wherein the first four tertiary does 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.”

208. As explained above with respect to claim 5, Adis discloses that the VIEW1 and VIEW2 clinical trials will last at least a year. (*See, e.g.*, Ex.1007, Adis, 263 (“The primary endpoint will be the proportion of patients treated with aflibercept who maintain vision *at the end of 1 year* . . . .”) (emphasis added)). One year of dosing on an every-8-week dosing schedule after three monthly doses would result in at least 5 “tertiary” doses administered at least 8 weeks after the immediately preceding dose.

209. Thus, for these reasons, as well as for the reasons discussed above for claims 5 and 14, it is my opinion that claim 19 of the ’338 patent is anticipated by Adis.

11. Dependent claims 21-23 are anticipated by Adis.

210. Dependent claim 21 depends from claim 14 and recites "wherein all doses of the VEGF antagonist are administered to the patient by topical administration or by intraocular administration."

211. Claim 22 depends from claim 21 and specifies intraocular administration.

212. Claim 23 depends from claim 22 and specifies that "the intraocular administration is intravitreal administration."

213. As discussed above with respect to claims 8-10, Adis discloses that the VIEW trials, and the treatment arms used therein, were assessing intravitreally-administered aflibercept. (*See, e.g.*, Ex.1007, Adis, 263 ("VIEW1 . . . will evaluate the safety and efficacy of intravitreal aflibercept . . . .")). Adis therefore expressly discloses intravitreal administration of the VEGF antagonist.

214. Therefore, for these reasons, as well as for the reasons discussed above for claims 8-10 and 14, it is my opinion that claims 21-23 are anticipated by Adis.

12. Dependent claims 24 and 26 are anticipated by Adis.

215. Dependent claim 24 depends from claim 23 and recites "wherein all doses of the VEGF antagonist comprise from about 0.5 mg to about 2 mg of the VEGF antagonist." Dependent claim 26 depends from claim 24 and specifies "wherein all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist."

216. As discussed above with respect to claims 11 and 13, Adis discloses that the VIEW1 and VIEW2 studies were intended to assess a 2.0 mg dose. (*See*, *e.g.*, Ex.1007, Adis, 263). Adis therefore expressly discloses a 2.0 mg doses of VEGF Trap-Eye/aflibercept.

217. Therefore, for these reasons, as well as the reasons set forth above for claims 11 and 13, and the claims from which claims 24 and 26 depend, it is my opinion that claims 24 and 26 are anticipated by Adis.

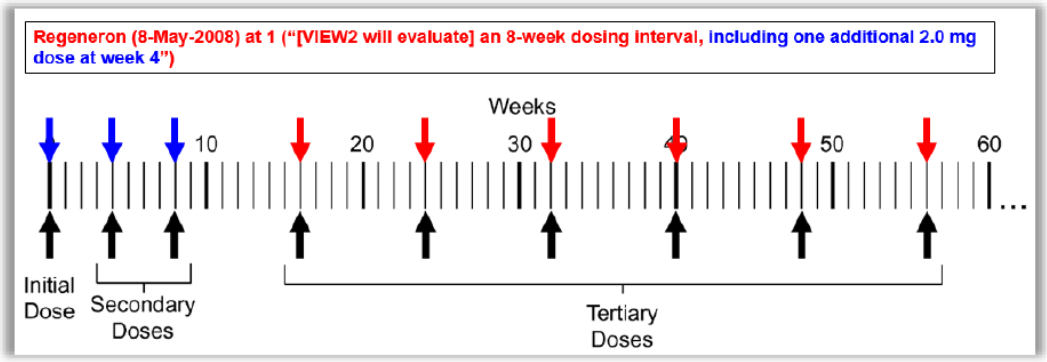
C. Claims 1, 3-11, 13, 14, 16-24, and 26 of the '338 Patent Are Anticipated by the Regeneron Press Release Dated May 8, 2008 (Regeneron (8-May-2008) (Ex.1013).

1. Independent claim 1 of the '338 patent is anticipated by Regeneron (8-May-2008).

218. I have been asked to review the challenged claims of the '338 patent and compare them to the disclosures of the Regeneron Press Release, dated May 8, 2008. It is my opinion that Regeneron (8-May-2008) discloses every element of the claimed method(s) and thus anticipates each of the challenged claims of the '338 patent.

219. For example, like Dixon and Adis above, Regeneron (8-May-2008) discloses the VIEW Phase 3 trials being conducted with VEGF Trap-Eye, and explains that VIEW2 will assess VEGF Trap-Eye at "2.0 mg at an 8-week dosing interval, including one additional 2.0 mg dose at week four." (Ex.1013, Regeneron

(8-May-2008), 1). This has been illustrated using the same overlay presented above, in which I have used Figure 1 of the '338 patent to illustrate how Regeneron (8-May-2008) discloses the exact dosing regimen set forth in Figure 1 of the '338 patent, as well as that which is claimed in the challenged claims of the '338 patent, as depicted here:



(Ex.1001, '338 patent, Fig.1 (modifications added)). In other words, dosing "at an 8-week dosing interval" would result in doses at day 0 and at week 8, and when adding "one additional 2.0 mg dose at week 4," this would result in three monthly doses (**blue arrows**) (i.e., doses at day 0 (i.e. "initial dose") and at weeks 4 and 8 (i.e., "secondary doses")). Thereafter, an eight-week dosing interval will result in injections at weeks 16, 24, 32, 40, and 48 (**red arrows**) (i.e., "tertiary doses")).

220. Regeneron (8-May-2008) further states that "[a]fter the first year of treatment, patients will continue to be followed and treated for another year on a flexible, criteria-based extended regimen with a dose administered at least every 12

weeks, but not more often than every 4 weeks." (Ex.1013, Regeneron (8-May-2008), 1).

221. With respect to the VEGF antagonist element of claim 1, as I discuss above, it is merely a recitation of the molecular architecture of the "VEGF Trap-Eye" disclosed in Regeneron (8-May-2008), a fact that was disclosed well before January 2011. (*See, e.g.*, Ex.1006, Dixon, 1575-76, Fig.1; Ex.1010, '758 patent, Fig.24A-C (disclosing the nucleotide sequence and deduced amino acid sequence, as well as a description of each molecular component therein (i.e., the signal sequence, the FLT1 Ig domain 2, the FLK1 Ig domain 3, and the FcΔC1 domain), 10:15-17 (specifying that this molecule is termed "VEGFR1R2-FcΔC1(a).")); Ex.1033, Dix, [0013]-[0014], [0030]; Ex.1039, '095 patent, 1:45-54; Ex.1021, 2009 10-Q, 20 (using VEGF Trap and aflibercept interchangeably and explaining that "VEGF Trap-Eye is a specially purified and formulated form of VEGF Trap for use in intraocular applications"); Ex.1007, Adis, 261 (indicating in the title that aflibercept, VEGF Trap (R1R2) and VEGF Trap-Eye, among other terms, are understood by a person of ordinary skill in the art to refer, interchangeably, to the same drug); Ex.1093). As a result, through Regeneron (8-May-2008)'s disclosure

of VEGF Trap-Eye/aflibercept, Regeneron (8-May-2008) discloses this aspect of claim 1. .[20]

222. Accordingly, for at least these reasons, it is my opinion that claim 1 is anticipated by Regeneron (8-May-2008).

2. Dependent claims 3 and 4 are anticipated by Regeneron (8-May-2008).

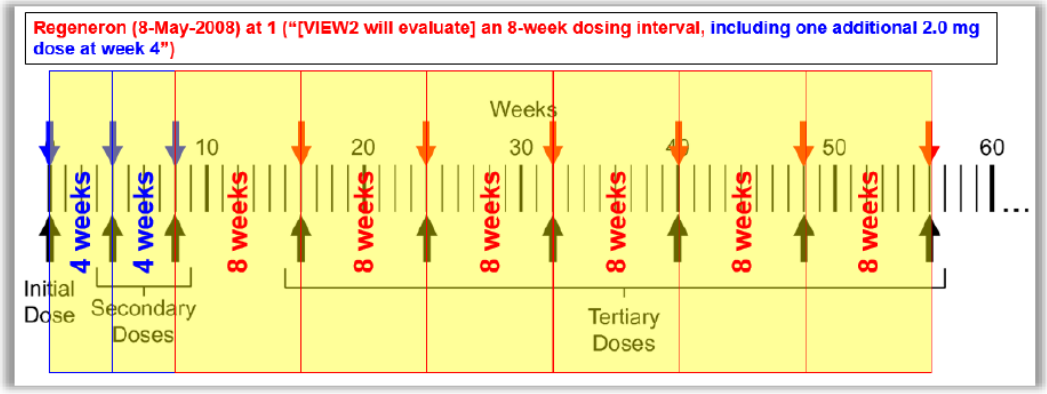
223. Dependent claim 3 claims the method of claim 1, "wherein only two secondary doses are administered to the patient, and wherein each secondary dose is administered 4 weeks after the immediately preceding dose."

224. Claim 4 claims the method of claim 3, "wherein each tertiary dose is administered 8 weeks after the immediately preceding dose."

225. As illustrated in my modified Figure 1 of the '338 patent below, Regeneron (8-May-2008) discloses the elements of claims 3 and 4. In discussing the first year of the VIEW2 study, Regeneron (8-May-2008) states patients will be administered "2.0 mg at an 8-week dosing interval, including one additional 2.0 mg

[20] Regarding the preamble, *see, e.g.*, *supra* note 18; Ex.1013, Regeneron (8-May-2008), 1 ("[P]atients 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.").

dose at week four." (Ex.1013, Regeneron (8-May-2008), 1). In my opinion, and consistent with the figure below, this dosing schedule consists of a 2.0 mg dose at day 0 (i.e., an "initial dose"), 2.0 mg doses at weeks 4 and 8 (i.e., "secondary doses"), and 2.0 mg doses every 8 weeks (i.e., "tertiary doses") for the remainder of the year:



(Ex.1001, '338 patent, Fig.1 (modifications added (initial and secondary doses indicated by **blue arrows** and tertiary doses indicated by **red arrows**)).

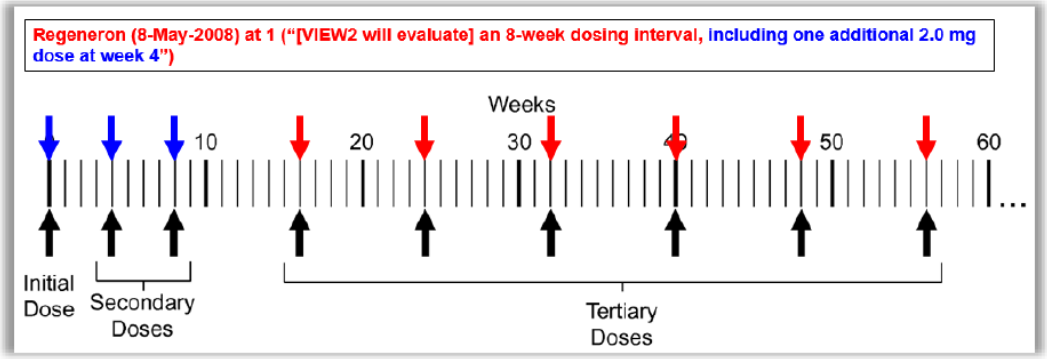
226. Thus, for these reasons, as well as the reasons discussed above for claim 1, it is my opinion that claims 3 and 4 are anticipated by Regeneron (8-May-2008).

3. Dependent claim 5 is anticipated by Regeneron (8-May-2008).

227. For the same reasons as above for claims 3 and 4, Regeneron (8-May-2008) discloses the elements of claim 5. Dependent claim 5 recites "[t]he 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 does 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."

228. Regeneron (8-May-2008) discloses that the VIEW2 clinical trial will last at least a year. (Ex.1013, Regeneron (8-May-2008), 1 ("In the ***first year***, the VIEW 2 . . . study will evaluate the safety and efficacy of VEGF Trap-Eye at doses of . . . 2.0 mg at an 8-week dosing interval . . . ." (emphasis added))). As illustrated in my modified Figure 1 of the '338 patent, an 8-week dosing interval over the course of one year, after the initial dose and 2 secondary doses, would result in at least 5 tertiary doses administered at least 8 weeks after the immediately preceding dose, at weeks 16, 24, 32, 40, and 48 (**red arrows**):



(Ex.1001, '338 patent, Fig.1 (modifications added)).

229. Accordingly, for these reasons, as well as for the reasons discussed above for claim 1, it is my opinion that claim 5 is anticipated by Regeneron (8-May-2008).

4. Dependent claims 6 and 7 are anticipated by Regeneron (8-May-2008).

230. Claim 6 of the ’338 patent recites the method of claim 1, “wherein the angiogenic eye disorder is selected from the group consisting of” several well-known eye disorders, including AMD.

231. Claim 7 further limits the method of claim 6 to recite “wherein the angiogenic eye disorder is age related macular degeneration.”

232. Regeneron (8-May-2008) expressly discloses that VIEW2 is an investigation of efficacy and safety of VEGF Trap-Eye in wet AMD, which is a well-known angiogenic eye disorder. (Ex.1013, Regeneron (8-May-2008), 1; *see also id.*, Title).

233. Thus, for these reasons, as well as for the reasons discussed above for claim 1, it is my opinion that claims 6 and 7 are anticipated by Regeneron (8-May-2008).

5. Dependent claims 8-10 are anticipated by Regeneron (8-May-2008).

234. Claim 8 depends from claim 1 and recites “wherein all doses of the VEGF antagonist are administered to the patient by topical administration or by intraocular administration.”

235. Claim 9 depends from claim 8 and specifies that all doses be administered by “intraocular administration.”

236. Claim 10 depends from claim 9 and specifies that "the intraocular administration is intravitreal administration."

237. Regeneron (8-May-2008) discloses that "[b]oth VIEW 1 and VIEW 2 are designed to evaluate the efficacy and safety of VEGF Trap-Eye administered by intravitreal injection." (Ex.1013, Regeneron (8-May-2008), 1). This element is therefore expressly disclosed and taught by Regeneron (8-May-2008).

238. Therefore, for these reasons, as well as for the reasons discussed above for claim 1, it is my opinion that claims 8-10 are anticipated by Regeneron (8-May-2008).

6. Dependent claims 11 and 13 are anticipated by Regeneron (8-May-2008).

239. Dependent claim 11 further limits the method of claim 10 to "wherein all doses of the VEGF antagonist comprise from about 0.5 mg to about 2 mg of the VEGF antagonist."

240. Claim 13 depends from claim 11 and recites "wherein all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist."

241. Regeneron (8-May-2008) discloses that the "VIEW 2 (VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD) study will evaluate the safety and efficacy of VEGF Trap-Eye at" a dose of 2.0 mg. (Ex.1013, Regeneron

(8-May-2008), 1). Regeneron (8-May-2008) therefore expressly discloses the doses of claims 11 and 13.

242. Accordingly, for these reasons, as well as for the reasons discussed above for claim 1 and the claims from which claims 11 and 13 depend, it is my opinion that claims 11 and 13 are anticipated by Regeneron (8-May-2008).

7. Independent claim 14 is anticipated by Regeneron (8-May-2008).

243. Claim 14 of the '338 patent is identical to claim 1 with the only exception being in the third "wherein" clause.

244. First, claim 14 recites the same dosing regimen as that recited in claim 1: "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." Thus, for the same reasons discussed above with respect to claim 1, (*see* ¶¶ 218-22), it is also my opinion that Regeneron (8-May-2008) discloses these identical elements in claim 14.

245. Second, in my opinion, Regeneron (8-May-2008) discloses the VEGF antagonist element of claim 14. Just as for claim 1, Regeneron (8-May-2008) expressly discloses VEGF Trap-Eye/aflibercept, and the sequence aspect of claim 14 was widely published in the prior art. (*See, e.g.*, Ex.1006, Dixon, 1575-76, Fig.1; Ex.1010, '758 patent, Fig.24A-C (disclosing the nucleotide sequence and deduced

amino acid sequence, as well as a description of each molecular component therein (i.e., the signal sequence, the FLT1 Ig domain 2, the FLK1 Ig domain 3, and the FcΔC1 domain), 10:15-17 (specifying that this molecule is termed "VEGFR1R2-FcΔC1(a).")); Ex.1033, Dix, [0013]-[0014], [0030]; Ex.1039, '095 patent, 1:45-54; Ex.1021, 2009 10-Q, 20 (using VEGF Trap and aflibercept interchangeably and explaining that "VEGF Trap-Eye is a specially purified and formulated form of VEGF Trap for use in intraocular applications"); Ex.1007, Adis, 261 (indicating in the title that aflibercept, VEGF Trap (R1R2), and VEGF Trap-Eye, among other terms, are understood by a person of ordinary skill in the art to refer, interchangeably, to the same drug); Ex.1094).

246. Therefore, for these reasons, as well as the reasons set forth above for claim 1, it is my opinion that claim 14 is anticipated by Regeneron (8-May-2008).

8. Dependent claims 16 and 17 are anticipated by Regeneron (8-May-2008).

247. Claim 16 depends from claim 14 and recites "wherein only two secondary doses are administered to the patient, and wherein each secondary dose is administered 4 weeks after the immediately preceding dose."

248. Claim 17 further limits the method of claim 16 to "wherein each tertiary dose is administered 8 weeks after the immediately preceding dose."

249. As discussed with respect to claims 3 and 4 above, Regeneron (8-May-2008) discloses the elements of claims 16 and 17. Regeneron (8-May-2008) states patients will be administered "2.0 mg at an 8-week dosing interval, including one additional 2.0 mg dose at week four." (Ex.1013, Regeneron (8-May-2008), 1). In my opinion, this dosing schedule consists of an initial 2.0 mg dose, a first secondary 2.0 mg dose at week 4, a second secondary 2.0 mg dose at week 8, and tertiary 2.0 mg doses every 8 weeks for the remainder of the year.

250. For these reasons, as well as the reasons discussed above for claims 3, 4, and 14, it is my opinion that claims 16 and 17 are anticipated by Regeneron (8-May-2008).

9. Dependent claims 18 and 20 are anticipated by Regeneron (8-May-2008).

251. Claim 18 depends from claim 17, which ultimately depends from claim 14 and recites "wherein the angiogenic eye disorder is age related macular degeneration."

252. Claim 20 recites the method of claim 14, "wherein the angiogenic eye disorder is selected from the group consisting of" several well-known eye disorders, including AMD.

253. As discussed with claims 6 and 7 above, Regeneron (8-May-2008) discloses that VIEW2 is an investigation of efficacy and safety of VEGF Trap-Eye

in wet AMD. (Ex.1013, Regeneron (8-May-2008), 1; *see also id.*, Title). Regeneron (8-May-2008) therefore expressly discloses treating AMD, an angiogenic eye disorder.

254. Therefore, for these reasons, as well as for the reasons discussed above for claims 6, 7, 14, 16, and 17, it is my opinion that claims 18 and 20 are anticipated by Regeneron (8-May-2008).

10. Dependent claim 19 is anticipated by Regeneron (8-May-2008).

255. Dependent claim 19 further limits the method of claim 14 to "wherein at least 5 tertiary doses of the VEGF antagonist are administered to the patient, and wherein the first four tertiary does 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."

256. As discussed with claim 5, Regeneron (8-May-2008) discloses that the VIEW2 clinical trial will last at least a year. (Ex.1013, Regeneron (8-May-2008), 1 ("In the ***first year***, the VIEW 2 . . . study will evaluate the safety and efficacy of VEGF Trap-Eye at doses of . . . 2.0 mg at an 8-week dosing interval . . . ." (emphasis added))). An 8-week dosing interval over the course of one year, after the initial dose and 2 secondary doses, would result in at least 5 tertiary doses administered at least 8 weeks after the immediately preceding dose, at weeks 16, 24, 32, 40, and 48.

257. Accordingly, for these reasons, as well as for the reasons discussed above for claims 5 and 14, it is my opinion that claim 19 is anticipated by Regeneron (8-May-2008).

11. Dependent claims 21-23 are anticipated by Regeneron (8-May-2008).

258. Dependent claim 21 further limits the method of claim 14 and recites "wherein all doses of the VEGF antagonist are administered to the patient by topical administration or by intraocular administration."

259. Claim 22 depends from claim 21 and specifies that all doses be administered by "intraocular administration."

260. Claim 23 depends from claim 22 and specifies that "the intraocular administration is intravitreal administration."

261. As discussed with claims 8-10 above, Regeneron (8-May-2008) discloses that "[b]oth VIEW 1 and VIEW 2 are designed to evaluate the efficacy and safety of VEGF Trap-Eye administered by intravitreal injection." (Ex.1013, Regeneron (8-May-2008), 1). Regeneron (8-May-2008) therefore expressly discloses intravitreal administration of the VEGF antagonist.

262. Thus, for these reasons, as well as for the reasons discussed above for claims 8-10 and 14, it is my opinion that claims 21-23 are anticipated by Regeneron (8-May-2008).

12. Dependent claims 24 and 26 are anticipated by Regeneron (8-May-2008).

263. Claim 24 depends from claim 23 and recites "wherein all doses of the VEGF antagonist comprise from about 0.5 mg to about 2 mg of the VEGF antagonist."

264. Claim 26 depends from claim 24 and specifies "wherein all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist."

265. As discussed with claims 11 and 13 above, Regeneron (8-May-2008) discloses that the "VIEW 2 (VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD) study will evaluate the safety and efficacy of VEGF Trap-Eye at" a dose of 2.0 mg. (Ex.1013, Regeneron (8-May-2008), 1). Regeneron (8-May-2008) therefore expressly discloses the claimed doses.

266. Accordingly, for these reasons, as well as the reasons set forth above for claims 11 and 13, and the claims from which claims 24 and 26 depend, it is my opinion that claims 24 and 26 are anticipated by Regeneron (8-May-2008).

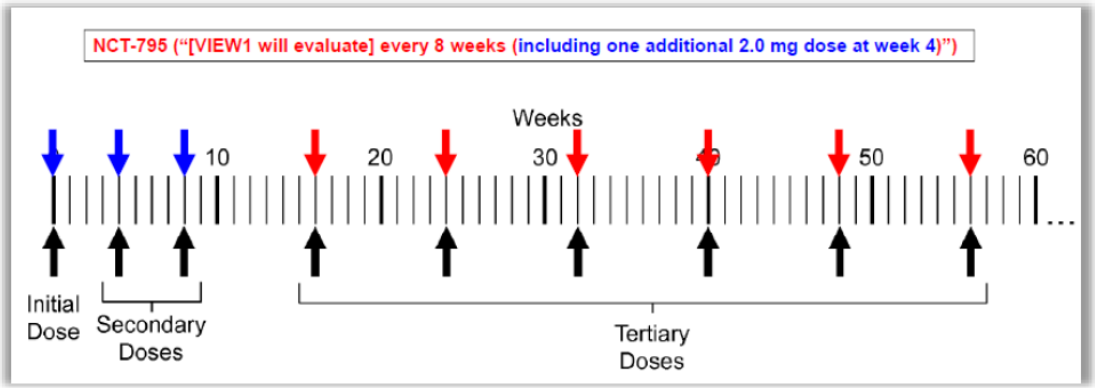
D. Claims 1, 3-11, 13, 14, 16-24, and 26 of the '338 Patent Are Anticipated by NCT00509795 (NCT-795) (Ex.1014).

1. Independent claim 1 of the '338 patent is anticipated by NCT-795.

267. I have been asked to review the challenged claims of the '338 patent and compare them to the disclosures of NCT-795. As with the other references

above that disclose Regeneron's VIEW trials and the dosing regimens used in those trials, it is my opinion that NCT-795 discloses every element of the claimed method(s) and thus anticipates each of the challenged claims of the '338 patent.

268. For example, NCT-795 describes VIEW1 as a Phase 3 trial being conducted with VEGF Trap-Eye in patients with AMD and including a treatment arm in which 2.0 mg of VEGF Trap-Eye will be "administered every 8 weeks (including one additional 2.0 mg dose at week 4)." (Ex.1014, NCT-795, 8). This has been illustrated using the same overlay presented above, in which I have used Figure 1 of the '338 patent to illustrate how NCT-795 discloses the exact dosing regimen set forth in Figure 1 of the '338 patent, as well as that which is claimed in the challenged claims of the '338 patent, as depicted here:



(Ex.1001, '338 patent, Fig.1 (modifications added)). In other words, dosing every eight weeks would result in doses at day 0 and at week 8, and when adding one additional dose at week 4, this would result in three monthly doses (**blue arrows**)

(i.e., doses at day 0 (i.e., "initial dose") and at weeks 4 and 8 (i.e., "secondary doses")). Thereafter, an eight-week dosing interval will result in injections at weeks 16, 24, 32, 40, and 48 (**red arrows**) (i.e., "tertiary doses")).

269. With respect to the last element of claim 1, as I discuss above, it is merely a recitation of the molecular architecture of the "VEGF Trap-Eye" disclosed in NCT-795, a fact that was disclosed well before January 2011. (*See, e.g.*, Ex.1006, Dixon, 1575-76, Fig.1; Ex.1010, '758 patent, Fig.24A-C (disclosing the nucleotide sequence and deduced amino acid sequence, as well as a description of each molecular component therein (i.e., the signal sequence, the FLT1 Ig domain 2, the FLK1 Ig domain 3, and the FcΔC1 domain), 10:15-17 (specifying that this molecule is termed "VEGFR1R2-FcΔC1(a).")); Ex.1033, Dix, [0013]-[0014], [0030]; Ex.1039, '095 patent, 1:45-54; Ex.1021, 2009 10-Q, 20 (using VEGF Trap and aflibercept interchangeably and explaining that "VEGF Trap-Eye is a specially purified and formulated form of VEGF Trap for use in intraocular applications"); Ex.1007, Adis, 261 (indicating in the title that aflibercept, VEGF Trap (R1R2), and VEGF Trap-Eye, among other terms, are understood by a person of ordinary skill in the art to refer, interchangeably, to the same drug); Ex.1093).[21]

[21] Regarding the preamble, *see, e.g.*, *supra* note 18.

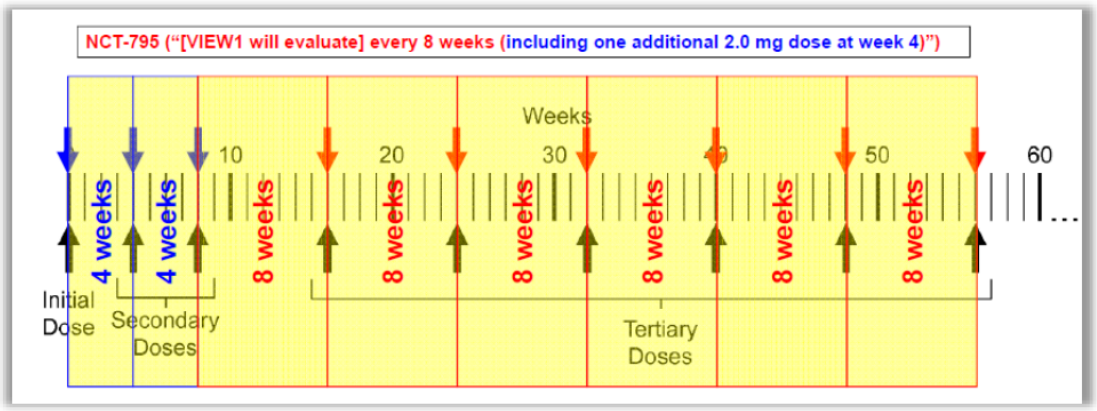
270. Accordingly, for at least these reasons, it is my opinion that claim 1 is anticipated by NCT-795.

2. Dependent claims 3 and 4 are anticipated by NCT-795.

271. Dependent claim 3 recites "[t]he 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."

272. Claim 4 additionally limits the method of claim 3 to "wherein each tertiary dose is administered 8 weeks after the immediately preceding dose."

273. As illustrated in my modified Figure 1 of the '338 patent below, NCT-795 discloses the elements of claims 3 and 4. NCT-795 discloses a treatment arm wherein subjects are 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." (Ex.1014, NCT-795, 8). In my opinion, this dosing schedule consists of an "initial" 2.0 mg dose, a first "secondary" 2.0 mg dose at week 4, a second "secondary" 2.0 mg dose at week 8, and "tertiary" 2.0 mg doses every 8 weeks for the remainder of the year:



(Ex.1001, '338 patent, Fig.1 (modifications added)).

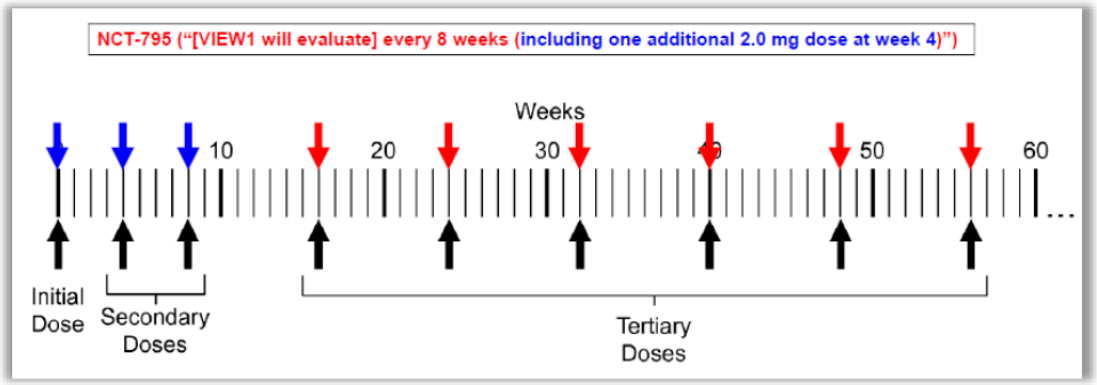
274. Thus, for these reasons, as well as the reasons discussed above for claim 1, it is my opinion that claims 3 and 4 are anticipated by NCT-795.

3. Dependent claim 5 is anticipated by NCT-795.

275. For the same reasons as above for claims 3 and 4, NCT-795 discloses the elements of claims 5. Dependent claim 5 recites "[t]he 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 does 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."

276. NCT-795 discloses the clinical study will last at least a year. (Ex.1014, NCT-795, 8 ("2.0 mg VEGF Trap-Eye administered every 8 weeks (including one additional 2.0 mg dose at week 4) ***during the first year***." (emphasis added))). As

illustrated in my modified Figure 1 of the '338 patent, an 8-week dosing interval over the course of one year, after the initial dose and 2 secondary doses, would result in at least 5 tertiary doses administered at least 8 weeks after the immediately preceding dose, at weeks 16, 24, 32, 40, and 48 (**red arrows**):



(Ex.1001, '338 patent, Fig.1 (modifications added)).

277. Accordingly, for these reasons, as well as for the reasons discussed above for claim 1, it is my opinion that claim 5 is anticipated by NCT-795.

4. Dependent claims 6 and 7 are anticipated by NCT-795.

278. Claim 6 of the '338 patent recites the method of claim 1, "wherein the angiogenic eye disorder is selected from the group consisting of" several well-known eye disorders, including AMD.

279. Claim 7 further limits the method of claim 6 to "wherein the angiogenic eye disorder is age related macular degeneration."

280. NCT-795 discloses that the title of the Phase 3 clinical study is "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). Thus, NCT-795 expressly discloses the treatment of AMD, which was known to be an angiogenic eye disorder.

281. Thus, for these reasons, as well as for the reasons discussed above for claim 1, it is my opinion that claims 6 and 7 are anticipated by NCT-795.

5. Dependent claims 8-10 are anticipated by NCT-795.

282. Claim 8 depends from claim 1 and recites "wherein all doses of the VEGF antagonist are administered to the patient by topical administration or by intraocular administration."

283. Claim 9 depends from claim 8 and specifies that all doses be administered by "intraocular administration."

284. Claim 10 depends from claim 9 and specifies that "the intraocular administration is intravitreal administration."

285. NCT-795 discloses that the Phase 3 study will test repeated doses of intravitreal VEGF Trap in subjects with AMD." (Ex.1014, NCT-795, 3). NCT-795 therefore expressly discloses intravitreal administration.

286. Therefore, for these reasons, as well as for the reasons discussed above for claim 1, it is my opinion that claims 8-10 are anticipated by NCT-795.

6. Dependent claims 11 and 13 are anticipated by NCT-795.

287. Dependent claim 11 further limits the method of claim 10 to "wherein all doses of the VEGF antagonist comprise from about 0.5 mg to about 2 mg of the VEGF antagonist."

288. Claim 13 depends from claim 11 and recites "wherein all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist."

289. NCT-795 discloses Phase 3 treatment arms using 2.0 mg of VEGF Trap-Eye. (Ex.1014, NCT-795, 6-8). NCT-795 therefore expressly discloses doses of claims 11 and 13.

290. Accordingly, for these reasons, as well as for the reasons discussed above for claims 1 and 8-10, it is my opinion that claims 11 and 13 are anticipated by NCT-795.

7. Independent claim 14 is anticipated by NCT-795.

291. Claim 14 of the '338 patent is identical to claim 1 with the only exception being in the third "wherein" clause.

292. First, claim 14 recites the same dosing regimen as that recited in claim 1: "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." Thus, for the same reasons discussed above with respect to claim 1, (*see* ¶¶ 267-70), it is also my opinion that NCT-795 discloses these identical elements in claim 14.

293. Second, in my opinion, NCT-795 discloses the VEGF antagonist element of claim 14. Just as for claim 1, NCT-795 expressly discloses VEGF Trap-Eye/aflibercept, and the sequence aspect of claim 14 was widely published in the prior art. (*See, e.g.*, Ex.1006, Dixon, 1575-76, Fig.1; Ex.1010, '758 patent, Fig.24A-C (disclosing the nucleotide sequence and deduced amino acid sequence, as well as a description of each molecular component therein (i.e., the signal sequence, the FLT1 Ig domain 2, the FLK1 Ig domain 3, and the FcΔC1 domain), 10:15-17 (specifying that this molecule is termed "VEGFR1R2-FcΔC1(a).")); Ex.1033, Dix, [0013]-[0014], [0030]; Ex.1039, '095 patent, 1:45-54; Ex.1021, 2009 10-Q, 20 (using VEGF Trap and aflibercept interchangeably and explaining that "VEGF Trap-Eye is a specially purified and formulated form of VEGF Trap for use in intraocular applications"); Ex.1007, Adis, 261 (indicating in the title that aflibercept, VEGF Trap (R1R2), and VEGF Trap-Eye, among other terms, are understood by a person of ordinary skill in the art to refer, interchangeably, to the same drug); Ex.1094). .

294. Therefore, for these reasons, as well as the reasons set forth above for claim 1, it is my opinion that claim 14 is anticipated by NCT-795.

8. Dependent claims 16 and 17 are anticipated by NCT-795.

295. Claim 16 depends from claim 14 and recites "wherein only two secondary doses are administered to the patient, and wherein each secondary dose is administered 4 weeks after the immediately preceding dose."

296. Claim 17 further limits the method of claim 16 to "wherein each tertiary dose is administered 8 weeks after the immediately preceding dose."

297. As discussed with respect to claims 3 and 4 above, NCT-795 discloses the elements of claims 16 and 17. (Ex.1014, NCT-795, 8). In my opinion, it was well established that the VIEW1 dosing schedule consists of an initial 2.0 mg dose, a first secondary 2.0 mg dose at week 4, a second secondary 2.0 mg dose at week 8, and tertiary 2.0 mg doses every 8 weeks for the remainder of the year.

298. Therefore, for these reasons, as well as the reasons discussed above for claims 3, 4, and 14, it is my opinion that claims 16 and 17 are anticipated by NCT-795.

9. Dependent claims 18 and 20 are anticipated by NCT-795.

299. Claim 18 depends from claim 17, which ultimately depends from claim 14 and recites "wherein the angiogenic eye disorder is age related macular degeneration."

300. Claim 20 recites the method of claim 14, "wherein the angiogenic eye disorder is selected from the group consisting of" several well-known eye disorders, including AMD.

301. As discussed with claims 6 and 7 above, NCT-795 discloses the title of the VIEW1 clinical study as "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). NCT-795 therefore expressly discloses treating AMD, an angiogenic eye disorder.

302. Therefore, for these reasons, as well as the reasons discussed above for claims 6, 7, 14, 16, and 17, it is my opinion that claims 18 and 20 are anticipated by NCT-795.

10. Dependent claim 19 is anticipated by NCT-795.

303. Dependent claim 19 further limits the method of claim 14 to "wherein at least 5 tertiary doses of the VEGF antagonist are administered to the patient, and wherein the first four tertiary does 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."

304. As discussed with claim 5, NCT-795 discloses that the VIEW1 clinical study will last at least a year. (Ex.1014, NCT-795, 8 ("2.0 mg VEGF Trap-Eye

administered every 8 weeks (including one additional 2.0 mg dose at week 4) ***during the first year***." (emphasis added))). As illustrated above in my modified Figure 1 of the '338 patent, an 8-week dosing interval over the course of one year, after the initial dose and 2 secondary doses called for in the VIEW1 trial, would result in at least 5 tertiary doses administered at least 8 weeks after the immediately preceding dose, at weeks 16, 24, 32, 40, and 48.

305. Accordingly, for these reasons, as well as the reasons discussed above for claims 5 and 14, it is my opinion that claim 19 is anticipated by NCT-795.

11. Dependent claims 21-23 are anticipated by NCT-795.

306. Dependent claim 21 further limits the method of claim 14 and recites "wherein all doses of the VEGF antagonist are administered to the patient by topical administration or by intraocular administration."

307. Claim 22 depends from claim 21 and specifies that all doses be administered by "intraocular administration."

308. Claim 23 depends from claim 22 and specifies that "the intraocular administration is intravitreal administration."

309. As discussed with claims 8-10 above, NCT-795 discloses that the VIEW1 Phase 3 study will test repeated doses of intravitreal VEGF Trap in subjects with AMD. (Ex.1014, NCT-795, 3). NCT-795 therefore discloses intravitreal administration of VEGF Trap-Eye/aflibercept.

310. Thus, for these reasons, as well as the reasons discussed above for claims 8-10 and 14, it is my opinion that claims 21-23 are anticipated by NCT-795.

12. Dependent claims 24 and 26 are anticipated by NCT-795.

311. Claim 24 depends from claim 23 and recites "wherein all doses of the VEGF antagonist comprise from about 0.5 mg to about 2 mg of the VEGF antagonist."

312. Claim 26 depends from claim 24 and specifies "wherein all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist."

313. As discussed with claims 11 and 13 above, NCT-795 discloses VIEW1 Phase 3 treatment arms using 2.0 mg of VEGF Trap-Eye. (Ex.1014, NCT-795, 6-8). NCT-795 therefore expressly discloses the claimed doses.

314. Accordingly, for these reasons, as well as the reasons set forth above for claims 11 and 13, and the claims from which claims 24 and 26 depend, it is my opinion that claims 24 and 26 are anticipated by NCT-795.

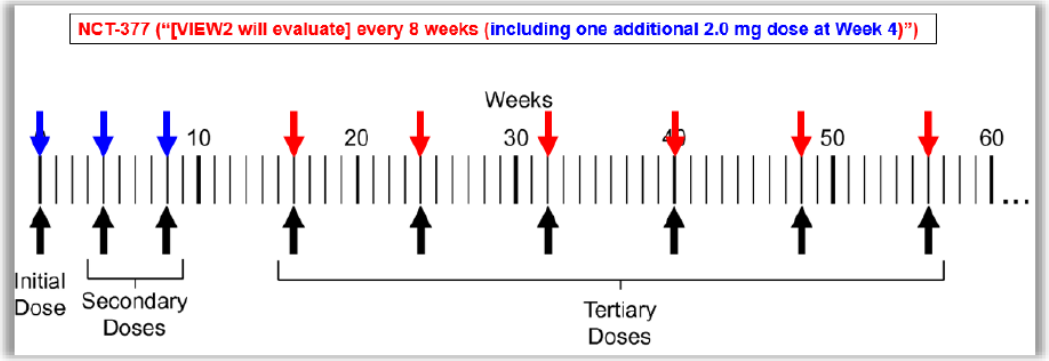
E. Claims 1, 3-11, 13, 14, 16-24, and 26 of the '338 Patent Are Anticipated by NCT00637377 (NCT-377) (Ex.1015).

1. Independent claim 1 of the '338 patent is anticipated by NCT-377.

315. I have been asked to review the challenged claims of the '338 patent and compare them to the disclosures of NCT-377. As with the other references above that disclose Regeneron's VIEW trials and the dosing regimens used in those

trials, it is my opinion that NCT-377 discloses every element of the claimed method(s) and thus anticipates each of the challenged claims of the '338 patent.

316. For example, NCT-377 discloses the VIEW2 Phase 3 trial being conducted with VEGF Trap-Eye in patients with AMD and including a treatment arm in which 2.0 mg of VEGF Trap-Eye will be "administered every 8 weeks (including one additional 2.0 mg dose at Week 4) during the first year." (Ex.1015, NCT-377, 5-6). This has been illustrated using the same overlay presented above, in which I have used Figure 1 of the '338 patent to illustrate how NCT-377 discloses the exact dosing regimen set forth in Figure 1 of the '338 patent, as well as that which is claimed in the challenged claims of the '338 patent, as depicted here:



(Ex.1001, '338 patent, Fig.1 (modifications added)). In other words, dosing every eight weeks would result in doses at day 0 and at week 8, and when adding one additional dose at week 4, this would result in three monthly doses (**blue arrows**) (i.e., doses at day 0 (i.e., "initial dose") and at weeks 4 and 8 (i.e., "secondary

doses")). Thereafter, an eight-week dosing interval will result in injections at weeks 16, 24, 32, 40, and 48 (**red arrows**) (i.e., "tertiary doses")).

317. NCT-377 further states that subjects will 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. Thereafter a dose may be administered as frequently as every 4 weeks, but no less frequently than every 12 weeks." (Ex.1015, NCT-377, 6).

318. With respect to the last element of claim 1, as I discuss above, it is merely a recitation of the molecular architecture of the "VEGF Trap-Eye" disclosed in NCT-377, a fact that was disclosed well before January 2011. (*See*, *e.g.*, Ex.1006, Dixon, 1575-76, Fig.1; Ex.1010, '758 patent, Fig.24A-C (disclosing the nucleotide sequence and deduced amino acid sequence, as well as a description of each molecular component therein (i.e., the signal sequence, the FLT1 Ig domain 2, the FLK1 Ig domain 3, and the FcΔC1 domain), 10:15-17 (specifying that this molecule is termed "VEGFR1R2-FcΔC1(a).")); Ex.1033, Dix, [0013]-[0014], [0030]; Ex.1039, '095 patent, 1:45-54; Ex.1021, 2009 10-Q, 20 (using VEGF Trap and aflibercept interchangeably and explaining that "VEGF Trap-Eye is a specially purified and formulated form of VEGF Trap for use in intraocular applications"); Ex.1007, Adis, 261 (indicating in the title that aflibercept, VEGF Trap (R1R2), and

VEGF Trap-Eye, among other terms, are understood by a person of ordinary skill in the art to refer, interchangeably, to the same drug); Ex.1093).[22]

319. For at least these reasons, it is my opinion that claim 1 is anticipated by NCT-377.

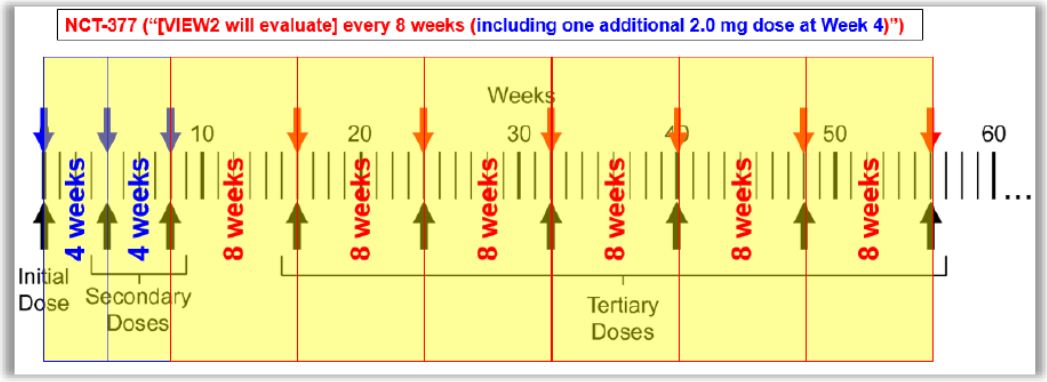
2. Dependent claims 3 and 4 are anticipated by NCT-377.

320. Claim 3 recites "[t]he 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."

321. Claim 4 additionally limits the method of claim 3 to "wherein each tertiary dose is administered 8 weeks after the immediately preceding dose."

322. As illustrated in my modified Figure 1 of the '338 patent below, NCT-377 discloses the elements of claims 3 and 4. NCT-377 states that subjects in one of the four treatment arms will 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." (Ex.1015, NCT-377, 6). In my opinion, this dosing schedule consists of an "initial" 2.0 mg dose, a first "secondary" 2.0 mg dose at week 4, a second "secondary" 2.0 mg dose at week 8, and "tertiary" 2.0 mg doses every 8 weeks for the remainder of the year:

[22] Regarding the preamble, *see, e.g.*, *supra* note 18.



(Ex.1001, '338 patent, Fig.1 (modifications added)).

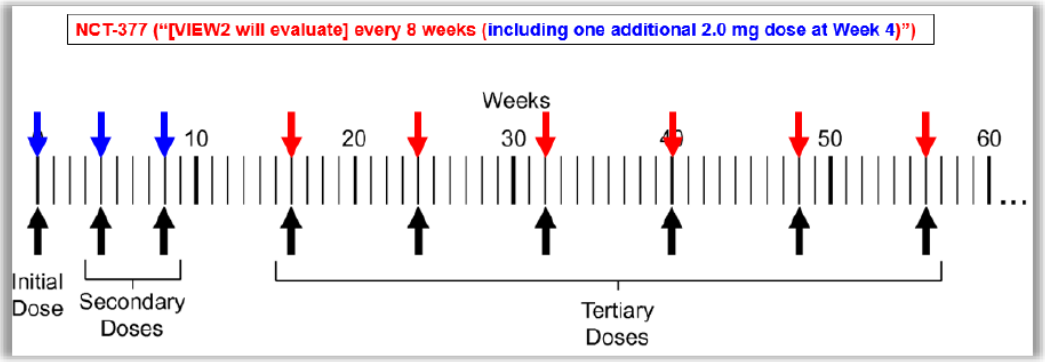
323. Thus, for these reasons, as well as the reasons discussed above for claim 1, it is my opinion that claims 3 and 4 are anticipated by NCT-377.

3. Dependent claim 5 is anticipated by NCT-377.

324. For the same reasons as above for claims 3 and 4, NCT-377 discloses the elements of claim 5. Dependent claim 5 recites "[t]he 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 does 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."

325. NCT-377 discloses that the VIEW2 clinical study will last at least a year. (Ex.1015, NCT-377, 6 ("2.0 mg VEGF Trap-Eye administered every 8 weeks (including one additional 2.0 mg dose at Week 4) ***during the first year***." (emphasis added))). As illustrated in my modified Figure 1 of the '338 patent, an 8-week

dosing interval over the course of one year, after the initial dose and 2 secondary doses, would result in at least 5 tertiary doses administered at least 8 weeks after the immediately preceding dose, at weeks 16, 24, 32, 40, and 48 (**red arrows**):



(Ex.1001, '338 patent, Fig.1 (modifications added)).

326. Accordingly, for these reasons, as well as for the reasons discussed above for claim 1, it is my opinion that claim 5 is anticipated by NCT-377.

4. Dependent claims 6 and 7 are anticipated by NCT-377.

327. Claim 6 of the '338 patent recites the method of claim 1, "wherein the angiogenic eye disorder is selected from the group consisting of" several well-known eye disorders, including AMD.

328. Claim 7 further limits the method of claim 6 to "wherein the angiogenic eye disorder is age related macular degeneration."

329. NCT-377 discloses the title of the clinical study as "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)." (Ex.1015, NCT-377, 3-4). NCT-377 thus discloses the treatment of AMD, which was known to be an angiogenic eye disorder.

330. Thus, for these reasons, as well as for the reasons discussed above for claim 1, it is my opinion that claims 6 and 7 are anticipated by NCT-377.

5. Dependent claims 8-10 are anticipated by NCT-377.

331. Claim 8 depends from claim 1 and recites "wherein all doses of the VEGF antagonist are administered to the patient by topical administration or by intraocular administration."

332. Claim 9 depends from claim 8 and specifies that all doses be administered by "intraocular administration."

333. Claim 10 depends from claim 9 and specifies that "the intraocular administration is intravitreal administration."

334. NCT-377 discloses the title of the VIEW2 clinical study as "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)." (Ex.1015, NCT-377, 3-4 (emphasis added)). NCT-377 thus expressly discloses intravitreal administration.

335. Therefore, for these reasons, as well as for the reasons discussed above for claim 1, it is my opinion that claims 8-10 are anticipated by NCT-377.

6. Dependent claims 11 and 13 are anticipated by NCT-377.

336. Dependent claim 11 further limits the method of claim 10 to "wherein all doses of the VEGF antagonist comprise from about 0.5 mg to about 2 mg of the VEGF antagonist."

337. Claim 13 depends from claim 11 and recites "wherein all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist."

338. NCT-377 discloses that subjects in one of the VIEW2 treatment arms will 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." (Ex.1015, NCT-377, 6). NCT-377 thus expressly discloses the claimed doses.

339. Accordingly, for these reasons, as well as for the reasons discussed above for claim 1 and the claims from which claims 11 and 13 depend, it is my opinion that claims 11 and 13 are anticipated by NCT-377.

7. Independent claim 14 is anticipated by NCT-377.

340. Claim 14 of the '338 patent is identical to claim 1 with the only exception being in the third "wherein" clause.

341. First, claim 14 recites the same dosing regimen as that recited in claim 1: "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." Thus, for the same reasons discussed above with respect to claim 1, (*see* ¶¶ 315-19), it is also my opinion that NCT-377 discloses these identical elements in claim 14.

342. Second, in my opinion, NCT-377 discloses the VEGF antagonist element of claim 14. Just as for claim 1, NCT-377 expressly discloses VEGF Trap-Eye/aflibercept, and the sequence aspect of claim 14 was widely published in the prior art. (*See, e.g.*, Ex.1006, Dixon, 1575-76, Fig.1; Ex.1010, '758 patent, Fig.24A-C (disclosing the nucleotide sequence and deduced amino acid sequence, as well as a description of each molecular component therein (i.e., the signal sequence, the FLT1 Ig domain 2, the FLK1 Ig domain 3, and the FcΔC1 domain), 10:15-17 (specifying that this molecule is termed "VEGFR1R2-FcΔC1(a).")); Ex.1033, Dix, [0013]-[0014], [0030]; Ex.1039, '095 patent, 1:45-54; Ex.1021, 2009 10-Q, 20 (using VEGF Trap and aflibercept interchangeably and explaining that "VEGF Trap-Eye is a specially purified and formulated form of VEGF Trap for use in intraocular applications"); Ex.1007, Adis, 261 (indicating in the title that aflibercept, VEGF Trap (R1R2), and VEGF Trap-Eye, among other terms, are understood by a person of ordinary skill in the art to refer, interchangeably, to the same drug); Ex.1094).

343. Thus, for these reasons, as well as the reasons set forth above for claim 1, it is my opinion that claim 14 is anticipated by NCT-377.

8. Dependent claims 16 and 17 are anticipated by NCT-377.

344. Claim 16 depends from claim 14 and recites "wherein only two secondary doses are administered to the patient, and wherein each secondary dose is administered 4 weeks after the immediately preceding dose."

345. Claim 17 further limits the method of claim 16 to "wherein each tertiary dose is administered 8 weeks after the immediately preceding dose."

346. As discussed with respect to claims 3 and 4 above, NCT-377 discloses the elements of claims 16 and 17. NCT-377 states that subjects in one of the four VIEW2 treatment arms will 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." (Ex.1015, NCT-377, 6). In my opinion, this VIEW2 dosing schedule consists of an "initial" 2.0 mg dose, a first "secondary" 2.0 mg dose at week 4, a second "secondary" 2.0 mg dose at week 8, and "tertiary" 2.0 mg doses every 8 weeks for the remainder of the year.

347. For these reasons, as well as the reasons discussed above for claim 14, it is my opinion that claims 16 and 17 are anticipated by NCT-377.

9. Dependent claims 18 and 20 are anticipated by NCT-377.

348. Claim 18 depends from claim 17, which ultimately depends from claim 14 and recites "wherein the angiogenic eye disorder is age related macular degeneration."

349. Claim 20 recites the method of claim 14, "wherein the angiogenic eye disorder is selected from the group consisting of" several well-known eye disorders, including AMD.

350. As discussed with claims 6 and 7 above, NCT-377 discloses the title of the VIEW2 clinical study as "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)." (Ex.1015, NCT-377, 3-4). NCT-377 therefore expressly discloses treating AMD, which was known to be an angiogenic eye disorder.

351. Therefore, for these reasons, as well as the reasons discussed above for claims 6, 7, 14, 16, and 17, it is my opinion that claims 18 and 20 are anticipated by NCT-377.

10. Dependent claim 19 is anticipated by NCT-377.

352. Dependent claim 19 further limits the method of claim 14 to "wherein at least 5 tertiary doses of the VEGF antagonist are administered to the patient, and wherein the first four tertiary does 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."

353. As discussed with claim 5, NCT-377 discloses that the VIEW2 clinical study will last at least a year. (Ex.1015, NCT-377, 6 ("2.0 mg VEGF Trap-Eye administered every 8 weeks (including one additional 2.0 mg dose at Week 4) ***during the first year***." (emphasis added))). As illustrated in my modified Figure 1 of the '338 patent, an 8-week dosing interval over the course of one year, after the initial dose and 2 secondary doses, would result in at least 5 tertiary doses administered at least 8 weeks after the immediately preceding dose, at weeks 16, 24, 32, 40, and 48.

354. Accordingly, for these reasons, as well as the reasons discussed above for claims 5 and 14, it is my opinion that claim 19 is anticipated by NCT-377.

11. Dependent claims 21-23 are anticipated by NCT-377.

355. Dependent claim 21 further limits the method of claim 14 and recites "wherein all doses of the VEGF antagonist are administered to the patient by topical administration or by intraocular administration."

356. Claim 22 depends from claim 21 and specifies that all doses be administered by "intraocular administration."

357. Claim 23 depends from claim 22 and specifies that "the intraocular administration is intravitreal administration."

358. As discussed with claims 8-10 above, NCT-377 discloses the title of the VIEW2 clinical study as "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)." (Ex.1015, NCT-377, 3-4 (emphasis added)). NCT-377 therefore expressly discloses intravitreal administration.

359. Thus, for these reasons, as well as the reasons discussed above for claims 8-10 and 14, it is my opinion that claims 21-23 are anticipated by NCT-377.

12. Dependent claims 24 and 26 are anticipated by NCT-377.

360. Claim 24 depends from claim 23 and recites "wherein all doses of the VEGF antagonist comprise from about 0.5 mg to about 2 mg of the VEGF antagonist."

361. Claim 26 depends from claim 24 and specifies "wherein all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist."

362. As discussed with claims 11 and 13 above, NCT-377 discloses that subjects in one of the VIEW2 treatment arms will 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." (Ex.1015, NCT-377, 6). NCT-377 therefore expressly discloses the claimed doses.

363. Accordingly, for these reasons, as well as the reasons set forth above for claims 11 and 13, and the claims from which claims 24 and 26 depend, it is my opinion that claims 24 and 26 are anticipated by NCT-377.

F. Claims 1, 3-11, 13, 14, 16-24, and 26 of the '338 Patent Are Obvious in View of Dixon, Either Alone or in Combination with the '758 Patent or Dix.

1. Independent claim 1.

364. I have set forth above the disclosures in Dixon that I believe anticipate the challenged claims, and I incorporate those disclosures herein. In my opinion, in addition to anticipating the challenged claims, Dixon also would make the subject matter of the challenged claims obvious.

365. First, one of ordinary skill in the art would have been motivated to explore dosing regimens that reduce the frequency of intravitreal injections administered in a monthly dosing scheme. This was a widely discussed concern at the time, and is evident from the Dixon reference itself. (Ex.1006, Dixon, 1574, 1577 (noting the "time and financial burden of monthly injections" and "[d]esirable attributes for emerging therapies for neovascular AMD include . . . decreased dosing intervals")).

366. Second, one of ordinary skill in the art would have observed in Dixon, and in the many other publicly available reports of the initiation of the VIEW Phase 3 trials, that a solution to the dosing frequency issue was presented therein in the

form of the publicly disclosed VIEW regimens involving every-8-week dosing following three monthly loading doses. (*Id.* at 1576).

367. Third, one of ordinary skill in the art would have had a reasonable expectation of success using the VIEW regimens for treating AMD. Dixon, in addition to reporting on the Phase 3 VIEW regimens, also provides a summary of the Phase 2 VEGF Trap-Eye results. For example, Dixon reports that the Phase 2 PRN regimen of 2.0 mg doses resulted in a mean increase of 9.0 ETDRS letters, with 29% gaining greater than or equal to 15 ETDRS letters at 52 weeks. (*Id.*). Those patients also experienced a mean decrease in retinal thickness of 143 µm. (*Id.*). A comparison to the results eventually reported for VIEW1/VIEW2 further illustrates why a person of ordinary skill in the art would have been justified in having a reasonable expectation of success based on the Phase 2 data:

Measure	Phase 2 4 monthly + PRN (as reported in Dixon)	Phase 3 (VIEW1, VIEW2) 3 monthly + every-8-week (as reported in Heier-2012)
BCVA letter gain	+9.0	+7.9, +8.9
Retinal thickness (µm)	-143	-128.5, -149.2
Number of doses (first year)	5.6	8

368. As Dixon further notes, patients on the Phase 2 PRN regimen received, on average, 1.6 doses during the PRN dosing phase. (*Id.*). This means that, combined with the 4 monthly loading doses, patients in this group received, on average, 5.6 doses over the course of the first year. On the other hand, a patient would receive 8 doses in the first year under the Phase 3 VIEW dosing regimen (3 monthly loading doses followed by 5 every-8-week doses (i.e., doses at months 0, 1, 2, 4, 6, 8, 10, and 12)). The reasonable expectation of success is confirmed by Regeneron itself, who stated that the Phase 2 studies "indicat[e] that an 8-week dosing schedule may be feasible." (Ex.1036, Regeneron (28-April-2008), 1). Indeed, after the Phase 2 results, Regeneron did in fact go with the 3 monthly loading dose/every-8-week dosing regimen for its Phase 3 trial. In my opinion, Regeneron would not have settled on that regimen without having a reasonable expectation that it would be successful. In sum, it is my opinion that a person of ordinary skill in the art, in light of the Phase 2 results, would have indeed had a reasonable expectation of success that the Phase 3 regimen would be capable of treating AMD.

369. Fourth, with respect to the amino acid sequence and protein domains recited in claim 1, I discuss these disclosures in depth in the sections above and incorporate that discussion into this analysis. VEGF Trap-Eye/aflibercept was a well-known molecule among those of ordinary skill in the art, and a description of its molecular structure and sequence could be found throughout the prior art. (*See,*

e.g., Ex.1010, ’758 patent, Fig.24A-C (disclosing the nucleotide sequence and deduced amino acid sequence, as well as a description of each molecular component therein (i.e., the signal sequence, the FLT1 Ig domain 2, the FLK1 Ig domain 3, and the FcΔC1 domain), 10:15-17 (specifying that this molecule is termed “VEGFR1R2-FcΔC1(a).”); Ex.1033, Dix, [0013]-[0014], [0030]; Ex.1093).

370. Accordingly, it is my opinion that the disclosures of Dixon, either alone, or in combination with the disclosures of the VEGF Trap domain architecture and VEGF Trap amino acid and nucleotide sequences in the ’758 patent and Dix, makes claim 1 of the ’338 patent obvious.

2. Dependent claims 3 and 4.

371. Dependent claim 3 limits the method of claim 1 to “wherein only two secondary doses are administered to the patient, and wherein each secondary dose is administered 4 weeks after the immediately preceding dose.” And, claim 4 further limits the method of claim 3 to “wherein each tertiary dose is administered 8 weeks after the immediately preceding dose.”

372. As discussed above, Dixon discloses the elements of claim 3 (each secondary dose is administered 4 weeks after the immediately preceding dose) and claim 4 (each tertiary dose is administered 8 weeks after the immediately preceding dose) in the discussion of the VIEW study arms. (*See, e.g.*, Ex.1006, Dixon, 1576 (“2.0 mg at an 8 week dosing interval (following three monthly doses)”)).

373. Accordingly, and for the reasons discussed above with respect to claim 1, it is my opinion that Dixon, either alone, or in combination with the disclosures of the VEGF Trap domain architecture and VEGF Trap amino acid and nucleotide sequences in the '758 patent and Dix, makes claims 3 and 4 of the '338 patent obvious.

3. Dependent claim 5.

374. Claim 5 claims 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 does 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."

375. Dixon discloses that the VIEW1 and VIEW2 clinical trials were to last at least a year. (Ex.1006, Dixon, 1576 ("*After the first year* of the study, patients will enter a second year of p.r.n. dosing . . . . [T]he primary outcome will be the proportion of patients who maintain vision *at week 52* . . . ." (emphasis added)). As discussed above in the anticipation section, over the course of a year, and following the three monthly doses, the "8 week dosing interval" disclosed in Dixon for the VIEW studies would result in "at least 5 tertiary doses," administered at weeks 16, 24, 32, 40, and 48.

376. Thus, for these reasons, as well as for the reasons discussed above for claim 1, it is my opinion that Dixon, either alone, or in combination with the disclosures of the VEGF Trap domain architecture and VEGF Trap amino acid and nucleotide sequences in the ’758 patent and Dix, makes claim 5 of the ’338 patent obvious.

4. Dependent claims 6 and 7.

377. Claim 6 is dependent on claim 1 and recites “wherein the angiogenic eye disorder is selected from the group consisting of” several well-known eye disorders, including AMD. Claim 7, which depends from claim 6, recites “wherein the angiogenic eye disorder is age related macular degeneration.”

378. The Dixon reference is drawn to disclosures of VEGF Trap’s use in treating AMD, which was known to be an angiogenic eye disorder. Dixon reported on the results of the Phase 1 and Phase 2 VEGF Trap-Eye AMD studies and set forth the dosing regimens being tested in the Phase 3 AMD trial, including the dosing regimen of 3 monthly doses followed by every-8-week dosing. (*See, e.g.*, Ex.1006, Dixon, 1576).

379. Thus, for these reasons, as well as for the reasons discussed above for claim 1, it is my opinion that Dixon, either alone, or in combination with the disclosures of the VEGF Trap domain architecture and VEGF Trap amino acid and

nucleotide sequences in the ’758 patent and Dix, makes claims 6 and 7 of the ’338 patent obvious.

5. Dependent claims 8-10.

380. Dependent claim 8 depends from claim 1 and recites “wherein all doses of the VEGF antagonist are administered to the patient by topical administration or by intraocular administration.”

381. Claim 9 depends from claim 8 and specifies intraocular administration.

382. Claim 10 depends from claim 9 and specifies that “the intraocular administration is intravitreal administration.”

383. Dixon expressly discloses that the VEGF Trap was intravitreally administered, reporting that the VIEW1 and VIEW2 Phase 3 studies “will evaluate the safety and efficacy of ***intravitreal*** VEGF Trap-Eye.” (Ex.1006, Dixon, 1575-76 (emphasis added)). Intravitreal injection is a type of intraocular administration—more specifically, administration directly into the vitreous of the eye.

384. Thus, for these reasons, as well as for the reasons discussed above for claim 1, it is my opinion that Dixon, either alone, or in combination with the disclosures of the VEGF Trap domain architecture and VEGF Trap amino acid and nucleotide sequences in the ’758 patent and Dix, makes claims 8-10 of the ’338 patent obvious.

6. Dependent claims 11 and 13.

385. Dependent claim 11 depends from claim 10 and recites "wherein all doses of the VEGF antagonist comprise from about 0.5 mg to about 2 mg of the VEGF antagonist." Dependent claim 13 depends from claim 11 and specifies "wherein all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist."

386. Dixon expressly discloses that the treatment arms in the VIEW studies will employ a 2.0 mg dose. (*See, e.g.*, Ex.1006, Dixon, 1576 (disclosing "intravitreal VEGF Trap-Eye at . . . 2.0 mg at an 8-week dosing interval (following three monthly doses)")).

387. Therefore, for these reasons, as well as the reasons set forth above for claims 1 and 10, it is my opinion that Dixon, either alone, or in combination with the disclosures of the VEGF Trap domain architecture and VEGF Trap amino acid and nucleotide sequences in the '758 patent and Dix, makes claims 11 and 13 of the '338 patent obvious.

7. Independent claim 14.

388. Claim 14 of the '338 patent is identical to claim 1 with the only exception being in the third "wherein" clause.

389. First, claim 14 recites the same dosing regimen as that recited in claim 1: "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." Thus, for the same reasons discussed above with respect to claim 1, (*see* ¶¶ 364-70), it is also my opinion that Dixon discloses these identical elements in claim 14.

390. Second, as discussed above, in my opinion, Dixon discloses the VEGF antagonist element of claim 14. Just as for claim 1, Dixon expressly discloses VEGF Trap-Eye/aflibercept, and the sequence aspect of claim 14 was widely published in the prior art. (*See, e.g.*, Ex.1010, '758 patent, Fig.24A-C (disclosing the nucleotide sequence and deduced amino acid sequence, as well as a description of each molecular component therein (i.e., the signal sequence, the FLT1 Ig domain 2, the FLK1 Ig domain 3, and the FcΔC1 domain), 10:15-17 (specifying that this molecule is termed "VEGFR1R2-FcΔC1(a).")); Ex.1033, Dix, [0013]-[0014], [0030]; Ex.1039, '095 patent, 1:45-54; Ex.1021, 2009 10-Q, 20 (using VEGF Trap and aflibercept interchangeably and explaining that "VEGF Trap-Eye is a specially purified and formulated form of VEGF Trap for use in intraocular applications"); Ex.1007, Adis, 261 (indicating in the title that aflibercept, VEGF Trap (R1R2), and VEGF Trap-Eye, among other terms, are understood by a person of ordinary skill in the art to refer, interchangeably, to the same drug); Ex.1094). Therefore, for the same reasons discussed above, it is my opinion that this aspect of claim 14 is obvious.

391. Therefore, it is my opinion that Dixon, either alone, or in combination with the disclosures of the VEGF Trap domain architecture and VEGF Trap amino acid and nucleotide sequences in the '758 patent and Dix, makes claim 14 of the '338 patent obvious.

8. Dependent claims 16 and 17.

392. Claim 16 limits the method of claim 14 to "wherein only two secondary doses are administered to the patient, and wherein each secondary dose is administered 4 weeks after the immediately preceding dose." Claim 17 further limits the method of claim 16 to "wherein each tertiary dose is administered 8 weeks after the immediately preceding dose."

393. I note that aside from the independent claims from which they depend, claims 16 and 17 are similar to claims 3 and 4. Accordingly, for the reasons discussed above for claim 14 and for claims 3 and 4, it is my opinion that Dixon, either alone, or in combination with the disclosures of the VEGF Trap domain architecture and VEGF Trap amino acid and nucleotide sequences in the '758 patent and Dix, makes claims 16 and 17 of the '338 patent obvious.

9. Dependent claims 18 and 20.

394. Claim 18 is dependent on claim 17, which ultimately depends from claim 14, and recites "wherein the angiogenic eye disorder is age related macular degeneration." Claim 20 is dependent on claim 14 and recites "wherein the

angiogenic eye disorder is selected from the group consisting of" several well-known eye disorders, including AMD.

395. Aside from the independent claims from which they depend, claim 18 is similar to claim 7 and claim 20 is similar to claim 6. Accordingly, for the reasons discussed above for claims 6, 7, 14, 16, and 17, it is my opinion that the disclosures of Dixon, either alone, or in combination with the disclosures of the VEGF Trap domain architecture and VEGF Trap amino acid and nucleotide sequences in the '758 patent and Dix, makes claims 18 and 20 of the '338 patent obvious.

10. Dependent claim 19.

396. Claim 19 claims the method of claim 14, "wherein at least 5 tertiary doses" are administered, and "wherein the first four tertiary does 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."

397. Aside from the independent claims from which they depend, claim 19 is similar to claim 5. Accordingly, for the reasons discussed above for claims 5 and 14, it is my opinion that Dixon, either alone, or in combination with the disclosures of the VEGF Trap domain architecture and VEGF Trap amino acid and nucleotide sequences in the '758 patent and Dix, makes claim 19 of the '338 patent obvious.

11. Dependent claims 21-23.

398. Dependent claim 21 depends from claim 14 and recites "wherein all doses of the VEGF antagonist are administered to the patient by topical administration or by intraocular administration."

399. Claim 22 depends from claim 21 and specifies intraocular administration.

400. Claim 23 depends from claim 22 and specifies that "the intraocular administration is intravitreal administration."

401. Aside from the independent claims from which they depend, claims 21-23 are similar to claims 8-10. Accordingly, for the reasons discussed above for claims 8-10, and 14, it is my opinion that Dixon, either alone, or in combination with the disclosures of the VEGF Trap domain architecture and VEGF Trap amino acid and nucleotide sequences in the '758 patent and Dix, makes claims 21-23 of the '338 patent obvious.

12. Dependent claims 24 and 26.

402. Dependent claim 24 depends from claim 23 and recites "wherein all doses of the VEGF antagonist comprise from about 0.5 mg to about 2 mg of the VEGF antagonist." Dependent claim 26 depends from claim 24 and specifies "wherein all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist."

403. Aside from the independent claims from which they depend, claims 24 and 26 are similar to claims 11 and 13. Accordingly, for the reasons discussed above for claims 11 and 13, and the claims from which claims 24 and 26 depend, it is my opinion that Dixon, either alone, or in combination with the disclosures of the VEGF Trap domain architecture and VEGF Trap amino acid and nucleotide sequences in the '758 patent and Dix, makes claims 24 and 26 of the '338 patent obvious.

IX. SECONDARY CONSIDERATIONS.

404. I understand that a patent owner may in some circumstances rely on so-called "secondary considerations of non-obviousness" to attempt to refute a finding of obviousness of a claim.[23] I also understand that there are several categories of secondary considerations, which might include alleged unexpected results or a "long-felt but unmet need." Notwithstanding that the unpatentability of the challenged claims is supported by strong evidence, including the numerous Regeneron disclosures and public announcements of its dosing regimens for VEGF Trap-Eye/aflibercept well prior to the filing date of the '338 patent, it is my opinion that there are no unexpected results or a "long-felt but unmet need" that would refute the strong case of obviousness against the challenged claims.

[23] I understand that any showing of "secondary considerations" by the patent owner is not relevant to an anticipation analysis.

405. For example, I was asked to review Regeneron's statement to the U.S. Patent and Trademark Office, dated September 11, 2015. Therein, Regeneron argues that "improved unexpected results" were observed and thereafter described in the working examples of the '338 patent and a 2012 publication reporting on the results of the VIEW studies (Ex.1019, Heier-2012). Regeneron characterizes the standard of care prior to the filing of the '338 patent as once per month dosing. (Ex.1017, '338 FH, 9/11/2015 Remarks, 6). They further characterize the results reported in Heier-2012 as surprising, dramatic, and unexpected since the every-eight-week dosing group exhibited outcomes similar to those receiving monthly injections.

406. First, I note that the applicants admit that the VIEW1/2 every-8-week dosing regimen falls squarely within the scope of the claims of the '338 patent. This is the same regimen that was disclosed and disseminated before the filing date of the '338 patent, as I discuss at length above. (*See, e.g.*, Ex.1006, Dixon; Ex.1007, Adis; Ex.1013, Regeneron (8-May-2008); Ex.1014, NCT-795; Ex.1015, NCT-377; and the detailed discussion above of the disclosures of the VIEW1 and/or VIEW2 studies in each of these references).

407. Second, in my experience and that a person of ordinary skill in the art, as of 2010, monthly dosing was not the regimen typically used in standard clinical practice. By 2010, as I discuss above, the discomfort, inconvenience, and risks

experienced by patients [24] receiving intravitreal injections led most in the ophthalmology community to reduce the frequency of administration whenever possible. For example, my typical practice, together with the typical practice of the skilled person, when administering intravitreal anti-VEGF agents, involved the administration of a few loading dose injections, typically spaced a month apart. Thereafter, we would usually bring back patients for monthly visits to assess visual acuity and retinal swelling and only administer injections on those monthly visits where there appeared to be loss in visual acuity or increase in retinal swelling.

408. Third, in addition to that approach being common practice among practicing ophthalmologists and persons of ordinary skill in the art, it was the trend among industry leaders at the time as well. For example, after Genentech's monthly dosing studies of ranibizumab (MARINA and ANCHOR), they embarked on a clinical trial campaign directed to investigating dosing regimens with less frequent injections. For example, Genentech began, as early as 2007, to assess dosing

[24] This is a point on which I agree with Regeneron. (*See, e.g.*, Ex.1017, '338 FH, 9/11/2015 Remarks at 6 (stating that once-per-month injections are "(1) expensive; (2) painful to the patient; (3) inconvenient for the patient as well as the patient's family; (4) psychologically and physically traumatic to the patient; and (5) subjects the patient to potential adverse effects such as infection with each treatment event")).

regimens that included three monthly loading doses, followed by a period of individualized (i.e., as-needed/PRN) dosing, or fixed quarterly dosing. (*See, e.g.*, SUSTAIN (PRN dosing after 3 monthly loading doses); EXCITE (quarterly dosing after 3 monthly loading doses); PrONTO (PRN dosing after three monthly loading doses); SAILOR (PRN dosing after 3 monthly loading doses); and PIER (quarterly dosing after 3 monthly loading doses); Ex.1030, Mitchell, 6-7 (providing a summary of each of the above studies). From these studies, the authors concluded that while fixed quarterly dosing may be inferior to monthly dosing (though still more effective than placebo), the individualized regimens could achieve outcomes similar to that observed for monthly dosing. (*See, e.g.*, Ex.1030, Mitchell, 6-7).

409. Fourth, in my opinion, the results reported in Heier-2012, and which Regeneron relies upon in their remarks to the Patent Office, were not unexpected in light of the positive results reported for Regeneron's Phase 2 study of VEGF Trap-Eye in AMD. In that study, Regeneron used two treatment arms: (1) quarterly dosing for 12 weeks followed by PRN dosing; and (2) fixed monthly dosing for 12 weeks followed by PRN dosing. The latter group, when dosed with 2 mg, achieved on average a gain in visual acuity of 9 letters and a mean decrease in retinal thickness of 143 μm. (Ex.1006, Dixon, 1576). The results of the VIEW studies as reported in Heier-2012 included a mean gain in visual acuity of 7.9 letters and a mean decrease in retinal thickness of 128.5 μm. (Ex.1019, Heier-2012, 2542). In my opinion, these

results from the VIEW studies would not have been surprising or unexpected in light of the results reported for the Phase 2 CLEAR-IT-2 study. This is confirmed by Regeneron itself, who stated that the Phase 2 studies "indicat[e] that an 8-week dosing schedule may be feasible." (Ex.1036, Regeneron (28-April-2008), 1; *see also id.* ("Due to its high affinity for all isoforms of VEGF-A and PIGF . . . as well as its long residence time in the eye, it is anticipated that VEGF Trap-Eye may be able to be dosed at a frequency less than once monthly . . . . These emerging Phase 2 clinical data seem to support the concept of durability of VEGF Trap-Eye.")).

410. Lastly, I disagree that there were "an infinite number of different treatment protocols" when deciding on dosing regimens to investigate. Given the concern (shared by Regeneron) over the frequency of monthly dosing, monthly injections would have been avoided if possible, and anything more frequent than monthly would not have been reasonably considered by skilled artisans. The ranibizumab studies were showing that quarterly (i.e., every 3 month) regimens had trouble maintaining gains in visual acuity in some cases. As a result, if monthly was disfavored, and every 3 months was seen as less effective in some cases, a person of ordinary skill in the art naturally would have considered dosing every 2 months, which is precisely what Regeneron used in their VIEW studies. Regarding the number of loading doses, the trend in the industry was that three monthly loading doses could achieve substantial gains in visual acuity and decreases in retinal

thickness. (*See, e.g.*, Ex.1030, Mitchell, 6-7). Therefore, in my opinion, there was nothing new or non-obvious about the regimen Regeneron settled upon, and its claims to the Patent Office that there were "an infinite number of different treatment protocols" was not true given the state of the art and the practical realities of treating AMD patients with intravitreal injections.

411. In sum, a person of ordinary skill in the art would have expected the claimed dosing regimen to work based on the positive Phase 1 and Phase 2 trial results. Thus, it would have been expected that following the dosing regimen set forth in the '338 patent would have led to at least some level of "treating" an angiogenic eye disorder. The dosing regimens claimed in the '338 patent were not unexpected in my opinion, and the arguments presented by the patentees to the Patent Office do not support their claims of unexpected results.

412. Moreover, to the extent that the inventors would claim an unmet and long-felt need was fulfilled with the '338 patent, in my opinion, this is not the case. While I agree that there may have been a need for VEGF antagonists prior to their development, in my opinion, once those antagonists were developed, and especially after the dosing knowledge was gleaned from ranibizumab and the early trials of VEGF Trap-Eye, arriving at a dosing regimen that extended the administration beyond once-monthly was obvious, had already been noted in the literature and put into actual practice, and served no "unmet" need. This is particularly so given that

the dosing regimen was already publicly disclosed as early as 2009, meaning that any "unmet" need had already been met by Regeneron's own public disclosures well before the '338 patent was filed.

413. I further understand that there may be commercial products that the patent owner may attempt to assert are encompassed by the claims, one potential example being Eylea®. However, in my opinion, none of the claimed dosing regimens covered by the '338 patent that I have discussed above are responsible for any commercial success of Eylea®, and I have seen no evidence that the commercial success of Eylea® has been due to anything outside of marketing and promotional activities or regulatory exclusivity. To the extent that Regeneron or their technical expert raise secondary considerations arguments, I reserve the right to address and respond to those arguments in a future declaration.

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

Dated: 5/4/21

By: _____
Dr. Thomas A. Albini