

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MYLAN PHARMACEUTICALS INC.,
Petitioner,

v.

REGENERON PHARMACEUTICALS, INC.,
Patent Owner.

Inter Partes Review No.: IPR2022-01226

U.S. Patent No. 10,888,601 B2
Filed: April 29, 2019
Issued: January 12, 2021
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. 10,888,601 B2**

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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 opinions regarding the patentability of claims 1-9, 34-39, 41-43, and 45 of U.S. Patent No. 10,888,601 (Ex.1001, “the ’601 patent”), which I understand is assigned to Regeneron Pharmaceuticals, Inc. (“Regeneron”). I further understand that Petitioner is petitioning for *inter partes* review of the ’601 patent, and is requesting that the United States Patent and Trademark Office cancel claims 1-9, 34-39, 41-43, and 45 of the ’601 patent as unpatentable. My opinions in this expert declaration support Petitioner’s request for *inter partes* review of the ’601 patent and the cancellation of claims 1-9, 34-39, 41-43, and 45 (the “challenged claims”).

2. I am the same Dr. Albini who submitted declarations in support of Mylan in connection with the currently-pending *inter partes* reviews of U.S. Patent Nos. 9,669,069 B2 (“the ’069 patent”) and 9,254,338 B2 (“the ’338 patent”), instituted as IPR2021-00880 and IPR2021-00881, respectively. I understand that the ’069 and ’338 patents are related to the ’601 patent being challenged here.

I. QUALIFICATIONS AND BACKGROUND.

A. Education and Experience.

3. 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.

4. 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.

5. 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.

6. 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.

7. 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.

8. 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.

9. 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.

10. 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.

11. 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.

12. 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.

13. I have been retained by Petitioner as an expert in this matter to provide my various opinions regarding the '601 patent. I receive compensation 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 the named inventor on the '601 patent.

II. LEGAL STANDARDS.

14. 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:

15. **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.

16. **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 at the time of the invention, 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.

17. **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.

18. **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.

19. I have further been instructed that one cannot use the challenged patent itself (here, the '601 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.

20. 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.

21. 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.

22. 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.

23. 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.

24. 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.

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

26. **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 '601 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.

27. 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.

28. 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.

29. 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.¹

¹ In the context of the related '338 patent, the Board preliminarily found that "Petitioner's definition of one of ordinary skill in the art is reasonable and consistent

IV. SUMMARY OF OPINIONS.

30. It is my opinion that Dixon anticipates the challenged claims of the '601 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).

31. It is my opinion that Adis anticipates the challenged claims of the '601 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).

32. It is my opinion that Regeneron's May 2008 Press Release ("Regeneron (8-May-2008)") anticipates the challenged claims of the '601 patent through the reference's disclosure of the dosing regimen used by Regeneron in its Phase 3 VIEW2 AMD trial (3 monthly doses of 2 mg, followed by 2 mg every eight weeks).

33. It is my opinion that Regeneron's publicly accessible clinicaltrials.gov submission NCT-795 anticipates the challenged claims of the '601 patent through

with the '338 patent and the prior art of record." (IPR2021-00881, Paper 21, 16). In my opinion, this definition of one of ordinary skill in the art is likewise consistent with the '601 patent (which shares a specification with the related '338 patent) and the prior art of record (which overlaps for both the '338 patent and the '601 patents).

its disclosure of the dosing regimen used by Regeneron in its Phase 3 VIEW1 and VIEW2 AMD trials (3 monthly doses of 2 mg, followed by 2 mg every eight weeks).

34. It is my opinion that the public disclosures of Regeneron's VIEW1/VIEW2 trials make the challenged claims obvious, because they expressly or inherently 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 the '173 patent), 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.

35. It is my opinion that one of ordinary skill in the art would have been aware of Dixon and would have been aware of Rosenfeld-2006. These references were germane to the relevant field; accordingly, a skilled artisan would have been motivated to combine the teachings of Dixon with Rosenfeld-2006, and would have considered challenged claims 9 and 36 of the '601 patent obvious in light of the combination of Dixon and Rosenfeld-2006.

36. It is my opinion that one of ordinary skill in the art would have been aware of several available guidelines for the administration of intravitreal injections, including Heimann-2007, and would have been motivated to combine the teachings

of Dixon with Heimann-2007. It is also my opinion that the skilled artisan would have considered challenged claims 9 and 36 of the '601 patent obvious in light of the combination of Dixon and Heimann-2007.

37. It is also my opinion that there are no “secondary considerations” that would support the patentability of the challenged claims of the '601 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 '601 patent claims. Second, in the context of obviousness, it is my opinion that there is nothing surprising or unexpected about the VIEW1/VIEW 2 results, especially given the positive and promising results publicly reported for the Phase 2 trial and public disclosure of the Phase 3 dosing regimen. Nor is there any support, in my opinion, for a finding of long-felt need or commercial success, for the reasons I discuss below.

V. THE '601 PATENT (Ex.1001).

38. I have read the '601 patent, which is titled “Use of a VEGF Antagonist to Treat Angiogenic Eye Disorders,” including the issued claims, specification and prosecution history. The '601 patent pertains to dosing regimens for treating angiogenic eye disorders, including AMD, in patients, via administering approximately 2 mg aflibercept every four weeks for the first 3 months, followed by continuing to administer approximately 2 mg aflibercept once every 8 weeks or once

every 2 months. (*See* Ex.1001, '601 patent, 21:41-46 (claim 1)). Dependent claims of the '601 patent specify, *inter alia*: the angiogenic eye disorder is neovascular (wet) AMD (*e.g., id.*, 21:47-48 (claim 2)); efficacy limitations based on the Best Corrected Visual Acuity (BCVA) score (*e.g., id.*, 21:49-51 (claim 3)); and patients not meeting any of two exclusion criteria: (i) active intraocular inflammation and (ii) active ocular or periocular infection (*e.g., id.*, 21:65-67 (claim 9)). I am very familiar with the state of the art at the time the first application for the '601 patent was filed, which I have been asked to assume is January 13, 2011.² The '601 patent lists George D. Yancopoulos as the sole inventor.

² I understand the following from the cover page of the '601 patent: (i) Application No. 16/397,267 (“the '267 application”) issued as the '601 patent on or about January 12, 2021; (ii) the '267 application was filed April 29, 2019; (iii) the '267 application was filed as a “continuation” of application No. 16/159,282, which is a “continuation” of application No. 15/471,506, now U.S. Patent No. 10,130,691, which is a “continuation” of application No. 14/972,560, now the '069 patent, which is a “continuation” of application No. 13/940,370, now the '338 patent, which is a “continuation-in-part” of application No. PCT/US2012/020855, filed on January 11, 2012; and (iv) the '601 patent lists three “provisional” applications filed,

39. I have reviewed the '601 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 1-9, 34-39, 41-43, and 45.

40. Claims 1 and 34 are the only independent challenged claims and read as follows:

1. A method for treating age related macular degeneration in a patient in need thereof, comprising intravitreally administering, to said patient, an effective amount of aflibercept which is 2 mg approximately every 4 weeks for the first 3 months, followed by 2 mg approximately once every 8 weeks or once every 2 months.

* * *

respectively, on (a) January 13, 2011; (b) January 21, 2011; and (c) November 21, 2011, as "Related U.S. Application Data." (*See* Ex.1001, '601 patent at Cover). I have been asked to assume that the priority date of the '601 patent is January 13, 2011. I have formed no opinion regarding the merit of the '601 patent's claim to that date.

34. A method for treating an angiogenic eye disorder in a patient in need thereof, said method comprising administering to the patient an effective sequential dosing regimen of a single initial dose of a VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonist; wherein each secondary dose is administered 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered 8 weeks after the immediately preceding dose; wherein the VEGF antagonist is a receptor-based chimeric molecule comprising an immunoglobulin-like (Ig) domain 2 of a first VEGF receptor which is VEGFR1 and an Ig domain 3 of a second VEGF receptor which is VEGFR2, and a multimerizing component.

(Ex.1001, '601 patent, 21:41-46 (claim 1); *id.*, 24:4-19 (claim 34)).

41. Challenged claims 2-9 each depend, either directly or indirectly, from claim 1.

42. Challenged claims 35-39, 41-43, and 45 each depend, either directly or indirectly, from claim 34.

A. Claim Construction.

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

1. “Initial Dose,” “Secondary Dose,” and “Tertiary Dose.”

44. Independent claim 34 recites a dosing regimen via administering a single “initial dose” of a VEGF antagonist (VEGF Trap-Eye or aflibercept), followed by one or more “secondary doses” administered 4 weeks after the

immediately preceding dose, followed by one or more “tertiary doses” administered 8 weeks after the immediately preceding dose. (*See* Ex.1001, ’601 patent, 24:4-19 (Claim 34)).

45. 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 ’601 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, ’601 patent, 3:42-49). The ’601 patent further states that “[t]he initial, secondary, and tertiary doses...will generally differ from one another in terms of frequency of administration.” (*Id.*, 3:49-52). For example, the ’601 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.*, 3:57-62). The ’601 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.*, 3:62-67).

46. In my opinion, the specification is clear and unmistakable in its definition of “initial dose,” “secondary doses,” and “tertiary doses” as the temporal sequence of administration of the VEGF antagonist. (Ex.1001, ’601 patent, 3:42-44). I believe the person of ordinary skill in the art (“POSA”) would recognize that the specification defines “initial dose” as “the dose which is administered at the beginning of the treatment regimen (also referred to as the ‘baseline dose’); the “secondary doses” as “the doses which are administered after the initial dose”; and the “tertiary doses” as “the doses which are administered after the secondary doses.” (Ex.1001, ’601 patent, 3:44-49). In my opinion, the POSA would be able to apply these definitions to the patent claims with no further construction or guidance, and these are the meanings I have applied to these terms in formulating my opinions.³

³ My opinions in this regard are consistent with the Board’s preliminary findings regarding the same claim terms in the context of the related ’338 patent. (*See* IPR2021-00881, Paper 21, 23 (“Based on those express definitions, we do not find cause to construe the terms differently.”)). In so finding, the Board rejected Regeneron’s arguments to the contrary: “In particular, we do not find that the

2. “A method for treating age related macular degeneration in a patient in need thereof” and “A method for treating an angiogenic eye disorder in a patient in need thereof.”

47. Independent challenged claims 1 and 34 each recite a “method for treating” preamble: “[a] method for treating age related macular degeneration in a patient in need thereof” (claim 1), and “[a] method for treating an angiogenic eye disorder in a patient in need thereof” (claim 34). 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.⁴ In my opinion, if the Board finds the “method of treating”

Specification requires the ‘tertiary doses’ to maintain any efficacy gain achieved after the initial and secondary doses, or that the term ‘connotes a specific level of efficacy’ for the reasons urged by Patent Owner.” (*Id.*). As the ’601 patent shares the same specification as the ’338 patent, Regeneron’s arguments as to any degree of maintained efficacy similarly fail, and “tertiary doses” means “the doses which are administered after the secondary doses.” (*Id.*; Ex.1001, ’601 patent, 3:48-49).

⁴ I reviewed the Board’s institution decision in co-pending IPR2021-00881, Paper 21, regarding the related ’338 patent, which I understand claims priority to the same application and shares the same specification as the ’601 patent. Like the Challenged

preamble phrases to be limiting, a person of ordinary skill in the art would apply a plain and customary meaning to these phrases, which would include administering a therapeutic agent to a patient and would not require any particular level of efficacy. I hold this opinion for at least the following reasons.

48. First, I have analyzed the '601 patent specification and claims and have not seen any parameters set forth in the Challenged Claims or any guidance from the claims themselves that would inform a POSA as to some specialized meaning for

Claims of the '601 patent, the '338 patent claims are similarly directed to “a method for treating” an angiogenic eye disorder in a patient. (*Compare* Ex.1001, '601 patent at Claims, *with* Ex.1071, '338 patent at Claims). With respect to the '338 patent, I understand that the Board preliminarily found that the “method for treating” preamble does not require “the recited method steps to provide an *effective* treatment.” (IPR2021-00881, Paper 21, 21). I agree with the Board that the term “method for treating an angiogenic eye disorder in a patient” does not require any particular level of efficacy in the context of the '338 patent. As the '601 patent shares the same specification as the '338 patent, it is my opinion that the same construction should be applied for the '601 patent—i.e., the “method for treating” preamble does not require any particular level of efficacy.

the “method for treating” preamble claim term. Given the lack of any express definition for the “method of treating” preamble term in the ’601 patent specification, it is my opinion that a POSA would rely on the specification’s disclosure that “beneficial therapeutic effects *can be* achieved in patients suffering from angiogenic eye disorders by administering a VEGF antagonist”—not that such effects *must be* achieved. (Ex.1001, ’601 patent, 2:11-17 (emphasis added)).⁵ According to the patent’s disclosure, a “VEGF antagonist administered to the patient in each dose is, *in most cases* [i.e., not all], a therapeutically effective amount.” (Ex.1001, ’601 patent, 6:58-60 (emphasis added)). In addition, the ’601 patent specification provides FIG. 1 as an “exemplary dosing regimen of the present invention,” (Ex.1001, ’601 patent, 2:63-64), which Figure focuses on the temporal sequence of administration of the VEGF antagonist, not efficacy outcomes.

49. I also note that the ’601 patent specification discloses multiple methods that do not achieve a so-called “high level of efficacy,” which suggests that no particular level of efficacy is required by any of the covered methods. The ’601 patent Examples, which demonstrate a large variety of effective (and ineffective)

⁵ I understand that my opinion in this regard is consistent with what the Board found in the context of the related ’338 patent. (See IPR2021-00881, Paper 21, 20-21).

treatments⁶, would further support the POSA's conclusion that the Challenged Claims do not require any particular level of efficacy.

50. Second, to the extent Regeneron (or its experts) argues that the “method for treating” preamble term must be construed as one that is non-inferior to the standard of care for that particular angiogenic eye disorder at the time of patent filing, I disagree. The '601 patent specification does not provide the POSA any guidance as to what level of efficacy would be considered “non-inferior to the standard of care.” This is particularly true considering that the standard of care is apparently “specific to the angiogenic eye disorder that is being treated,” as well as the specific timeframe, patient population, and physician. (*See* Ex.1016, IPR2021-00881, Ex.1109, 162:9-16 (agreeing there's potentially a different “standard of care” for each disorder), 160:20-161:3; *compare* Ex.1019, IPR2021-00881 Ex.2051, ¶68 with Ex.1068, 1 (describing “focal laser treatment” as “the current [September 2009]

⁶ Notably, Regeneron has publicly conceded that certain subpopulations of patients do not respond to the claimed regimen and thus do not receive a “method for treating” even when administered doses according to the claimed regimen. (IPR2021-00881, Paper 41, 44-45). Thus, Regeneron's own statements further support that the claimed regimens result in both effective, and ineffective, treatments.

standard of care in DME”); Ex.1016, IPR2021-00881 Ex.1109, 100:5-18 (“it depends on what the standard of care was at that time.”), 164:13-18 (same); Ex.1022, IPR2021-00881, Ex.1110, 110:2-22 (“The standard of care ... really depended on what access the patients had.”), *id.* (“[Lucentis or off-label Avastin] is the standard of care, ***if you could get it***”) (emphasis added)), 143:21-144:10 (“standard of care” in clinical practice has been “treat and extend” since 2007)).

51. Moreover, the skilled person would have understood at the relevant time that non-inferiority is a population-based clinical trial statistical determination, and a POSA would not use a *population-based* statistical determination such as “non-inferior to the standard of care” to measure the efficacy of a given treatment for a *single patient*. As such, in my opinion, the ’601 patent provides a skilled person with no guidance or clarity as to how to ascertain what level of efficacy would constitute “non-inferior to the standard of care” for the claimed person’s treatment.

52. I note that the ’601 patent specification defines the term “efficacy.” In my opinion, to the extent the preamble “method of treatment” phrases are construed to require some particular level of efficacy, a POSA would apply the definition of “efficacy” expressly provided in the ’601 patent specification (which is consistent with a POSA’s knowledge, skill and experience):

Treatment Population and Efficacy

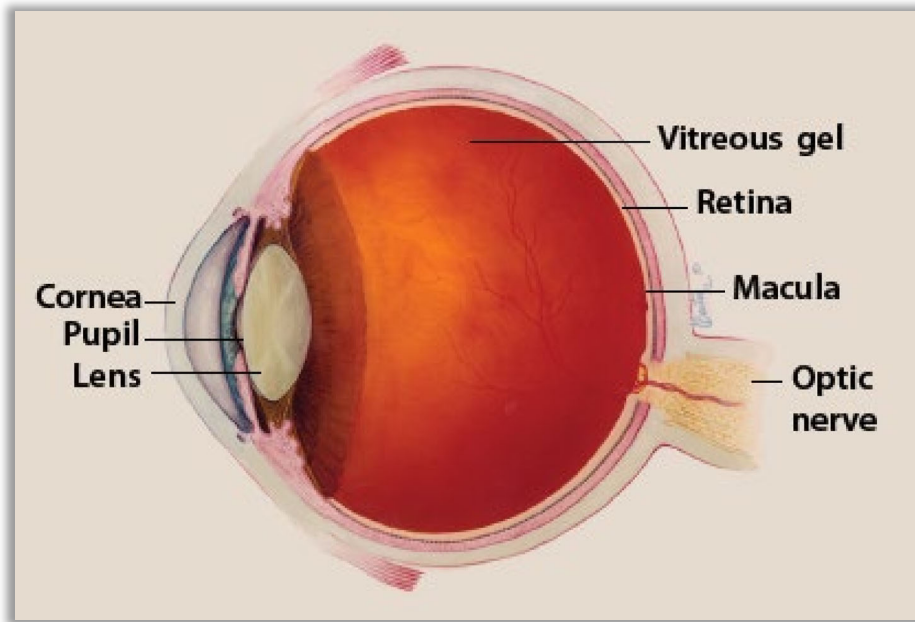
The methods of the present invention are useful for treating angiogenic eye disorders in patients that have been diagnosed with or are at risk of being afflicted with an angiogenic eye disorder. Generally, the methods of the present invention demonstrate efficacy within 104 weeks of the initiation of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

(Ex.1001, '601 patent, 7:26-43). Accordingly, while it is my opinion that claims 1 and 34 do not require any particular level of efficacy, if a determination is made that they do, then in my opinion, a POSA would look to the discussion of efficacy in the specification and apply the definition provided therein—i.e., efficacy within 104 weeks from initiation, and that the patients exhibit a loss of 15 or fewer letters on the ETDRS visual acuity chart.

VI. BACKGROUND.

A. Vitreoretinal Disorders.

53. 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.

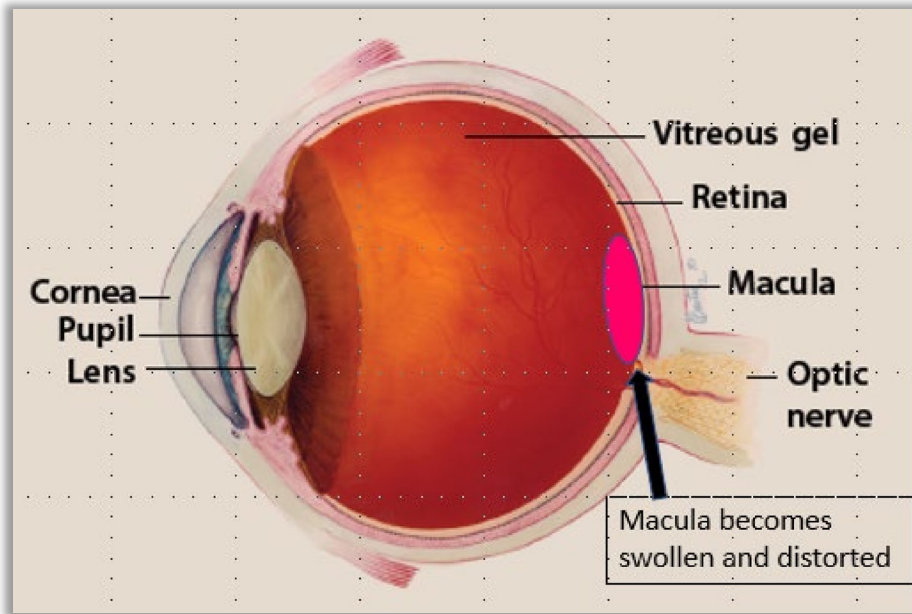
54. Vitreoretinal disorders such as AMD and diabetic retinopathy (DR) are the leading causes of visual impairment in developed countries, and the prevalence

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).

55. 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).

56. AMD can be classified as either “dry” (nonexudative) or “wet” (exudative). (*See, e.g.,* Ex.1012, 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.1012, 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.

57. 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).

58. 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).

59. 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).

60. 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).

61. 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.

62. 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.1012, 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. (Ex.1046, Ferrara-2005, 971).

63. 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).

64. 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).

65. 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.

66. 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.

67. It was widely known to practicing ophthalmologists that bevacizumab and ranibizumab were different active pharmaceutical ingredients. While they both were known to bind to VEGF, it also was well known that they possessed different molecular structures. (*See, e.g.,* Ex.1084, IPR2021-00881 Ex.2055, 862-66).

68. The LUCENTIS® prescribing information available in 2006 also suggested a regimen of less frequent dosing following four monthly intravitreal

injections. (Ex.1048, Lucentis, 1). Less frequent dosing was a preferred option due to the nature of intravitreal injections. (See, e.g., Ex.1034, Fung, 581-83 (“A decrease in the number of injections would reduce the potential risk of injection-related complications, and an increase in the injection-free interval would reduce the burden of frequent follow-up evaluations.”)).

69. 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.

70. In addition, as discussed further below, potential complications that can occur from intravitreal injections include subconjunctival hemorrhage, infection, and inflammation. (Ex.1006, Dixon, 1577 (each intravitreal injection “subjects patients to risks of cataract, intraocular inflammation, retinal detachment, and endophthalmitis”)). Risk of infection occurs with intravitreal injections because naturally occurring surface bacteria (typically *Propionibacterium* or *Staphylococcus*) can be carried into the eye via the syringe or through the puncture site created by the syringe. In the case of a pre-existing or current infection, there is greater risk due to the presence of pathogenic microorganisms. While the risk of infection is generally small, the consequences can be devastating. Endophthalmitis, for example, is a potentially serious infection of the ocular tissues, which, in some cases can lead to blindness. (Ex.1057, Jager-2004, 678 (endophthalmitis presenting

“the greatest likelihood for acute and irreversible vision loss”); Ex.1040, Heimann-2007, 69, 74-75 (identifying endophthalmitis as one of “the most serious side effects of intravitreal injections” and that “[o]ther important, potentially sight-threatening complications of injections are intraocular inflammation”)).

71. 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.

72. 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

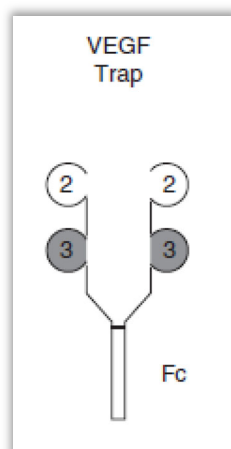
loading doses); EXCITE (quarterly dosing after 3 monthly loading doses); PrONTO (PRN dosing after three monthly loading doses); SAILOR (PRN dosing after 3 monthly loading doses); and PIER (quarterly dosing after 3 monthly loading doses)). PrONTO, in particular, showed that “flexible OCT-guided retreatment could sustain visual acuity gain with fewer injections” than monthly regimens. (Ex.1030, Mitchell, 6-7; *see, e.g.*, Ex.1035, Lalwani, 43-44 (“observations from the patients in the [ranibizumab] extension study served as the basis for investigating whether a variable-dosing OCT-guided regimen with ranibizumab could result in fewer injections and similar clinical outcomes when compared with the phase III regimen that used monthly injections”)). Indeed, PrONTO-style extended dosing regimens were widely adopted after the results were reported for that study. (Ex.1025, 1369 (“PrONTO-style dosing has become popular.”)).

73. 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; Ex.1090, IPR2-21-00881 Ex.2103, 2-3).

74. 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.1012, 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.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.

75. VEGF Trap-Eye is a VEGF blocker developed by Regeneron. Unlike the VEGF blocker ranibizumab, which is a humanized monoclonal antibody fragment, 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.1012, 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 (PlGF).”)).

76. 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).

77. 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).

78. 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).

79. 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.*).

80. 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. (*See, e.g.,* Ex.1018, Heier-2012, 2539 (“The binding affinity of intravitreal aflibercept to VEGF is substantially greater than that of bevacizumab or ranibizumab” and the “greater affinity could translate into...a substantially longer duration of action in the eye, allowing for less frequent dosing, as supported by early clinical trials.”)).

81. 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).

82. 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; *see also* Ex.1091, Rudge-2008, 417-18).

83. It was common knowledge among ophthalmologists as of 2010 that Regeneron’s anti-VEGF agent was aflibercept, and that VEGF Trap-Eye was another term for this agent. This was clear from a review of the literature directed to ophthalmologists at the time, including Dixon, the authors of which noted that for the treatment of AMD “[o]ne promising new drug is aflibercept (VEGF Trap-Eye).” (Ex.1006, Dixon, 1573).

84. The identity of VEGF Trap-Eye (aflibercept)—including the fact that the terms VEGF Trap-Eye and aflibercept referred to the same agent—was further confirmed by Regeneron’s prior art publications and patents. (*See, e.g.*, Ex.1008, ’173 patent, 1:48-52 (Regeneron prior art patent disclosing that “[i]n a specific and

preferred embodiment, the VEGF trap is VEGFR1R2-FcΔC1(a) (also termed VEGF trap_{R1R2}) comprising the nucleotide sequence set forth in SEQ ID NO: 1 and the amino acid sequence set forth in SEQ ID NO: 2”); Ex.1004, Holash, 11397 (“Herein we describe the engineering of an anti-VEGF agent, termed VEGF-Trap_{R1R2}.”); Ex.1026, Rudge-2007, 18363, 18370 (discussing VEGF Trap, including “aflibercept” as a keyword, and citing back to Holash (ref. 20))). POSAs prior to 2011 understood VEGF Trap-Eye to refer to the same molecule disclosed in Holash, and understood it to be the same molecule as aflibercept. Heier-2009(a) included a description of the pharmacokinetics of VEGF Trap-Eye and for that discussion cited back to the data presented in Holash 2002 for VEGF Trap_{R1R2}. (Ex.1028, IPR2021-00881 Ex.2080, 2, 5). Other articles using the term aflibercept refer back to Holash 2002 and its description of VEGF Trap_{R1R2}. (Ex.1029, Gomez-Manzano, 940, 945 (“a new anti-VEGF agent, VEGF Trap/aflibercept (henceforth referred to as VEGF Trap), has been developed by incorporating domains of both VEGF receptor 1 (VEGFR1) and VEGFR-2 fused to the constant region of human immunoglobulin G1,” and citing Holash))).

85. In view of these disclosures, a POSA would have understood the VEGF Trap_{R1R2} nomenclature to reference a single molecule, which a POSA would have understood was the single agent that Regeneron had in clinical trials and which Regeneron was calling both aflibercept and VEGF Trap-Eye.

86. Dixon reported that VEGF Trap-Eye and aflibercept (the oncology product) have the same molecular structure, but also reported that there are differences between their formulations. (Ex.1006, Dixon, 1575 (“VEGF Trap-Eye and aflibercept (the oncology product) have the same molecular structure, but there are substantial differences between the preparation of the purified drug product and their formulations.”)). Regeneron’s public statements were consistent with this understanding, and expressly represented that the only differences between Regeneron’s oncology and ophthalmology products were the purification and formulation steps. (Ex.1021, 2009 10-Q, 19 (“VEGF Trap-Eye is a specially purified and formulated form of VEGF Trap for use in intraocular applications.”); Ex.1003, Gerritsen ¶¶ 91-100; Ex.1041, Regeneron (26-February-2009), 1; Ex.1003, Gerritsen ¶¶ 44-47, 72-73, 76-78). No mention is made of any changes or alterations to the active pharmaceutical ingredient.

E. Regeneron’s Press Releases and Clinical Trials.

87. In the mid-2000’s, Regeneron began reporting on its clinical trials of VEGF Trap-Eye in AMD patients. Regeneron press releases, and other publications and materials, disclosed that VEGF Trap-Eye had completed Phase 1 and 2 clinical trials, and was in Phase 3 clinical trials by 2009.

88. 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) ⁷	Monthly through week 8, followed by every 8 weeks

⁷ The VIEW1 and VIEW2 trials were discussed in numerous Regeneron press releases between August 2007 and the time the '601 patent priority applications were filed in 2011. Regeneron (8-May-2008) is provided here as an illustrative example.

Trial	Name	Reference(s)	Dosing Regimen
			(0.5 and 2 mg doses)

89. 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:

Trial⁸	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

⁸ A summary of these trials also can be found in Ex.1030, Mitchell.

90. In connection with Regeneron's VEGF Trap clinical program, Regeneron issued a series of press releases, beginning around 2007, disclosing, in 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)	<u>Phase 2 trial</u> : 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; Ex.1003, Gerritsen ¶¶ 44-47, 64-65, 76-78).
2 Aug. 2007 (Ex.1054)	<u>Phase 2 trial</u> : 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; Ex.1003, Gerritsen ¶¶ 44-47, 66, 76-78). <u>Phase 3 trial</u> : VIEW1 trial initiated, testing the safety and efficacy of VEGF Trap-Eye dosed at either <u>4 week intervals</u> (0.5 and 2.0 mg) or <u>8 week intervals</u> (2.0 mg). (<i>Id.</i>).
28 Apr. 2008 (Ex.1012)	<u>Phase 2 trial</u> : Previously reported gains in visual acuity and decreases in retinal thickness for week 12 were maintained out

Press Release	Representative Disclosure
	to week 32 when using a PRN (i.e., <i>pro re nata</i> or as-needed) dosing schedule after week 12. (Ex.1012, Regeneron (28-April-2008), 1; Ex.1003, Gerritsen ¶¶ 44-47, 67-69, 76-78). <u>Phase 3 trials (VIEW1 & 2):</u> 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.” (<i>Id.</i>, 2).
8 May 2008 (Ex.1013)⁹	<u>Phase 3 trials (VIEW1 & 2):</u> 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; Ex.1003, Gerritsen ¶¶ 44-55, 76-78).
19 Aug. 2008 (Ex.1089)	<u>Phase 2 trial:</u> 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

⁹ The same information was reported by Regeneron’s partner, Bayer, in its own press release, dated the same day. (*See, e.g.*, Ex.1032, Bayer (8-May-2008)).

Press Release	Representative Disclosure
	after one year. (Ex.1089, Regeneron (19-August-2008), 1; Ex.1003, Gerritsen ¶¶ 44-47, 70-71, 76-78). <u>Phase 3 trials (VIEW1 & 2):</u> 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. (<i>Id.</i>).
28 Sept. 2008 (Ex.1056)	<u>Phase 2 trial:</u> 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.¹⁰ (Ex.1056, Regeneron (28-September-2008), 1; Ex.1003, Gerritsen ¶¶ 44-47, 56-63, 76-78). <u>Phase 3 trials (VIEW1 & 2):</u> Studies involve “2.0 mg [VEGF Trap-Eye] every 8 weeks (following three monthly doses)”—

¹⁰ 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.

Press Release	Representative Disclosure
	i.e., doses at weeks 0, 4, and 8, followed by doses at weeks 16, 24, 32, 40, and 48. ¹¹ (<i>Id.</i> , 2).
14 Sep. 2009 (Ex.1068)	<u>Phase 3 trials (VIEW1 & 2)</u> : 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; Ex.1003, Gerritsen ¶¶ 44-47, 74-75, 76-78).

F. Risks Associated with Intravitreal Injections.

91. As noted above, it was well understood by those of ordinary skill in the art well before January 2011 that intravitreal administration could be associated with

¹¹ The Phase 3 VIEW1 and VIEW2 studies reported in the above disclosures appear to correspond to the Phase 3 study reported in the '601 patent at Example 4. (*Compare* Ex.1056, Regeneron (28-September-2008), 2, *with* Ex.1001, '601 patent, 9:21 – 14:5 (Example 4)).

serious side effects if proper, aseptic technique is not adhered to. (*See, e.g.*, Ex.1006, Dixon, 1577 (“Each injection subjects patients to risks of cataract, intraocular inflammation, retinal detachment and endophthalmitis.”); Ex.1040, Heimann-2007, 67 (reporting that while adverse events are rare, “the rate can increase significantly if certain standards for intraocular interventions are not followed”); *see also* Ex.1018, Heier-2012, 2537 (recognizing the “risk of rare but serious adverse events resulting from the intravitreal procedure”)). Endophthalmitis in particular, was a significant concern amongst POSAs, with it being one of the conditions having “the greatest likelihood for acute and irreversible vision loss.” (Ex.1057, Jager-2004, 678; *see also* Ex.1040, Heimann-2007, 67, 76 (“[e]ndophthalmitis is the most feared complication of intravitreal injections” due to its “potentially devastating consequences”); Ex.1057, Jager-2004, 686 (“Endophthalmitis manifests as severe inflammation usually after ocular trauma or surgery or in the setting of a known endogenous source for infection”)).

92. In addition to the widely-known side effects and risks associated with intravitreal injections, numerous references at the relevant time reported on the existence of “[s]everal guidelines on the technique for intravitreal injections,” instructing that “[s]trict adherence to these guidelines is advisable.” (Ex.1040, Heimann-2007, 67; *see also id.*, 76 (emphasizing “the importance of appropriate hygiene standards and techniques for intraocular injections,” and advising that

“preparation of the ocular surface should aim to minimize the bacterial contamination during the injection”)).

93. Persons of ordinary skill in the art thus recognized, and reported on, the need to avoid injecting eyes that are infected or show signs of infection (i.e., inflammation). (*See, e.g.*, Ex.1040, Heimann-2007, 76 (“Patients with acute or chronic infections of the anterior segment and ocular adnexa, e.g., conjunctivitis or blepharitis, should first undergo treatment of the infectious diseases before proceeding to the injection.”); *id.*, 81 (noting that “concomitant eye diseases,” such as bacterial infections, “should be treated before performing an intravitreal injection,” and advising that pre-operation assessments be done “to rule out possible contraindications...that might complicate the injection”)). It was therefore well understood that some patients should be excluded from treatment administered via intravitreal injection, particularly those patients at increased risk for infection or inflammation. (*See* Ex.1040, Heimann-2007, 85 (“Exclude patients with suspected bacterial infections of the anterior segment (e.g. blepharitis, conjunctivitis))). The exclusion of patients with, for example, uveitis (a form of intraocular inflammation) from methods of treatment involving intraocular injections was known and published to POSAs before the earliest filing date of the ’601 patent. (*See, e.g.*, Ex.1025, Engelbert-2010, 1370).

94. In addition, a skilled artisan would have been aware of, and understood, the eligibility criteria for clinical studies of other intravitreally administered agents for the treatment of vitreoretinal disorders like AMD, including the seminal MARINA Phase 3 clinical trial assessing monthly LUCENTIS (ranibizumab) in the treatment of AMD. Rosenfeld-2006, for example, disclosed the “complete list of eligibility criteria” for the LUCENTIS (ranibizumab) Phase 3 MARINA trial, including several exclusion criteria directed to infection and inflammation, such as “[i]nfectious conjunctivitis, keratitis, scleritis, or endophthalmitis in either eye.” (Ex.1058, Rosenfeld-2006, Appx. 2-3). Likewise, one of ordinary skill in the art also would have consulted the publicly-available FDA approval package for LUCENTIS (ranibizumab), and found within the Medical Review (“MR”) a list of exclusion criteria that included the following “concurrent ocular conditions”:

2. Active intraocular inflammation (grade trace or above) in the study eye
3. Current vitreous hemorrhage in the study eye
4. History of rhegmatogenous retinal detachment or macular hole (Stage 3 or 4) in the study eye
5. History of idiopathic or autoimmune-associated uveitis in either eye
6. Infectious conjunctivitis, keratitis, scleritis, or endophthalmitis in either eye

(Ex.1037, Lucentis MR, 62 (Report of Rhea Lloyd, MD at 33) (emphasis added)).

95. Conjunctivitis, keratitis, scleritis, and endophthalmitis were well known by those of ordinary skill in the art to be ocular and/or periocular types of infections or inflammations, usually caused by bacteria, viruses, or fungi. (*See, e.g.,*

Ex.1040, Heimann-2007, 76, 85 (conjunctivitis is a “bacterial infection” of the “anterior segment and ocular adnexa” that must be treated prior to any injection); *id.*, 67 (endophthalmitis “is usually caused by bacterial contamination during or immediately after the injection”); *id.*, 77 (“The spectrum of cultured organism shows a greater variation of different bacterial species causing endophthalmitis.”); Ex.1082, Wilhelmus-1988, 105 (“Multiple microorganisms are capable of producing corneal infection,” such as keratitis, including bacteria, fungi and yeasts); Ex.1083, Wirbelauer-2006, 304 (“scleritis is a...painful localized inflammation of the sclera itself,” while “[k]eratitis is an inflammation of the cornea with many possible causes, including viruses such as herpes simplex and adenovirus [or] bacterial infection of a corneal ulcer”)).

96. Similar exclusion criteria were publicly reported in connection with the ranibizumab Phase 2b PrONTO clinical trial evaluating a variable dosing regimen guided by optical coherence tomography (OCT). For example, the 2009 publication, Lalwani, identified “major eligibility criteria for enrollment into the [Phase 2] PrONTO study” for LUCENTIS (ranibizumab), including exclusion of patients having a “[h]istory of idiopathic or autoimmune-associated uveitis in either eye.” (Ex.1035, Lalwani, 44; *see also* Ex.1034, Fung, 567 (same)). A POSA would have understood idiopathic uveitis to be inflammation. (*See, e.g.*, Ex.1060, Mueller, 66 (uveitis refers to “[i]nflammation of the uveal structures [and] can be a primary,

idiopathic process, or can occur secondary to other ophthalmologic infections or inflammatory conditions”)).

97. In turning to the body of literature relating to LUCENTIS (ranibizumab), the leading AMD treatment at the relevant time, one of ordinary skill in the art would have also observed that the LUCENTIS (ranibizumab) prescribing information disclosed that one of the contraindications is “ocular or periocular infections.” (Ex.1048, Lucentis, 1, 2). A POSA would have therefore been aware that the LUCENTIS (ranibizumab) clinical trials employed exclusion criteria that included, among other relevant criteria, active intraocular inflammation in the study eye; history of idiopathic or autoimmune-associated uveitis (inflammation) in either eye; and infectious conjunctivitis, keratitis, scleritis, or endophthalmitis in either eye, (Ex.1037, Lucentis MR, 62; *see also* Ex.1048, Lucentis, 2 (“LUCENTIS is contraindicated in patients with ocular or periocular infections”))), and that the same exclusion criteria were also employed in Regeneron’s VIEW studies for aflibercept (which included a monthly ranibizumab arm). Indeed, Regeneron designed its Phase 3 VIEW clinical trials for aflibercept (VEGF Trap) to include the same inclusion and exclusion criteria as those employed in the ranibizumab (LUCENTIS) trials to “maintain consistency with the pivotal trials for the reference drug ranibizumab, consistent with regulatory guidelines for noninferiority studies.” (Ex.1018, Heier-2012, 2540).

98. Furthermore, ocular or periocular infections in the 2 weeks prior to screening would have been understood by a POSA to be a condition that would contraindicate the use of an intravitreally administered agent or affect the interpretation of the results of administering an agent. As, such, a POSA would have understood the importance of performing a thorough pre-operative assessment of the patient before proceeding to the injection in order to avoid known complications associated with the intravitreal injection procedure. (*See* Ex.1040, Heimann-2007, 81 (advising preoperative assessment “to rule out possible contraindications or to detect conditions that might complicate the injection”)).

99. Well before 2011, it was also widely understood amongst POSAs that recent infection could negatively impact a clinical trial in a number of ways, including (1) increasing the risk of a serious adverse event (e.g., endophthalmitis) that puts a patient’s sight at risk and/or causes the patient to have to drop out of the study; (2) influencing baseline measures of visual acuity, retinal thickness, and/or other anatomic assessments; (3) influencing the subsequent post-administration measures of visual acuity, retinal thickness, and/or other anatomic assessments; (4) and influencing the pharmacokinetics of intravitreally administered drugs (Ex.1057, Jager 2004, 680).

100. Regarding (2) and (3) above, infections and inflammation have the ability to either mask or mimic some of the anatomic characteristics associated with

AMD, including swelling and the presence of fluid. (*See* Ex.1040, Heimann-2007, 75 (disclosing that sometimes “severe intraocular inflammatory reactions can be seen” following intravitreal injections, and noting that it can be “extremely difficult, to differentiate a sterile inflammatory process from an inflammatory reaction associated with infectious endophthalmitis”); Ex.1057, Jager-2004, 680 (noting that the “pharmacokinetic properties of compounds in the vitreous have been observed to change in the setting of inflammation or infection”)).

VII. SCOPE AND CONTENT OF THE PRIOR ART REFERENCES.

A. Dixon (Ex.1006).

101. Dixon was published in 2009. I understand that because Dixon published before the earliest priority date of the '601 patent,¹² it is prior art. I have reviewed Dixon. Dixon is an article summarizing the current state of AMD therapies 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

¹² As noted, I have been asked by counsel for Petitioner to use January 13, 2011, as the priority date of the '601 patent for purposes of my declaration. I understand that counsel for Petitioner reserves the right to challenge whether there is sufficient support in the priority document for Regeneron to properly rely on this date.

Dixon that, in my opinion, are relevant to the method(s) of treatment claimed in the '601 patent:

102. 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). Dixon discloses that in the context of AMD treatments, “[o]ne promising new drug is aflibercept (VEGF Trap-Eye).” (*Id.* (emphasis added)). Dixon discloses VEGF Trap-Eye/aflibercept as “a fusion protein that blocks all isoforms of VEGF-A and placental growth factors-1 and -2.” (*Id.* (emphasis added)).

103. Dixon discloses that “VEGF Trap-Eye and aflibercept (the oncology product) have the same molecular structure, but there are substantial differences between the preparation of the purified drug product and their formulations.” (Ex.1006, Dixon, 1575). While Dixon reports differences between their formulations, a POSA would have understood that the active ingredient, aflibercept, was the same in both presentations. (*See, e.g., id.* 1575 (discussing half-lives of aflibercept in both systemic (e.g., oncology) and intravitreal (e.g., eye disorder) contexts)).

104. Dixon teaches that VEGF Trap-Eye is an “anti-VEGF therapy, with Phase I and II trial data indicating safety, tolerability and efficacy for the treatment

of neovascular AMD.” (Ex.1006, Dixon, 1573). 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.*).

105. 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.¹³ (*Id.*). Regeneron’s VEGF

¹³ 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.

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).

106. Among other VEGF Trap related disclosures,¹⁴ 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);
- 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.*).

¹⁴ 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.

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]¹⁵ basis.” (*Id.*).

107. 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, ≥ 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

¹⁵ 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. My experience is consistent with what was reported in the prior art with respect to ranibizumab (LUCENTIS). (*See, e.g.*, Ex.1035, Lalwani, 43 (extension study “provided continued intravitreal injections of ranibizumab performed at the discretion of the investigator” based upon optical coherence tomography (OCT) to “monitor the resolution and recurrence of fluid in eyes as ranibizumab therapy was started and stopped”); Ex. 1073, Anderson, 274 (“current practice is to administer three doses [of ranibizumab] at four-week intervals, then to administer according to clinical need”)). 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).

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.*).

108. Dixon also reported on Regeneron’s Phase 3 AMD studies, named VIEW1 and VIEW2, which were intended to be non-inferiority studies 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.*).

109. 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)).

110. 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).

111. Further, Dixon expressly discloses the well-known risks associated with intravitreal injections, including that “[e]ach injection subjects patients to risks of cataract, intraocular inflammation, retinal detachment and endophthalmitis.”¹⁶ (Ex.1006, Dixon, 1577).

¹⁶ Endophthalmitis is a serious and potentially devastating bacterial or fungal infection known to be one of the more serious adverse side effects of intravitreal injections and other invasive ocular surgical procedures. (Ex.1040, Heimann-2007, 76 (“[i]nfectious endophthalmitis is the most feared complication of intravitreal injections”); *id.*, 77 (“[t]he most commonly isolated organism was *Staphylococcus aureus*” for endophthalmitis cases reported in connection with “the three major trials published on intravitreal anti-VEGF therapy”)).

B. Adis (Ex.1007).

112. The Adis reference was published in 2008. I understand because the Adis reference published before January 13, 2011, the earliest priority date of the '601 patent, it is prior art.

113. 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 IgG₁,” 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 (providing synonyms for aflibercept, including VEGF Trap-Eye)).

114. 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).

115. According to Adis, the VIEW1 and VIEW2 trials were initiated to evaluate the safety and efficacy of aflibercept administered as (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.”)).¹⁷

116. 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.*).

117. Adis also covers the Regeneron Phase 2 AMD trial results, reporting that at the 32-week point, “157 patients receiving either 0.5 or 2.0 mg followed by

¹⁷ Notably, Adis cites Regeneron and Bayer Press Releases from 2005 to 2008, retrieved online from the companies’ respective websites. (Ex.1007, Adis, 263-64, 268, Ref. Nos. 10-19). 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.

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.*). Retinal thickness was a primary indicator used in AMD treatment at the relevant time.

118. 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).

119. Regeneron (8-May-2008) is dated May 8, 2008. Because Regeneron (8-May-2008) published¹⁸ before January 13, 2011, the earliest priority date of the '601 patent, it is my understanding that Regeneron (8-May-2008) qualifies as prior art to the '601 patent.

¹⁸ 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. (Ex.1003, Gerritsen ¶¶ 44-55, 76-78).

120. 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 ’601 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.*).

121. 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.*).

122. 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).

123. 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.

124. [Clinicaltrials.gov](https://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.

125. 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.

126. 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

127. 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**.

128. 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.

129. 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 '601 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).¹⁹

2. NCT-795 discloses the VIEW1 regimen.

130. NCT-795 was originally submitted on July 31, 2007. (*See, e.g.*, Ex.1014, NCT-795, 1, 3; Ex.1003, Gerritsen ¶¶ 79-90). 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).

131. 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

¹⁹ Citations to the clinicaltrials.gov records for NCT00509795 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).

132. 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).

133. 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
<i>Drug: VEGF Trap-Eye</i> <i>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.</i>

(*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. '758 Patent (Ex.1010).

134. U.S. Patent No. 7,374,758 (“the ’758 patent”) 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 ’601 patent because it issued prior to January 13, 2011, the earliest possible priority date of the ’601 patent.

135. 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 potential utility of aflibercept in treating eye disorders such as AMD. (*Id.*, 15:50 – 16:6; *see also id.*, 3:5-29). The '758 patent discloses the VEGF fusion polypeptide (i.e., VEGF Trap-Eye/aflibercept) 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).”)).

F. '173 patent (Ex.1008).

136. U.S. Patent No. 7,531,173 B2 (“the '173 patent”) issued May 12, 2009, from Application No. 11/998,746, filed on November 30, 2007, and is assigned, on its face, to Regeneron Pharmaceuticals, Inc. I understand that the '173 patent qualifies as prior art to the '601 patent because it issued prior to January 13, 2011, the earliest possible priority date of the '601 patent.

137. The '173 patent is drawn to methods of reducing angiogenesis through the administration of a VEGF antagonist fusion protein. (Ex.1008, '173 patent, 1:42-56, SEQ ID NOS:1 and 2). The '173 patent further discloses that “[i]n a specific and preferred embodiment, the VEGF trap is VEGFR1R2-FcΔC1(a) (also termed VEGF trap_{R1R2}) comprising the nucleotide sequence set forth in SEQ ID NO: 1 and the amino acid sequence set forth in SEQ ID NO: 2.” (*Id.*, 1:48-52). The nucleotide and amino acid sequences for the VEGF antagonist fusion protein disclosed in the '173 patent are identical to the VEGF antagonist sequences required by the Challenged Claims of the '601 patent. (*Compare* Ex.1001, '601 patent, SEQ ID NO:1 and SEQ ID NO:2, *with* Ex.1008, '173 patent, 1:42-56, SEQ ID NOS:1 and 2).

G. Rosenfeld-2006 (Ex.1058).

138. The Rosenfeld-2006 reference was published in 2006. I understand because the Rosenfeld-2006 reference published before January 13, 2011, the earliest priority date of the '601 patent, it is prior art.

139. Rosenfeld-2006 disclosed that ranibizumab is “a recombinant, humanized monoclonal antibody Fab that neutralizes all active forms of [VEGF-A].” (Ex.1058, Rosenfeld-2006, 1419).

140. Rosenfeld-2006 reported on the results of the seminal Phase 3 MARINA (Minimally Classic/Occult Trial of the Anti-VEGF Antibody

Ranibizumab in the Treatment of Neovascular AMD) clinical trial assessing monthly dosing of LUCENTIS (ranibizumab) compared to sham (placebo) injections in the treatment of AMD. (Ex.1058, Rosenfeld-2006, 1420-27).

141. Rosenfeld-2006 included a Supplementary Appendix that provided additional information about the clinical trial, including eligibility criteria, among which were several exclusion criteria directed to infection and inflammation. (Ex.1058, Rosenfeld-2006, Appx., 1-3). Table 1 of the Rosenfeld-2006 Supplementary Appendix disclosed the full list of exclusion criteria. (*Id.*, Table 1). For example, Rosenfeld-2006 disclosed exclusion criteria including:

- “Active intraocular inflammation (grade trace or above) in the study eye”;
- “History of idiopathic or autoimmune-associated uveitis in either eye”;
- “Infectious conjunctivitis, keratitis, scleritis, or endophthalmitis in either eye”; and
- “History of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that might affect interpretation of the results of the study or render the subject at high risk for treatment complications.”

(Ex.1058, Rosenfeld-2006, Appx., 2-3).

H. Heimann-2007 (Ex.1040).

142. Heimann-2007 is a book chapter published in 2007. I understand because the Heimann-2007 reference published before January 13, 2011, the earliest priority date of the '601 patent, it is prior art.

143. Heimann-2007 summarizes some of the major complications potentially stemming from, and guidelines for, intravitreal injections. For example, Heimann-2007 advises that “[b]acterial infections of the anterior segment and ocular adnexa increase the risk of endophthalmitis and should be treated *before performing an intravitreal injection*,” and that pre-operation assessments be done “to rule out possible contraindications...that might complicate the injection.” (Ex.1040, Heimann-2007, 81 (emphasis added); *id.*, 85 (“[e]xclude patients with suspected bacterial infections or the anterior segment (e.g., blepharitis, conjunctivitis).”)). Heimann-2007 further instructs that “preparation of the ocular surface should aim to minimize bacterial contamination during the injection.” (*Id.*, 76).

144. Heimann-2007 discloses that “[e]ndophthalmitis is the most feared complication of intravitreal injections,” (*id.*, 67), due to its “potentially devastating consequences.” (*Id.*, 76; *id.* (further noting that endophthalmitis prevention is “one of the key issues” regarding intravitreal injections)). Heimann-2007 also discloses that sometimes “severe intraocular inflammatory reactions can be seen” following intravitreal injections, and notes that it can be “extremely difficult, to differentiate a

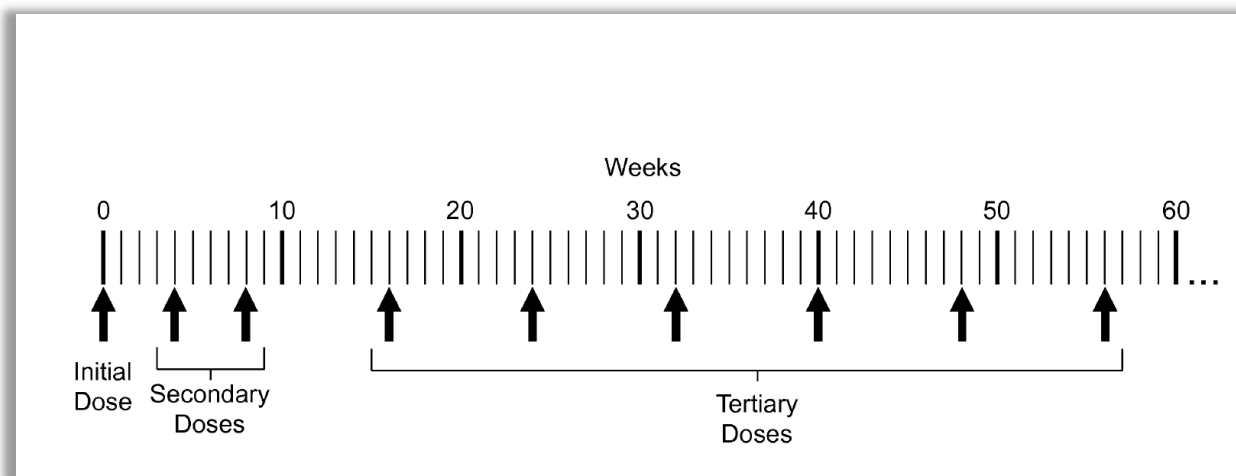
sterile inflammatory process from an inflammatory reaction associated with infectious endophthalmitis.” (*Id.*, 75).

VIII. UNPATENTABILITY OF THE '601 PATENT.

A. Claims 1-9, 34-39, 41-43, and 45 of the '601 Patent Are Anticipated by Dixon (Ex.1006).

145. I was asked to review the challenged claims of the '601 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 '601 patent.

146. First, Figure 1 of the '601 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, '601 patent, Fig.1, 2:62 – 3:2).

147. Based upon my reading of the patent specification, including Figure 1, and the claims of the '601 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 '601 patent states that FIG. 1 “shows an exemplary dosing regimen of the present invention.” (*Id.*, 2:63-64). In addition, the '601 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.” (*Id.*, 2:64 – 3:2). Because I will be using a modified version of Figure 1 of the '601 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 '601 patent correspond to Figure 1 of the '601 patent.

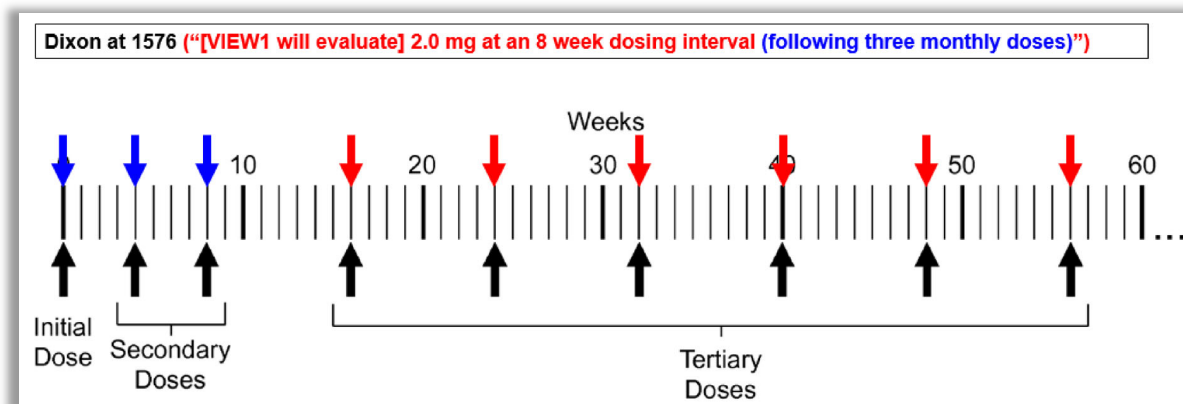
Figure 1	Claim 1	Claim 34
“a single ‘initial dose’ of VEGF antagonist (‘VEGFT’) is administered at the beginning of the treatment regimen (i.e. at ‘week 0’)”	“intravitreally administering, to said patient, an effective amount of aflibercept ... approximately every 4 weeks for the first 3 months”	“a single initial dose of a VEGF antagonist”

Figure 1	Claim 1	Claim 34
(Ex.1001, '601 patent, 2:64-66).		
“two ‘secondary doses’ are administered at weeks 4 and 8, respectively” (<i>Id.</i> , 2:66-67).	See above, e.g., “every 4 weeks for the first 3 months”	“followed by one or more secondary doses of the VEGF antagonist . . . wherein each secondary dose is administered 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.” (<i>Id.</i> , 3:1-2).	“followed by 2 mg approximately once every 8 weeks or once every 2 months”	“followed by one or more tertiary doses of the VEGF antagonist . . . wherein each tertiary dose is administered 8 weeks after the immediately preceding dose”

148. In addition, I note that dependent claim 7 purports to offer a narrower version of claim 1, specifying “wherein approximately every 4 weeks comprises approximately every 28 days or approximately monthly.” Compare to the Figure 1 legend: “two ‘secondary doses’ are administered at weeks 4 and 8, respectively.” (*Id.*, 2:58-60). Therefore, in my opinion, claim 7 represents a dosing regimen falling within the scope of claim 1, and also corresponds precisely to the dosing regimen portrayed in Figure 1 of the '601 patent, and reproduced above.

149. Because the Figure 1 dosing regimen corresponds to the narrowest dosing regimen claim, it also is representative of claim 1, from which claim 7 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.

150. To illustrate why Dixon anticipates the challenged claims, I have prepared the following *modified* version of Figure 1 from the '601 patent (set forth below), to show how Dixon discloses the exact dosing regimen set forth in Figure 1 of the '601 patent, as well as that which is claimed in the challenged claims of the '601 patent:



(Ex.1001, '601 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).

151. I note that the dosing regimen set forth in independent claims 1 and 34 are similar, and thus the analysis is largely the same. Claim 34, however, includes the additional element of claim 34—"wherein the VEGF antagonist is a VEGF receptor-based chimeric molecule comprising an immunoglobulin-like (Ig) domain 2 of a first VEGF receptor which is VEGFR1 and an Ig domain 3 of a second VEGF receptor which is VEGFR2, and a multimerizing component." In my opinion, this additional element of claim 34 is merely a recitation of the domain composition 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.1003, Gerritsen ¶¶ 91-100; 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.1092, AA Alignment vs 758 and 173 patents). As a result, through Dixon’s disclosure of VEGF Trap-Eye/aflibercept, Dixon discloses this aspect of claim 34.

1. Independent claims 1 and 34 are anticipated by Dixon.

152. 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 ²⁰ age related macular degeneration in a patient in need thereof,	“VEGF Trap-Eye is a novel anti-VEGF therapy, with Phase I and Phase II trial data indicating safety, tolerability and

²⁰ 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, and physicians typically use the term in this way even though there is often a fraction of the treated patients that does not respond to the treatment. Further, the VEGF Trap-Eye Phase 2 data showed effective treatment of AMD, an angiogenic eye disorder, with a

Claim 1	Dixon
	efficacy for the treatment of neovascular AMD.” (Ex.1006, Dixon, 1573, 1577). AMD is well known to be an angiogenic eye disorder Phase 2 patients “treated with 2.0 mg 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, ≥ 15 ETDRS letters at 52 weeks.” (<i>Id.</i>, 1576). “[P]atients . . . demonstrated stabilization of their vision that was similar to previous studies of ranibizumab at 1 year.” (<i>Id.</i>, 1577).

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 '601 patent. The Phase 2 results were publicly available well before the priority date of the '601 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).

Claim 1	Dixon
	“Two Phase III studies in wet AMD [VIEW1/VIEW2] are currently under way and seek to compare monthly ranibizumab to monthly or bimonthly VEGF Trap-Eye.” (<i>Id.</i>, 1577). “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 (following three monthly doses).” (<i>Id.</i>, 1576).
comprising intravitreally administering, to said patient	“[A]ll anti-VEGF agents for neovascular AMD are administered only by <i>intravitreal injection</i>.” (Ex.1006, Dixon, 1574 (emphasis added)). “The highest intravitreal dose being used in pivotal trials for VEGF Trap-Eye is 2 mg/month, which corresponds to at least a 280-fold lower potential systemic exposure than in the oncology setting.” (<i>Id.</i>, 1575). “The safety, tolerability and biological activity of intravitreal VEGF Trap-Eye in treatment of neovascular AMD was evaluated in the two-part Clinical Evaluation of Anti-angiogenesis in the Retina-I (CLEAR-IT-I) study.” (<i>Id.</i>, 1575). The VIEW1 and VIEW2 studies “will evaluate the safety and efficacy of

Claim 1	Dixon
	intravitreal VEGF Trap-Eye.” (<i>Id.</i> , 1576).
an effective amount of aflibercept which is 2 mg	Patients treated with monthly loading doses of 2.0 mg followed by PRN dosing “achieved mean improvements of 9.0...ETDRS letters with 29%...gaining... ≥ 15 ETDRS letters at 52 weeks.” (Ex.1006, Dixon, 1576). Patients in this arm also displayed mean decreases in retinal thickness of 143 μM compared to baseline. (<i>Id.</i>). “One promising new [angiogenesis inhibiting] drug is aflibercept (VEGF Trap-Eye), a fusion protein that blocks all isoforms of VEGF-A and placental growth factors-1 and -2.” (<i>Id.</i>, 1573 (Abstract)). “VEGF Trap-Eye and aflibercept (the oncology product) have the same molecular structure.” (<i>Id.</i>, 1575). “The aflibercept dose that is administered in oncology settings is either 4 mg/kg every 2 weeks or 6 mg/kg every 3 weeks, which corresponds to 2 mg/(kg week) with either schedule. The highest intravitreal dose being used in pivotal trials for VEGF Trap-Eye is 2 mg/month, which corresponds to at least a 280-fold lower potential systemic exposure than in the oncology setting.” (<i>Id.</i>, 1575).

Claim 1	Dixon
approximately every 4 weeks for the first 3 months, followed by 2 mg approximately once every 8 weeks or once every 2 months.	“[Phase 3] will evaluate the safety and efficacy of . . . 2.0 mg at an 8 week dosing interval (<i>following three monthly doses</i>).” (Ex.1006, Dixon, 1576 (emphasis added)).

As a result, Dixon anticipates claim 1 of the '601 patent.

153. The analysis for claim 34 is nearly identical to that of claim 1, as set forth below:

Claim 34	Dixon
A method for treating ²¹ an angiogenic eye disorder in a patient in need thereof,	“VEGF Trap-Eye is a novel anti-VEGF therapy, with Phase I and Phase II trial data indicating safety, tolerability and efficacy for the treatment of neovascular AMD.” (Ex.1006, Dixon, 1573, 1577). AMD is well known to be an angiogenic eye disorder.

²¹ See footnote 20, *supra*. As noted above, the VIEW Phase 3 results using the every-8-week dosing regimen confirm that the 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 34	Dixon
	Phase 2 patients “treated with 2.0 mg 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, ≥ 15 ETDRS letters at 52 weeks.” (<i>Id.</i>, 1576). “[P]atients . . . demonstrated stabilization of their vision that was similar to previous studies of ranibizumab at 1 year.” (<i>Id.</i>, 1577). “Two Phase III studies in wet AMD [VIEW1/VIEW2] are currently under way and seek to compare monthly ranibizumab to monthly or bimonthly VEGF Trap-Eye.” (<i>Id.</i>, 1577 (describing DME and RVO studies)).
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;	“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 (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 4 weeks after the immediately preceding dose; and	“2.0 mg at an 8 week dosing interval (<i>following three monthly doses</i>).” (Ex.1006, Dixon, 1576 (emphasis added)). As I explain above, “three monthly doses” involves a dose at baseline, i.e., day 0, as well as a

Claim 34	Dixon
	“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 <i>at an 8 week dosing interval</i> (following three monthly doses).” (Ex.1006, Dixon, 1576 (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 receptor-based chimeric molecule comprising an immunoglobulin-like (Ig) domain 2 of a first VEGF receptor which is VEGFR1 and an Ig domain 3 of a second VEGF receptor which is VEGFR2, and a multimerizing component.	“One promising new drug is aflibercept (VEGF Trap-Eye), a fusion protein that blocks all isoforms of VEGF-A and placental growth factors-1 and -2.” (Ex.1006, Dixon, 1573). “VEGF Trap-Eye and aflibercept (the oncology product) have the same molecular structure.” (<i>Id.</i>, 1575). “Structurally, VEGF Trap-Eye is a fusion protein of key binding domains of human VEGFR-1 and -2 combined with a human IgG Fc fragment.” (<i>Id.</i>, 1575).²²

²² 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. VI.D.).

Claim 34	Dixon
	VEGF Trap-Eye is “a fusion protein of binding domains of VEGF receptors-1 and -2 attached to the Fc fragment of human IgG.” (<i>Id.</i> , 1576 & Fig. 1).

As a result, Dixon anticipates claim 34 of the '601 patent.

2. Dependent claim 7 is anticipated by Dixon.

154. I have been informed that claim 7 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.

155. Claim 7 purports to further limit the claimed dosing regimen of claim 1 to “wherein approximately every 4 weeks comprises approximately every 28 days or approximately monthly.”

156. Dixon discloses that “[Phase 3] will evaluate the safety and efficacy of . . . 2.0 mg at an 8 week dosing interval (*following three monthly doses*).” (Ex.1006, Dixon, 1576 (emphasis added)).

157. Thus, for this reason, as well as the reasons discussed above for claim 1, it is my opinion that claim 7 of the '601 patent is anticipated by Dixon.

3. Dependent claims 2 and 8 are anticipated by Dixon.

158. Claims 2 and 8 depend from claims 1 and 7, respectively, and each specifies that “the age-related macular degeneration is neovascular (wet).”

159. The Dixon reference indicates in the title that VEGF Trap-Eye was being studied for the “treatment of neovascular age-related macular degeneration.” (Ex.1006, Dixon, 1573). 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 neovascular (wet) AMD, as required by claims 2 and 8.

160. Thus, for these reasons, as well as for the reasons discussed above for claims 1 and 7, it is my opinion that claims 2 and 8 of the '601 patent are anticipated by Dixon.

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

161. Claim 3 limits the method of claim 1 to “wherein the patient loses less than 15 letters of Best Corrected Visual Acuity (BCVA) score.” And, claim 4, further limits the method of claim 3 to “wherein Best Corrected Visual Acuity

(BCVA) is according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.”

162. Dixon discloses that in Phase 2 “[p]atients initially treated with 2.0 . . . mg of VEGF Trap-Eye monthly achieved mean improvements of 9.0 ($p < 0.0001$) . . . ETDRS [BCVA] letters with 29[%] . . . gaining . . . ≥ 15 ETDRS letters at 52 weeks.” (Ex.1006, Dixon, 1576). A gain of ≥ 15 ETDRS BCVA letters necessarily encompasses a loss of less than 15 letters. Dixon also discloses that for Phase 3 (VIEW), “the primary outcome will be the proportion of patients who maintain vision at week 52 (defined as a loss of < 15 ETDRS letters).” (*Id.*, 1576). Thus, Dixon anticipates this aspect of claims 3 and 4.

163. Dixon disclosed the same VIEW clinical trial regimen with the same drug now claimed in claim 1 (from which claims 3 and 4 depend). In my opinion, the claimed visual acuity measures would have been a natural result flowing from the prior art Phase 3 regimen, i.e., treating patients with 2 mg of aflibercept, with a regimen involving 3 monthly loading doses followed by every every-8-week fixed dosing. Thus, through Dixon’s disclosure of the dosing regimen used in the VIEW trials, Dixon anticipates this aspect of claims 3 and 4.

164. In addition, I have reviewed publications disclosing the results of the VIEW clinical trials. In Heier-2012, for example, the authors report that most patients achieved the claimed BCVA measures, providing additional evidence that

such measures are a natural result of the dosing regimen set forth in claims 3 and 4. (See Ex.1018, Heier-2012, 2542).

165. 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 '601 patent are anticipated by Dixon.

5. Dependent claims 5 and 6 are anticipated by Dixon.

166. Claim 5 depends from claim 2 and recites “wherein the patient gains at least 15 letters of Best Corrected Visual Acuity (BCVA) score.” Claim 6 depends from claim 5 and further limits the claimed method to “wherein Best Corrected Visual Acuity (BCVA) is according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.”

167. Dixon discloses that in Phase 2 “[p]atients initially treated with 2.0 . . . mg of VEGF Trap-Eye monthly achieved mean improvements of 9.0 ($p < 0.0001$) . . . ETDRS [BCVA] letters with 29[%] . . . gaining . . . ≥ 15 ETDRS letters at 52 weeks.” (Ex.1006, Dixon, 1576). Accordingly, Dixon discloses the added limitations, and thus anticipates this aspect of claims 5 and 6.

168. As discussed above for claims 3 and 4, Dixon disclosed the same VIEW clinical trial regimen with the same drug now claimed in claim 1 (from which claims 5 and 6 depend). In my opinion, the claimed visual acuity measures would have been a natural result flowing from the prior art Phase 3 regimen, i.e., treating patients

with 2 mg of aflibercept, with a regimen involving 3 monthly loading doses followed by every every-8-week fixed dosing. Thus, through Dixon's disclosure of the dosing regimen used in the VIEW trials, Dixon anticipates this aspect of claims 5-6.

169. In addition, I have reviewed publications disclosing the results of the VIEW clinical trials. In Heier-2012, for example, the authors report that patients achieved the claimed BCVA measures, providing additional evidence that such measures are a natural result of the dosing regimen set forth in claims 5 and 6. (*See* Ex.1018, Heier-2012, 2542).

170. Thus, for these reasons, as well as for the reasons discussed above for claims 1 and 2, it is my opinion that claims 5 and 6 of the '601 patent is anticipated by Dixon.

6. Dependent claim 35 is anticipated by Dixon.

171. Dependent claim 35 further limits the claimed dosing regimen of independent claim 34 as follows: "wherein the VEGF antagonist is aflibercept."

172. As discussed above, Dixon discloses that "VEGF Trap-Eye and aflibercept (the oncology product) have the same molecular structure," (Ex.1006, Dixon, 1575), and in fact are the same molecule: "***One*** promising new [angiogenesis inhibiting] drug is aflibercept (VEGF Trap-Eye), ***a*** fusion protein that blocks all isoforms of VEGF-A and placental growth factors-1 and -2," (*id.*, 1573 (Abstract) (emphasis added)). To a person of ordinary skill in the art, it was well understood

that Regeneron had a single agent in clinical trials, which agent Regeneron was calling both aflibercept and VEGF Trap-Eye.

173. Thus, for these reasons, as well as the reasons discussed above for claim 34, it is my opinion that claim 35 is anticipated by Dixon.

7. Dependent claims 9 and 36 are anticipated by Dixon.

174. Dependent claim 9 recites the method of claim 8, “wherein exclusion criteria for the patient include (1) active intraocular inflammation; or (2) active ocular or periocular infection.” Claim 36, which depends from claim 35, recites “wherein exclusion criteria for the patient include (1) active intraocular inflammation; or (2) active ocular or periocular infection.”

175. I have been informed that the exclusion criteria elements constitute mental steps and/or written material, and thus are not entitled to patentable weight. But regardless of whether the exclusion criteria elements are considered in the patentability analysis, the exclusion of patients with, for example active intraocular inflammation and/or active ocular or periocular infection from methods of treatment involving administration of intraocular injections was known and published to POSAs well before the priority date of the '601 patent. Dixon discloses, for

example, that “[e]ach injection subjects patients to risks of cataract, intraocular inflammation, retinal detachment and endophthalmitis.” (Ex.1006, Dixon, 1577).²³

176. Furthermore, the “exclusion criteria” listed in claims 9 and 36 were necessarily and inevitably applied in connection with practicing the VIEW clinical trial protocol, because in the context of clinical trials, clinical trial investigators are required to apply each of the exclusion criteria listed in the protocol. (*See, e.g.*, Ex.1050, Eylea MR, 112-14 (listing 37 exclusion criteria, including the two “exclusion criteria” listed in claims 9 and 36); Ex.1018, Heier-2012, Appendix 2). The application of the “exclusion criteria” recited in claims 9 and 36, therefore, was a natural result flowing from the application of the VIEW trial study protocol. Thus, Dixon inherently discloses this aspect of claims 9 and 36.

177. For these reasons, as well as for reasons discussed above for the claims from which claims 9 and 36 depend, it is my opinion that claims 9 and 36 are anticipated by Dixon.

²³ As discussed above, it was well known and widely understood amongst skilled artisans that patients with ocular or periocular infection and/or inflammation should be excluded from treatment methods involving direct injection of medication into the eye.

8. Dependent claims 37 and 38 are anticipated by Dixon.

178. Claim 37 depends from claim 34 and recites “wherein all doses of the VEGF antagonist are administered to the patient by intraocular administration.” Claim 38, which depends from claim 37, specifies that the “intraocular administration is intravitreal administration.”

179. To a person of ordinary skill in the art, it was 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. In Dixon’s disclosure of the VIEW1 and VIEW2 studies, Dixon stated that the studies “will evaluate the safety and efficacy of *intravitreal* VEGF Trap-Eye.” (Ex.1006, Dixon, 1576 (emphasis added)). This element is therefore expressly disclosed by Dixon.

180. Therefore, for these reasons, as well as the reasons set forth for claim 34 above, it is my opinion that claims 37 and 38 are anticipated by Dixon.

9. Dependent claims 39, 41, and 45 are anticipated by Dixon.

181. Dependent claim 39 depends from claim 38, which ultimately depends from claims 34 and 37, and recites “wherein all doses of the VEGF antagonist comprise from about 0.5 mg to about 2 mg of the VEGF antagonist.” Claim 41 depends from claim 39 and specifies “wherein all doses of the VEGF antagonist

comprise 2 mg of the VEGF antagonist.” Claim 45 is dependent on claim 43, and recites “wherein all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist.”

182. 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; *see also id.* (reporting that another treatment arm of the VIEW1 and VIEW2 studies included “0.5 mg every 4 weeks”)). Dixon thus expressly discloses the doses of claims 39, 41, and 45.

183. Therefore, for these reasons, as well as the reasons set forth above for the claims from which claims 39, 41 and 45 depend, it is my opinion that claims 39, 41, and 45 are anticipated by Dixon.

10. Dependent claims 42 and 43 are anticipated by Dixon.

184. Claim 42 is dependent on claim 34, and recites “wherein the angiogenic eye disorder is selected from the group consisting of” several well-known eye disorders, including AMD. Claim 43 depends on claim 34, and recites “wherein the angiogenic eye disorder is age related macular degeneration.”

185. As explained above with respect to claims 2 and 8, 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 42 and 43.

186. Thus, for these reasons, as well as for the reasons discussed above for claim 34, it is my opinion that claims 42 and 43 of the '601 patent are anticipated by Dixon.

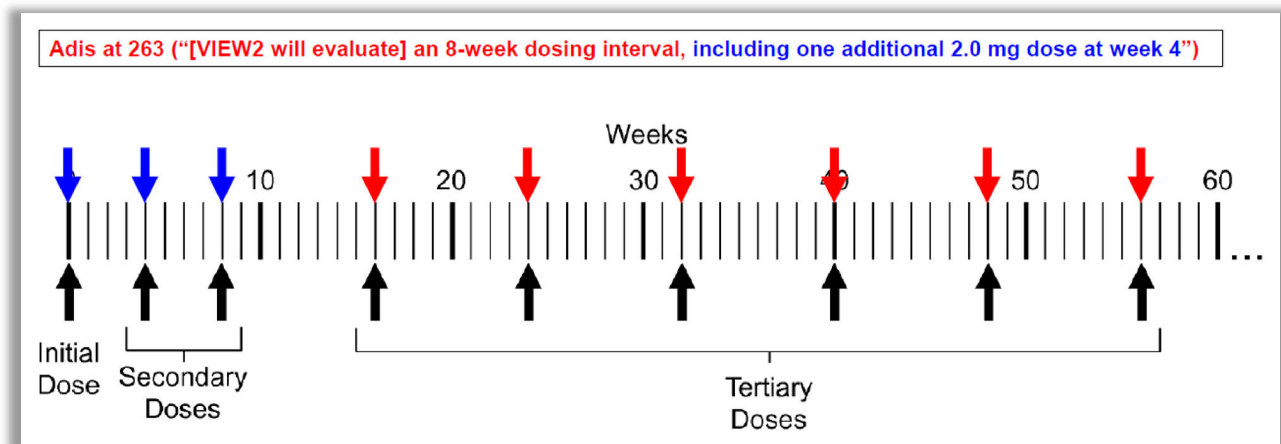
B. Claims 1-9, 34-39, 41-43, and 45 of the '601 Patent Are Anticipated by Adis (Ex.1007).

1. Independent claims 1 and 34 of the '601 patent are anticipated by Adis.

187. I was asked to review the challenged claims of the '601 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 '601 patent.

188. Claims 1 and 34 of the '601 patent have been set forth above.

189. Adis describes Phase 1, 2, and 3 clinical trials studying VEGF Trap-Eye as a therapy for treating angiogenic eye disorders such as AMD. 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 (or, "every 4 week") doses. This has been shown using the same overlay presented above, in which I have used Figure 1 of the '601 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 '601 patent, as well as that which is claimed in the challenged claims of the '601 patent, as depicted here:



(Ex.1001, '601 patent, Fig.1 (modifications added)).

190. One of ordinary skill in the art readily would have recognized that the claimed dosing regimen consisting of doses administered “approximately every 4 weeks for the first 3 months, followed by...once every 8 weeks or once every 2 months,” could be found in Adis’ disclosure of “an 8-week dosing interval,” (**red arrows**), including one additional 2.0 mg dose at week 4,” (**blue arrows**). (*See, e.g.,* Ex.1007, Adis, 263 (emphasis added)).

191. In my opinion, the VIEW dosing regimen described in Adis is the precise dosing regimen that was described in Figure 1 in the ’601 patent and which falls squarely within the scope of the challenged claims.²⁴

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

Claim 1:	Adis:
A method for treating age related macular degeneration in a patient in need thereof,	“Regeneron and Bayer are developing the agent [i.e., aflibercept] for eye disorders.” (Ex.1007, Adis, 261; <i>id.</i> , 263).

²⁴ Regarding the preamble, *see, e.g., supra* note 20; 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.”).

Claim 1:	Adis:
	“Blockade of VEGF can also prevent blood vessel formation and vas[cu]lar leakage associated with wet [AMD].” (<i>Id.</i>, 261). “A second phase III trial (VIEW 2) in wet AMD began with the first patient dosed in May 2008.” (<i>Id.</i>, 263). “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 Analysis of data demonstrated that all five doses of aflibercept met the primary endpoint of a statistically significant reduction in retinal thickness after 12 weeks and 32 weeks of treatment compared with baseline.” (<i>Id.</i>; <i>see also id.</i>, 267-68).
comprising intravitreally administering, to said patient,	“The non-inferiority, [VIEW1]...study will evaluate the safety and efficacy of intravitreal aflibercept” (Ex.1007, Adis, 263).
an effective amount of aflibercept which is 2 mg approximately every 4 weeks for the first 3 months, followed by 2 mg approximately once every 8 weeks or once every 2 months.	“The non-inferiority, [VIEW1]...study will evaluate the safety and efficacy of intravitreal aflibercept at...<i>2.0 mg at an 8-week dosing interval</i>” (Ex.1007, Adis, 263 (emphasis added)). “[VIEW 2] will evaluate the safety and efficacy of aflibercept at 0.5 mg and 2.0 mg administered at . . . <i>2.0 mg at an 8-week dosing interval, including one</i>

Claim 1:	Adis:
	<i>additional 2.0 mg dose at week 4.” (Id. (emphasis added)).</i>

Accordingly, for these reasons, it is my opinion that claim 1 of the '601 patent is anticipated by Adis.

193. The analysis for claim 34 is nearly identical to that of claim 1, discussed above. The additional element of claim 34—wherein the VEGF antagonist is a VEGF receptor-based chimeric molecule comprising an immunoglobulin-like (Ig) domain 2 of a first VEGF receptor which is VEGFR1 and an Ig domain 3 of a second VEGF receptor which is VEGFR2, and a multimerizing component”—is merely a recitation of the domain composition of the “aflibercept” / “VEGF Trap-Eye” disclosed in Adis, a fact that was disclosed well before January 2011. (*See, e.g.*, 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.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.1003, Gerritsen ¶¶ 91-100; Ex.1092, AA Alignment vs 758 and 173 patents). As a result, through Adis’ disclosure of VEGF Trap-Eye/aflibercept, Adis discloses this additional aspect of claim 34.

194. Accordingly, for these reasons, it is my opinion that claims 1 and 34 of the ’601 patent are anticipated by Adis.

2. Dependent claim 7 is anticipated by Adis.

195. Claim 7 purports to limit the claimed dosing regimen of claim 1 to “wherein approximately every 4 weeks comprises approximately every 28 days or approximately monthly.”

196. Adis discloses that the “VIEW 1 study will evaluate the safety and efficacy of intravitreal aflibercept at doses of 0.5 mg and 2.0 mg administered at 4-week dosing intervals.” (Ex.1007, Adis, 263). A POSA would understand “4-week dosing intervals” to comprise “approximately every 28 days or approximately monthly.” Accordingly, Adis expressly disclosed and taught the added limitation of claim 7.

197. Therefore, for these reasons, as well as the reasons set forth for claim 1 above, it is my opinion that claim 7 is anticipated by Adis.

3. Dependent claims 2 and 8 are anticipated by Adis.

198. Claims 2 and 8 depend from claims 1 and 7, respectively, and each specifies that “the age-related macular degeneration is neovascular (wet).”

199. 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 patients with wet AMD. (*Id.*, 263 (“a phase III trial of aflibercept in approximately 1200 patients with the neovascular form of wet AMD”)). It is in the discussion of the VIEW1 and VIEW2 trials for wet AMD 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 wet AMD, a well-known angiogenic eye disorder.

200. Thus, for these reasons, as well as for the reasons discussed above for claims 1 and 7, it is my opinion that claims 2 and 8 of the ’601 patent are anticipated by Adis.

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

201. Claim 3 limits the method of claim 1 to “wherein the patient loses less than 15 letters of Best Corrected Visual Acuity (BCVA) score.” And, claim 4,

further limits the method of claim 3 to “wherein Best Corrected Visual Acuity (BCVA) is according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.”

202. Adis disclosed the same VIEW clinical trial regimen with the same drug now claimed in claim 1 (from which claims 3 and 4 depend). In my opinion, the claimed visual acuity measures would have been a natural result flowing from the prior art Phase 3 regimen, i.e., treating patients with 2 mg of aflibercept, with a regimen involving 3 monthly loading doses followed by every 8-week fixed dosing. Thus, through Adis’ disclosure of the dosing regimen used in the VIEW trials, Adis anticipates this aspect of claims 3 and 4.

203. In addition, I have reviewed publications disclosing the results of the VIEW clinical trials. In Heier-2012, for example, the authors report that most patients achieved the claimed BCVA measures, providing additional evidence that such measures are a natural result of the dosing regimen set forth in claims 3 and 4. (*See* Ex.1018, Heier-2012, 2542).

204. Accordingly, for these reasons, as well as the reasons presented for claim 1 above, it is my opinion that claims 3 and 4 of the ’601 patent are anticipated by Adis.

5. Dependent claims 5 and 6 are anticipated by Adis.

205. Claim 5 depends from claim 2 and recites “wherein the patient gains at least 15 letters of Best Corrected Visual Acuity (BCVA) score.” Claim 6 depends from claim 5 and specifies “wherein Best Corrected Visual Acuity (BCVA) is according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.”

206. As with dependent claims 3 and 4 discussed above, Adis disclosed the same VIEW clinical trial regimen with the same drug now claimed in claim 1 (from which claims 5 and 6 depend). In my opinion, the claimed visual acuity measures would have been a natural result flowing from the prior art Phase 3 regimen, i.e., treating patients with 2 mg of aflibercept, with a regimen involving 3 monthly loading doses followed by every every-8-week fixed dosing. Thus, Adis anticipates this aspect of claims 5 and 6.

207. In addition, I have reviewed publications disclosing the results of the VIEW clinical trials. In Heier-2012, for example, the authors report that patients achieved the claimed BCVA measures, providing additional evidence that such measures are a natural result of the dosing regimen set forth in claims 5 and 6. (*See* Ex.1018, Heier-2012, 2542).

208. Accordingly, for these reasons, as well as for the reasons discussed above for claims 1 and 2, it is my opinion that claims 5 and 6 of the '601 patent are anticipated by Adis.

6. Dependent claim 35 is anticipated by Adis.

209. Dependent claim 35 further limits the claimed dosing regimen of independent claim 34 as follows: “wherein the VEGF antagonist is aflibercept.”

210. As discussed above, Adis discloses that “[t]he non-inferiority, [VIEW1] . . . study will evaluate the safety and efficacy of intravitreal *aflibercept* . . .” (Ex.1007, Adis, 263 (emphasis added)). Adis further discloses that “[VIEW 2] will evaluate the safety and efficacy of *aflibercept* . . .” (*Id.* (emphasis added)).

211. Thus, for these reasons, as well as for the reasons discussed above for claim 34, it is my opinion that claim 35 of the ’601 patent is anticipated by Adis.

7. Dependent claims 9 and 36 are anticipated by Adis.

212. Dependent claim 9 recites the method of claim 8, “wherein exclusion criteria for the patient include (1) active intraocular inflammation; or (2) active ocular or periocular infection.” Claim 36, which depends from claim 35, recites “wherein exclusion criteria for the patient include (1) active intraocular inflammation; or (2) active ocular or periocular infection.”

213. I have been informed that the exclusion criteria elements constitute mental steps and/or written material, and thus are not entitled to patentable weight. But, as discussed above, regardless of whether the exclusion criteria elements are considered in the patentability analysis, it was well known and widely understood amongst skilled artisans that patients with ocular or periocular infection and/or

inflammation should be excluded from treatment methods involving direct injection of medication into the eye. (*See, e.g.*, Ex.1025, Engelbert-2010, 1370). As a result, through Adis' disclosure of the VIEW clinical trial, Adis discloses this aspect of claims 9 and 36.

214. In addition, the "exclusion criteria" listed in claims 9 and 36 were necessarily and inevitably applied in connection with practicing the VIEW clinical trial protocol because in the context of clinical trials, clinical trial investigators are required to apply each of the exclusion criteria listed in the protocol. (*See, e.g.*, Ex.1050, Eylea MR, 112-14 (listing 37 exclusion criteria, including the two "exclusion criteria" listed in claims 9 and 36); Ex.1018, Heier-2012, Appendix 2). Thus, Adis inherently discloses this aspect of claims 9 and 36.

215. Therefore, for these reasons, as well as for reasons discussed above for the claims from which claims 9 and 36 depend, it is my opinion that claims 9 and 36 are anticipated by Adis.

8. Dependent claims 37 and 38 are anticipated by Adis.

216. Claim 37 depends from claim 34 and recites "wherein all doses of the VEGF antagonist are administered to the patient by intraocular administration." Claim 38, which depends from claim 37, specifies that the "intraocular administration is intravitreal administration."

217. To a person of ordinary skill in the art, it was 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. (*See, e.g.*, Ex.1001, '601 patent, 2:47-50 (“Various administration routes are contemplated . . . including . . . intraocular administration (e.g., intravitreal administration).”)). Adis discloses “intravitreal injection [sic] as a route of administration.” (Ex.1007, Adis, 264). For example, in Adis’ disclosure of the VIEW studies, Adis states that the study “will evaluate the safety and efficacy of intravitreal aflibercept.” (*Id.*, 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.*). This element is therefore expressly disclosed and taught by Adis.

218. Thus, for these reasons, as well as for the reasons discussed above for claim 34, it is my opinion that claims 37 and 38 of the '601 patent are anticipated by Adis.

9. Dependent claims 39, 41, and 45 are anticipated by Adis.

219. Claim 39 depends from claim 38, which ultimately depends from claims 34 and 37, and recites “wherein all doses of the VEGF antagonist comprise from about 0.5 mg to about 2 mg of the VEGF antagonist.” Claim 41 depends from

claim 39 and specifies “wherein all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist.” Claim 45 is dependent on claim 43, and recites “wherein all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist.”

220. 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 39, 41, and 45.

221. Therefore, for these reasons, as well as the reasons set forth above for the claims from which claims 39, 41 and 45 depend, it is my opinion that claims 39, 41, and 45 are anticipated by Adis.

10. Dependent claims 42 and 43 are anticipated by Adis.

222. Claim 42 is dependent on independent claim 34, and recites “wherein the angiogenic eye disorder is selected from the group consisting of” several well-known eye disorders, including AMD. Claim 43 depends on claim 34, and recites “wherein the angiogenic eye disorder is age related macular degeneration.”

223. These elements are similar in scope to those discussed above with respect to claims 2 and 8, 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.

224. Thus, for these reasons, as well as for the reasons discussed above for claim 34, it is my opinion that claims 42 and 43 of the ’601 patent are anticipated by Dixon.

C. Claims 1-9, 34-39, 41-43, and 45 of the ’601 Patent Are Anticipated by the Regeneron Press Release Dated May 8, 2008 (Regeneron (8-May-2008) (Ex.1013)).

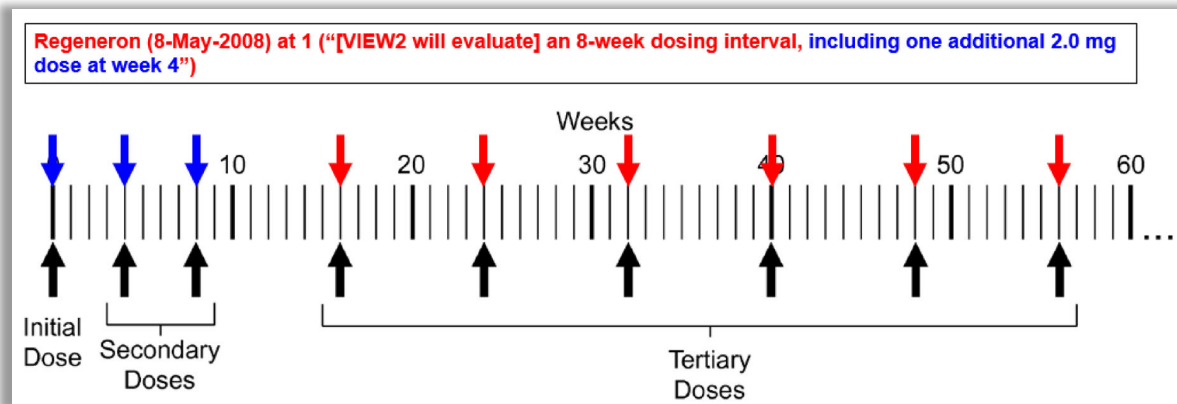
225. I have been asked to review the Challenged Claims of the ’601 patent and compare them to the disclosures of the Regeneron Press Release, dated May 8, 2008. It is my opinion that Regeneron (8-May-2008) discloses every element of the claimed method(s) and thus anticipates each of the challenged claims of the ’601 patent.

1. Independent claims 1 and 34 are anticipated by Regeneron (8-May-2008).

226. Claims 1 and 34 of the ’601 patent have been set forth above.

227. Regeneron (8-May-2008) describes Phase 2 and 3 trials of VEGF Trap-Eye in AMD using the claimed dosing regimens. 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 '601 patent to illustrate how Regeneron (8-May-2008) discloses the exact dosing regimen set forth in Figure 1 of the '601 patent, as well as that which is claimed in the challenged claims of the '601 patent, as depicted here:



(Ex.1001, '601 patent, Fig.1 (modifications added)).

228. One of ordinary skill in the art readily would have recognized that the claimed dosing regimen consisting of doses administered “approximately every 4 weeks for the first 3 months, followed by...once every 8 weeks or once every 2 months,” could be found in Regeneron (8-May-2008)’s disclosure of “an 8-week dosing interval,” (**red arrows**), including one additional 2.0 mg dose at week 4,” (**blue arrows**). (See, e.g., Ex.1013, Regeneron (8-May-2008), 1).

229. In my opinion, the VIEW dosing regimen described in Regeneron (8-May-2008) is the precise dosing regimen that was described in Figure 1 in the '601 patent and which falls squarely within the scope of the challenged claims.²⁵

230. Below, I have constructed a chart for the purpose of showing where each and every claim element from claim 1 is found in the Regeneron (8-May-2008) reference:

Claim 1:	Regeneron (8-May-2008):
A method for treating age related macular degeneration in a patient in need thereof,	“VIEW 2 (VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD) will enroll approximately 1,200 patients.” (Ex.1013, Regeneron (8-May-2008), 1). “Results from the Phase 2 study have shown that VEGF Trap-Eye has the potential to significantly reduce retinal thickness and improve vision.” (<i>Id.</i>, 1). “VEGF Trap-Eye met both primary and secondary key endpoints: a statistically significant reduction in retinal thickness (a measure of disease activity) after 12

²⁵ Regarding the preamble, *see, e.g., supra* note 20; Ex.1013, Regeneron (8-May-2008), 2 (“[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.”).

Claim 1:	Regeneron (8-May-2008):
	weeks of treatment compared with baseline and a statistically significant improvement from baseline in visual acuity (ability to read letters on an eye chart).” (<i>Id.</i>, 1-2). “Dosing of the first patient in this confirmatory Phase 3 trial is an important milestone for this compound intended to treat a devastating ocular disease that impacts millions of people worldwide.” (<i>Id.</i>, 1).
comprising intravitreally administering, to said patient,	“Both VIEW 1 and VIEW 2 are designed to evaluate the efficacy and safety of VEGF Trap-Eye administered by intravitreal injection, at dosing intervals of 4 and 8 weeks.” (Ex.1013, Regeneron (8-May-2008), 1).
an effective amount of aflibercept which is 2 mg approximately every 4 weeks for the first 3 months, followed by 2 mg approximately once every 8 weeks or once every 2 months.	The Phase 3 VIEW2 “study will evaluate the safety and efficacy of VEGF Trap-Eye at . . . <i>2.0 mg at an 8-week dosing interval, including one additional 2.0 mg dose at week four.</i>” (Ex.1013, Regeneron (8-May-2008), 1 (emphasis added)). In other words, doses at weeks 0, 4, 8, 16, 24, 32, 40, and 48.

Accordingly, for these reasons, it is my opinion that claim 1 of the '601 patent is anticipated by Regeneron (8-May-2008).

231. The analysis for claim 34 is nearly identical to that of claim 1, discussed above. The additional element of claim 34—wherein the VEGF antagonist is a VEGF receptor-based chimeric molecule comprising an immunoglobulin-like (Ig) domain 2 of a first VEGF receptor which is VEGFR1 and an Ig domain 3 of a second VEGF receptor which is VEGFR2, and a multimerizing component”—is merely a recitation of the domain composition of the “aflibercept” / “VEGF Trap-Eye” disclosed in Regeneron (8-May-2008), a fact that was disclosed well before January 2011. (*See, e.g.*, 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.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.1003, Gerritsen ¶¶ 91-100; Ex.1092, AA Alignment vs 758 and 173 patents). In addition, Regeneron (8-May-2008) discloses that “VEGF Trap-Eye is a fully human,

soluble VEGF receptor fusion protein that binds all forms of VEGF-A . . . and VEGF-B. VEGF Trap-Eye is a specific and highly potent blocker of these growth factors.” (Ex.1013, Regeneron (8-May-2008), 2). As a result, through Regeneron (8-May-2008)’s disclosure of VEGF Trap-Eye/aflibercept, Regeneron (8-May-2008) discloses this aspect of claim 34.²⁶

232. Accordingly, for these reasons, it is my opinion that claims 1 and 34 of the ’601 patent are anticipated by Regeneron (8-May-2008).

2. Dependent claim 7 is anticipated by Regeneron (8-May-2008).

233. Claim 7 purports to limit the claimed dosing regimen of claim 1 to “wherein approximately every 4 weeks comprises approximately every 28 days or approximately monthly.”

234. Regeneron (8-May-2008) discloses that the VIEW trial “will evaluate the safety and efficacy of VEGF Trap-Eye at doses of 0.5 milligrams (mg) and 2.0 mg administered at 4-week intervals.” (Ex.1013, Regeneron (8-May-2008), 1). A

²⁶ Regarding the preamble, *see, e.g., supra* note 20; Ex.1013, Regeneron (8-May-2008), 2 (“[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.”).

person of ordinary skill in the art would understand “4-week intervals” to comprise “approximately every 28 days or approximately monthly.” Accordingly, Regeneron (8-May-2008) expressly disclosed and taught the added limitation of claim 7.

235. Therefore, for these reasons, as well as the reasons set forth for claim 1 above, it is my opinion that claim 7 is anticipated by Regeneron (8-May-2008).

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

236. Claims 2 and 8 depend from claims 1 and 7, respectively, and each specifies that “the age-related macular degeneration is neovascular (wet).”

237. Regeneron (8-May-2008) expressly 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.* (“VIEW 2 (VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD) will enroll approximately 1,200 patients”)).

238. Thus, for these reasons, as well as for the reasons discussed above for claims 1 and 7, it is my opinion that claims 2 and 8 of the ’601 patent are anticipated by Regeneron (8-May-2008).

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

239. Claim 3 limits the method of claim 1 to “wherein the patient loses less than 15 letters of Best Corrected Visual Acuity (BCVA) score.” And, claim 4, further limits the method of claim 3 to “wherein Best Corrected Visual Acuity

(BCVA) is according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.”

240. Regeneron (8-May-2008) discloses that “[t]he primary endpoint of the [VIEW 2] study is the proportion of patients treated with VEGF Trap-Eye who maintain vision at the end of one year,” where “[m]aintenance of vision is defined as losing fewer than three lines (equivalent to 15 letters) on the ETDRS chart.” (Ex.1013, Regeneron (8-May-2008), 1). Thus, Regeneron (8-May-2008) anticipates this aspect of claims 3 and 4.

241. Regeneron (8-May-2008) disclosed the same VIEW clinical trial regimen with the same drug now claimed in claim 1 (from which claims 3 and 4 depend). In my opinion, the claimed visual acuity measures would have been a natural result flowing from the prior art Phase 3 regimen, i.e., treating patients with 2 mg of aflibercept, with a regimen involving 3 monthly loading doses followed by every every-8-week fixed dosing. Thus, through Regeneron (8-May-2008)’s disclosure of the dosing regimen used in the VIEW trials, Regeneron (8-May-2008) anticipates this aspect of claims 3 and 4.

242. In addition, I have reviewed publications disclosing the results of the VIEW clinical trials. In Heier-2012, for example, the authors report that most patients achieved the claimed BCVA measures, providing additional evidence that

such measures are a natural result of the dosing regimen set forth in claims 3 and 4. (See Ex.1018, Heier-2012, 2542).

243. Accordingly, for these reasons, as well as the reasons presented for claim 1 above, it is my opinion that claims 3 and 4 of the '601 patent are anticipated by Regeneron (8-May-2008).

5. Dependent claims 5 and 6 are anticipated by Regeneron (8-May-2008).

244. Claim 5 depends from claim 2 and recites “wherein the patient gains at least 15 letters of Best Corrected Visual Acuity (BCVA) score.” Claim 6 depends from claim 5 and specifies “wherein Best Corrected Visual Acuity (BCVA) is according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.”

245. Regeneron (8-May-2008) discloses that “[k]ey secondary endpoints [of VIEW 2] include the mean change from baseline in visual acuity as measured by ETDRS and the proportion of patients who gained at least 15 letters of vision at week 52.” (Ex.1013, Regeneron (8-May-2008), 1).

246. As with dependent claims 3 and 4 discussed above, Regeneron (8-May-2008) disclosed the same VIEW clinical trial regimen with the same drug now claimed in claim 1 (from which claims 3 and 4 depend). In my opinion, the claimed visual acuity measures would have been a natural result flowing from the prior art Phase 3 regimen, i.e., treating patients with 2 mg of aflibercept, with a regimen

involving 3 monthly loading doses followed by every every-8-week fixed dosing. Thus, Regeneron (8-May-2008) anticipates this aspect of claims 5 and 6.

247. In addition, I have reviewed publications disclosing the results of the VIEW clinical trials. In Heier-2012, for example, the authors report that patients achieved the claimed BCVA measures, providing additional evidence that such measures are a natural result of the dosing regimen set forth in claims 5 and 6. (*See* Ex.1018, Heier-2012, 2542).

248. Accordingly, for these reasons, as well as for the reasons discussed above for claims 1 and 2, it is my opinion that claims 5 and 6 of the '601 patent are anticipated by Regeneron (8-May-2008).

6. Dependent claim 35 is anticipated by Regeneron (8-May-2008).

249. Dependent claim 35 further limits the claimed dosing regimen of independent claim 34 as follows: “wherein the VEGF antagonist is aflibercept.”

250. Regeneron (8-May-2008) discloses that “VEGF Trap-Eye is a fully human, soluble VEGF receptor fusion protein that binds all forms of VEGF-A . . . and VEGF-B. VEGF Trap-Eye is a specific and highly potent blocker of these growth factors.” (Ex.1013, Regeneron (8-May-2008), 2). As discussed above, the skilled artisan would have understood and been aware of the identify of VEGF Trap-Eye as aflibercept.

251. Thus, for these reasons, as well as for the reasons discussed above for claim 34, it is my opinion that claim 35 of the '601 patent is anticipated by Regeneron (8-May-2008).

7. Dependent claims 9 and 36 are anticipated by Regeneron (8-May-2008).

252. Dependent claim 9 recites the method of claim 8, “wherein exclusion criteria for the patient include (1) active intraocular inflammation; or (2) active ocular or periocular infection.” Claim 36, which depends from claim 35, recites “wherein exclusion criteria for the patient include (1) active intraocular inflammation; or (2) active ocular or periocular infection.”

253. I have been informed that the exclusion criteria elements constitute mental steps and/or written material, and thus are not entitled to patentable weight. But, as discussed above, regardless of whether the exclusion criteria elements are considered in the patentability analysis, the exclusion of patients with, for example intraocular inflammation and/or infection from methods of treatment involving administration of intraocular injections was known and published to POSAs well before the priority date of the '601 patent. (*See, e.g.*, Ex.1025, Engelbert-2010, 1370). As a result, through Regeneron (8-May-2008)’s disclosure of the VIEW clinical trials, Regeneron (8-May-2008) discloses this aspect of claims 9 and 36.

254. Furthermore, the “exclusion criteria” listed in claims 9 and 36 were necessarily and inevitably applied in connection with practicing the VIEW clinical trial protocol, because in the context of clinical trials, clinical trial investigators are required to apply each of the exclusion criteria listed in the protocol. (*See, e.g.*, Ex.1050, Eylea MR, 112-14 (listing 37 exclusion criteria, including the two “exclusion criteria” listed in claims 9 and 36); Ex.1018, Heier-2012, Appendix 2). The application of the “exclusion criteria” recited in claims 9 and 36, therefore, was a natural result flowing from the application of the VIEW trial study protocol. Thus, Regeneron (8-May-2008) inherently discloses this aspect of claims 9 and 36.

255. Accordingly, for these reasons, as well as for reasons discussed above for the claims from which claims 9 and 36 depend, it is my opinion that claims 9 and 36 are anticipated by Regeneron (8-May-2008).

8. Dependent claims 37 and 38 are anticipated by Regeneron (8-May-2008).

256. Claim 37 depends from claim 34 and recites “wherein all doses of the VEGF antagonist are administered to the patient by intraocular administration.” Claim 38, which depends from claim 37, specifies that the “intraocular administration is intravitreal administration.”

257. To a person of ordinary skill in the art, it was 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. (*See, e.g.*, Ex.1001, '601 patent, 2:47-50 (“Various administration routes are contemplated . . . including . . . intraocular administration (e.g., intravitreal administration).”)). 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).

258. Thus, for these reasons, as well as for the reasons discussed above for claim 34, it is my opinion that claims 37 and 38 of the '601 patent are anticipated by Regeneron (8-May-2008).

9. Dependent claims 39, 41, and 45 are anticipated by Regeneron (8-May-2008).

259. Dependent claim 39 depends from claim 38, which ultimately depends from claims 34 and 37, and recites “wherein all doses of the VEGF antagonist comprise from about 0.5 mg to about 2 mg of the VEGF antagonist.” Claim 41 depends from claim 39 and specifies “wherein all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist.” Claim 45 is dependent on claim 43, and

recites “wherein all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist.”

260. 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 39, 41, and 45.

261. Therefore, for these reasons, as well as the reasons set forth above for the claims from which claims 39, 41 and 45 depend, it is my opinion that claims 39, 41, and 45 are anticipated by Regeneron (8-May-2008).

10. Dependent claims 42 and 43 are anticipated by Regeneron (8-May-2008).

262. Claim 42 is dependent on independent claim 34, and recites “wherein the angiogenic eye disorder is selected from the group consisting of” several well-known eye disorders, including AMD. Claim 43 depends on claim 34, and recites “wherein the angiogenic eye disorder is age related macular degeneration.”

263. These elements are similar in scope to those discussed above with respect to claims 2 and 8, and as I explained with respect to those claims, 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).

264. Thus, for these reasons, as well as for the reasons discussed above for claim 34, it is my opinion that claims 42 and 43 of the '601 patent are anticipated by Dixon.

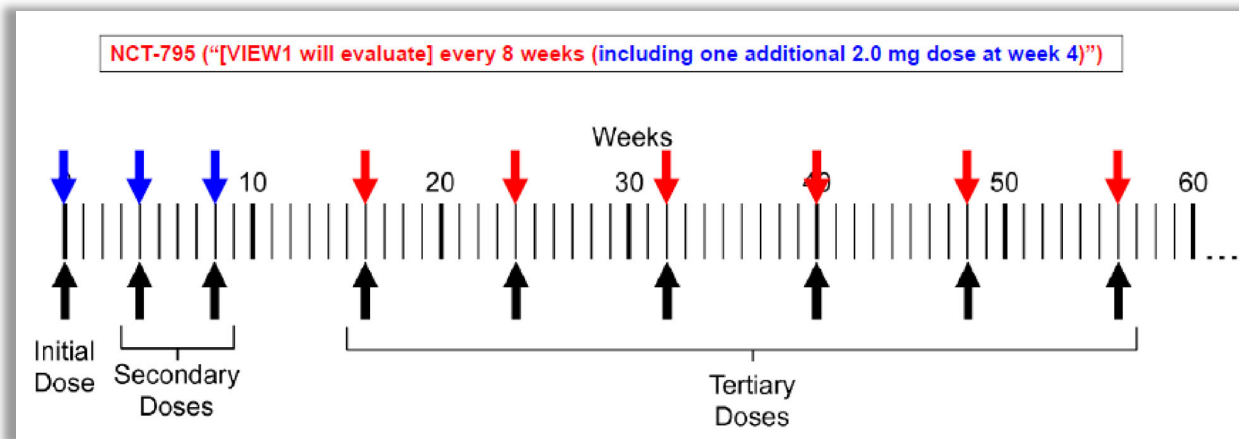
D. Claims 1-9, 34-39, 41-43, and 45 of the '601 Patent Are Anticipated by NCT00509795 (NCT-795) (Ex.1014).

1. Independent claims 1 and 34 of the '601 patent are anticipated by NCT-795.

265. I have been asked to review the challenged claims of the '601 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 '601 patent.

266. 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 '601 patent to illustrate how NCT-795 discloses the exact dosing

regimen set forth in Figure 1 of the '601 patent, as well as that which is claimed in the challenged claims of the '601 patent, as depicted here:



(Ex.1001, '601 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”).

267. With respect to the additional element of claim 34, as I discuss above, it is merely a recitation of the domain composition 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.1003, Gerritsen ¶¶ 91-100; 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.1092, AA Alignment vs 758 and 173 patents).²⁷

268. Accordingly, for at least these reasons, it is my opinion that claims 1 and 34 are anticipated by NCT-795.

2. Dependent claim 7 is anticipated by NCT-795.

269. Claim 7 purports to limit the claimed dosing regimen of claim 1 to “wherein approximately every 4 weeks comprises approximately every 28 days or approximately monthly.”

270. NCT-795 discloses that disclose the VIEW eight-week dosing arm as requiring doses “every 8 weeks (including one additional 2.0 mg dose at week 4).” (Ex.1014, NCT-795, 8). In other words, NCT-795 discloses doses at 0, 4, and 8

²⁷ Regarding the preamble, *see, e.g., supra* note 20.

weeks, i.e., every 4 weeks. A POSA would understand that “every 4 weeks” is approximately every 28 days or approximately monthly. Accordingly, NCT-795 expressly disclosed and taught the added limitation of claim 7.

271. Therefore, for these reasons, as well as the reasons set forth for claim 1 above, it is my opinion that claim 7 is anticipated by NCT-795.

3. Dependent claims 2 and 8 are anticipated by NCT-795.

272. Claims 2 and 8 depend from claims 1 and 7, respectively, and each specifies that “the age-related macular degeneration is neovascular (wet).”

273. NCT-795 expressly 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.

274. Thus, for these reasons, as well as for the reasons discussed above for claims 1 and 7, it is my opinion that claims 2 and 8 of the ’601 patent are anticipated by NCT-795.

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

275. Claim 3 limits the method of claim 1 to “wherein the patient loses less than 15 letters of Best Corrected Visual Acuity (BCVA) score.” And, claim 4,

further limits the method of claim 3 to “wherein Best Corrected Visual Acuity (BCVA) is according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.”

276. NCT-795 discloses the VIEW primary outcome measure of “[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.” (Ex.1014, NCT-795, 9). The skilled artisan would have understood that ETDRS is a well-known measure of BCVA.

277. NCT-795 disclosed the same VIEW clinical trial regimen with the same drug now claimed in claim 1 (from which claims 3 and 4 depend). In my opinion, the claimed visual acuity measures would have been a natural result flowing from the prior art Phase 3 regimen, i.e., treating patients with 2 mg of aflibercept, with a regimen involving 3 monthly loading doses followed by every every-8-week fixed dosing. Thus, through NCT-795’s disclosure of the dosing regimen used in the VIEW trials, NCT-795 anticipates this aspect of claims 3 and 4.

278. In addition, I have reviewed publications disclosing the results of the VIEW clinical trials. In Heier-2012, for example, the authors report that most patients achieved the claimed BCVA measures, providing additional evidence that such measures are a natural result of the dosing regimen set forth in claims 3 and 4. (See Ex.1018, Heier-2012, 2542).

279. Accordingly, for these reasons, as well as the reasons presented for claim 1 above, it is my opinion that claims 3 and 4 of the '601 patent are anticipated by NCT-795.

5. Dependent claims 5 and 6 are anticipated by NCT-795.

280. Claim 5 depends from claim 2 and recites “wherein the patient gains at least 15 letters of Best Corrected Visual Acuity (BCVA) score.” Claim 6 depends from claim 5 and specifies “wherein Best Corrected Visual Acuity (BCVA) is according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.”

281. NCT-795 discloses that one of the VIEW secondary outcome measures of “[t]he proportion of subjects who gain at least 15 letters of vision at Week 52.” (Ex.1014, NCT-795, 9). A POSA would have been understood that the letter measure was BCVA and assessed according to ETDRS, a well-known measure of BCVA. (*See, e.g.*, Ex.1014, NCT-795, 9 (“Mean change from baseline in BCVA as measured by ETDRS”)).

282. As with dependent claims 3 and 4 discussed above, NCT-795 disclosed the same VIEW clinical trial regimen with the same drug now claimed in claim 1 (from which claims 5 and 6 depend). In my opinion, the claimed visual acuity measures would have been a natural result flowing from the prior art Phase 3 regimen, i.e., treating patients with 2 mg of aflibercept, with a regimen involving 3 monthly loading doses followed by every every-8-week fixed dosing. Thus, through

NCT-795's disclosure of the dosing regimen used in the VIEW trials, NCT-795 anticipates this aspect of claims 5 and 6.

283. In addition, I have reviewed publications disclosing the results of the VIEW clinical trials. In Heier-2012, for example, the authors report that patients achieved the claimed BCVA measures, providing additional evidence that such measures are a natural result of the dosing regimen set forth in claims 5 and 6. (*See* Ex.1018, Heier-2012, 2542).

284. Accordingly, for these reasons, as well as for the reasons discussed above for claims 1 and 2, it is my opinion that claims 5 and 6 of the '601 patent are anticipated by NCT-795.

6. Dependent claim 35 is anticipated by NCT-795.

285. Dependent claim 35 further limits the claimed dosing regimen of independent claim 34 as follows: "wherein the VEGF antagonist is aflibercept."

286. As discussed above, NCT-795's recitation of VEGF Trap-Eye discloses this claim element, as the skilled artisan understood Regeneron's VEGF Trap-Eye and aflibercept to be names directed to the same active agent. Indeed, the identity of VEGF Trap-Eye and aflibercept was published in the prior art and known to POSAs.

287. Thus, for these reasons, as well as for the reasons discussed above for claim 34, it is my opinion that claim 35 of the '601 patent is anticipated by NCT-795.

7. Dependent claims 9 and 36 are anticipated by NCT-795.

288. Claim 9 is dependent on claim 8, which ultimately depends from claim 1, and recites the method of claim 8, “wherein exclusion criteria for the patient include (1) active intraocular inflammation; or (2) active ocular or periocular infection.” Claim 36, which depends from claim 35, recites “wherein exclusion criteria for the patient include (1) active intraocular inflammation; or (2) active ocular or periocular infection.”

289. I have been informed that the exclusion criteria elements constitute mental steps and/or written material, and thus are not entitled to patentable weight. But, as discussed above, regardless of whether the exclusion criteria elements are considered in the patentability analysis, the exclusion of patients with, for example intraocular inflammation and/or infection from methods of treatment involving administration of intraocular injections was known and published to POSAs well before the priority date of the '601 patent. (*See, e.g.*, Ex.1025, Engelbert-2010, 1370). As a result, through NCT-795’s disclosure of the VIEW clinical trials, NCT-795 discloses this aspect of claims 9 and 36.

290. Furthermore, the “exclusion criteria” listed in claims 9 and 36 were necessarily and inevitably applied in connection with practicing the VIEW clinical trial protocol, because in the context of clinical trials, clinical trial investigators are required to apply each of the exclusion criteria listed in the protocol. (*See, e.g.,* Ex.1050, Eylea MR, 112-14 (listing 37 exclusion criteria, including the two “exclusion criteria” listed in claims 9 and 36); Ex.1018, Heier-2012, Appendix 2). The application of the “exclusion criteria” recited in claims 9 and 36, therefore, was a natural result flowing from the application of the VIEW trial study protocol. Thus, NCT-795 inherently discloses this aspect of claims 9 and 36.

291. Accordingly, for these reasons, as well as for reasons discussed above for the claims from which claims 9 and 36 depend, it is my opinion that claims 9 and 36 are anticipated by NCT-795.

8. Dependent claims 37 and 38 are anticipated by NCT-795.

292. Claim 37 depends from claim 34 and recites “wherein all doses of the VEGF antagonist are administered to the patient by intraocular administration.” Claim 38, which depends from claim 37, specifies that the “intraocular administration is intravitreal administration.”

293. To a person of ordinary skill in the art, it was (and still 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. (*See, e.g.*, Ex.1001, '601 patent, 2:47-50 (“Various administration routes are contemplated . . . including . . . intraocular administration (e.g., intravitreal administration).”)). 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.

294. Thus, for these reasons, as well as for the reasons discussed above for claim 34, it is my opinion that claims 37 and 38 of the '601 patent are anticipated by NCT-795.

9. Dependent claims 39, 41, and 45 are anticipated by NCT-795.

295. Dependent claim 39 depends from claim 38, which ultimately depends from claims 34 and 37, and recites “wherein all doses of the VEGF antagonist comprise from about 0.5 mg to about 2 mg of the VEGF antagonist.” Claim 41 depends from claim 39 and specifies “wherein all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist.” Claim 45 is dependent on claim 43, and recites “wherein all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist.”

296. 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 39, 41, and 45.

297. Therefore, for these reasons, as well as the reasons set forth above for the claims from which claims 39, 41 and 45 depend, it is my opinion that claims 39, 41, and 45 are anticipated by NCT-795.

10. Dependent claims 42 and 43 are anticipated by NCT-795.

298. Claim 42 is dependent on independent claim 34, and recites “wherein the angiogenic eye disorder is selected from the group consisting of” several well-known eye disorders, including AMD. Claim 43 depends on claim 34, and recites “wherein the angiogenic eye disorder is age related macular degeneration.”

299. These elements are similar in scope to those discussed above with respect to claims 2 and 8, and as I explained with respect to those claims 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.

300. Thus, for these reasons, as well as for the reasons discussed above for claim 34, it is my opinion that claims 42 and 43 of the '601 patent are anticipated by NCT-795.

E. Claims 1-9, 34-39, 41-43, and 45 of the '601 Patent Are Obvious in View of Dixon, Either Alone or in Combination with the '758 Patent or the '173 Patent.

1. Independent claims 1 and 34.

301. 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 renders the subject matter of the challenged claims obvious for the reasons discussed below.

302. *Motivation to explore extended dosing regimens.* One of ordinary skill in the art would have been motivated to use dosing regimens that reduced 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”); *id.* (“Each injection subjects patients to risks of cataract, intraocular inflammation, retinal detachment and endophthalmitis.”)).

303. Additionally, Dixon reported the initiation of the VIEW Phase 3 trials, which included an extended dosing regimen as a solution to the dosing frequency issue, through its disclosure of three monthly loading doses followed by every-8-week dosing. (*Id.*, 1576). Thus, in my opinion, a person of ordinary skill in the art would have been motivated to adopt the disclosed Phase 3 regimen as a solution to the need for less frequent injections.

304. ***Reasonable expectation of success.*** It is my opinion that a person of ordinary skill in the art would have had a reasonable expectation of success using the VIEW regimens for treating wet AMD.

305. First, Dixon, in addition to reporting on the Phase 3 VIEW regimens, also disclosed a summary of Regeneron's CLEAR-IT-2 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.*, 1576). 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

306. As Dixon further notes, during the PRN dosing phase, which covered 40 weeks, patients only required, on average, 1.6 doses during the PRN dosing phase. (Ex.1006, Dixon, 1576).²⁸ 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

²⁸ Dixon reported these results in 2009 and Regeneron reported these results in 2008 at a Retina Society Meeting. Among other things, Regeneron publicly reported that the maximum number of injections received by a patient in the monthly loading/PRN treatment arm was 4 injections, (Ex.1055, Retina Society Meeting Presentation, slide 12), which averages out to about one injection every 10 weeks. Some patients required zero injections after the loading dose phase (*id.*).

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)). When patients are having their AMD managed with an average of only 1.6 injections over a 40-week period, there is more than a reasonable expectation that an 8-week fixed dosing regimen will show success.

307. In my opinion, the very positive Phase 2 results would have provided a POSA with a reasonable expectation of success, especially given that the Phase 3 trial would actually result in *more injections* per year (8) than in the Phase 2 monthly/PRN arm (5.6).

308. Second, this 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.1012, Regeneron (28-April-2008), 1). Indeed, after the Phase 2 results, Regeneron did in fact decide to go with a regimen of three monthly loading doses followed by every-8-week dosing for its Phase 3 trial *and* publicly announced this decision. (*Id.*, 1-2). Despite clinical trials being expensive, and that Regeneron was a small company undergoing financial hardships at the time of starting the VIEW trials,²⁹ Regeneron still made the decision to go ahead with the 2Q8 arm of the VIEW trial.

²⁹ Ex.1085, IPR2021-00881 Ex.2050, ¶¶79, 117.

309. Notably, PO's experts testified that Regeneron could have gotten approval of aflibercept purely based on the 4-week VEGF Trap-Eye dosing arms. (Ex.1085, IPR2021-00881 Ex.2050, ¶126 (based on preliminary Phase 2 data from CLEAR-IT-2 "[Dr. Brown and Dr. Heier] thought monthly dosing of VEGF Trap-Eye would likely work (*i.e.*, be noninferior to Lucentis monthly dosing)" in Regeneron's Phase 3 VIEW trials); *see also* Ex.1016, IPR2021-00881 Ex.1109, 171:19-172:3 ("I believe the Example 5, which was a Phase 2 clinical trial, provided a very positive signal that VEGF-Trap given every eight weeks after initial and secondary doses was highly efficacious in improving visual acuity, as stated in the table at Week 24 and 52.")). This further supports my opinion that if Regeneron did not have a reasonable expectation of success, it would not have initiated the 2Q8 arm of the trial.

310. Regeneron's own expectation that the 2Q8 arm would be successful is also supported by the FDA's finding that an "8-week dosing interval could potentially maintain the effect of VEGF Trap-Eye in Phase-3 studies." (Ex.1086, IPR2021-00881 Ex.2098, 7 (stating that the combination of VEGF Trap's binding affinity being higher than native VEGF receptors and, "unlike other anti-VEGF molecules, VEGF Trap also binds to PlGF, with higher binding affinity than does its native receptor" was "expected to potentially contribute to longer lasting action, thereby leading to a dosing interval longer than once monthly"))).

311. 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, along with the fact that Regeneron initiated Phase 3 testing, would have indeed had a reasonable expectation of success that a Q8 dosing regimen would be effective.

312. *The aflibercept (VEGF-Trap) molecule was known in the art.* With respect to the aflibercept (VEGF-Trap) molecule recited in claims 1 and 34, 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 domain composition 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.1008, '173 patent, 1:42-52 (“In a specific and preferred embodiment, the VEGF Trap is VEGFR1R2-FcΔC1(a) (also termed VEGF Trap_{R1R2}) comprising the nucleotide sequence set forth in SEQ ID NO:1 and the amino acid sequence set forth in SEQ ID NO:2.”); Ex.1092, AA Alignment vs 758 and 173 patents).

313. In sum, 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 the '173 patent, makes claims 1 and 34 of the '601 patent obvious.

2. Dependent claim 7.

314. Claim 7 purports to limit the claimed dosing regimen of claim 1 to “wherein approximately every 4 weeks comprises approximately every 28 days or approximately monthly.”

315. As discussed above, Dixon discloses the element of claim 7 (“wherein approximately every 4 weeks comprises approximately every 28 days or approximately monthly”) in the reference’s express teaching of the VIEW “monthly” loading doses. (Ex.1006, Dixon, 1576).

316. 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 the '173 patent, makes claim 7 of the '601 patent obvious.

3. Dependent claims 2 and 8.

317. Claims 2 and 8 depend from claims 1 and 7, respectively, and each specifies that “the age-related macular degeneration is neovascular (wet).”

318. As discussed above in the anticipation section, 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).

319. Thus, for these reasons, as well as for the reasons discussed above for claims 1 and 7, 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 the '173 patent, makes claims 2 and 8 of the '601 patent obvious.

4. Dependent claims 3 and 4.

320. Claim 3 limits the method of claim 1 to "wherein the patient loses less than 15 letters of Best Corrected Visual Acuity (BCVA) score." And, claim 4, further limits the method of claim 3 to "wherein Best Corrected Visual Acuity (BCVA) is according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score."

321. In my opinion, a POSA would have had a reasonable expectation of success of achieving those BCVA criteria, based upon the results of the Phase 2 clinical trials, also disclosed in Dixon. For example, Dixon discloses that in Phase

2, a regimen employing *even fewer doses* than the number planned for the Phase 3 trials, “[p]atients initially treated with 2.0 . . . mg of VEGF Trap-Eye monthly achieved mean improvements of 9.0 ($p < 0.0001$) . . . ETDRS [BCVA] letters with 29[%] . . . gaining . . . ≥ 15 ETDRS letters at 52 weeks.” (Ex.1006, Dixon, 1576).

322. 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 the ’173 patent, makes claims 3 and 4 of the ’601 patent obvious.

5. Dependent claims 5 and 6.

323. Claim 5 depends from claim 2 and recites “wherein the patient gains at least 15 letters of Best Corrected Visual Acuity (BCVA) score.” Claim 6 depends from claim 5 and specifies “wherein Best Corrected Visual Acuity (BCVA) is according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.”

324. Dixon discloses that in Phase 2 “[p]atients initially treated with 2.0 . . . mg of VEGF Trap-Eye monthly achieved mean improvements of 9.0 ($p < 0.0001$) . . . ETDRS [BCVA] letters with 29[%] . . . gaining . . . ≥ 15 ETDRS letters at 52 weeks.” (Ex.1006, Dixon, 1576). In my opinion, the promising results of Dixon’s reported Phase 2 trials would have provided the person of ordinary skill in the art with a reasonable expectation of success of achieving those BCVA criteria.

325. Accordingly, for this reason, as well as for the reasons discussed above for claims 1 and 2, 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 the '173 patent, makes claims 5 and 6 obvious.

6. Dependent claim 35.

326. Dependent claim 35 further limits the claimed dosing regimen of independent claim 34 as follows: “wherein the VEGF antagonist is aflibercept.”

327. As discussed above, Dixon expressly discloses that “VEGF Trap-Eye and aflibercept (the oncology product) have the same molecular structure,” (Ex.1006, Dixon, 1575), and in fact are the same molecule: “***One*** promising new [angiogenesis inhibiting] drug is aflibercept (VEGF Trap-Eye), ***a*** fusion protein that blocks all isoforms of VEGF-A and placental growth factors-1 and -2,” (*id.*, 1573 (Abstract) (emphasis added); *id.*, 1576 (Fig. 1)).

328. Thus, for these reasons, as well as for the reasons discussed above for claim 34, 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 the '173 patent, makes claim 35 of the '601 patent obvious.

7. Dependent claims 9 and 36.

329. Claim 9 is dependent on claim 8, which ultimately depends from claim 1, and recites the method of claim 8, “wherein exclusion criteria for the patient include (1) active intraocular inflammation; or (2) active ocular or periocular infection.” Claim 36, which depends from claim 35, recites “wherein exclusion criteria for the patient include (1) active intraocular inflammation; or (2) active ocular or periocular infection.”

330. A POSA administering the VIEW1/VIEW2 dosing regimens to wet AMD patients would have applied the same exclusion criteria—(1) active intraocular inflammation and (2) active ocular or periocular infection—in order to avoid risking known complications or exacerbating an existing infection in patients. A POSA naturally would have avoided injecting eyes exhibiting signs of infection or inflammation, and Dixon’s disclosure of the risks associated with intraocular injections is consistent with that practice. (Ex.1006, Dixon, 1577 (each intravitreal injection “subjects patients to risks of cataract intraocular inflammation, retinal detachment, and endophthalmitis”))).

331. As discussed above, endophthalmitis is a potentially serious infection of the ocular tissues, which, in some cases can lead to blindness. The POSA would have understood that risk of infection occurs with intravitreal injections because naturally occurring surface bacteria (typically *Propionibacterium* or

Staphylococcus) can be carried into the eye via the syringe or through the puncture site created by the syringe. It was also widely understood amongst skilled artisans that, in the case of a pre-existing or current infection, the risk is even greater due to the presence of pathogenic microorganisms.

332. It was equally known and published well before the earliest possible priority date for the '601 patent, that patients having intraocular inflammation, such as uveitis, should be excluded from intraocular injection treatment methods. (*See, e.g., Ex.1025, Engelbert-2010, 1370; Ex.1035, Lalwani, 44*).

333. Accordingly, it would have been common sense to a POSA to avoid risking complications by excluding patients with intraocular inflammation or infection from a dosing regimen of intraocular injections given that it was widely understood in the art at the relevant time that eye infections were a problem associated with intraocular injections.

334. In sum, for these reasons and the reasons discussed above with respect to the claims from which claims 9 and 36 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 the '173 patent, makes claims 9 and 36 obvious.

8. Dependent claims 37 and 38.

335. Claim 37 depends from claim 34 and recites “wherein all doses of the VEGF antagonist are administered to the patient by intraocular administration.” Claim 38, which depends from claim 37, specifies that the “intraocular administration is intravitreal administration.”

336. 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.

337. Thus, for these reasons, as well as for the reasons discussed above for claim 34, 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 the ’173 patent, makes claims 37 and 38 of the ’601 patent obvious.

9. Dependent claims 39, 41, and 45.

338. Dependent claim 39 depends from claim 38, which ultimately depends from claims 34 and 37, and recites “wherein all doses of the VEGF antagonist comprise from about 0.5 mg to about 2 mg of the VEGF antagonist.” Claim 41 depends from claim 39 and specifies “wherein all doses of the VEGF antagonist

comprise 2 mg of the VEGF antagonist.” Claim 45 is dependent on claim 43, and recites “wherein all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist.”

339. 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)”)).

340. Therefore, for these reasons, as well as the reasons set forth above for claims 34 and 37-38, 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 the ’173 patent, makes claims 39, 41, and 45 of the ’601 patent obvious.

10. Dependent claims 42 and 43.

341. Claim 42 is dependent on claim 34, and recites “wherein the angiogenic eye disorder is selected from the group consisting of” several well-known eye disorders, including AMD. Claim 43 depends on claim 34, and recites “wherein the angiogenic eye disorder is age related macular degeneration.”

342. As explained above in connection with claims 2 and 8, 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).

343. Accordingly, for the reasons discussed above for claims 2 and 8, and the claims from which claims 42 and 43 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 the '173 patent, makes claims 42 and 43 of the '601 patent obvious.

F. Claims 9 and 36 of the '601 Patent Are Obvious Over Dixon in Combination with Rosenfeld-2006 (Ground 7), or in Combination with Heimann-2007 (Ground 8) (and, If Necessary, in Combination with the '758 Patent and the '173 Patent).

344. Dependent claim 9 recites the method of claim 8, “wherein exclusion criteria for the patient include (1) active intraocular inflammation; or (2) active ocular or periocular infection.” Claim 36, which depends from claim 35, recites “wherein exclusion criteria for the patient include (1) active intraocular inflammation; or (2) active ocular or periocular infection.”

345. I have set forth above the disclosures in Dixon that I believe anticipate and render obvious each of the Challenged Claims, and I incorporate those disclosures herein. In my opinion, claims 9 and 36 of the '601 patent also are rendered obvious in view of Dixon in combination with prior art disclosing exclusion

of patients from receiving intravitreal injections where those patients have ocular or periocular infections, or signs of such infection (i.e., inflammation).

346. First, as discussed above, the risks and potential complications of intravitreal injections were widely known amongst POSAs. For example, Dixon discloses that each intravitreal injection “subjects patients to risks of cataract, intraocular inflammation, retinal detachment, and endophthalmitis.” (Ex.1006, Dixon, 1577). Similarly, Heimann-2007 discloses that the “potentially sight-threatening complications of injections are intraocular inflammation.” (Ex.1040, Heimann-2007, 69). Consequently, persons of ordinary skill in the art recognized, and reported on, the need to avoid injecting eyes that were currently or recently infected or show signs of potential infection (i.e., “intraocular inflammation”) in order to avoid exacerbating pre-existing conditions affecting the eye.

347. The exclusion of patients having infected and/or inflamed eyes in the LUCENTIS clinical trials (MARINA/ANCHOR) was expressly disclosed in Rosenfeld-2006. (Ex.1058, Rosenfeld-2006, Appx., 2-3). Rosenfeld-2006 reports that the exclusion criteria for the MARINA clinical trial included: “[a]ctive intraocular inflammation (grade trace or above) in the study eye,” “[h]istory of idiopathic or autoimmune-associated uveitis in either eye,” “[i]nfectious conjunctivitis, keratitis, scleritis, or endophthalmitis in either eye,” and “[h]istory of other disease, metabolic dysfunction, physical examination finding, or clinical

laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that might affect interpretation of the results of the study or render the subject at high risk for treatment complications.” (*Id.*, Appx., 2-3). Heimann-2007 similarly discloses the exclusion of “patients with suspected bacterial infections of the anterior segment (e.g., blepharitis conjunctivitis)” from intravitreal injections generally. (Ex.1040, Heimann-2007, 85; *id.*, 69 (“Potentially sight-threatening complications of injections are intraocular inflammation....”)).

348. These disclosures are consistent with my typical practice prior to 2011, and, in my opinion, it would have been obvious to, and a POSA would have been motivated to, incorporate the same precautions for VEGF Trap-Eye treatment regimens in order to avoid exacerbating existing, potentially serious, conditions. Second, as Dixon expressly reports, one of the primary aims in the aflibercept VIEW trials was to assess the non-inferiority of aflibercept compared to monthly ranibizumab (LUCENTIS). (Ex.1006, Dixon, 1576 (“This non-inferiority study will evaluate...VEGF Trap-Eye...compared with 0.5 mg of ranibizumab administered every 4 weeks.”)). A POSA would have been motivated to use the same or very similar set of eligibility criteria in VIEW as were used in the ranibizumab MARINA and ANCHOR clinical trials in order to maintain consistency across, and enable meaningful comparison with the outcomes of, the VIEW and MARINA/ANCHOR

trials. (Ex.1059, Christensen, 953 (“An equivalence or non-inferiority trial should mirror as closely as possible the methods used in previous superiority trials assessing the effect of the control therapy versus placebo.” “[I]t is important that the inclusion and *exclusion criteria*, which define the patient population...are the same as in the preceding superiority trials, which have evaluated the reference therapy being used in the comparison.” (emphasis added))).

349. It would have been obvious for a POSA to consult the MARINA/ANCHOR trials (which were highly public and widely recognized by those of ordinary skill in the art) for guidance in designing a Phase 3 study of aflibercept in AMD patients that involved intravitreal administration. Even if not necessary for purposes of comparison to ranibizumab, a POSA would have understood that existing or recent inflammation/infection events could confound the analysis of the clinical efficacy and safety of aflibercept in the VIEW trials, and could potentially lead to more unwanted adverse events.

350. Third, as reported by Dixon, a POSA was motivated to minimize injections and thus adopt dosing regimens that allowed for less frequent intravitreal injections than the FDA-approved monthly dosing for Lucentis. (Ex.1006, Dixon, 1577 (“significant time and financial burden falls on patients during their [monthly] treatment course” and “[d]esirable attributes for emerging therapies for neovascular AMD include . . . decreased dosing intervals”)). Dixon also reported the known

“time and financial burden[s] of monthly injections” and disclosed “the initiation of studies to examine the efficacy of *alternative dosing schedules*.” (Ex.1006, Dixon, 1574 (emphasis added)).

351. Finally, Dixon’s disclosures further provided a POSA with a reasonable expectation of success, particularly in light of Dixon’s reported increases in visual acuity and mean decreases in retinal thickness resulting from the Phase 2 regimen, which consisted of four monthly loading doses followed by PRN dosing, as well as Dixon’s disclosure that Phase 2 patients required on average only 1.6 additional injections after the four monthly loading doses during the one-year study. (Ex.1006, Dixon, 1576). Consequently, a POSA would have reasonably expected success in administering the VIEW1/VIEW 2 dosing regimens to AMD patients in light of the positive Phase 2 AMD trial results, as reported in Dixon.

352. Accordingly, it is my opinion that the disclosures of Dixon in combination with the disclosures of Rosenfeld-2006 or Heimann-2007, and, if necessary, in combination with the disclosures of the VEGF Trap domain architecture and VEGF Trap amino acid and nucleotide sequences in the ’758 patent and the ’173 patent, make claims 9 and 36 of the ’601 patent obvious.

IX. SECONDARY CONSIDERATIONS.

353. 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.³⁰ 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 ’601 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.

354. For example, to the extent Regeneron asserts unexpected results were obtained with the VIEW1/VIEW2 regimen and thereafter described in Example 4 of the ’601 patent, I disagree. As I discuss above, Dixon reports Phase 2 data showing mean visual acuity gains of nine (9.0) letters and a mean decrease in retinal thickness of 143 μm using a regimen that resulted in fewer average doses (average of 5.6 injections/year) than their Phase 3 every-eight-week regimen (8 injections/year). (Ex.1006, Dixon, 1576). Accordingly, in light of these Phase 2 results, there is nothing unexpected about the every-eight-week results obtained by Regeneron in connection with the VIEW trials.

³⁰ I understand that any showing of “secondary considerations” by the patent owner is not relevant to an anticipation analysis.

355. 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 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. Thus, should Regeneron attempt to characterize the standard of care at the relevant time as monthly dosing to argue the purported unexpectedness of the results from the claimed every-eight-week dosing regimen, this would ignore the actual real-world practice of ophthalmologists. (*See, e.g.*, Ex.1090, IPR2021-00881 Ex.2103, 2-3).

356. 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 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); Ex.1003, Gerritsen ¶¶ 42-43). 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 (i.e., PRN) regimens could achieve outcomes similar to that observed for monthly dosing, while employing fewer injections. (*See, e.g.,* Ex.1030, Mitchell, 6-7; *compare* Fig. 1(e) with Fig. 1(a) and (b); 6 (“this study [PrONTO] suggests that flexible OCT-guided retreatment could sustain visual gain with fewer injections.”)).

357. Fourth, in my opinion, the results reported in Heier-2012 were not unexpected in light of the positive results reported in the prior art, including in Dixon, 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.1018, 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.1012, Regeneron (28-April-2008), 1; *see also id.* (“Due to its high affinity for all isoforms of VEGF-A and PlGF . . . 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.”)).

358. Fifth, in my opinion, there was nothing new or non-obvious about the regimen Regeneron settled upon given the state of the art and the practical realities of treating wet AMD patients with intravitreal injections. 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). In sum, the dosing regimens claimed in the '601 patent were not unexpected in my opinion.

359. Moreover, to the extent that the inventors would claim an unmet and long-felt need was fulfilled with the '601 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 '601 priority application(s) was filed.

360. 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 '601 patent that I have discussed above are responsible for any commercial success of Eylea®. In my opinion, any advantage of Eylea® over its competitors is due to the molecule, and the attributes inherent in the drug, which I understand was covered by earlier Regeneron patents that pre-date the '601 patent. To the extent that Regeneron or their technical expert(s) 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: 6/30/22

By: 
Dr. Thomas A. Albini