Exhibit 25

IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF WEST VIRGINIA
AT CLARKSBURG

REGENERON PHARMACEUTICALS, INC., Plaintiff, v. MYLAN PHARMACEUTICALS INC., Defendant.	Case No. 1:22-cv-00061-TSK **HIGHLY CONFIDENTIAL**

OPENING EXPERT REPORT OF DR. THOMAS A. ALBINI

I. INTRODUCTION AND QUALIFICATIONS.

1. I, Dr. Thomas A. Albini, have been retained to testify as an expert on behalf of Mylan Pharmaceuticals Inc. ("Mylan") in the above-captioned action. If called upon, I am prepared to testify as an expert witness in the area of vitreoretinal disorders and treatments of the same. I expect to testify about my background, qualifications, and experience, as well as about the issues set forth in this report, including in rebuttal to testimony by any experts testifying on behalf of Plaintiff Regeneron Pharmaceuticals, Inc., or any other party.

2. As I understand it, Plaintiff presently asserts the following patent claims against Mylan: claims 5-9, 11-12, 15-17, 19, 21, 23-25, 27, 28, 31-33, and 36 of U.S. Patent No. 10,888,601 ("601 patent"); claims 4, 7, 9, 11, and 14-18 of U.S. Patent No. 11,084,865 ("865 patent"); claims 2-4, 6, and 12-16 of U.S. Patent No. 11,104,715 ("715 patent"); and claims 1-23 and 25-30 of U.S. Patent No. 11,253,572 ("572 patent").

3. While some of the scientific discussions I include in this report may have some relevance to the 865 patent and/or the 715 patent, this report addresses claims 5-9, 11-12, 15-17, 19, 21, 23-25, 27, 28, 31-33, and 36 of the 601 patent ("601 patent Asserted Claims") and claims 1-23 and 25-30 of the 572 patent ("572 patent Asserted Claims").

4. This report, including the attached exhibits, contains my opinions and the factual bases for those opinions; information I considered in forming those opinions; my qualifications (including a list of publications authored or co-authored by me); and compensation for my time. The opinions and facts set forth in this report are based upon information made available to me, as well as my knowledge and experience in treating vitreoretinal disorders and the prescription, and intravitreal administration, of VEGF antagonists. I reserve the right to supplement or amend this report based on additional information obtained by or made available to me (such as documents and deposition transcripts), including in light of any additional fact discovery that might take place

and ongoing expert discovery, or in order to clarify the information provided herein. I specifically reserve the right to supplement or amend this report in response to any arguments made by Plaintiff or any expert for Plaintiff or any other party, or based on any relevant Court rulings, and expect to supplement or amend this report in response to, at the very least, arguments made by one or more experts for Plaintiff. I further reserve the right to rely upon the reports and/or opinions of any expert for Mylan or any other party. While I use various headings in my report, they are for convenience only; headings do not limit or otherwise impact my ability to rely on any information in this report to support any point or opinion in this report, regardless of where found, and I reserve the right to do so.

5. 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.

6. 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.

7. 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.

8. 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.

9. 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.

10. 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.

11. 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.

12. 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.

13. 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.

14. Additional details concerning my background, training and experience are contained in my current *curriculum vitae*, attached hereto as **Exhibit 1**.

15. I have been asked by Mylan to opine on several subjects in this case, including, but not limited to, those detailed in this report.

16. In forming the opinions set forth in this report, I considered and relied upon my education, background, and years of experience in the fields of vitreoretinal disorders and treatments of the same, including through the use of VEGF antagonists. I also reviewed and considered the documents cited in this report and/or listed as part of this report in **Exhibit 2.** As noted above, I reserve the right to supplement or amend this report based on additional information obtained by or made available to me (such as documents and deposition transcripts), including in light of any additional fact discovery that might take place and ongoing expert discovery, or in order to clarify the information provided herein. I specifically reserve the right to supplement or amend this report in response to any arguments made by Plaintiff or any expert for Plaintiff or any other party.

II. DISCUSSION.

17. I understand that the 601 and 572 patents come from the same patent family. I also understand that Plaintiff was asked to identify, for each claim of the 601 and 572 patents, the date

that the claimed subject matter was first conceived and the date it was reduced to practice. I understand that Plaintiff stated in response that "Dr. Yancopoulos conceived of the inventions in the asserted claims of the '572 and '601 patents and began diligent reduction to practice no later than January 13, 2010, or in the alternative no later than November 2010, or in the alternative no later than December 2010, or in the alternative no later than January 2011, or in the alternative no later than November 21, 2011."

18. I have been asked by counsel to use January 13, 2011, as the priority date of the 601 patent and the 572 patent for purposes of my report. As indicated below, I have been asked for my opinion regarding the invalidity of certain claims under the assumption that those claims have a priority date of July 12, 2013. If Plaintiff attempts to assert earlier or different invention dates and/or filing dates for any of the 601 patent Asserted Claims or 572 patent Asserted Claims, I reserve the right to respond.

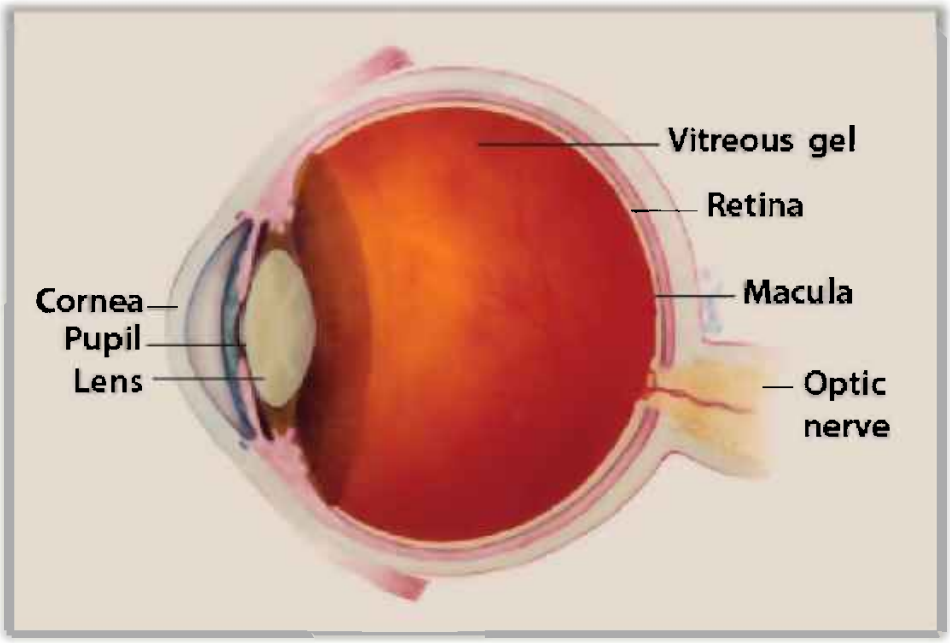
19. I reserve the right to provide further opinions and/or to rely on additional references in the event that I am asked to do so, for example, if Plaintiff or its experts challenge that any references or products cited in this report are within the prior art. I also reserve the right to respond to any evidence of an earlier invention date (including evidence of conception, reduction to practice, and/or diligence), and/or any evidence of an earlier or different filing date, should Plaintiff attempt to rely on any earlier or different invention/filing dates.

A. Background.

20. The following provides a brief background regarding vitreoretinal disorders and treatments of the same, including through the use of VEGF antagonists. I can, and reserve the right to, discuss these issues in more detail.

1. Vitreoretinal Disorders.

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



(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.

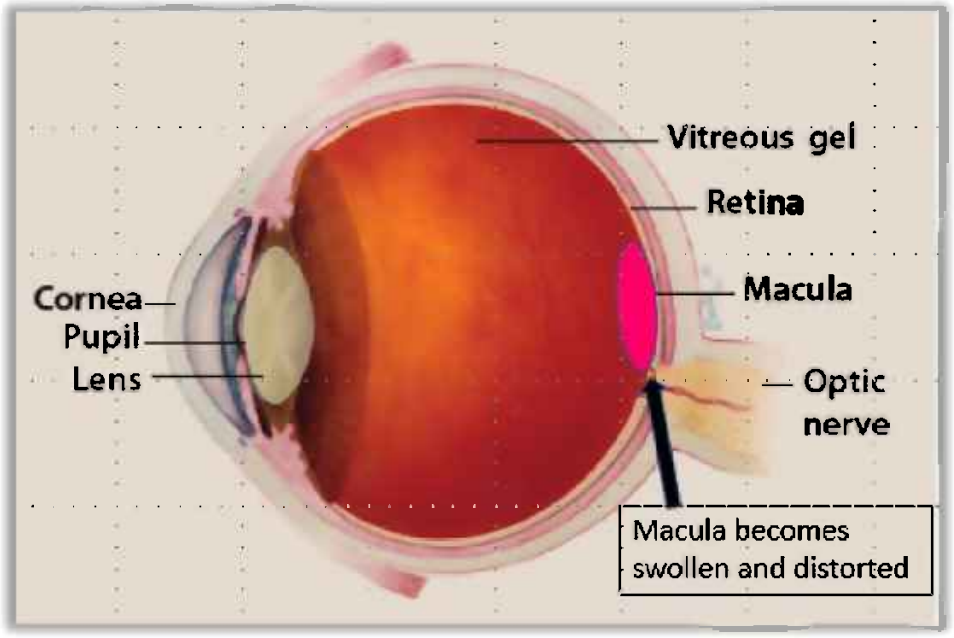
22. Vitreoretinal disorders such as AMD and diabetic retinopathy (DR) are the leading causes of visual impairment in developed countries, and the prevalence of these disorders is expected to rise with the increase in the aged population. (*See* Dixon, 1573).

a. Age-related macular degeneration (AMD).

23. 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." (NIH AMD, 1).

24. AMD can be classified as either "dry" (nonexudative) or "wet" (exudative). (*See, e.g.*, 4-28-2008 Regeneron Press Release, 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:



(NIH AMD, 2 (modified to illustrate neovascular (wet) AMD); *see also* 4-28-2008 Regeneron Press Release, 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.

25. 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." (Dixon, 1573).

26. 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* Brown 2007, 627; Dixon, 1573 ("[Patients treated with photodynamic therapy] continued to experience a decline in visual acuity and the treatment was of questionable cost and effectiveness.")).

b. Diabetic retinopathy (DR).

27. DR "occurs when diabetes damages the tiny blood vessels in the retina, which is the light-sensitive tissue at the back of the eye." (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).

c. Diabetic macular edema (DME).

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

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

29. 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* 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.*, 1359-61).

3. VEGF Antagonists.

30. 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," (4-28-2008 Regeneron Press Release, 2), additional research also identified a role for VEGF in tumor angiogenesis, with studies showing an upregulation of VEGF in various tumor types, (Ferrara 2005, 968). As a result, anti-angiogenic VEGF inhibitors were identified as potential therapies, and were soon developed and entered clinical testing. (Ferrara 2005, 971).

31. 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).

32. 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; 4-28-2008 Regeneron Press Release, 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.*, Bashshur 2006, 1-2; Bashshur 2008, 250).

33. 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.

34. 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.

35. 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.*, Ferrara 2006, 862-66).

36. The LUCENTIS® prescribing information available in 2006 also suggested a regimen of less frequent dosing following four monthly intravitreal injections. (Lucentis, 1). Less frequent dosing was a preferred option due to the nature of intravitreal injections. (*See, e.g.*, 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.")).

37. 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.

38. In addition, as discussed further below, potential complications that can occur from intravitreal injections include subconjunctival hemorrhage, infection, and inflammation. (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 *Streptococcus* 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. (Jager 2004, 678 (endophthalmitis presenting "the greatest likelihood for acute and irreversible vision loss"); 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 [include] intraocular inflammation")).

39. 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.

40. 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.*, Mitchell, 6-7 (summarizing 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. (Mitchell, 6-7; *see, e.g.*, Lalwani 2009, 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. (Engelbert, 1369 ("PrONTO-style dosing has become popular.")).

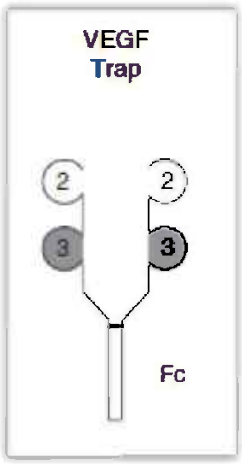
41. Also, in my experience, by 2010/2011 very few physicians were engaging in straight monthly dosing of VEGF antagonists. The typical practice was to either (1) treat with 2 or 3 monthly loading doses, followed by as-needed dosing thereafter, based on OCT and visual acuity assessments; or (2) engage 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.*, Spaide, 305; Spielberg, 24; Retinal Physician I, 2-3).

42. 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.*, Dixon, 1574; 4-28-2008 Regeneron Press Release, 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); Keane, 592 ("[M]uch effort has focused on the development of alternative treatment regimens, which would reduce the number of injections required . . . .")).

4. VEGF Trap-Eye/Aflibercept.

43. 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:



(Dixon, 1575-76, Fig.1; *see also* 4-28-2008 Regeneron Press Release, 2 ("VEGF Trap-Eye is a fully human, soluble VEGF receptor fusion protein that binds all forms of VEGF-A along with the related Placental Growth Factor (PIGF).")).

44. 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. (Holash 2002, 11393).

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

46. 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).

47. The Holash 2002 authors concluded that VEGF Trap may be useful in the treatment of retinopathies, given the contribution of pathological angiogenesis to such disorders. (*See id.*).

48. 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.*, 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.")).

49. 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. (Rudge 2005, 411).

50. 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* Nguyen-2006, 1522.e10). The authors also noted that the VEGF Trap was in the process of entering even more clinical trials related to vascular eye diseases. (Rudge 2005, 415; *see also* Rudge 2008, 417-18).

51. 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)." (Dixon, 1573; *see also, e.g.*, Adis, 261 ("Aflibercept....VEGF Trap-Eye"; "Aflibercept is in clinical development....Regeneron and Bayer are developing the agent for eye disorders.")).

52. 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.*, 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 SEQID NO: 2"); Holash 2002, 11397 ("Herein we describe the engineering of an anti-VEGF agent, termed VEGF-Trap$_{R1R2}$."); Rudge 2007, 18363, 18370 (discussing VEGF Trap, including "aflibercept" as a keyword, and citing back to Holash 2002 (ref. 20))). Persons having ordinary skill in the art ("POSAs") prior to 2011 understood VEGF Trap-Eye to refer to the same molecule disclosed in Holash 2002, and understood it to be the same molecule as aflibercept. Heier 2009A 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$_{R1R2}$. (Retinal Physician II, 2, 5). Other articles using the term aflibercept refer back to Holash

2002 and its description of VEGF Trap$_{R1R2}$. (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 2002 (ref. 5))).

53. 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.

54. 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. (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. (2009 Regeneron 10-Q, 19 ("VEGF Trap-Eye is a specially purified and formulated form of VEGF Trap for use in intraocular applications."); IPR2022-01226 Ex.1003, Gerritsen Decl. ("Gerritsen IPR Decl.") ¶¶ 91-100; 2-26-2009 Regeneron Press Release, 1; Gerritsen IPR Decl. ¶¶ 44-47, 72-73, 76-78). No mention is made of any changes or alterations to the active pharmaceutical ingredient.

B. The 601 Patent and 572 Patent Asserted Claims.

55. I have read the 601 patent, which is titled "Use of a VEGF Antagonist to Treat Angiogenic Eye Disorders," as well as the issued claims. I am very familiar with the state of the art at the time this patent was filed, which I have been asked to assume is January 13, 2011.[1]

56. I have read the 572 patent, which is titled "Use of a VEGF Antagonist to Treat Angiogenic Eye Disorders," as well as the issued claims. I am very familiar with the state of the art at the time this patent was filed, which I have been asked to assume is January 13, 2011.[2]

57. Both the 601 patent and the 572 patent list George Yancopoulos as the sole inventor.

1. The 601 and 572 Patents' Shared Specification.

58. I understand that the 601 patent and the 572 patent share a common specification.

59. The 601 and 572 patents' specification states:

> The present invention relates to the field of therapeutic treatments of eye disorders. More specifically, the invention relates to the administration of VEGF antagonists to treat eye disorders caused by or associated with angiogenesis.

(601 patent, 1:24-27).[3]

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[1] As indicated below, I have been asked for my opinion regarding the invalidity of certain claims under the assumption that those claims have a priority date of July 12, 2013. If Plaintiff attempts to assert earlier or different invention dates and/or filing dates for any of the 601 patent Asserted Claims or 572 patent Asserted Claims, I reserve the right to respond.

[2] As indicated below, I have been asked for my opinion regarding the invalidity of certain claims under the assumption that those claims have a priority date of July 12, 2013. If Plaintiff attempts to assert earlier or different invention dates and/or filing dates for any of the 601 patent Asserted Claims or 572 patent Asserted Claims, I reserve the right to respond.

[3] Throughout this section I have include citations to the specification of the 601 patent, but I note that the 601 and 572 patents share a specification and thus the same disclosures are also found in the 572 patent specification.

60. The specification also discloses:

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

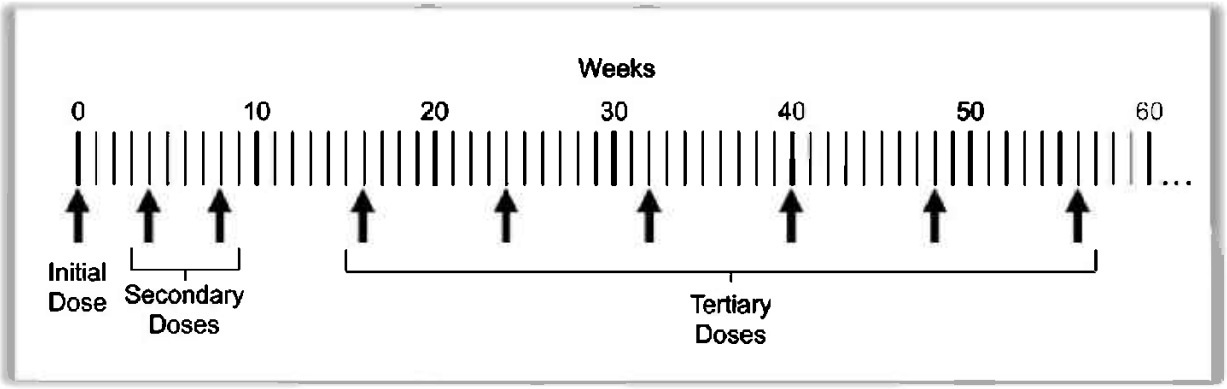
(*Id.* at 2:33-36).

61. The specification provides the following definition:

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

(*Id.* at 3:42-56).

62. In addition, the specification discloses the prior art VIEW1/VIEW2 regimen, which became the FDA-approved regimen for EYLEA® (i.e., VEGF Trap-Eye/aflibercept). (*See, e.g.*, *id.* at 21:41-46). The VIEW1/VIEW2 dosing regimen is depicted in Figure 1 of the 601 patent and is described as "an exemplary dosing regimen of the present invention":



(*Id.*, Fig. 1, 2:61 – 3:2; *see also id.*, 4:10-12).

63. The specification also sets forth seven examples. A brief summary of the examples is below.

64. ***Example 1.*** A Phase I neovascular AMD study, in which patients received a single dose of VEGFT, is reported in Example 1. (*Id.*, 8:9-27). At the end of the Example 1 study BCVA measurements were taken. (*Id.*).

65. ***Example 2.*** A Phase II neovascular AMD study, in which patients received a 3 doses of VEGFT at 4-week and/or 12-week intervals is reported in Example 2. (*Id.*, 8:34-59). Retina thickness was measured at the end of the study. (*Id.*).

66. ***Example 3.*** A Phase I neovascular AMD study, in which patients received a 4 doses of VEGFT or a placebo over 8-weeks is reported in Example 3. (*Id.*, 8:66 – 9:20). BCVA measurements were taken at the end of the study. (*Id.*).

67. ***Example 4.*** Two parallel Phase III neovascular AMD clinical trial is reported in Example 4. (*Id.*, 9:27 – 14:4). "The primary objective of these studies was to assess the efficacy of IVT administered VEGFT compared to ranibizumab." (*Id.*, 9:31-33). Subjects were randomly assigned to "1 of 4 dosing regimens: (1) 2 mg VEGFT administered every 4 weeks (2Q4); (2) 0.5 mg VEGFT administered every 4 weeks (0.5Q4); (3) 2 mg VEGFT administered every 4 weeks

to week 8 and then every 8 weeks (with sham injection at the interim 4-week visits when study drug was not administered (2Q8); and (4) 0.5 mg ranibizumab administered every 4 weeks (RQ4)" administered to patients. (*Id.*, 9:58-65). Specific inclusion and exclusion criteria were applied during the study. (*Id.*, 10:50 – 12:22). The 52-week results from both studies are summarized in Table 1:

TABLE 1

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

[a]Following three initial monthly doses

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

(*Id.*, 13:20-46).

68. ***Example 5.*** A Phase II clinical trial of VEGFT in subjects with DME is reported in Example 5. (*Id.*, 14:9-54). Below is the clinical trial dosing schedule:

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

(*Id.*, 14:9-23). Mean gains in visual acuity versus baseline were shown in Table 2:

TABLE 2

	n	Mean change in visual acuity at week 24 versus baseline (letters)	Mean change in visual acuity at week 52 versus baseline (letters)
Laser	44	2.5	−1.3
VEGFT 0.5 mg monthly (0.5Q4)	44	8.6**	11.0**
VEGFT 2 mg monthly (2Q4)	44	11.4**	13.1**
VEGFT 2 mg every 8 weeks[a] (2Q8)	42	8.5**	9.7**
VEGFT 2 mg as needed[a] (PRN)	45	10.3**	12.0**

[a]Following three intial monthly doses
**p < 0.01 versus laser

69. ***Example 6.*** A Phase III study, in which Naive Patients with Macular Edema Secondary to CRVO is reported in Example 6. (*Id.*, 14:60 – 15:34). Below is the clinical trial dosing schedule:

> In this randomized, double-masked, Phase 3 study, patients received 6 monthly injections of either 2 mg intravitreal VEGFT (114 patients) or sham injections (73 patients). From Week 24 to Week 52, all patients received 2 mg VEGFT as-needed (PRN) according to retreatment criteria. Thus, "sham-treated patients" means patients who received sham injections once every four weeks from Week 0 through Week 20, followed by intravitreal VEGFT as needed from Week 24 through Week 52. "VEGFT-treated

(*Id.*, 14:60 – 15:1).

70. ***Example 7.*** Example 7 purports to set forth "[s]pecific, non-limiting examples of dosing regimens within the scope of the present invention." (*Id.*, 15:38-39). In total, twenty such "dosing regimens" are set forth in Example 7. (*See generally id.*, 15:35 – 17:27). According to Example 7:

> Any of the foregoing administration regimens may be used for the treatment of, e.g., age-related macular degeneration (e.g., wet AMD, exudative AMD, etc.), retinal vein occlusion (RVO), central retinal vein occlusion (CRVO; e.g., macular edema following CRVO), branch retinal vein occlusion (BRVO), diabetic macular edema (DME), choroidal neovascularization (CNV; e.g., myopic CNV), iris neovascularization, neovascular glaucoma, post-surgical fibrosis in glaucoma, proliferative vitreoretinopathy (PVR), optic disc neovascularization, corneal neovascularization, retinal neovascularization, vitreal neovascularization, pannus, pterygium, vascular retinopathy, etc.

(*Id.*, 15:38 – 17:27). However, Example 7 does not include any data regarding patients with any of the listed disorders receiving any of the listed "administration regimens."

2. Priority History of the 601 and 572 Patents.

71. I understand that the 601 patent issued on January 12, 2021, from U.S. Patent Application No. 16/397,267 ("267 application"), filed on April 29, 2019, as a purported continuation of U.S. Patent Application No. 16/159,282, filed on October 12, 2018, as a purported

continuation of U.S. Patent Application No. 15/471,506, filed on March 28, 2017, as a purported continuation of U.S. Patent Application No. 14/972,560, filed on December 17, 2015, as a purported continuation of U.S. Patent Application No. 13/940,370, filed on July 12, 2013, as a purported continuation-in-part of International Application No. PCT/US2012/020855, filed on January 11, 2012. The 601 patent also purports to claim priority to U.S. Provisional Patent Application Nos. 61/432,245 ("245 application"), filed on January 13, 2011; 61/434,836 ("836 application"), filed on January 21, 2011, and 61/561,957 ("957 application"), filed on November 21, 2011.

72. I understand that the 572 patent issued on issued on February 22, 2022, from U.S. Patent Application No. 17/352,892, filed on June 21, 2021, as a purported continuation of U.S. Patent Application No. 17/350,958, filed on June 17, 2021, as a purported continuation of U.S. Patent Application No. 17/112,404, filed on December 4, 2020, as a purported continuation of U.S. Patent Application No. 17/072,417, filed on October 16, 2020, as a purported continuation of U.S. Patent Application No. 16/055,847, filed on August 6, 2018, as a purported continuation of U.S. Patent Application No. 16/397,267, filed on April 29, 2019, as a purported continuation of U.S. Patent Application No. 16/159,282, filed on October 12, 2018, as a purported continuation of U.S. Patent Application No. 15/471,506, filed on March 28, 2017, as a purported continuation of U.S. Patent Application No. 14/972,560, filed on December 17, 2015, as a purported continuation of U.S. Patent Application No. 13/940,370, filed on July 12, 2013, as a purported continuation-in-part of International Application No. PCT/US2012/020855, filed on January 11, 2012. The 572 patent also purports to claim priority to the 245 application, filed on January 13, 2011; the 836 application, filed on January 21, 2011; and the 957 application, filed on November 21, 2011.

3. The 601 and 572 Patent Asserted Claims.

73. I understand that Plaintiff is currently asserting 21 claims from the 601 patent and 29 claims from the 572 patent. I understand that some of those claims are so-called dependent claims. As I understand it, a dependent claim contains all of the limitations recited in that claim, as well as all of the limitations recited in the claim(s) from which it depends. For example, asserted claim 5 of the 601 patent depends from claim 2, which depends from claim 1, of that patent. Claim 5 of the 601 patent therefore includes the limitations from claim 1 and 2 of that patent.

4. The 601 Patent Asserted Claims.

74. 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.

75. I understand that Plaintiff is asserting claims 5-9, 11-12, 15-17, 19, 21, 23-25, 27, 28, 31-33, and 36 of the 601 patent. Those claims (in **bold** below), including any unasserted claims from which they depend (not bolded below), recite:

> 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.
>
> 2. The method of claim 1, wherein the age-related macular degeneration is neovascular (wet).
>
> * * *
>
> **5. The method of claim 2 wherein the patient gains at least 15 letters of Best Corrected Visual Acuity (BCVA) score.**
>
> **6. The method of claim 5 wherein Best Corrected Visual Acuity (BCVA) is according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.**
>
> **7. The method of claim 1, wherein approximately every 4 weeks**

comprises approximately every 28 days or approximately monthly.

8. The method of claim 7, wherein the age-related macular degeneration is neovascular (wet).

9. The method of claim 8 wherein exclusion criteria for the patient include (1) active intraocular inflammation; or (2) active ocular or periocular infection.

10. A method for treating diabetic macular edema 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 5 injections followed by 2 mg approximately once every 8 weeks or once every 2 months.

11. The method of claim 10, wherein approximately every 4 weeks comprises approximately every 28 days or approximately monthly.

12. The method of claim 10, further comprising, after 20 weeks, administering, via intravitreal injection, 2 mg of aflibercept once every 4 weeks.

* * *

15. The method of claim 10 wherein the patient gains at least 15 letters of Best Corrected Visual Acuity (BCVA) score.

16. The method of claim 15 wherein Best Corrected Visual Acuity (BCVA) is according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

17. The method of claim 10 wherein exclusion criteria for the patient include (1) active intraocular inflammation; or (2) active ocular or periocular infection.

18. A method for treating diabetic retinopathy 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 5 injections followed by 2 mg approximately once every 8 weeks or 2 months.

19. The method of claim 18, wherein approximately every 4 weeks comprises approximately every 28 days or approximately monthly.

* * *

21. The method of claim 18, further comprising, after 20 weeks, administering, via intravitreal injection, 2 mg of aflibercept once every 4 weeks.

* * *

23. The method of claim 18 wherein the patient gains at least 15 letters of Best Corrected Visual Acuity (BCVA) score.

24. The method of claim 23 wherein Best Corrected Visual Acuity (BCVA) is according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

25. The method of claim 18 wherein exclusion criteria for the patient include (1) active intraocular inflammation; or (2) active ocular or periocular infection.

26. A method for treating diabetic retinopathy in a patient with diabetic macular edema, who is in need of such treatment, comprising intravitreally administering, to said patient, an effective amount of aflibercept which is 2 mg approximately every 4 weeks for the first 5 injections followed by 2 mg approximately once every 8 weeks or 2 months.

27. The method of claim 26, wherein approximately every 4 weeks comprises approximately every 28 days or approximately monthly.

28. The method of claim 26, further comprising, after 20 weeks, administering, via intravitreal injection, 2 mg of aflibercept once every 4 weeks.

* * *

31. The method of claim 26 wherein the patient gains at least 15 letters of Best Corrected Visual Acuity (BCVA) score.

32. The method of claim 31 wherein Best Corrected Visual Acuity (BCVA) is according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

33. The method of claim 26 wherein exclusion criteria for the patient include (1) active intraocular inflammation; or (2) active ocular or periocular infection.

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 immunoglobin-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.

35. The method of claim 34 wherein the VEGF antagonist is aflibercept.

36. The method of claim 35 wherein exclusion criteria for the patient include (1) active intraocular inflammation; or (2) active ocular or periocular infection.

(601 patent at claims).

5. The 572 Patent Asserted Claims.

76. I understand that Plaintiff is currently asserting claims 1-23 and 25-30 of the 572 patent, which recite:

1. A method of treating an angiogenic eye disorder in a patient in need thereof comprising sequentially administering to the patient by intravitreal injection a single initial dose of 2 mg of aflibercept, followed by one or more secondary doses of 2 mg of aflibercept, followed by one or more tertiary doses of 2 mg of aflibercept; wherein each secondary dose is administered approximately 4 weeks following the immediately preceding dose; and wherein each tertiary dose is administered approximately 8 weeks following the immediately preceding dose; wherein the patient achieves a gain in visual acuity within 52 weeks following the initial dose.

2. The method of claim 1 wherein the patient achieves a gain in Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

3. The method of claim 2 wherein the patient gains at least 7 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

4. The method of claim 3 wherein the patient achieves the gain in visual acuity within 24 weeks following the initial dose.

5. The method of claim 3 wherein only two secondary doses are administered to the patient.

6. The method of claim 3 wherein the aflibercept is formulated as an isotonic solution.

7. The method of claim 3 wherein the aflibercept is formulated with a nonionic surfactant.

8. The method of claim 2 wherein the patient gains at least 8 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

9. The method of claim 8 wherein the patient achieves the gain in visual acuity within 24 weeks following the initial dose.

10. The method of claim 2 wherein the patient gains at least 9 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

11. The method of claim 10 wherein only two secondary doses are administered to the patient.

12. The method of claim 10 wherein the aflibercept is formulated as an isotonic solution.

13. The method of claim 10 wherein the aflibercept is formulated with a nonionic surfactant.

14. The method of claim 1 wherein exclusion criteria for the patient include both of: (1) active ocular inflammation; and (2) active ocular or periocular infection.

15. A method of treating diabetic macular edema in a patient in need thereof comprising sequentially administering to the patient a single initial dose of 2 mg of aflibercept, followed by one or more secondary doses of 2 mg of aflibercept, followed by one or more tertiary doses of 2 mg of aflibercept; wherein each secondary dose is administered to the patient by intravitreal injection approximately

4 weeks following the immediately preceding dose; and wherein each tertiary dose is administered to the patient by intravitreal injection approximately 8 weeks following the immediately preceding dose.

16. The method of claim 15 wherein the patient achieves a gain in visual acuity within 52 weeks following the initial dose.

17. The method of claim 16 wherein the patient gains at least 9 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

18. The method of claim 17 wherein the aflibercept is formulated as an isotonic solution.

19. The method of claim 17 wherein the aflibercept is formulated with a non-ionic surfactant.

20. The method of claim 17 wherein the patient achieves a gain in visual acuity within 24 weeks following the initial dose.

21. The method of claim 16 wherein the patient gains at least 8 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

22. The method of claim 21 wherein the aflibercept is formulated as an isotonic solution.

23. The method of claim 21 wherein the aflibercept is formulated with a nonionic surfactant.

* * *

25. The method of claim 15 wherein four secondary doses are administered to the patient.

26. A method of treating age related macular degeneration in a patient in need thereof comprising sequentially administering to the patient a single initial dose of 2 mg of aflibercept, followed by one or more secondary doses of 2 mg of aflibercept, followed by one or more tertiary doses of 2 mg of aflibercept; wherein each secondary dose is administered to the patient by intravitreal injection approximately 4 weeks following the immediately preceding dose; and wherein each tertiary dose is administered to the patient by intravitreal injection approximately 8 weeks following the immediately preceding dose; wherein the method is as effective in achieving a gain in visual acuity as monthly administration of 0.5

mg of ranibizumab by intravitreal injection in human subjects with age-related macular degeneration at 52 weeks following the initial dose.

27. The method of claim 26 wherein only two secondary doses are administered to the patient.

28. The method of claim 26 wherein the gain in visual acuity is measured using the Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

29. A method of treating age-related macular degeneration in a patient in need thereof comprising sequentially administering to the patient a single initial dose of 2 mg of aflibercept, followed by one or more secondary doses of 2 mg of aflibercept, followed by one or more tertiary doses of 2 mg of aflibercept; wherein each secondary dose is administered to the patient by intravitreal injection approximately 4 weeks following the immediately preceding dose; and wherein each tertiary dose is administered to the patient by intravitreal injection approximately 8 weeks following the immediately preceding dose; wherein the method is as effective in maintaining visual acuity as monthly administration of 0.5 mg of ranibizumab by intravitreal injection in human subjects with age-related macular degeneration at 52 weeks following the initial dose.

30. The method of claim 29 wherein maintenance of visual acuity means loss of less than 15 letters Best Corrected Visual Acuity (BCVA) as measured by using the Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

(572 patent at claims).

C. Claim Construction.

77. I understand that Regeneron and Mylan have proposed the below constructions for two claim terms appearing in the 601 and 572 patent claims. It is also my understanding that the Court has not yet issued a ruling on this matter:

- **"best corrected visual acuity"**[4]
    - Regeneron's Proposed Construction: The best visual acuity that can be achieved with the use of a corrective lens
    - Mylan's Proposed Construction: Plain and ordinary meaning: Best Corrected Visual Acuity (BCVA) measured in letters, a clinical trial endpoint / measurement
- **"wherein exclusion criteria for the patient include"**[5]
    - Regeneron's Proposed Construction: The claim limitations are appropriately construed as: assessing the patient for (1) active ocular inflammation; and (2) administering aflibercept to the patient on the basis of the foregoing assessment. The "patient" is not limited to a clinical trial subject.
    - Mylan's Proposed Construction: To the extent the Court determines that this term should be accorded patentable weight, it should be construed as follows: wherein exclusion criteria for the patent to be eligible in the clinical study of the said method for treating include

78. Regardless of which construction is applied for each claim term, my invalidity opinions set forth herein remain unchanged. I reserve the right to amend and/or supplement my invalidity opinions to address and/or respond to any claim construction order issued by the Court and/or in response to any statements made by Plaintiff in any post-Markman briefing.

[4] The claim term "best corrected visual acuity" appears in the 601 patent at claims 5-6, 15-16, 23-24, and 31-32; and in the 572 patent at claims 2-3, 8, 10, 17, 21, and 30.

[5] The "exclusion criteria" claim term appears in the 601 patent at claims 9, 17, 25 and 33; and in the 572 patent at claim 14.

D. Legal Standards

79. For my opinions in this report, 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:

80. ***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.

81. ***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.

82. I have further been instructed that one cannot use the asserted patents themselves (here, the 601 patent and the 572 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.

83. 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.

84. I understand that before reaching any final conclusion on obviousness, the obviousness analysis requires consideration of objective indicia of nonobviousness, 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 nonobviousness 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.

85. 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.

86. 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.

87. 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.

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

E. The Person Of Ordinary Skill In The Art.

89. 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.

90. 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.

91. After considering the above-mentioned factors, it is my opinion that a person of ordinary skill in the art in the context of both the 601 patent and the 572 patent 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.

92. I understand that Plaintiff has previously taken the position that the person of ordinary skill in the art in the context of the related 338 patent is "an ophthalmologist with experience in treating angiogenic eye disorders, including through the use of VEGF antagonists." (338 IPR Final Written Decision, IPR2021-00881, Paper 94 (PTAB Nov. 9, 2022) ("338 FWD"), at 10; *see also id.* ("According to [Plaintiff's expert], 'only an ophthalmologist would have the firsthand experience of diagnosing and treating angiogenic eye disorders to which the patent is

plainly directed'")). I note that Plaintiff's proposed definition would exclude Yancopoulous—the sole, named inventor of the 338, 601, and 572 patents—who admitted he never was an ophthalmologist. (Yancopoulos Tr. at 26:23-27:3; *see also id.* at 14:8-19:13). I also understand that the Patent Trial and Appeal Board rejected Plaintiff's proposed definition, and adopted Mylan's. (*Id.* at 10-11).

93. In determining the education and experience level of the person of ordinary skill in the art, I considered several factors, including the subject matter of the 601 patent and 572 patent; the 601 patent Asserted Claims and 572 patent Asserted Claims; the prior art cited in the patents and their file histories; the technology at issue; and my over 15 years of hands-on clinical and research experience specializing in treating vitreoretinal disorders.

94. I am—and was on January 13, 2011—a person with at least ordinary skill in the art and am qualified to render opinions from the perspective of a person of ordinary skill in the art.

III. Opinions Regarding Invalidity of the 601 Patent Asserted Claims.

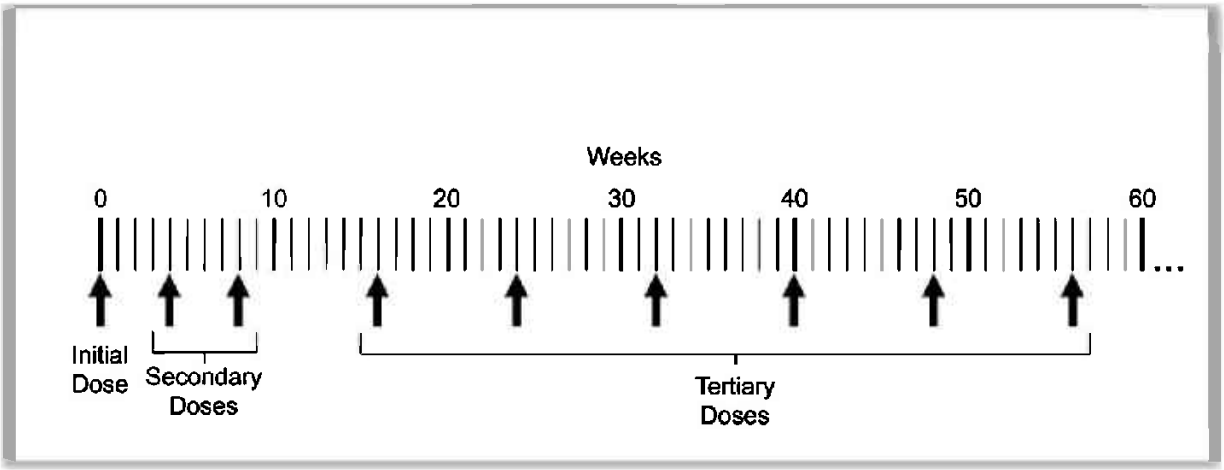
A. Anticipation of the 601 Patent Asserted Claims.

1. Claims 1-2, 5-9, 34, and 36 of the 601 Patent Are Anticipated by Several Prior Art References and Documents, Including Dixon.

95. I was asked to review the 601 patent Asserted Claims and compare them to the disclosures of the prior art. It is my opinion that each of the below references discloses every element of the claimed method(s) and thus anticipates each of the Asserted Claims of the 601 patent.

96. 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."



(601 patent, Fig. 1, 2:61 – 3:2; *see also id.*, 4:10-12).

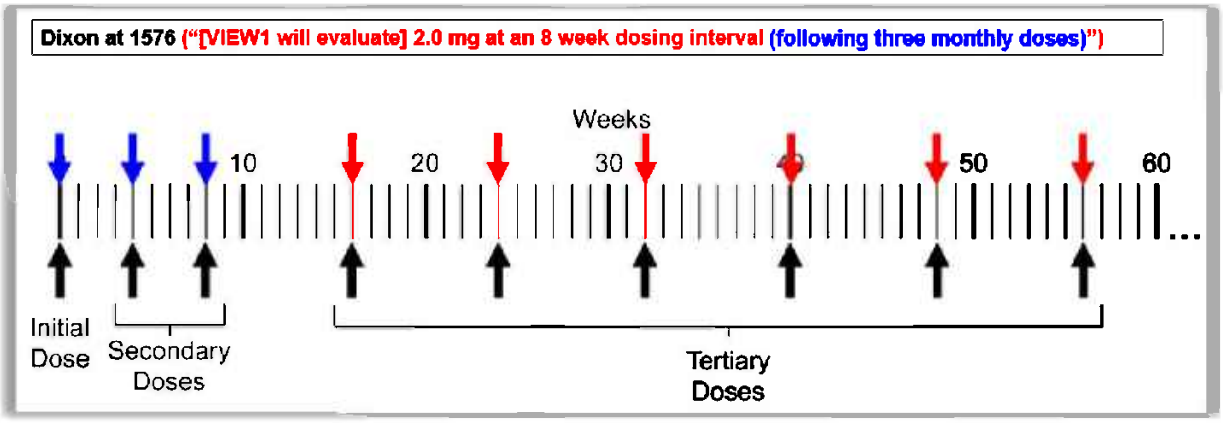
97. Based upon my reading of the patent specification, including Figure 1, and the claims of the 601 patent, it is my opinion that Figure 1 represents a dosing regimen that falls squarely within the scope of the challenged claims, including claim 1. For example, the 601 patent states that FIG. 1 "shows 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')" (601 patent, 2:64-66).	"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"
"two 'secondary doses' are administered at weeks 4 and 8, respectively" (*Id.*, 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." (*Id.*, 2:67-3:2).	"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"

98. 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 that to the Figure 1 legend: "two 'secondary doses' are administered at weeks 4 and 8, respectively." (601 patent, 2:66-67). 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.

99. 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 other claims directed to dosing regimens (i.e., claims 1, 34). I also note that this regimen comes straight from the VIEW1/VIEW2 Phase 3 studies. (*See, e.g.*, Dixon, 1576).

100. To illustrate why Dixon and the other VIEW references anticipate the challenged claims, I have prepared the following *modified* version of Figure 1 from the 601 patent (set forth below), to show how Dixon (as just one example) 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:



(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. (Dixon, 1576). 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." (Dixon, 1576).

101. 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—"wherein the VEGF antagonist is a receptor-based chimeric molecule comprising an immunoglobin-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.*, Dixon, 1575-76, Fig.1; 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)"); Dix, [0013]-[0014], [0030]; 095 patent, 1:45-54; 9-30-2009 Regeneron 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"); Gerritsen IPR Decl. ¶¶ 91-100; 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); IPR2022-01226 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.

a. Independent claims 1 and 34 are anticipated by Dixon and other references disclosing the VIEW clinical trial.

102. Below, I have constructed charts for the purpose of showing where each and every claim element from claim 1 is found in the Dixon and VIEW references:

Claim 1	Dixon[6]
A method for treating[7] age related macular degeneration in a patient in need thereof,	"VEGF Trap-Eye is a novel anti-VEGF therapy, with Phase I and II trial data indicating

[6] I have reviewed Dixon, which published in 2009. I have been informed that because Dixon published in 2009, which is more than one year prior to the earliest priority date claimed by the 601 and 572 patents, Dixon is prior art to the 601 and 572 patents.

[7] 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

Claim 1	Dixon[6]
	safety, tolerability and efficacy for the treatment of neovascular AMD." (Dixon, 1573). AMD is well known to be an angiogenic eye disorder Phase 2 patients "treated with 2.0 or 0.5 mg of VEGF Trap-Eye monthly achieved mean improvements of 9.0 ($p < 0.0001$) and 5.4 ($p < 0.085$) ETDRS letters with 29 and 19% gaining, respectively, $\geq$ 15 ETDRS letters at 52 weeks." (*Id.*, 1576). "[P]atients . . . demonstrated stabilization of their vision that was similar to previous studies of ranibizumab at 1 year." (*Id.*, 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." (*Id.*, 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)." (*Id.*, 1576).
comprising intravitreally administering, to said patient	"[A]ll anti-VEGF agents for neovascular AMD are administered only by *intravitreal injection*." (Dixon, 1574 (emphasis added)).

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 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.*, Dixon, 1576; Adis, 263, 267-68; 5-8-2008 Regeneron Press Release, 1-2; 9-28-2008 Regeneron Press Release, 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. (Heier 2012, 2541-45).

Claim 1	Dixon[6]
	"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." (*Id.*, 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-1 (CLEAR-IT-1) study." (*Id.*, 1575). The VIEW1 and VIEW2 studies "will evaluate the safety and efficacy of intravitreal VEGF Trap-Eye." (*Id.*, 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." (Dixon, 1576). Patients in this arm also displayed mean decreases in retinal thickness of 143 µm compared to baseline. (*Id.*). "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 (Background)). "VEGF Trap-Eye and aflibercept (the oncology product) have the same molecular structure." (*Id.*, 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

Claim 1	Dixon[6]
	280-fold lower potential systemic exposure than in the oncology setting." (*Id.*, 1575).
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 (*following three monthly doses*)." (Dixon, 1576 (emphasis added)).

Claim 1	Other VIEW References[8]
A method for treating[9] age related macular degeneration in a patient in need thereof,	"Regeneron and Bayer inititiated [sic] a phase III trial of aflibercept in approximately 1200 patients with the neovascular form of wet AMD in August 2007." (Adis, 263). (*See also, e.g.*, NCT 795, 3-4; NCT 377, 3, 5; 4-28-2008 Regeneron Press Release, 1; 5-8-2008 Regeneron Press Release, 1; 8-19-2008 Regeneron Press Release, 1; 9-28-2008 Regeneron Press Release, 1-2; 9-14-2009 Regeneron Press Release, 1; 2009 Regeneron 10-K, 3-4; 3-31-2009 Regeneron 10-Q, 13-14; 6-30-2009 Regeneron 10-Q, 19-20; 9-30-2009 Regeneron 10-Q, 20-21; 5-8-2008 Bayer Press Release, 1-3; 8-19-2008 Bayer Press Release, 1, 3-4).
comprising intravitreally administering, to said patient	"The noninferiority, VIEW 1 (VEGF Trap: Investigation of Efficacy and safety in Wet age-related macular degeneration) study will

[8] I have reviewed each of the above references, each of which published or were available by 2009. I have been informed that because the references published or were available by 2009, which is more than one year prior to the earliest priority date claimed by the 601 and 572 patents, each of those references are prior art to the 601 and 572 patents.

[9] 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, receiving treatment, 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.

Claim 1	Other VIEW References[8]
	evaluate the safety and efficacy of ***intravitreal*** aflibercept…" (Adis, 263). (*See also, e.g.*, NCT 795, 3, 6-8; NCT 377, 4, 6; 4-28-2008 Regeneron Press Release; 5-8-2008 Regeneron Press Release, 1; 8-19-2008 Regeneron Press Release, 1; 9-28-2008 Regeneron Press Release, 1; 9-14-2009 Regeneron Press Release, 1; 2009 Regeneron 10-K, 37; 3-31-2009 Regeneron 10-Q, 20; 6-30-2009 Regeneron 10-Q, 26; 9-30-2009 Regeneron 10-Q, 27; 5-8-2008 Bayer Press Release, 1; 8-19-2008 Bayer Press Release, 2).
an effective amount of aflibercept which is 2 mg	"This study will evaluate the safety and efficacy of aflibercept at 0.5 mg and 2.0 mg administered at 4-week intervals and 2.0 mg at an 8-week dosing interval, including one additional 2.0 mg dose at week 4." (Adis, 263). (*See also, e.g.*, NCT 795, 6-8; NCT 377, 6; 4-28-2008 Regeneron Press Release, 1-2; 5-8-2008 Regeneron Press Release, 1; 8-19-2008 Regeneron Press Release, 1; 9-28-2008 Regeneron Press Release, 1; 9-14-2009 Regeneron Press Release, 1; 2009 Regeneron 10-K, 3-4; 3-31-2009 Regeneron 10-Q, 13-14; 6-30-2009 Regeneron 10-Q, 19-20; 9-30-2009 Regeneron 10-Q, 20-21; 5-8-2008 Bayer Press Release, 2; 8-19-2008 Bayer Press Release, 2-3).
approximately every 4 weeks for the first 3 months, followed by 2 mg approximately once every 8 weeks or once every 2 months.	"This study will evaluate the safety and efficacy of aflibercept at 0.5 mg and 2.0 mg administered at 4-week intervals and 2.0 mg at an 8-week dosing interval, including one additional 2.0 mg dose at week 4." (Adis, 263). (*See also, e.g.*, NCT 795, 6-8; NCT 377, 6; 4-28-2008 Regeneron Press Release, 1-2; 5-8-2008 Regeneron Press Release, 1; 8-19-2008 Regeneron Press Release, 1; 9-28-2008

Claim 1	Other VIEW References[8]
	Regeneron Press Release, 2; 9-14-2009 Regeneron Press Release, 1; 2009 Regeneron 10-K, 3; 3-31-2009 Regeneron 10-Q, 13; 6-30-2009 Regeneron 10-Q, 19; 9-30-2009 Regeneron 10-Q, 20; 5-8-2008 Bayer Press Release, 2; 8-19-2008 Bayer Press Release, 3).

103. As a result, Dixon, as well as each of the other VIEW references above, anticipate claim 1 of the 601 patent.

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

Claim 34	Dixon
A method for treating[10] an angiogenic eye disorder in a patient in need thereof,	"VEGF Trap-Eye is a novel anti-VEGF therapy, with Phase I and II trial data indicating safety, tolerability and efficacy for the treatment of neovascular AMD." (Dixon, 1573). AMD is well known to be an angiogenic eye disorder. Phase 2 patients "treated with 2.0 or 0.5 mg of VEGF Trap-Eye monthly achieved mean improvements of 9.0 ($p < 0.0001$) and 5.4 ($p < 0.085$) ETDRS letters with 29 and 19% gaining, respectively, $\geq$ 15 ETDRS letters at 52 weeks." (*Id.*, 1576). "[P]atients . . . demonstrated stabilization of their vision that was similar to previous studies of ranibizumab at 1 year." (*Id.*, 1577). "Two Phase III studies in wet AMD [VIEW1/VIEW2] are currently under way and seek to compare monthly ranibizumab to

[10] *See* footnote 7, *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. (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
	monthly or bimonthly VEGF Trap-Eye." (*Id.*, 1577 (describing DME and RVO studies)).
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;	"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)." (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 (*following three monthly doses*)." (Dixon, 1576 (emphasis added)). As I explain above, "three monthly doses" involves a dose at baseline, i.e., day 0, as well as a "secondary dose" one month later (i.e., "4 weeks after the immediately preceding dose"), and another "secondary dose" one month after that (i.e., "4 weeks after the immediately preceding dose").
wherein each tertiary dose is administered 8 weeks after the immediately preceding dose;	"2.0 mg *at an 8 week dosing interval* (following three monthly doses)." (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 immunoglobin-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." (Dixon, 1573 (Background)). "VEGF Trap-Eye and aflibercept (the oncology product) have the same molecular structure." (*Id.*, 1575). "Structurally, VEGF Trap-Eye is a fusion protein of key binding domains of human

Claim 34	Dixon
	VEGFR-1 and -2 combined with a human IgG Fc fragment." (*Id.*, 1575).[11] VEGF Trap-Eye is "a fusion protein of binding domains of VEGF receptors-1 and -2 attached to the Fc fragment of human IgG." (*Id.*, 1576 & Fig. 1).

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

b. Dependent claim 7 is anticipated by Dixon and the other VIEW references.

106. 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.

107. 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."

108. 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*)." (Dixon, 1576 (emphasis added)).

109. Also, in my opinion, as a practicing physician and ophthalmologist, I view the terms "approximately every 4 weeks" and "approximately monthly" as meaning the same thing in the context of anti-VEGF dosing regimens. Thus, when I see the term "approximately every 4 weeks," I understand that to be approximately monthly, and vice versa. I note that the patent itself notes that "'monthly' dosing is equivalent to dosing once every four weeks." (601 patent, 8:1-2). I also note that Regeneron itself, and the named inventor, used the terms interchangeably in its public

[11] 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* ¶¶ 43-54, 101).

disclosures of the VIEW clinical trials. (*See, e.g.*, 4-28-2008 Regeneron Press Release, 2 (G. Yancopoulos: "These studies are evaluating the clinical efficacy and safety of VEGF Trap-Eye, using 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."); *see also, e.g.*, 8-19-2008 Regeneron Press Release, 1 ("the companies are evaluating VEGF Trap-Eye dosed 0.5 mg every 4 weeks, 2 mg every 4 weeks, or 2 mg every 8 weeks (following three monthly doses)"); *compare also, e.g.*, 8-19-2008 Regeneron Press Release, 1 ("in direct comparison with ranibizumab (Lucentis®, a registered trademark of Genentech, Inc.) administered 0.5 mg ***every four weeks*** according to its U.S. label") (emphasis added), *with*, Lucentis PI 2006, 2 ("LUCENTIS 0.5 mg (0.05 mL) is recommended to be administered by intravitreal injection ***once a month***.") (emphasis added)).

110. Accordingly, whether set forth in weeks or months, a person of ordinary skill in the art reading the VIEW references would have understood the dosing regimen, whether that regimen was set forth in weeks or months. Accordingly, the other VIEW references also disclose this aspect of the VIEW dosing regimen. (*See, e.g.*, Adis, 263; NCT 795, 6-8; NCT 377, 6; 4-28-2008 Regeneron Press Release, 1-2; 5-8-2008 Regeneron Press Release, 1; 8-19-2008 Regeneron Press Release, 1; 9-28-2008 Regeneron Press Release, 1-2; 9-14-2009 Regeneron Press Release, 1; 11-22-2010 Regeneron Press Release, 2; 2009 Regeneron 10-K, 3; 3-31-2009 Regeneron 10-Q, 13; 6-30-2009 Regeneron 10-Q, 19; 9-30-2009 Regeneron 10-Q, 20; 3-31-2010 Regeneron 10-Q, 17; 6-30-2010 Regeneron 10-Q, 16; 9-30-2010 Regeneron 10-Q, 16; 5-8-2008 Bayer Press Release, 2; 8-19-2008 Bayer Press Release, 3).

111. 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 and each of the other VIEW references.

c. Dependent claims 2 and 8 are anticipated by Dixon and the other VIEW references.

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

113. The Dixon reference indicates in the title that VEGF Trap-Eye was being studied for the "treatment of neovascular age-related macular degeneration." (Dixon, 1573). Likewise, the bulk of the reference discusses VEGF Trap-Eye as it relates to the treatment of neovascular age-related macular degeneration (wet 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; and the Phase 3 VIEW1 and VIEW2 clinical trials in wet AMD. 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. (*See id.*, 1576). Dixon therefore expressly discloses treating neovascular (wet) AMD, as required by claims 2 and 8.

114. Similarly, each of the VIEW references discloses that the VIEW study was being conducted with patients with wet AMD. (*See, e.g.*, Adis, 263 ("neovascular form of wet AMD" and "in wet AMD"); NCT 795, 3; NCT 377, 1; 4-28-2008 Regeneron Press Release, 1-2; 5-8-2008 Regeneron Press Release, 1-2; 8-19-2008 Regeneron Press Release, 1-2; 9-28-2008 Regeneron Press Release, 1-2; 9-14-2009 Regeneron Press Release, 1-2; 11-22-2010 Regeneron Press Release, 2; 2009 Regeneron 10-K, 3-5; 3-31-2009 Regeneron 10-Q, 13-14; 6-30-2009 Regeneron

10-Q, 19-20; 9-30-2009 Regeneron 10-Q, 20-21; 3-31-2010 Regeneron 10-Q, 16-17; 6-30-2010 Regeneron 10-Q, 16-17; 9-30-2010 Regeneron 10-Q, 16-17; 5-8-2008 Bayer Press Release, 1-2; 8-19-2008 Bayer Press Release, 1-4).

115. 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 and each of the other VIEW references

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

116. 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."

117. I have been informed that Mylan is taking the legal position that the visual acuity elements recited in claims 5 and 6 constitute statements of intended results of the claimed methods that do not result in a manipulative difference in the steps of the claim, and thus should be deemed non-limiting. Furthermore, in my opinion, the recited BCVA criteria are commonly used outcome measures in clinical trials assessing AMD patients who are receiving anti-VEGF treatment, and thus represent nothing more than the intended result of those trials, or the natural result flowing from those clinical trials. (*See, e.g.*, Nguyen 2009a, 2141-43, 2145-46; Dixon, 1575-76; Heier 2009A, 45; Brown 2006, 1433; Rosenfeld 2006, 1420, 1426). Indeed, there is nothing in the claims that instruct how to achieve the visual acuity measures recited in the claims. The claims merely recite a prior art dosing regimen, and then recite commonly used visual acuity metrics. But there are no modifications or adjustments to the dosing regimen included in the claims.

118. 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." (Dixon, 1576; *see also, e.g.*, 5-8-2008 Regeneron Press Release, 1-2; 9-14-2009 Regeneron Press Release, 1; 5-8-2008 Bayer Press Release, 2). Dixon also discloses the use of the BCVA ETDRS criteria in connection with the assessment of AMD patients. (Dixon, 1575-76; *see also, e.g.*, Retina Society Meeting Presentation, 3; 11-22-2010 Regeneron Press Release, 1-2; 12-20-2010 Regeneron Press Release, 1-2; 1-18-2011 Regeneron Press Release, 2; Heier 2012, 2538-39). Also, references such as NCT-377 and NCT-795 disclosed that the proportion of patients who gain at least 15 letters of vision at week 52 was an outcome measure of the VIEW clinical trials. (NCT-377 at 6-7; NCT-795 at 9; *see also, e.g.*, 5-8-2008 Regeneron Press Release at 1; 9-14-2009 Regeneron Press Release, 1; 5-8-2008 Bayer Press Release, 2). Accordingly, Dixon and the other VIEW references, including at least NCT-377 and NCT-795 disclose the added limitations, and thus anticipate this aspect of claims 5 and 6.

119. Dixon and the other VIEW references 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-8-week fixed dosing. In addition, the outcome measure of gain of 15 letters in BCVA is expressly set forth in several of the VIEW prior art references. Thus, through Dixon's disclosure, and the other VIEW references' disclosures, of the dosing regimen used in the VIEW trials, Dixon and the other VIEW references anticipate this aspect of claims 5-6.

120. 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* Heier 2012, 2542).

121. 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 are anticipated by Dixon, as well as each of the other VIEW references, including at least NCT 795 and NCT 377.

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

122. 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."

123. 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 clinical trials involving administration of intraocular injections was known and published to POSAs well before the priority date of the 601 patent. (*See, e.g.*, Lucentis Medical Review, 32-33 (MYL-AFL0007147-49)).[12]

124. 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.*, Eylea® Medical Review, 112-14 (listing 37 exclusion

[12] It was well known and widely understood amongst skilled artisans at the time that patients with ocular or periocular infection and/or inflammation should be excluded from treatment methods involving direct injection of medication into the eye.

criteria, including the two "exclusion criteria" listed in claims 9 and 36); 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 and each of the VIEW references disclosing the VIEW clinical trial and dosing regimen inherently disclose this aspect of claims 9 and 36.

125. Lastly, the VIEW clinical trial references make clear that the VIEW clinical trials were being conducted at least as early as 2008. (*See* Heier 2012, 2539). I am not aware of any confidentiality restrictions or obligations that would have been applicable to the exclusion criteria in that clinical trial, including at least because the exclusion criteria were largely carried over from the earlier-conducted ranibizumab studies. (*See, e.g.*, Heier 2012, 2540). Consequently, in my opinion, the subject matter of claims 9 and 36 would have been in public use or otherwise available to the public before 2010.

126. 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.

2. Claims 10-12, and 15-17 of the 601 Patent Are Anticipated by the 747 Patent and/or the 9-14-2009 Regeneron Press Release.

127. Independent claim 10 of the 601 patent recites: "A method for treating diabetic macular edema 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 5 injections followed by 2 mg approximately once every 8 weeks or once every 2 months."

128. I was asked to review claims 10-12 and 15-17 of the 601 patent and compare them to the disclosures of the 747 patent. I was also asked to review claims 10-12 and 15-17 of the 601 patent and compare them to the disclosures of the 9-14-2009 Regeneron Press Release. For the

reasons set forth herein, it is my opinion that the 747 patent and the 9-14-2009 Regeneron Press Release each anticipate claims 10-12 and 15-17 of the 601 patent, either alone, or in combination.

a. Independent claim 10 of the 601 patent is anticipated by the 747 Patent.

129. The 747 patent[13] discloses a method of treating eye disorders, including diabetic retinopathy ("DR"). (747 patent, Title, Abstract, 1:49-54, 2:9-35, 5:39-51, 6:8-24, 6:64 – 7:3). One of the complications associated with diabetic retinopathy is retinal edema (i.e., diabetic macular edema ("DME")).

130. The 747 patent further discloses treatment with VEGFR1R2-FcΔC1(a)) (i.e., VEGF Trap-Eye or aflibercept). (747 patent, SEQ ID NO:6, 2:1-2, 2:9-35, 5:28-51, 7:5-63). The 747 patent further discloses intravitreal administration of the VEGF trap protein, and treatment with 25-4000 micrograms of the VEGF trap (i.e., 2 mg). (747 patent, 2:9-35; 7:5-63; 20:15-67; 21:1 - 22:42).

131. In addition, the 747 patent discloses treatment on a monthly basis, with a preferred embodiment including an initial treatment followed by subsequent treatments between 1-6 months apart (*see, e.g.*, 747 patent, 20:62-67), which a person of ordinary skill in the art would understand could encompass monthly treatment for a series of loading doses (e.g., 5 loading doses), followed by a series of less frequent dosing every 8 weeks.

132. In addition, claim 12 depends from claim 10, and thus, as I understand it, is included in the scope of claim 10. Claim 12 is directed essentially to monthly dosing, because through its dependency on claim 10 it includes the monthly injections through week 20; but then claim 12 recites that dosing is to continue after that point on a monthly basis. The 747 patent discloses

[13] I have reviewed the 747 patent, which issued Dec. 4, 2007. I have been informed that because the 747 patent issued in 2007, which is more than one year prior to the earliest priority date claimed by the 601 and 572 patents, the 747 patent is prior art to the 601 and 572 patents.

treatment of diabetic retinopathy (and thus its underlying complications, such as diabetic macular edema), at monthly intervals. (*See, e.g.*, 747 patent, 20:62-67).

133. For at least the reasons discussed above, claim 10 is anticipated by the 747 patent.

b. Independent claim 10 of the 601 patent is anticipated by the 9-14-2009 Regeneron Press Release.

134. Independent claim 10 of the 601 patent recites: "A method for treating diabetic macular edema 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 5 injections followed by 2 mg approximately once every 8 weeks or once every 2 months."

135. The 9-14-2009 Regeneron Press Release[14] discloses VEGF Trap-Eye (aflibercept) as a drug intended for intravitreal administration. (*See, e.g.*, 9-14-2009 Regeneron Press Release, 1). The press release also discloses a phase 2 clinical trial in which aflibercept is administered to patients with DME in 2 mg doses for 3 monthly loading doses. (*Id.*, 1-2). After the 3 monthly loading doses, patients are treated with fixed every-8-week injections or PRN (i.e., as needed) injections. (*Id.*, 2).

136. A person of ordinary skill in the art would immediately envision a regimen that involves 3 monthly loading doses followed by PRN dosing could easily result in patients receiving 5 total monthly injections and one or more injections that are 8 weeks apart.

137. In addition, claim 12 depends from claim 10, and thus, as I understand it, is included in the scope of claim 10. Claim 12 is directed essentially to monthly dosing, because through its dependency on claim 10 it includes the monthly injections through week 20; but then claim 12

[14] I have reviewed the 9-14-2009 Regeneron Press Release, which is dated 2009. I have been informed that because the 9-14-2009 Regeneron Press Release was released in 2009, which is more than one year prior to the earliest priority date claimed by the 601 and 572 patents, the 9-14-2009 Regeneron Press Release is prior art to the 601 and 572 patents.

recites that dosing is to continue after that point on a monthly basis. The 9-14-2009 Regeneron Press Release discloses treatment of DME with VEGF Trap-Eye dosed at "2 mg monthly." (*See, e.g.*, 9-14-2009 Regeneron Press Release, 2).

138. For at least the reasons discussed above, claim 10 is anticipated by the 9-14-2009 Regeneron Press Release.

c. Dependent claims 11 and 12 of the 601 patent are anticipated by the 747 patent and the 9-14-2009 Regeneron Press Release.

139. I was asked to review claims 11 and 12 of the 601 patent and compare them to the disclosures of the prior art.

140. Claim 11 purports to further limit the claimed dosing regimen of claim 10 to "wherein approximately every 4 weeks comprises approximately every 28 days or approximately monthly."

141. Claim 12 purports to limit the claimed dosing regimen of claim 10 to "further comprising, after 20 weeks, administering, via intravitreal injection, 2 mg of aflibercept once every 4 weeks."

142. The 747 patent uses the terms "monthly" and "4 weeks" in a manner that would make clear to a person of ordinary skill in the art that the terms were synonymous. (*See, e.g.*, 747 patent at 41:4 – 42:3 (claims 5 and 6)).

143. The 9-14-2009 Regeneron Press Release also uses the terms interchangeably. (*See, e.g.*, 9-14-2009 Regeneron Press Release, 1-2 ("three monthly doses" and "administered 0.5 mg every four weeks…")).

144. Also, in my opinion, as a practicing physician and ophthalmologist, I view the terms "approximately every 4 weeks" and "approximately monthly" as meaning the same thing in the context of anti-VEGF dosing regimens. Thus, when I see the term "approximately every 4 weeks,"

I understand that to be approximately monthly, and vice versa. I note that the patent itself notes that "'monthly' dosing is equivalent to dosing once every four weeks." (601 patent, 8:1-2). I also note that Regeneron itself used the terms interchangeably in its public disclosures of the DME phase 2 clinical trials. (*See, e.g.*, 9-14-2009 Regeneron Press Release, 1).

145. Accordingly, whether set forth in weeks or months, a person of ordinary skill in the art reading the 747 patent and the 9-14-2009 Regeneron Press Release would have understood the dosing regimen, whether that regimen was set forth in weeks or months.

146. As for claim 12, I read that claim as being directed to monthly dosing after the first 5 monthly doses. This appears to conflict with claim 10, from which it depends, making the exact scope of claims 10 and 12 unclear. However, despite the lack of clarity, the prior art disclosed monthly dosing for the treatment of DME.

147. For example, Regeneron has represented to the public and the Patent Office that, as of the relevant time period, monthly dosing was the standard of care for angiogenic eye disorders. (*See, e.g.*, 338 patent prosecution history ("338 PH"), 9-11-2015 Applicant Remarks, 6). I disagree that monthly dosing was the standard of care. However, Regeneron also knew that monthly dosing, while not the majority practice, was nevertheless a long-practiced regimen. This is also evident from the 9-14-2009 Regeneron Press Release. (9-14-2009 Regeneron Press Release, 1 ("evaluat[ing] whether further improvements in vision and/or longer dosing intervals than *monthly* administration are possible.") (emphasis added)).

148. Monthly dosing was an approved regimen for treating angiogenic eye disorders with the existing therapy (i.e., Lucentis), and in my experience, some doctors (though not many), were using fixed monthly dosing to treat these disorders prior to the filing of the 601 patent.

149. In addition, the DME phase 2 references disclose the administration of 2 mg of aflibercept, including at monthly intervals. (*See, e.g.*, 9-14-2009 Regeneron Press Release, 2 ("VEGF Trap-Eye dosed at … 2 mg monthly")).

150. Thus, in my opinion, there is nothing novel about claiming monthly dosing with aflibercept for the treatment of an angiogenic eye disorder such as DME, or the use of 2 mg of aflibercept to do so.

151. Thus, for this reason, as well as the reasons discussed above for claim 10, it is my opinion that claims 11 and 12 of the 601 patent are anticipated by the 747 patent and the 9-14-2009 Regeneron Press Release.

d. Dependent claims 15 and 16 are anticipated by the 9-14-2009 Regeneron Press Release.

152. I was asked to review claims 15 and 16 of the 601 patent and compare them to the disclosures of the prior art. Claim 15 purports to further limit the claimed dosing regimen of claim 10 to "wherein the patient gains at least 15 letters of Best Corrected Visual Acuity (BCVA) score," and claim 16 purports to limit the method of claim 15 to wherein the BCVA is according to the ETDRS letter score.

153. I have been informed that Mylan is taking the legal position that the visual acuity elements recited in claims 15 and 16 constitute statements of intended results of the claimed methods that do not result in a manipulative difference in the steps of the claim, and thus should be deemed non-limiting. Furthermore, in my opinion, the recited BCVA criteria are commonly used outcome measures in clinical trials assessing patients with angiogenic eye disorders who are receiving anti-VEGF treatment, and thus represent nothing more than the intended result of those trials, or the natural result flowing from those clinical trials. (*See, e.g.*, Nguyen 2009a, 2141-43, 2145-46; Dixon, 1575-76; Heier 2009A, 45; Brown 2006, 1433; Rosenfeld 2006, 1426). Indeed,

there is nothing in the claims that instruct how to achieve the visual acuity measures recited in the claims. The claims merely recite a prior art dosing regimen, and then recite commonly used visual acuity metrics. But there are no modifications or adjustments to the dosing regimen included in the claims.

154. Regardless of whether the BCVA elements are considered in the patentability analysis, they are expressly set forth in the prior art. For example, the 9-14-2009 Regeneron Press Release discloses the use of ETDRS in assessing angiogenic eye disorders, which a person of ordinary skill in the art would have understood to be measuring BCVA. (9-14-2009 Regeneron Press Release, 1; *see also, e.g.*, Do 2009, Abstract, 147 & Fig. 1 (assessing BCVA ETDRS in the aflibercept phase 1 DME trial)).

155. In addition, the results of the VIVID and VISTA phase 3 clinical trials show that a significant fraction of the patient population experienced gains of at least 15 letters in visual acuity based on ETDRS score. (*See, e.g.*, Korobelnik 2014 DME, 2247). This result was not surprising in view of the earlier clinical trial results with aflibercept, and would have indicated to a person of ordinary skill in the art that a population of treated patients necessarily would have experienced such gains.

156. Thus, for this reason, as well as the reasons discussed above for claim 10, it is my opinion that claims 15 and 16 of the 601 patent are anticipated by the 9-14-2009 Regeneron Press Release.

e. Dependent claim 17 of the 601 patent is anticipated by the 9-14-2009 Regeneron Press Release.

157. I was asked to review claim 17 of the 601 patent and compare it to the disclosures of the prior art.

158. Claim 17 purports to further limit the claimed dosing regimen of claim 10 to "wherein exclusion criteria for the patient include (1) active intraocular inflammation; or (2) active ocular or periocular infection."

159. 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 clinical trials involving administration of intraocular injections was known and published to POSAs well before the priority date of the 601 patent. (*See, e.g.*, Lucentis Medical Review, 32-33).

160. Claim 17 sets forth common criteria for excluding patients from clinical trials that involve the intravitreal administration of a drug. In fact, the phase 2 DME clinical trial included the application of these criteria, which would necessarily have been applied during the enrollment of patients in that trial, which began in 2008. (*See, e.g.*, Do 2011, 1820 (disclosing ocular inflammation, and infectious blepharitis, keratitis, scleritis, or conjunctivitis as exclusion criteria in the phase 2 DME trial)).

161. Thus, in my opinion the conduct of the phase 2 DME trials described in the 9-14-2009 Regeneron Press Release would have necessarily involved the application of one or both of the exclusion criteria listed in claim 17.

3. Claims 18-19, 21, and 23-25 of the 601 Patent Are Anticipated by the 747 Patent and/or the 9-14-2009 Regeneron Press Release.

a. Independent claim 18 of the 601 patent is anticipated by the 747 patent.

162. I was asked to review claim 18 of the 601 patent and compare it to the disclosures of the 747 patent. It is my opinion that the 747 patent discloses every element of the claimed method(s) and thus anticipates.

163. The 747 patent discloses a method of treating eye disorders, including diabetic retinopathy ("DR"). (747 patent, Title, Abstract, 1:49-54, 2:9-35, 5:39-51, 6:8-24, 6:64 – 7:3).

164. The 747 patent further discloses treatment with VEGFR1R2-FcΔC1(a) (i.e., VEGF Trap-Eye or aflibercept). (747 patent, SEQ ID NO:6, 2:1-2, 2:9-35, 5:28-51, 7:5-63). The 747 patent further discloses intravitreal administration of the VEGF trap protein, and treatment with 25-4000 micrograms of the VEGF trap (i.e., 2 mg). (747 patent, 2:9-35; 7:5-63; 20:15-67; 21:1 – 22:42).

165. In addition, the 747 patent discloses treatment on a monthly basis, with a preferred embodiment including an initial treatment followed by subsequent treatments between 1-6 months apart (*see, e.g.*, 747 patent, 20:62-67), which a person of ordinary skill in the art would understand could encompass monthly treatment for a series of loading doses (e.g., 5 loading doses), followed by a series of less frequent dosing every 8 weeks.

166. In addition, claim 21 depends from claim 18, and thus, as I understand it, is included in the scope of claim 18. Claim 21 is directed essentially to monthly dosing, because through its dependency on claim 18 it includes the monthly injections through week 20; but then claim 21 recites that dosing is to continue after that point on a monthly basis. The 747 patent discloses treatment of diabetic retinopathy at monthly intervals. (*See, e.g.*, 747 patent, 20:62-67).

167. Accordingly, for at least these reasons, claim 18 is anticipated by the 747 patent.

b. Independent claim 18 of the 601 patent is anticipated by the 9-14-2009 Regeneron Press Release.

168. I was asked to review claim 18 of the 601 patent and compare it to the disclosures of the 9-14-2009 Regeneron Press Release. It is my opinion that the 9-14-2009 Regeneron Press Release discloses every element of the claimed method(s) and thus anticipates claim 18 of the 601 patent.

169. For example, the 9-14-2009 Regeneron Press Release discloses VEGF Trap-Eye (aflibercept) as a drug intended for intravitreal administration. (*See, e.g.*, 9-14-2009 Regeneron Press Release, 1).

170. The press release also discloses a phase 2 clinical trial in which aflibercept is administered to patients with diabetic macular edema (DME) in 2 mg doses for three monthly loading doses. After the monthly loading doses, patients are treated with fixed every-8-week injections or PRN (i.e., as needed) injections. In my opinion, persons of ordinary skill in the art understood by 2009 that DME was a complication of diabetic retinopathy (DR). This also is clear from the publications that report on the very phase 2 DME clinical trial that I discuss above and below. For example, Do 2011 states that "[d]iabetic macular edema (DME) is the most common vision-threatening manifestation of diabetic retinopathy." (Do 2011, 1819). Thus, a person of ordinary skill in the art, when treating DME, would have understood that they would also be treating DR, given that DME is a common manifestation of DR.

171. Further, a person of ordinary skill in the art would have immediately envisioned that a regimen that involves 3 monthly loading doses followed by PRN dosing could easily result in patients receiving 5 total monthly injections, followed by one or more injections that are 8 weeks apart.

172. In addition, claim 21 depends from claim 18, and thus, as I understand it, is included in the scope of claim 18. Claim 21 is directed essentially to monthly dosing, because through its dependency on claim 18 it includes the monthly injections through week 20; but then claim 21 recites that dosing is to continue after that point on a monthly basis. The 9-14-2009 Regeneron Press Release discloses treatment of DME with VEGF Trap-Eye dosed at "2 mg monthly." (*See, e.g.*, 9-14-2009 Regeneron Press Release, 2).

173. For at least the reasons discussed above, claim 18 is anticipated by the 9-14-2009 Regeneron Press Release.

c. Dependent claims 19 and 21 of the 601 patent are anticipated by the 747 patent and the 9-14-2009 Regeneron Press Release.

174. I was asked to review claims 19 and 21 of the 601 patent and compare them to the disclosures of the prior art.

175. Claim 19 purports to further limit the claimed dosing regimen of claim 18 to "wherein approximately every 4 weeks comprises approximately every 28 days or approximately monthly."

176. Claim 21 purports to limit the claimed dosing regimen of claim 18 to "further comprising, after 20 weeks, administering, via intravitreal injection, 2 mg of aflibercept once every 4 weeks."

177. The 747 patent uses the terms "monthly" and "4 weeks" in a manner that would make clear to a person of ordinary skill in the art that the terms were synonymous. (*See, e.g.*, 747 patent, 41:4 – 42:3 (claims 5 and 6)).

178. The 9-14-2009 Regeneron Press Release also uses the terms interchangeably. (*See, e.g.*, 9-14-2009 Regeneron Press Release, 1 ("three monthly doses" and "administered 0.5 mg every four weeks…")).

179. Also, in my opinion, as a practicing physician and ophthalmologist, I view the terms "approximately every 4 weeks" and "approximately monthly" as meaning the same thing in the context of anti-VEGF dosing regimens. Thus, when I see the term "approximately every 4 weeks," I understand that to be approximately monthly, and vice versa. I note that the patent itself notes that "'monthly' dosing is equivalent to dosing once every four weeks." (601 patent, 8:1-2). I also note that Regeneron itself used the terms interchangeably in its public disclosures of the DME phase 2 clinical trials. (*See, e.g.*, 9-14-2009 Regeneron Press Release, 1).

180. Accordingly, whether set forth in weeks or months, a person of ordinary skill in the art reading the 747 patent and the 9-14-2009 Regeneron Press Release would have understood the dosing regimen, whether that regimen was set forth in weeks or months.

181. As for claim 21, I read that claim as being directed to monthly dosing after the first 5 monthly doses. This appears to conflict with claim 18, from which it depends, making the exact scope of claims 18 and 21 unclear. However, despite the lack of clarity, the prior art disclosed monthly dosing for the treatment of DME.

182. For example, Regeneron has represented to the public and the Patent Office that, as of the relevant time period, monthly dosing was the standard of care for angiogenic eye disorders. (*See, e.g.*, 338 PH, 9-11-2015 Applicant Remarks, 6). I disagree that monthly dosing was the standard of care. However, Regeneron also knew that monthly dosing, while not the majority practice, was nevertheless a long-practiced regimen. This is also evident from the 9-14-2009 Regeneron Press Release. (9-14-2009 Regeneron Press Release, 1 ("evaluat[ing] whether further improvements in vision and/or longer dosing intervals than *monthly* administration are possible") (emphasis added)).

183. Monthly dosing was an approved regimen for treating angiogenic eye disorders with the existing therapy (i.e., Lucentis), and in my experience, some doctors (though not many), were using fixed monthly dosing to treat these disorders, prior to the filing of the 601 patent.

184. In addition, the DME phase 2 references disclose the administration of 2 mg of aflibercept, including at monthly intervals. (*See, e.g.*, 9-14-2009 Regeneron Press Release, 2 ("VEGF Trap-Eye dosed at … 2 mg monthly")). Likewise, the 747 patent discloses dosing of aflibercept at monthly intervals. (*See, e.g.*, 747 patent, 20:62-67).

185. In addition, both the 747 patent and DME phase 2 references disclose the administration of 2 mg of aflibercept. (*See, e.g.*, 747 patent, 2:9-35, 7:52-55, 20:43-48, 39:64 – 40:67; 5-8-2008 Regeneron Press Release, 1; 9-14-2009 Regeneron Press Release, 1; 12-20-2010 Regeneron Press Release, 1; 5-8-2008 Bayer Press Release, 2).

186. Thus, in my opinion, there is nothing novel about claiming monthly dosing with aflibercept for the treatment of an angiogenic eye disorder such as DME/DR, or the use of 2 mg of aflibercept to do so.

187. Thus, for this reason, as well as the reasons discussed above for claim 18, it is my opinion that claims 19 and 21 of the 601 patent are anticipated by the 747 patent and the 9-14-2009 Regeneron Press Release.

d. Dependent claims 23 and 24 are anticipated by the 9-14-2009 Regeneron Press Release.

188. I was asked to review claims 23 and 24 of the 601 patent and compare them to the disclosures of the prior art. Claim 23 purports to further limit the claimed dosing regimen of claim 18 to "wherein the patient gains at least 15 letters of Best Corrected Visual Acuity (BCVA) score," and claim 24 purports to limit claim 23 to "wherein Best Corrected Visual Acuity (BCVA) is according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score."

189. I have been informed that Mylan is taking the legal position that the visual acuity elements recited in claims 23 and 24 constitute statements of intended results of the claimed methods that do not result in a manipulative difference in the steps of the claim, and thus should be deemed non-limiting. Furthermore, in my opinion, the recited BCVA criteria are commonly used outcome measures in clinical trials assessing patients with angiogenic eye disorders who are receiving anti-VEGF treatment, and thus represent nothing more than the intended result of those trials, or the natural result flowing from those clinical trials. (*See, e.g.*, Nguyen 2009a, 2141-43, 2145-46; Dixon, 1575-76; Heier 2009A, 45; Brown 2006, 1433; Rosenfeld 2006, 1420, 1426). Indeed, there is nothing in the claims that instruct how to achieve the visual acuity measures recited in the claims. The claims merely recite a prior art dosing regimen, and then recite commonly used visual acuity metrics. But there are no modifications or adjustments to the dosing regimen included in the claims.

190. Regardless of whether the BCVA elements are considered in the patentability analysis, they are expressly set forth in the prior art. For example, the 9-14-2009 Regeneron Press Release discloses the use of ETDRS in assessing angiogenic eye disorders, which a person of ordinary skill in the art would have understood to be measuring BCVA. (9-14-2009 Regeneron Press Release, 1; *see also, e.g.*, Do 2009, Abstract, 147 & Fig. 1 (assessing BCVA ETDRS in the aflibercept phase 1 DME trial)).

191. In addition, the results of the VIVID and VISTA phase 3 clinical trials show that a significant fraction of the patient population who received 5 monthly loading doses followed by every-8-week dosing experienced gains of at least 15 letters in visual acuity based on ETDRS score. (*See, e.g.*, Korobelnik 2014 DME, 2247). This result was not surprising in view of the earlier clinical trial results with aflibercept, and would have indicated to a person of ordinary skill

in the art that a population of treated patients in the phase 2 DME clinical trial who received the same or similar dosing necessarily would have experienced such gains.

192. Thus, for this reason, as well as the reasons discussed above for claim 18, it is my opinion that claims 23 and 24 of the 601 patent are anticipated by the 9-14-2009 Regeneron Press Release.

e. Dependent claim 25 of the 601 patent is anticipated by the 747 patent and the 9-14-2009 Regeneron Press Release.

193. I was asked to review claim 25 of the 601 patent and compare it to the disclosures of the prior art.

194. Claim 25 purports to further limit the claimed dosing regimen of claim 18 to "wherein exclusion criteria for the patient include (1) active intraocular inflammation; or (2) active ocular or periocular infection."

195. 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 clinical trials involving administration of intraocular injections was known and published to POSAs well before the priority date of the 601 patent. (*See, e.g.*, Lucentis Medical Review, 32-33 (MYL-AFL0007147-49)).

196. Claim 25 sets forth common criteria for excluding patients from clinical trials that involve the intravitreal administration of a drug. In fact, the phase 2 DME clinical trial included the application of these criteria, which would necessarily have been applied during the enrolment of patients in that trial, which began in 2008. (*See, e.g.*, Do 2011, 1820 (disclosing ocular

inflammation, and infectious blepharitis, keratitis, scleritis, or conjunctivitis as exclusion criteria in the phase 2 DME trial)).

197. Thus, in my opinion the conduct of the phase 2 DME trials described in the 9-14-2009 Regeneron Press Release, and performance of the methods disclosed in the 747 patent, would have necessarily involved the application of the exclusion criteria listed in claim 25.

4. Claims 26-28, and 31-33 of the 601 Patent Are Anticipated by the 747 patent and/or the 9-14-2009 Regeneron Press Release.

a. Independent claim 26 of the 601 patent is anticipated by the 747 patent.

198. I was asked to review claim 26 of the 601 patent and compare it to the disclosures of the 747 patent. It is my opinion that the 747 patent discloses every element of the claimed method(s) and thus anticipates claim 26 of the 601 patent.

199. The 747 patent discloses a method of treating eye disorders, including diabetic retinopathy ("DR"). (747 patent, Title, Abstract, 1:49-54, 2:9-35, 5:39-51, 6:8-24, 6:64 – 7:3). In my opinion, this would have included treating one of the major complications of DR: DME, i.e., treating diabetic retinopathy in a patient with diabetic macular edema.

200. The 747 patent further discloses treatment with VEGFR1R2-FcΔC1(a)) (i.e., VEGF Trap-Eye or aflibercept). (747 patent at SEQ ID NO:6, 2:1-2, 2:9-35, 5:28-51, 7:5-63). The 747 patent further discloses intravitreal administration of the VEGF trap protein, and treatment with 25-4000 micrograms of the VEGF trap (i.e., 2 mg). (747 patent, 2:9-35; 7:5-63; 20:15-67; 21:1 – 22:42).

201. In addition, the 747 patent discloses treatment on a monthly basis, with a preferred embodiment including an initial treatment followed by subsequent treatments between 1-6 months apart (*see, e.g.*, 747 patent, 20:62-67), which a person of ordinary skill in the art would understand

could encompass monthly treatment for a series of loading doses (e.g., 5 loading doses), followed by a series of less frequent dosing of one or more injections 8 weeks apart.

202. In addition, claim 28 depends from claim 26, and thus, as I understand it, is included in the scope of claim 26. Claim 28 is directed essentially to monthly dosing, because through its dependency on claim 26 it includes the monthly injections through week 20; but then claim 28 recites that dosing is to continue after that point on a monthly basis. The 747 patent discloses treatment of diabetic retinopathy (and thus its underlying complications, such as diabetic macular edema), at monthly intervals. (*See, e.g.*, 747 patent, 20:62-67).

203. For at least the reasons discussed above, claim 26 is anticipated by the 747 patent.

b. Independent claim 26 of the 601 patent is anticipated by the 9-14-2009 Regeneron Press Release.

204. I was asked to review claim 26 of the 601 patent and compare it to the disclosures of the 9-14-2009 Regeneron Press Release.

205. It is my opinion that the 9-14-2009 Regeneron Press Release discloses every element of the claimed method(s) and thus anticipates claim 26 of the 601 patent.

206. For example, the 9-14-2009 Regeneron Press Release discloses VEGF Trap-Eye (aflibercept) as a drug intended for intravitreal administration. (*See, e.g.*, 9-14-2009 Regeneron Press Release, 1).

207. The press release also discloses a phase 2 clinical trial in which aflibercept is administered to patients with diabetic macular edema (DME) in 2 mg doses for three monthly loading doses. After the monthly loading doses, patients are treated with fixed every-8-week injections or PRN (i.e., as needed) injections. In my opinion, persons of ordinary skill in the art understood by 2009 that DME was a complication of diabetic retinopathy (DR). This also is clear from the publications that report on the very phase 2 DME clinical trial that I discuss above and

below. For example, Do 2011 states that "[d]iabetic macular edema (DME) is the most common vision-threatening manifestation of diabetic retinopathy." (Do 2011, 1819). Thus, a person of ordinary skill in the art, when treating DME, would have understood that they would also be treating DR, given that DME is a common manifestation of DR.

208. Further, a person of ordinary skill in the art would have immediately envisioned that a regimen that involves 3 monthly loading doses followed by PRN dosing could easily result in patients receiving 5 total monthly injections, followed by one or more injections that are 8 weeks apart.

209. In addition, claim 28 depends from claim 26, and thus, as I understand it, is included in the scope of claim 26. Claim 28 is directed essentially to monthly dosing, because through its dependency on claim 26 it includes the monthly injections through week 20; but then claim 28 recites that dosing is to continue after that point on a monthly basis. The 9-14-2009 Regeneron Press Release discloses treatment of DME with VEGF Trap-Eye dosed at "2 mg monthly." (*See, e.g.*, 9-14-2009 Regeneron Press Release, 2).

210. For at least the reasons discussed above, claim 26 is anticipated by the 9-14-2009 Regeneron Press Release.

c. Dependent claims 27 and 28 of the 601 patent are anticipated by the 747 patent and the 9-14-2009 Regeneron Press Release.

211. I was asked to review claims 27 and 28 of the 601 patent and compare them to the disclosures of the prior art.

212. Claim 27 purports to further limit the claimed dosing regimen of claim 26 to "wherein approximately every 4 weeks comprises approximately every 28 days or approximately monthly."

213. Claim 28 purports to limit the claimed dosing regimen of claim 26 to "further comprising, after 20 weeks, administering, via intravitreal injection, 2 mg of aflibercept every 4 weeks."

214. The 747 patent uses the terms "monthly" and "4 weeks" in a manner that would make clear to a person of ordinary skill in the art that the terms were synonymous. (*See, e.g.*, 747 patent, 41:4 – 42:3 (claims 5 and 6)).

215. The 9-14-2009 Regeneron Press Release also uses the terms interchangeably. (*See, e.g.*, 9-14-2009 Regeneron Press Release, 1 ("three monthly doses" and "administered 0.5 mg every four weeks…")).

216. Also, in my opinion, as a practicing physician and ophthalmologist, I view the terms "approximately every 4 weeks" and "approximately monthly" as meaning the same thing in the context of anti-VEGF dosing regimens. Thus, when I see the term "approximately every 4 weeks," I understand that to be approximately monthly, and vice versa. I note that the patent itself notes that "'monthly' dosing is equivalent to dosing once every four weeks." (601 patent, 8:1-2). I also note that Regeneron itself used the terms interchangeably in its public disclosures of the DME phase 2 clinical trials. (*See, e.g.*, 9-14-2009 Regeneron Press Release, 1).

217. Accordingly, whether set forth in weeks or months, a person of ordinary skill in the art reading the 747 patent and the 9-14-2009 Regeneron Press Release would have understood the dosing regimen, whether that regimen was set forth in weeks or months.

218. As for claim 28, I read that claim as being directed to monthly dosing after the first 5 monthly doses. This appears to conflict with claim 26, from which it depends, making the exact scope of claims 26 and 28 unclear. However, despite the lack of clarity, the prior art disclosed monthly dosing for the treatment of DME.

219. For example, Regeneron has represented to the public and the Patent Office that as of the relevant time period monthly dosing was the standard of care for angiogenic eye disorders. (*See, e.g.*, 338 PH, 9-11-2015 Applicant Remarks, 6). I disagree that monthly dosing was the standard of care. However, Regeneron also knew that monthly dosing, while not the majority practice, was nevertheless a long-practiced regimen. This is also evident from the 9-14-2009 Regeneron Press Release. (9-14-2009 Regeneron Press Release, 1 ("evaluat[ing] whether further improvements in vision and/or longer dosing intervals than *monthly* administration are possible.") (emphasis added)).

220. Monthly dosing was an approved regimen for treating angiogenic eye disorders with the existing therapy (i.e., Lucentis), and in my experience, some doctors (though not many), were using fixed monthly dosing to treat these disorders, prior to the filing of the 601 patent.

221. In addition, the DME phase 2 references disclose the administration of 2 mg of aflibercept, including at monthly intervals. (*See, e.g.*, 9-14-2009 Regeneron Press Release, 2 ("VEGF Trap-Eye dosed at … 2 mg monthly")). Likewise, the 747 patent discloses dosing of aflibercept at monthly intervals. (*See, e.g.*, 747 patent, 20:62-67)

222. In addition, both the 747 patent and DME phase 2 references disclose the administration of 2 mg of aflibercept. (*See, e.g.*, 747 patent, 7:52-55, 20:43-48, 39:64 – 40:67; 5-8-2008 Regeneron Press Release, 1; 9-14-2009 Regeneron Press Release, 1; 12-20-2010 Regeneron Press Release, 1; 5-8-2008 Bayer Press Release, 2).

223. Thus, in my opinion, there is nothing novel about claiming monthly dosing with aflibercept for the treatment of an angiogenic eye disorder such as DME/DR, or the use of 2 mg of aflibercept to do so.

224. Thus, for this reason, as well as the reasons discussed above for claim 26, it is my opinion that claims 27 and 28 of the 601 patent are anticipated by the 747 patent and the 9-14-2009 Regeneron Press Release.

d. Dependent claims 31 and 32 are anticipated by the 9-14-2009 Regeneron Press Release.

225. I was asked to review claims 31 and 32 of the 601 patent and compare them to the disclosures of the prior art. Claim 31 purports to further limit the claimed dosing regimen of claim 26 to "wherein the patient gains at least 15 letters of Best Corrected Visual Acuity (BCVA) score," and claim 32 purports to limit claim 31 to "wherein Best Corrected Visual Acuity (BCVA) is according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score."

226. I have been informed that Mylan is taking the legal position that the visual acuity elements recited in claims 31 and 32 constitute statements of intended results of the claimed methods that do not result in a manipulative difference in the steps of the claim, and thus should be deemed non-limiting. Furthermore, in my opinion, the recited BCVA criteria are commonly used clinical trial measurements in trials assessing patients suffering from angiogenic eye disorders who are receiving anti-VEGF treatment, including primary outcome measures in the Phase 3 VIEW clinical, and thus represent nothing more than the intended result of those trials, or the natural result flowing from those clinical trials. (*See, e.g.*, Nguyen 2009a, 2141-43, 2145-46; Dixon, 1575-76; Heier 2009A, 45; Brown 2006, 1433; Rosenfeld 2006, 1420, 1426). Indeed, there is nothing in the claims that instruct how to achieve the visual acuity measures recited in the claims. The claims merely recite a prior art dosing regimen, and then recite commonly used visual acuity metrics. But there are no modifications or adjustments to the dosing regimen included in the claims.

227. Regardless of whether the BCVA elements are considered in the patentability analysis, the prior art expressly sets forth that BCVA criteria are commonly used clinical trial measurements for assessing patients suffering from angiogenic eye disorders who are receiving anti-VEGF treatment. For example, the 9-14-2009 Regeneron Press Release discloses the use of ETDRS in assessing angiogenic eye disorders, which a person of ordinary skill in the art would have understood to be measuring BCVA. (9-14-2009 Regeneron Press Release, 1; *see also, e.g.*, Do 2009, Abstract, 147 & Fig. 1 (assessing BCVA ETDRS in the aflibercept phase 1 DME trial)).

228. In addition, the results of the VIVID and VISTA phase 3 clinical trials show that a significant fraction of the patient population who received 5 monthly loading doses followed by every-8-week dosing experienced gains of at least 15 letters in visual acuity based on ETDRS score. (*See, e.g.*, Korobelnik 2014 DME, 2247). This result was not surprising in view of the earlier clinical trial results with aflibercept, and would have indicated to a person of ordinary skill in the art that a population of treated patients in the phase 2 DME clinical trial who received the same or similar dosing necessarily would have experienced such gains.

229. Thus, for this reason, as well as the reasons discussed above for claim 26, it is my opinion that claims 31 and 32 of the 601 patent are anticipated by the 9-14-2009 Regeneron Press Release.

e. Dependent claim 33 is anticipated by the 9-14-2009 Regeneron Press Release.

230. I was asked to review claim 33 of the 601 patent and compare it to the disclosures of the prior art.

231. Claim 33 purports to further limit the claimed dosing regimen of claim 26 to "wherein exclusion criteria for the patient include (1) active intraocular inflammation; or (2) active ocular or periocular infection."

232. Claim 33 sets forth common criteria for excluding patients from clinical trials that involve the intravitreal administration of a drug. In fact, the phase 2 DME clinical trial included the application of these criteria, which would necessarily have been applied during the enrollment of patients in that trial, which began in 2008. (*See, e.g.*, Do 2011, 1820 (disclosing ocular inflammation, and infectious blepharitis, keratitis, scleritis, or conjunctivitis as exclusion criteria in the phase 2 DME trial)).

233. Thus, in my opinion the conduct of the phase 2 DME trials described in the 9-14-2009 Regeneron Press Release would have necessarily involved the application of one or both of the exclusion criteria listed in claim 33.

5. Claims 5-9 and 36 of the 601 Patent Are Invalid for Being in Public Use or Otherwise Available to the Public.

234. For the reasons I discuss above, the public disclosures of the VIEW clinical trial design and dosing regimen disclose each and every aspect of claims 5-9 and 36, either expressly or inherently.

235. For the same reasons, the operation of the VIEW clinical trial also would have disclosed each and every aspect of claims 5-9 and 36. I am not aware of any confidentiality agreements or obligations relating to the VIEW clinical trial that would have extended to the dosing regimen, the exclusion criteria, or the outcome measures. According to Regeneron's own press releases, Regeneron began enrolling patients in the study in 2008, with enrollment completed in September 2009—enrollment necessarily would have entailed evaluating each enrolled patient for each of the exclusion criteria. (9-14-2009 Regeneron Press Release at 1). In addition, the press release notes that the one year data from VIEW will be available in the fourth quarter of 2010, meaning that dosing began in the fourth quarter of 2009 at the latest, over one year before the earliest filing dates of the 601 and 572 patents.

Accordingly, it is my opinion that the VIEW clinical trial, at least the aspects that appear in the Asserted Claims, would have been in public use or otherwise available to the public more than one year before the earliest filing date of the 601 patent.

B. The Asserted Claims of the 601 Patent Are Obvious.

236. For at least each of the multiple reasons discussed in this report, it is my opinion that each of the Asserted Claims of the 601 patent would have been obvious to a person of ordinary skill in the art at the time of the alleged invention of the patent. I reserve the right to supplement or amend these reasons in light of ongoing discovery, as well as in rebuttal or response to any opinions offered by any other expert, or in response to any claim construction orders entered by the Court.

237. At the time of the alleged invention of the 601 patent, a person of ordinary skill in the art would have been motivated to use the dosing regimens of the Asserted Claims of the 601 patent, and would have had a reasonable expectation of success in using such dosing regimens. Based on, among other things, my experience, the relevant prior art, and the reasons set forth herein, it is my opinion that the person of ordinary skill at the time would have been motivated to refine, and would have been able to successfully refine, dosing regimens falling within each of the Asserted Claims, and to use such regimens. In reaching my opinions, I did not use hindsight, but have performed my analysis from the perspective of one of ordinary skill in the art at the time of the alleged invention.

238. The prior art discloses (and disclosed at the relevant time), among other things:

- Methods of treating eye disorders, including age-related macular degeneration, diabetic retinopathy, and diabetic macular edema, including methods involving intravitreal administration of VEGF Trap-Eye (aflibercept) via dosing regimens encompassing an initial treatment, followed by subsequent treatments between 2-8 weeks, or 1-6 months apart and treatment with 25-4000 micrograms of the VEGF trap protein (i.e., 2 mg). (*See, e.g.*, 747 patent, 799 patent, 049 patent).

- Positive Phase 1 and Phase 2 results from a variety of regimens, including single intravitreal injections, for VEGF Trap-Eye/aflibercept. (*See, e.g.*, Adis; 6-30-2006 Regeneron 10-Q; 9-30-2006 Regeneron 10-Q; Brown 2011; Nguyen 2009a; Heier 2009; Dixon; Retina Society Meeting Presentation; 3-27-2007 Regeneron Press Release; 8-2-2007 Regeneron Press Release; 4-28-2008 Regeneron Press Release; 5-8-2008 Regeneron Press Release; 8-19-2008 Regeneron Press Release; 9-28-2008 Regeneron Press Release; 4-30-2009 Regeneron Press Release; 11-3-2009 Regeneron Press Release; 2008 Regeneron 10-K; 3-31-2008 Regeneron 10-Q; 6-30-2008 Regeneron 10-Q; 9-30-2008 Regeneron 10-Q; 2009 Regeneron 10-K; 3-31-2009 Regeneron 10-Q; 6-30-2009 Regeneron 10-Q; 9-30-2009 Regeneron 10-Q; Do 2007; Do 2009).

- Regeneron's Phase 2 clinical trial in patients with AMD, known as CLEAR-IT-2, including dosing VEGF Trap-Eye (aflibercept) on an initial, 12-week, fixed-dosing phase, followed by a PRN (as-needed) dosing schedule for another 40 weeks, with positive results, including maintenance of the statistically significant gain in visual acuity achieved after the initial fixed-dosing phase. (*See, e.g.*, 4-28-2008 Bayer Press Release; 8-19-2008 Bayer Press Release; 11-3-2009 Regeneron Press Release; 3-31-2007 Regeneron 10-Q; 6-30-2007 Regeneron 10-Q; 3-31-2008 Regeneron 10-Q; 6-30-2008 Regeneron 10-Q; 9-30-2008 Regeneron 10-Q; Benz; Brown 2011; Dixon).

- Regeneron's Phase 3 VIEW 1 and VIEW 2 clinical trials in patients with AMD, including that VEGF Trap-Eye (aflibercept) was administered to patients by intravitreal injection at dosing of 2 mg VEGF Trap-Eye (aflibercept) every eight weeks (following three monthly doses) compared with Lucentis (ranibizumab), with positive results, including a statistically significant mean improvement in visual acuity at week 52 versus baseline. (*See, e.g.*, Adis; 5-8-2008 Bayer Press Release; 9-30-2008 Regeneron 10-Q; 6-30-2009 Regeneron 10-Q; 9-14-2009 Regeneron Press Release; 9-30-2009 Regeneron 10-Q; Anderson; Brown 2011; Ciulla).

- Regeneron's Phase 1 VEGF Trap-Eye (aflibercept) clinical trial in DME, including positive results from administering to DME patients a single intravitreal injection of VEGF Trap-Eye, including improvements in BCVA and retinal thickness. (*See, e.g.*, 6-30-2007 Regeneron 10-Q; Adis; Dixon; Do 2007; Do 2009).

- Regeneron's Phase 2 DME clinical trial, known as DA VINCI, including positive results with administering VEGF Trap-Eye (aflibercept) intravitreally in 2 mg doses via three monthly loading doses, followed by dosing every eight weeks or on an as-needed (PRN) basis. (*See, e.g.*, 9-14-2009 Regeneron Press Release; 9-30-2009 Regeneron 10-Q; 11-3-2009 Regeneron Press Release; 2-18-2010 Bayer Press Release; 2-18-2010 Regeneron Press Release; 3-31-2010 Regeneron 10-Q; 9-30-2010 Regeneron 10-Q; 11-22-2010 Bayer Press Release; 12-20-2010 Bayer Press Release; 12-20-2010 Regeneron Press Release; Sharma 2010; Do 2011; Do 2012; Tolentino 2011; Boyer 2011).

- The Lucentis (ranibizumab) DME clinical trials, in which patients being treated with dosing regimens that included every other month dosing after a series of loading doses, experienced improvements in BCVA and retinal thickness, similar to the BCVA and retinal

thickness results observed in the use of ranibizumab to treat AMD. (*See, e.g.*, Chun 2006; Nguyen 2006b; Campochiaro 2006; Nguyen 2009b; Querques 2009; Rodriguez-Fontal 2009; Schwartz 2009; Hansen 2010; Schachat 2010; Waisbourd 2011).

- The use of the BCVA letter measure to assess patients in clinical trial relating to angiogenic eye disorder treatments, including the use of BCVA as a clinical trial measurement and/or endpoint in the VEGF Trap-Eye AMD and DME clinical trials. (*See, e.g.*, 9-30-2009 Regeneron 10-Q; 6-30-2010 Regeneron 10-Q; 9-30-2010 Regeneron 10-Q; Avila 2009; Benz; Boyer 2009; Brown 2011; Nguyen 2009a; Dixon; NCT 795; NCT 377; 5-8-2008 Regeneron Press Release; 9-14-2009 Regeneron Press Release; 11-22-2010 Regeneron Press Release; Retina Society Meeting Presentation; 3-27-2007 Regeneron Press Release; 8-2-2007 Regeneron Press Release; Lucentis Medical Review; Brown 2006; Rosenfeld 2006; Lalwani 2009; Bashshur 2008; Wu 2009; 5-8-2008 Bayer Press Release; Do 2007; 2-18-10 Regeneron Press Release; Do 2011; Do 2012; Chun 2006; Nguyen 2006b; Campochiaro 2006; Nguyen 2009b; Querques 2009; Hansen 2010).

- Improvement by > 15 letters as a metric in assessing treatment of angiogenic eye disorders, including AMD and DME, during the VEGF Trap-Eye clinical trials, including as an outcome measure for VIEW, VISTA, VIVID, and other clinical trials. (*See, e.g.*, Dixon; Heier 2012; NCT 795; NCT 377; 5-8-2008 Regeneron Press Release; 9-14-2009 Regeneron Press Release; 5-8-2008 Bayer Press Release).

- That the prior art clinical trials of VEGF Trap-Eye and other VEGF antagonists employed exclusion criteria that reflected basic safety precautions designed to minimize the known risks, including exclusion criteria directed to inflammation and/or infection in the eye. (*See, e.g.*, Do 2011; Lucentis Medical Review; Rosenfeld 2006; Brown 2006; NCT 836; NCT 594; Dixon; Chun 2006; CATT Study; Regillo 2008, MACTEL Study; Jaffe; Lucentis PI 2006; Retinal Physician II; Dixon; Jager 2004; Do 2011; Eylea® Medical Review; Heier 2012; Macugen Medical Review; Macugen Study Group; Gragoudas 2004).

239. As evidenced by at least the references discussed above, the person of ordinary skill in the art would have been aware of the results of the Phase 1 and Phase 2 VEGF Trap-Eye clinical trials in AMD and DME patients, which were made available to the public before the earliest priority date listed on the face of the 601 patent. For example, patients receiving a single intravitreal dose of 4 mg of VEGF Trap-Eye in the Phase 1 DME trial exhibited a mean increase in ETDRS BCVA. (*See, e.g.*, Do 2007, 1; Do 2009, 146-48). As another example, 29% of the patients receiving monthly 2.0 mg doses for three months, followed by as-needed dosing in the VEGF Trap-Eye Phase 2 AMD trial exhibited an increase in BCVA of ≥ 15 letters; and 30.6% of

the patients receiving three monthly doses followed by every-8-week dosing in the Phase 3 VIEW1 trial gained ≥ 15 letters. (*See, e.g.*, Dixon, 1576; Retina Society Meeting Presentation, 19).[15] The person of ordinary skill in the art, thus, would have had a reasonable expectation of success in view of the positive results observed in the publicly-disclosed, prior art trials.

240. It was known in the prior art that VEGF Trap, based on its molecular structure, binds VEGF-A with higher affinity than antibodies—having an approximately 140-fold higher affinity than that that of ranibizumab. (Csaky, 652). It was also known that VEGF Trap's higher affinity may make it active at lower concentrations and may reduce the frequency of dosing relative to other anti-VEGF agents. (Csaky, 652). The person of ordinary skill in the art would have also known that aflibercept has a longer half-life in the eye, relative to ranibizumab. (*See, e.g.*, Dixon, 1577; Do 2009, 144, 148). Thus, a person of ordinary skill in the art would have had a reasonable expectation of success with reducing the dosing frequency with VEGF-Trap Eye from monthly injections, i.e., the approved dosing regimen for ranibizumab, in view of aflibercept's higher binding affinity and longer half-life relative to ranibizumab.

241. For example, Regeneron's own press releases provide evidence of the reasonable expectation of success the ordinarily skilled artisan would have had at dosing VEGF Trap-Eye at a frequency less than once monthly, due to known qualities of the aflibercept molecule relative to ranibizumab. For example, the 4-28-2008 Regeneron Press Release quoted Quan Dong Nguyen, a primary investigator in the CLEAR-IT-2 Phase 2 AMD study, as saying: "Due to its high affinity for all isoforms of VEGF-A and PIGF, potent mediators of blood vessel overgrowth in wet AMD, as well as its long residence time in the eye, it is anticipated that VEGF Trap-Eye may be able to

[15] The disclosures set forth in later-dated references further confirm these positive results. (*See, e.g.*, 11-22-2010 Regeneron Press Release, 1-2; 12-20-2010 Regeneron Press Release, 1-2; Heier 2012, 2542-43).

be dosed at a frequency less than once monthly, especially on a chronic basis, without compromising visual acuity." (4-28-2008 Regeneron Press Release, 1).

242. The skilled person would have been motivated to refine existing dosing regimens to reduce the number of injections required in view of the "time and financial burden of monthly injections," which, as the prior art discloses, "has led to the initiation of studies to examine the efficacy of alternative dosing schedules." (Dixon, 1574; *see also id.*, 1577 (disclosing the "limitations" of current therapy including the need for frequent intraocular injections, as often as monthly, without a defined stopping point, and that "desirable attributes" include decreased dosing intervals); Keane, 592 (discussing the "practical and economic implications" of monthly dosing regimens)). The person of ordinary skill in the art would have also been motivated to adopt the claimed dosing regimens for VEGF Trap-Eye, which allow for dosing less frequently than monthly, in view of the understanding among those of ordinary skill in the art that less frequent dosing is preferred given the risks and potential complications associated with intravitreal administration. (*See, e.g.*, Dixon, 1577).

243. Further, the person of ordinary skill in the art understood that the exclusion criteria disclosed in the clinical trials of the leading prior art anti-VEGF intravitreal injection treatments, (e.g., the CATT, MACTEL, and PIER clinical trials) reflected basic safety precautions designed to minimize the known risks, and the person of ordinary skill in the art would have been motivated to adopt the exclusion criteria from these prior studies in order to mitigate potential complications for intravitreal injections of aflibercept, which posed the same potential risks as prior anti-VEGF agents that were administered intravitreally. (*See, e.g.*, Jaffe, 228; Lucentis PI 2006, 2, 5; Regillo 2008, 240, 248.e3-248.e4; Jager 2004, 680).

244. Similarly, the person of ordinary skill in the art would have also been motivated to adopt the exclusion criteria of the prior art Lucentis (ranimizumab) clinical trials for AMD and DME, including the exclusion of clinical trial subjects experiencing inflammation or infection in the eye. (*See, e.g.*, Lucentis Medical Review, 32-34; Rosenfeld 2006, 1420-21, Table 1; Brown 2006, 1433; NCT 836, 4-5; NCT 594, 5-7). Accordingly, it would have been obvious to adopt such exclusion criteria for the VEGF Trap-Eye clinical trials, particularly in light of the inclusion of monthly ranibizumab as a comparator arm in the VIEW clinical trials.

245. Thus, the purported inventor of the 601 patent claimed a known VEGF inhibitor (aflibercept), in a known dosage strength (2 mg) and route (intravitreal), for administration pursuant to a known dosing regimen (3 monthly loading doses, followed by every-8-weeks, i.e., the VIEW regimen), along with the intended results of performing the claimed method via a visual acuity measurement (BCVA / ETDRS letter score) that had already been disclosed in the prior art. Further, any adjustments to the number of loading doses in order to achieve, or come close to achieving, the results obtained with every-month dosing, would have been routine for those skilled in the art at the relevant time. As such, if not anticipated, the claimed regimens are nothing more than obvious embodiments of the disclosed regimens, representing nothing more than routine optimization by a person of ordinary skill in the art.

246. The Asserted Claims would have been obvious to one of ordinary skill in the art at the relevant time, at least in light of the teachings of the available prior art disclosing how to achieve the alleged invention. In other words, based on the relevant prior art, a person of ordinary skill at the time would have been motivated to investigate and use (and would have had an expectation of success in using) alternative dosing regimens for VEGF Trap-Eye, including extended-dosing schedules (including the every-8-week regimens of the Asserted Claims), and

would have had a high expectation of success at using the disclosed regimens; and would have had the skills necessary to investigate and administer such regimens.

247. For the reasons disclosed herein, each of the following prior art references and combinations would independently have taught the person of ordinary skill in the art at the time to develop the dosing methods of the Asserted Claims, using nothing more than his or her own knowledge in the art and, if necessary, well-known routine optimization techniques.

1. The Scope and Content of the Prior Art Relevant to the Asserted Claims.

248. The scope of the prior art for the 601 patent relates to the use of a VEGF antagonist for intravitreal administration pursuant to various dosing regimens, including the administration of VEGF antagonists to treat eye disorders caused by or associated with angiogenesis, e.g., age related macular degeneration, diabetic retinopathy, and diabetic macular edema.

249. In forming my opinions, I relied on, among other things, my knowledge of, and years of experience in, treating angiogenic eye disorders, and took into consideration the specification and claims of the 601 patent, as well as the prosecution history of the patent, including the art cited by the examiner during prosecution, and the deposition of the alleged inventor.

250. At a minimum, each of the prior art references and products discussed in this report, including in Appendix A to this report, falls within the scope of the prior art for the 601 patent and the Asserted Claims.

251. It is my understanding that the content of the prior art depends on legal conclusions dictated by the effective dates of the references and/or the dates of public sales, offers for sale, disclosures or uses. I have not undertaken to make legal determinations as to whether certain references are prior art. I have also been advised that the knowledge and information in the specification of the 601 and 572 patents concerning what was already known is admitted prior art.

252. As discussed herein, if Plaintiff or any of its experts attempt to dispute that any reference discussed herein is properly considered "prior art" to any Asserted Claim for any reason, I reserve the right to amend or supplement this report and my opinions set forth herein.

2. Comparison Between the Asserted Claims of the 601 Patent and the Prior Art.

253. The Asserted Claims of the 601 patent are generally directed to intravitreal administration of a VEGF antagonist and methods of treating angiogenic eye disorders by intravitreally administering the VEGF antagonist pursuant to dosing regimens that can generally be characterized as comprising sequential administration of multiple doses of the VEGF antagonist to a patient wherein the dosing regimen consists of an initial, monthly loading dose period, followed by a less frequent (every-8-week) maintenance period.

254. I have attached Appendix A as part of this report, which lists prior art references and products that are relevant to the subject matter of the Asserted Claims (and would have been so viewed by a person of ordinary skill in the art at the relevant time). My opinions set forth herein include and are applicable to the references and products disclosed in Appendix A.

255. For the reasons disclosed herein, each of the following prior art references, products, and combinations independently would have taught the person of ordinary skill at the time to administer VEGFT to angiogenic eye disorder patients pursuant to an every-8-week dosing regimen as set forth in the Asserted Claims. It is my opinion, for the reasons set forth below, that each and every Asserted Claim of the 601 patent, if not anticipated, as discussed above, is obvious in light of the relevant prior art.

3. Claims 1-2, 5-9, 34, and 36 of the 601 Patent are obvious over the prior art.

256. I was asked to review claims 1-2, 5-9, 34, and 36 of the 601 patent, and compare them to the disclosures of the prior art, including Dixon.

257. As discussed above, it is my opinion that Dixon discloses expressly or inherently each and every element of claims 1-2, 5-9, 34, and 36 in the 601 patent and thus anticipates them. I incorporate my discussion of the anticipation of claims 1-2, 5-9, 34, and 36 in light of Dixon, including my element-by-element claim analysis presented above for anticipation, and I will refer to those discussions with respect to my opinions regarding the obviousness of those claims based on Dixon. For the reasons I discuss herein, Dixon also makes obvious claims 1-2, 5-9, 34, and 36 of the 601 patent in light of the person of ordinary skill in the art's (i) clear motivation to use less frequent dosing; and (ii) reasonable expectation of success from the positive Phase 2 results.

a. Independent claims 1 and 34 are obvious over Dixon, and if necessary, in combination with the CLEAR-IT-2 References.

258. Independent claims 1 and 34 of the 601 patent are obvious in view of Dixon, and, if necessary, in combination with one or more of the references cited herein as disclosing the Phase 2 CLEAR-IT-2 results.[16]

259. Independent claims 1 and 34 recite:

[16] While I have provided specific citations to Dixon to illustrate the obviousness of the Asserted Claims, I reserve the right to rely upon any of the art identified in this report and/or in Appendix A to this report. For instance, instead of, or in addition to, Dixon, I reserve the right to rely on any of the VIEW References that disclose the dosing regimen and VEGF Trap-Eye/aflibercept used in the VIEW trials, including Adis; NCT 795; NCT 377; 4-28-2008 Regeneron Press Release; 5-8-2008 Regeneron Press Release; 8-19-2008 Regeneron Press Release; 9-28-2008 Regeneron Press Release; 9-14-2009 Regeneron Press Release; 11-22-2010 Regeneron Press Release; 2009 Regeneron 10-K; 3-31-2009 Regeneron 10-Q; 6-30-2009 Regeneron 10-Q; 9-30-2009 Regeneron 10-Q; 3-31-2010 Regeneron 10-Q; 6-30-2010 Regeneron 10-Q; 9-30-2010 Regeneron 10-Q; 5-8-2008 Bayer Press Release; and/or 8-19-2008 Bayer Press Release.

> 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.
>
> * * *
>
> 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 immunoglobin-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.

(601 patent, claims 1, 34).

260. As noted above, Dixon discloses each and every element of claims 1-2, 5-9 and 34-36 in the 601 patent. I incorporate my anticipation discussion regarding these claims, and I will refer to that discussion with respect to my opinions regarding claims 1 and 34 and their limitations.

261. Dixon discloses that "VEGF Trap-Eye is a novel anti-VEGF drug currently in commercial development for the treatment of neovascular AMD." (Dixon, 1575). Dixon further discloses that "[o]ne 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." (Dixon, 1573). Prior to the earliest filing date of the 601 patent, the identity of aflibercept was already disclosed in the

prior art, as confirmed by Dixon's disclosure that VEGF Trap-Eye and aflibercept, among others, are simply different names for the same active ingredient. (*See, e.g.*, Dixon, 1575 ("VEGF Trap-Eye and aflibercept (the oncology product) have the same molecular structure....")). Thus, in my opinion, the molecular structure of aflibercept was known to the skilled artisan.

262. Dixon also discloses that "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." (Dixon, 1573). Dixon teaches that the clinical trials sought to assess the improvements in visual acuity throughout the study period. (Dixon, 1576).

263. Dixon disclosed the favorable results of the Phase 2 AMD clinical trial, where the patients achieved gains in visual acuity within 52 weeks following the initial dose. (Dixon, 1576). Dixon also reported increases in visual acuity and mean decreases in retinal thickness resulting from the Phase 2 regimen, which consisted of, among other treatment arms, four monthly loading doses followed by PRN dosing, and further disclosed that the Phase 2 patients in that arm required on average only 1.6 additional injections after the four monthly loading doses during the one-year study. (Dixon, 1576).

264. Following the favorable Phase 2 results, Regeneron continued onto Phase 3. Dixon discloses the Phase 3 VIEW1/VIEW2 studies of VEGF Trap- Eye/aflibercept in patients with AMD. For example, Dixon discloses that "[t]wo Phase III studies in wet AMD, VIEW1 and VIEW2, are currently under way and seek to compare monthly ranibizumab to monthly or bimonthly VEGF Trap-Eye." (Dixon, 1577).

265. In addition to monthly dosing arms, the VIEW1/VIEW2 studies also included a treatment arm dosing 2 mg every eight weeks after 3 initial monthly injections, (Dixon, 1576), which is the precise dosing regimen Regeneron claimed years later in the 601 patent, (*see* 601

patent, Fig. 1; claims). (*See also* 601 patent, Example 4 (describing the same Phase 3 clinical trial described in Dixon, using aflibercept (referred to in the examples as VEGFT)). This choice to include a treatment arm of 3 monthly injections followed by dosing every 8 weeks was entirely consistent with the trend that had emerged in the treatment of patients with intravitreal VEGF blockers, and, indeed, consistent with Dixon's disclosure that "[t]he time and financial burden of monthly injections has led to the initiation of studies to examine the efficacy of alternative dosing schedules." (Dixon, 1574).

266. Although the final Phase 3 clinical trial data were not reported in the literature until after the priority date of the 601 patent, it is my opinion that Dixon's disclosure of the Phase 3 trial protocol and description of the claimed methods of treatment provided sufficient detail such that a POSA would be able to carry out the claimed methods.

267. ***Motivation to Explore Extended Dosing Regimens.*** The motivation to adopt the claimed dosing regimens for VEGF Trap-Eye comes from the references themselves, which persons of ordinary skill in the art would have appreciated set forth dosing regimens that allowed for dosing less frequently than monthly, as well as the understanding among those of ordinary skill in the art that less frequent dosing is preferred given the risks and potential complications associated with intravitreal administration.

268. One of ordinary skill in the art would have been motivated to explore and 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. (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.")).

269. One of ordinary skill in the art would have also observed in Dixon, and in the many other publicly available reports of the initiation of the VIEW Phase 3 trials, that a solution to the dosing frequency issue was presented therein in the form of the publicly disclosed VIEW regimens involving every-8-week dosing following three monthly loading doses. (Dixon, 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.

270. ***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 dosing regimens for treating wet AMD, at least because of the widely publicized results of the Phase 2 CLEAR-IT-2 data, which demonstrate success at treating AMD patients using *even fewer doses*, on average, than in the Phase 3 VIEW every-8-week dosing regimen. (*See, e.g.*, Dixon, 1575-76; *see also* Heier 2009A, 45).

271. 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. (Dixon, 1576). Those patients also experienced a mean decrease in retinal thickness of 143 μm. (*Id.*). A comparison of the Phase 2 AMD trial results, to those 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 (CLEAR-IT-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

(Dixon, 1576; Heier 2012, 2541-42).

272. As Dixon further notes, during the PRN dosing phase, which covered 40 weeks, patients only required, on average, 1.6 doses. (Dixon, 1576).[17] This means that, combined with the 4 monthly loading doses, patients in this group received, on average, 5.6 doses over the course of the first year. On the other hand, a patient would receive 8 doses in the first year under the Phase 3 VIEW dosing regimen (3 monthly loading doses followed by 5 every-8-week doses (i.e., doses at months 0, 1, 2, 4, 6, 8, 10, and 12)). 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.

273. In my opinion, a person of ordinary skill in the art would have reasonably expected success in administering the VIEW1/VIEW2 dosing regimens to AMD patients in light of the positive Phase 2 AMD trial results, as reported in Dixon, 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).

[17] Dixon reported these results in 2009 and Regeneron reported these results in 2008 at a Retina Society Meeting. (*See generally* Retina Society Meeting Presentation). Among other things, Regeneron publicly reported that the maximum number of injections received by a patient in the monthly loading/PRN treatment arm was 5 injections, (*Id.*, 12), which averages out to about one injection every 10 weeks. Some patients required zero injections after the loading dose phase. (*Id.*).

274. 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." (4-28-2008 Regeneron Press Release, 1). Additionally, Regeneron's President, and the 601 patent's named inventor, George Yancopoulos, publicly stated that the Phase 2 CLEAR-IT-2 "results further increase our confidence in the design of our Phase 3 clinical program for VEGF Trap-Eye in wet AMD." (4-28-2008 Regeneron Press Release, 1; *see also id.* (Phase 2 study's primary investigator quoted: "Due to its high affinity for all isoforms of VEGF-A and PIGF, potent mediators of blood vessel overgrowth in wet AMD, 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, especially on a chronic basis, without compromising visual acuity.")).[18]

275. 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, Regeneron still made the decision to go ahead with the 2Q8 arm of the VIEW trial.

276. Notably, Regeneron's internal documents confirm that. (*See, e.g.*, RGN-EYLEA-MYLAN-00526316, -317 (explaining the rationale for the 2Q8 arm, noting that "any fixed dose regimen greater than every 4 weeks that doesn't require interim monitoring for visual acuity is

[18] *See also* 4-28-2008 Press Release, 1; 5-8-2008 Regeneron Press Release, 1; Retina Society Meeting Presentation, 9, 28; 3-27-2007 Regeneron Press Release, 1; 6-30-2008 Regeneron 10-Q, 26 ("Presented positive extended follow-up data through 32 weeks from the Phase 2 trial in wet AMD"); 9-30-2008 Regeneron 10-Q, 22, 29; 2009 Regeneron 10-K, 3-4, 15; 3-31-2009 Regeneron 10-Q, 13-14; 6-30-2009 Regeneron 10-Q, 19-20; 9-30-2009 Regeneron 10-Q, 20-21; 8-2-2007 Regeneron Press Release, 1; 8-19-2008 Regeneron Press Release, 1; 9-28-2008 Regeneron Press Release, 1-2; 4-30-2009 Regeneron Press Release, 1; 11-3-2009 Regeneron Press Release, 2; 2008 Regeneron 10-K, 3-4, 33; 3-31-2008 Regeneron 10-Q, 17-18.

seen as desirable among physicians"); *Id.*, -316 (noting that the 2Q8 arm's purpose was to "maximize efficacy"); RGN-EYLEA-MYLAN-00527017 (relaying an analyst's commentary that the 8-week regimen "seems reasonable"); RGN-EYLEA-MYLAN-00527040, -041 (commenting on the market value of the "8q-weeks dosing"); RGN-EYLEA-MYLAN-00529944 ("The quarterly dosing arms seemed to sustain their effect on visual acuity out to eight weeks, providing the rationale for exploring an eight week dosing schedule in the Phase III program."); RGN-EYLEA-MYLAN-00532930 (discussing Phase 3 trial strategies after discussions with physicians and "Key Opinion Leaders" at the Association for Research in Vision and Ophthalmology)). 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.

277. 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." (CDER Statistical Reviews, MYL-AFL0089571; *see also id.*, MYL-AFL0089569 (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 P1GF, 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")).

278. 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.

* * *

279. Thus, based on Dixon's description of the VEGF Trap Phase 3 clinical trials (VIEW 1 and VIEW 2), and the results of the Phase 2 trials (CLEAR-IT-2), a POSA would have known how to administer, what dosing schedule to follow, and how much aflibercept to administer to a patient to treat angiogenic eye disorders. Further, a person of ordinary skill in the art would have been aware of the efforts to reduce dosing frequency, and would have been aware of the promising results already observed in the Phase 2 VEGF Trap-Eye trials. Thus, a person of ordinary skill in the art would have therefore been motivated to try—and would have had a reasonable of success in trying—treating an angiogenic eye disorder by administering VEGF Trap according to the claimed dosing regimen of three monthly loading doses, followed by every 8 week dosing.

280. For these reasons, it is my opinion that claims 1 and 34 of the 601 patent are made obvious by Dixon and, if necessary, in combination with one or more references disclosing the AMD Phase 2 results.

b. Dependent claim 7.

281. 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.

282. Claim 7 depends from claim 1 and recites "wherein approximately every 4 weeks comprises approximately every 28 days or approximately monthly."

283. In my opinion, as a practicing physician and ophthalmologist, I view the terms "approximately every 4 weeks" and "approximately monthly" as meaning the same thing in the context of anti-VEGF dosing regimens. Thus, when I see the term "approximately every 4 weeks," I understand that to be approximately monthly, and vice versa. I note that the patent itself notes that "'monthly' dosing is equivalent to dosing once every four weeks." (601 patent, 8:1-2).

284. A person of ordinary skill in the art would have also viewed and understood "approximately every 4 weeks" to be equivalent to "approximately every 28 days" and "approximately monthly." In addition, Regeneron itself, as well as authors in the field, would use weeks and months interchangeably. (*See, e.g.*, 9-14-2009 Regeneron Press Release, 2 ("2 mg monthly" and "2 mg every eight weeks after three monthly loading doses"); Dixon, 1576 ("Two groups received monthly doses of either 0.5 or 2.0 mg for 12 weeks (at weeks 0, 4, 8 and 12)"); Do 2012, 1660, Fig. 1 and legend (displaying every 4 week doses and monthly doses the same way and using the terms interchangeably ("3 initial monthly doses then every 8 weeks")).

285. 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 made obvious by Dixon.

c. Dependent claims 2 and 8.

286. Claims 2 and 8 depend from claims 1 and 7, respectively, and each further requires that "the age-related macular degeneration is neovascular (wet)." In my opinion, each of these claims would be obvious in view of the prior art teachings on the Phase 2 and Phase 3 clinical trials for AMD.

287. As discussed above, Dixon discloses each and every element of the claims upon which claims 2 and 8 depend. I incorporate my discussion of claims 1 and 7 of the 601 patent, and I will refer to that discussion with respect to my opinions regarding claims 2 and 8 and their limitations. In my view, the addition of the limitation of the age-related macular degeneration being neovascular (wet) would have been obvious to a POSA.

288. For example, the Dixon reference indicates in the title that VEGF Trap-Eye was being studied for the "treatment of neovascular age-related macular degeneration." (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. (*Id.*, 1575-76). 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. (*Id.*, 1576). Dixon therefore expressly discloses treating neovascular (wet) AMD, as required by claims 2 and 8.

289. Similarly, prior to 2011, numerous references disclosed that the VIEW study was being conducted with patients with wet AMD. (*See, e.g.*, Adis, 263 ("neovascular form of wet AMD" and "in wet AMD"); 4-28-2008 Regeneron Press Release, 1 ("Phase 2 study in the neovascular form of Age-related Macular Degeneration (wet AMD)")).[19]

290. Each of the VIEW References, including Dixon, would have taught the person of ordinary skill in the art at the time to use the claimed dosing regimen for the treatment of wet AMD. 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 made obvious by Dixon.

d. Dependent claim 5.

291. Claim 5 depends from claim 2 and recites "wherein the patient gains at least 15 letters of Best Corrected Visual Acuity (BCVA) score."

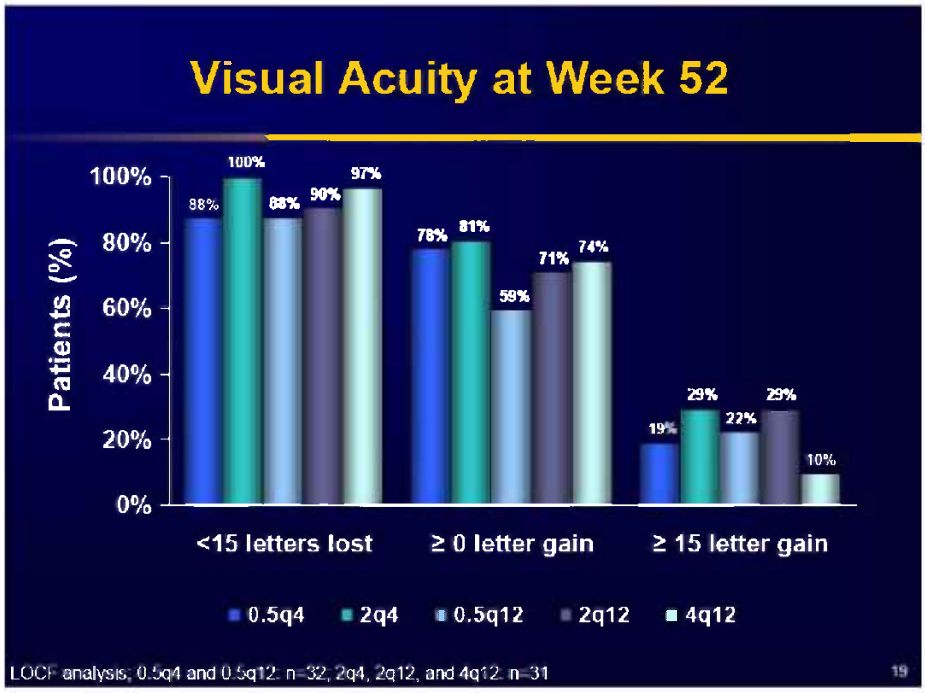
[19] In addition to the references cited in this paragraph, numerous other references disclosed to a person of ordinary skill in the art that the VIEW studies were being conducted with patients with wet AMD. (*See, e.g.*, NCT 795, 1-2; NCT 377, 1, 4; 5-8-2008 Regeneron Press Release, 1-2; 8-19-2008 Regeneron Press Release, 1-2; 9-28-2008 Regeneron Press Release, 2; 9-14-2009 Regeneron Press Release, 1-2; 2009 Regeneron 10-K, 3-5; 3-31-2009 Regeneron 10-Q, 13-14; 6-30-2009 Regeneron 10-Q, 19-20; 9-30-2009 Regeneron 10-Q, 20-21; 5-8-2008 Bayer Press Release, 1-3; 8-19-2008 Bayer Press Release, 1-4).

292. I have been informed that Mylan is taking the legal position that the additional element of claim 5 requiring that the "patient gains at least 15 letters of Best Corrected Visual Acuity (BCVA) score" constitutes a statement of intended results of the claimed methods that does not result in a manipulative difference in the steps of the claim, and thus should be deemed non-limiting. Furthermore, in my opinion, the recited BCVA criteria are commonly used outcome measures in clinical trials assessing AMD patients who are receiving anti-VEGF treatment, and thus represent nothing more than the intended result of those trials, or the natural result flowing from those clinical trials. (*See, e.g.*, Nguyen 2009a, 2141-43, 2145-46; Dixon, 1575-76; Heier 2009A, 45; Brown 2006, 1433; Rosenfeld 2006, 1420, 1426). Indeed, there is nothing in the claim that instructs how to achieve the visual acuity measures recited in the claim. The claim merely recites a prior art dosing regimen, and then recites commonly used visual acuity metrics. But there are no modifications or adjustments to the dosing regimen included in the claims.

293. Regardless of whether this element is limiting, it is set forth in the prior art. For example, the VIEW References identify improvement by ≥ 15 letters as a metric in assessing AMD treatment, including as a secondary outcome measure for the VIEW trials. (*See, e.g.*, NCT 795, 9 (listing "[t]he proportion of subjects who gain at least 15 letters of vision at Week 52" as a "secondary outcome measure" in the VIEW 1 trial); NCT 377, 6-7; 5-8-2008 Regeneron Press Release, 1). Therefore, a person of ordinary skill in the art reading each of the VIEW References would have understood and been aware of the secondary endpoint identified for those trials.

294. Further, a person of ordinary skill in the art would have understood from the prior art that the best corrected visual acuity (or BCVA) letter measure is an obvious choice to use when assessing patients in clinical trials relating to AMD treatments. (*See, e.g.*, Dixon, 1575-76; Heier 2009A, 45; Brown 2006, 1433; Rosenfeld 2006, 1420, 1426 & Suppl. App'x).

295. In addition, the results of the VEGF Trap-Eye Phase 2 AMD trial show that a significant fraction of the patient population experienced gains of at least 15 letters in visual acuity. (*See, e.g.*, Dixon, 1576 ("Patients 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.")). For example, the Retina Society Meeting Presentation discloses the visual acuity measurements taken at week 52 of the VEGF Trap-Eye Phase 2 AMD trial, including that 29% of patients in the 2q4 group (i.e., patients receiving four monthly 2.0 mg doses, followed by as-needed dosing) exhibited an increase in BCVA score of ≥ 15 letters:



(Retina Society Meeting Presentation, 19; *see also* Sharma 2010, 3 ("Of the patients enrolled in the [CLEAR-IT-2] extension study, . . . 30% gained 15 or more letters of visual acuity after treatment with VEGF Trap-Eye")). As such, a person of ordinary skill in the art would have had a reasonable expectation of success at meeting the BCVA criteria set forth in claim 5 when using

the recited regimen, in light of the positive VEGF Trap-Eye Phase 1 and Phase 2 AMD trial results reported in the prior art.

296. Further, the results of the VIEW phase 3 clinical trials, which utilized 3 monthly loading doses followed by every-8-week dosing, show that 30.6% of the patients receiving three monthly doses followed by every-8-week dosing in the Phase 3 VIEW1 trial gained ≥ 15 letters. (*See, e.g.*, Heier 2012, 2542 (Table 2)). This result was not surprising in view of the earlier clinical trial results with aflibercept, and would have indicated to a person of ordinary skill in the art that a population of treated patients necessarily would have experienced such gains. Accordingly, a person of ordinary skill in the art would have had a reasonable expectation of success at achieving such BCVA measures in view of the positive phase 1 and phase 2 AMD results with aflibercept, discussed above.

297. Thus, for these reasons, as well as for the reasons discussed above for claims 1 and 2, it is my opinion that claim 5 is obvious in view of at least Dixon, and, if necessary, in combination with one or more of the references cited above.

e. Dependent claim 6.

298. 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."

299. As with claim 5, above, I have been informed that the additional elements of claim 6 constitute non-limiting statements of intended results, and thus are not entitled to patentable weight. But regardless of whether this element is limiting, it is expressly set forth in the prior art.

300. A person of ordinary skill in the art would have known, from their background knowledge, and from the prior art cited above, that BCVA scores were assessed using an ETDRS

letter score when assessing patients in clinical trials relating to AMD treatments. (*See, e.g.*, Dixon, 1575-76; Nguyen 2009a, 2145; Heier 2009, 4; Lalwani 2009, 44; Rosenfeld 2006, 1420).

301. Thus, for these reasons, as well as for the reasons discussed above for claims 1, 2, and 5, it is my opinion that claim 6 is obvious in view of at least Dixon, and, if necessary, in combination with one or more of the references disclosing the use of BCVA (ETDRS) in assessing AMD, and/or results of the Phase 1, Phase 2, or Phase 3 trials, in view of the knowledge of a person of ordinary skill in the art.

f. Dependent claims 9 and 36 are obvious.

302. Claim 9 is dependent on claim 8, 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."

303. The claimed exclusion criteria were well known in the art for use in clinical trials involving intravitreal injections of VEGF antagonists. A POSA administering the VIEW1/VIEW2 dosing regimens to wet AMD patients in a clinical trial 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. To the extent "exclusion criteria" are found to apply in situations outside of clinical trials, 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. (Dixon, 1577 (each intravitreal injection "subjects patients to risks of cataract, intraocular inflammation, retinal detachment and endophthalmitis")).

304. 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 *Streptococcus* 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.

305. 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.*, Lalwani 2009b, 44).

306. Claims 9 and 36 are thus rendered obvious over the VIEW references, including Dixon, and, if necessary, in combination with references disclosing the exclusion criteria employed in the Lucentis ANCHOR and MARINA trials. For example, the Lucentis AMD MARINA and ANCHOR trials, involving monthly intravitreal administration of the VEGF antagonist Lucentis® (ranibizumab), employed exclusion criteria that included, among other relevant criteria, active intraocular inflammation in the study eye; history of idiopathic or autoimmune-associated uveitis in either eye; and infectious conjunctivitis, keratitis, scleritis, or endophthalmitis in either eye. (*See, e.g.*, Lucentis Medical Review, MYL-AFL0007147-49; Rosenfeld 2006, Appx., 2-3; NCT 836, 4-6; NCT 594, 5-7). The Lucentis Medical Review further disclosed that dose-holding criteria included intraocular inflammation and local or systemic infection, including infectious conjunctivitis, infectious keratitis, infectious scleritis, or endophthalmitis in either eye. (Lucentis Medical Review, MYL-AFL0007153, MYL-AFL0007171). Accordingly, it would have been

obvious to adopt such exclusion criteria for the VEGF Trap-Eye clinical trials, particularly in light of the inclusion of monthly ranibizumab as a comparator arm in the VIEW clinical trials.

307. Further, claims 9 and 36 of the 601 patent are also rendered obvious over the VIEW references, including Dixon, and, if necessary, in combination with references disclosing the exclusion criteria employed in the context of Macugen® (pegaptanib). For example, the pegaptanib trials involving intravitreal administration in treating AMD employed exclusion criteria that included, among other relevant criteria, choroiditis, and acute ocular or periocular infection. (*See, e.g.*, Macugen Medical Review, MYL-AFL0007406; Macugen Study Group, 1748). Accordingly, it would have been obvious to adopt such exclusion criteria for the VEGF Trap-Eye clinical trials, which also involved intravitreal administration to patients with angiogenic eye disorders.

308. In addition, claims 9 and 36 of the 601 patent are obvious in view of Dixon, and further in combination with references disclosing general guidelines, precautions, and general potential complications of intravitreal administration. For the reasons discussed above, that discussion incorporated herein, each VIEW reference, including Dixon, discloses expressly or inherently each and every claim element, and as discussed above, the recited exclusion criteria are not entitled to patentable weight and/or are inherent aspects of the VIEW study protocols. In addition to not being entitled to patentable weight, the claimed exclusion criteria also were obvious from the prior art. For example, it was known among those of ordinary skill in the art that intravitreal administration could be associated with serious side effects if proper, aseptic technique is not adhered to. Consequently, persons of ordinary skill in the art recognized, and reported on, the need to avoid injecting eyes that are infected or show signs of infection (i.e., inflammation). (*See, e.g.*, Aiello 2004, S4, 6-8, 17; Jager 2004, 688; De Caro, 878; Heimann, 67, 74-77, 80-81,

85). Accordingly, it would have been obvious to adopt exclusion criteria for the VEGF Trap-Eye clinical trials that included active intraocular inflammation or active ocular or periocular infection.

309. Further, claims 9 and 36 of the 601 patent are obvious because the claimed exclusion criteria were well known in the art for treatments involving intravitreal injections of VEGF antagonists. For example, with respect to the first claimed exclusion criterion, "active intraocular inflammation," the CATT, MACTEL, and PIER studies describe the exclusion criteria for clinical trials of the leading prior art anti-VEGF treatments—bevacizumab (Avastin) and ranibizumab (Lucentis). (*See, e.g.*, CATT Study, 6-7 (disclosing the criterion verbatim: "[a]ctive or recent (within 4 weeks) intraocular inflammation"); Regillo 2008, 248.e3 (disclosing the criterion verbatim: "[a]ctive intraocular inflammation (grade trace or above) in the study eye"); MACTEL Study, 4). With respect to the second claimed exclusion criterion, "active ocular or periocular infection," the prior art again includes nearly verbatim exclusion criteria. (*See id.*). The person of ordinary skill in the art understood that the exclusion criteria disclosed in the CATT, MACTEL, and PIER studies reflected basic safety precautions designed to minimize the known risks, and the person of ordinary skill in the art would have been motivated to adopt the exclusion criteria from these studies in order to mitigate potential complications for intravitreal injections of aflibercept, which posed the same potential risks as prior anti-VEGF agents that were administered intravitreally. (*See, e.g.*, Jaffe, 349-50; Lucentis PI 2006, 2; Regillo 2008, 248.e3; Retinal Physician II, 2, 5; Jager 2004, 688). Indeed, the person of ordinary skill in the art would have had a strong motivation to look to exclusion criteria from prior studies involving anti-VEGF intravitreal injections such as those disclosed by the CATT, MACTEL, and PIER studies, and to apply them to the aflibercept dosing regimen recited by Dixon. Further, because the known risks associated with intravitreal injections are common to all intravitreal injections, including injections

of VEGF antagonists, the person of ordinary skill in the art would reasonably expect that the exclusion criteria developed for prior art VEGF antagonists could be successfully applied to aflibercept. Accordingly, it would have been obvious to adopt exclusion criteria for the VEGF Trap-Eye clinical trials that included active intraocular inflammation or active ocular or periocular infection.

310. In sum, it would have been common sense to a POSA to avoid risking complications by excluding subjects 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.

311. 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 claims 9 and 36 are obvious.

4. Claims 10-12 and 15-17 of the 601 Patent Are Obvious in View of the Prior Art.

a. Independent claim 10 is obvious in view of the 747 patent and 9-14-2009 Regeneron Press Release alone, or in combination with Do 2009.

312. I was asked to review claims 10, 11, 12, 15, 16, and 17 of the 601 patent and compare them to the disclosures of the prior art, including the 747 patent, the 9-14-2009 Regeneron Press Release and Do 2009.

313. The 9-14-2009 Regeneron Press Release discloses VEGF Trap-Eye (aflibercept) as a drug intended for intravitreal administration. (9-14-2009 Regeneron Press Release, 1).

314. The press release also discloses a phase 2 clinical trial in which aflibercept is administered to patients with diabetic macular edema (DME) in 2 mg doses for three monthly loading doses. (*Id.*, 2). After the monthly loading doses, patients are treated with fixed every-8-week injections or PRN (i.e., as needed) injections. (*Id.*).

315. The 747 patent discloses a method of treating eye disorders, including diabetic retinopathy ("DR"). (747 patent, Title, Abstract, 1:49-54, 2:9-35, 5:39-51, 6:8-24, 6:64 – 7:3). One of the complications associated with diabetic retinopathy is retinal edema (i.e., diabetic macular edema ("DME"). The 747 patent also discloses treatment with VEGFR1R2-FcΔC1(a)) (i.e., VEGF Trap-Eye or aflibercept). (747 patent, SEQ ID NO:6, 2:1-2, 2:9-35, 5:28-51, 7:5-63). The 747 patent further discloses intravitreal administration of the VEGF trap protein, and treatment with 25-4000 micrograms of the VEGF trap (i.e., 2 mg). (747 patent, 2:9-35; 7:5-63; 20:15-67; 21:1 – 22:42).

316. A regimen of 5 monthly loading doses would have been obvious in view of the phase 2 dosing regimens. For example, from the positive results of the phase 1 DME trial, and the disclosed dosing regimens of the phase 2 clinical trial, a person of ordinary skill in the art would have been motivated to identify an optimal dosing regimen for the treatment of DME patients. In my experience, identifying an optimum dosing regimen for a VEGF antagonist such as aflibercept is a matter of routine optimization. A person of ordinary skill in the art would have been motivated to try a range of monthly loading doses, especially since a series of monthly loading doses followed by extended PRN/treat-and-extend dosing was the industry standard and that was the approach being used, with success, by those in clinical practice. (*See, e.g.*, Retinal Physician 2007, MYL-AFL0090401; *id.*, MYL-AFL0090402-03; MYL-AFL0091273).

317. I am aware that Regeneron was experimenting with 1, 3, and 4 monthly loading doses in its aflibercept clinical trials. For example, Regeneron tried 1 and 4 monthly loading doses in its phase 2 AMD trials, (Dixon, 1576); and 3 monthly loading doses in its phase 2 DME and phase 3 VIEW trials, (*see, e.g.*, 9-14-2009 Regeneron Press Release at 1, 2). This also is consistent

with internal Regeneron documents that indicated it was focusing its aflibercept DME program on no more than 3-6 monthly loading doses. (RGN-EYLEA-MYLAN-00631452 at -53; *see also* RGN-EYLEA-MYLAN-00495620 at -22 ("# loading doses (3 vs. 6 for 2q8")). Regeneron also used the phase 2 AMD CLEAR-IT-2 clinical trial results to guide its design of the phase 3 DME trial, explaining to EU authorities that:

> Other intravitreal anti-VEGF therapies (Macugen, Avastin, Lucentis) that are commonly used for AMD have suggested efficacy of this therapeutic principle also in treating DME in Phase I/II studies and investigator initiated studies. This is further supported by Phase III studies recently initiated by Genentech for their product ranibizumab in DME patients. Most notably the doses employed in these studies (0.3 and 0.5 mg given monthly) are the same doses which are used in the AMD indication.

(RGN-EYLEA-MYLAN-00531609 at -614). Regeneron continues, stating that:

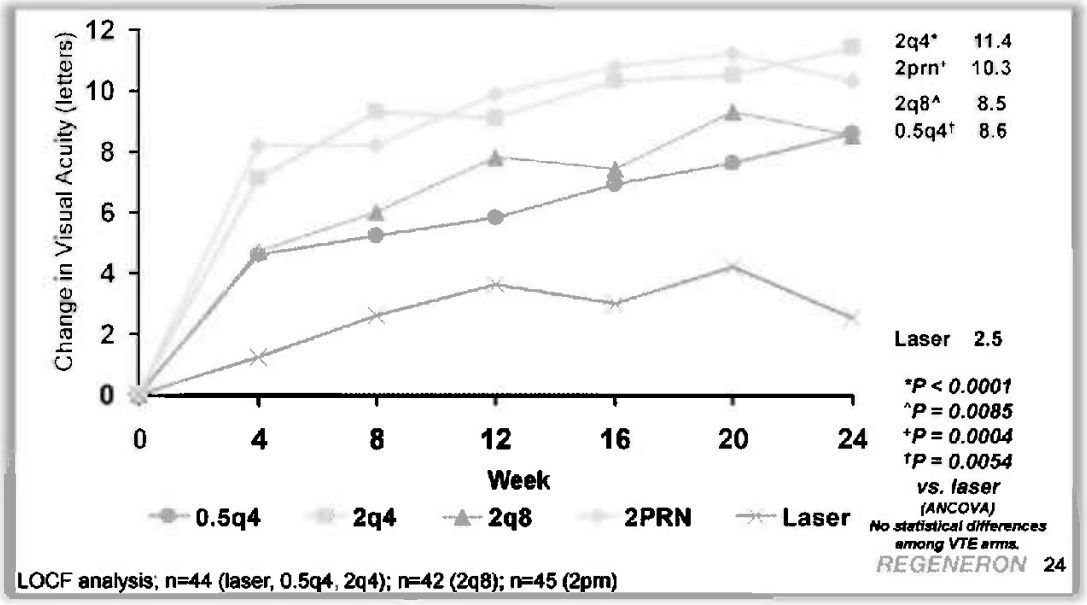
> Based on this experience we believe that the doses and dosing intervals for VEGF Trap-Eye for Phase III in DME can be selected based on the results of the Phase II study in patients with AMD (OD-0508, see Investigators Brochure, Vol. 14 , pg. 14) In this study, several doses of VEGF Trap-Eye have been assessed in 30 patients / treatment arm. The results suggested that 0.5mg VEGF Trap-Eye is effective in suppressing retinal edema if injected monthly and that 2mg are sufficient to suppress retinal edema for up to 8 weeks. We consider this Phase 2 study as providing an adequate basis for dose selection for the Phase 3 DME program and propose to use the 0.5mg dose in 4-weekly and the 2mg dose in 8-weekly intervals in the planned Phase 3 study (see outline of proposed Phase 3 studies in DME, Vol. 14 , pg. 14).

(RGN-EYLEA-MYLAN-00531609 at -614). In other words, Regeneron was relying on publicly available data and selecting an every-8-week dosing regimen that was already in the public domain for its phase 3 DME clinical trials. The selection of the 5 monthly loading doses was a matter of routine optimization, which began with Regeneron confining itself, as early as 2007/2008, to the use of 3-6 monthly loading doses. (*See, e.g.*, RGN-EYLEA-MYLAN-00631452 at -53; RGN-EYLEA-MYLAN-00531609 at -615 ("During an induction phase, VEGF Trap-Eye is administered by up to 6 intravitreal injections at intervals of 4 or 8 weeks until resolution of macular edema[.]")).

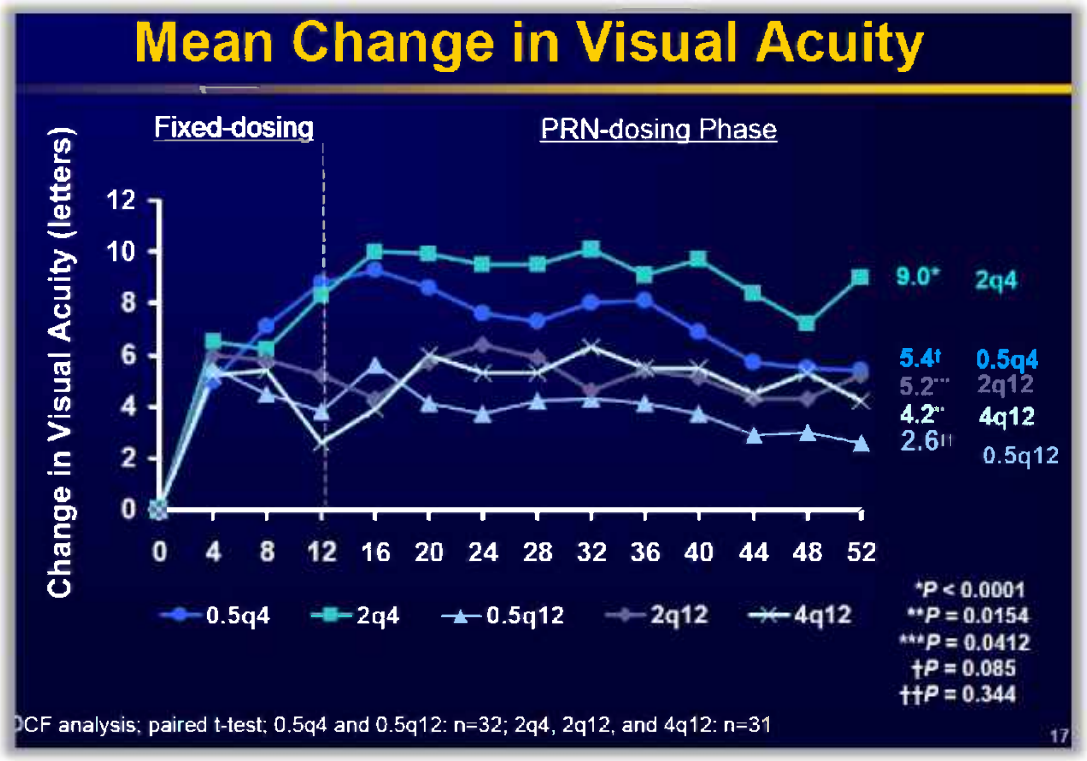
318. Further, in my clinical experience, DME patients tend to require more loading doses (compared to AMD patients) to achieve satisfactory retinal thickness and/or visual acuity measures.

319. Thus, in my opinion, putting DME patients on 4 or 5 monthly loading doses rather than three would have been obvious to try when conducting routine optimization of a loading dose regimen for DME. This is confirmed by my review of the data that came out of the phase 2 DA VINCI DME clinical trial.

320. For example, as Regeneron was designing its VIVID and VISTA phase 3 clinical trial in DME in which 5 monthly loading doses were to be tested, they had available to them the data from the phase 2 DME DA VINCI trial. A person of ordinary skill in the art would have immediately noticed that the 2Q8 arm patient group exhibited a lengthier time to plateau than what would have been observed with AMD. For example, I reviewed information from a March 2010 slide presentation provided by Regeneron. While not public at the time, this is used to illustrate the routine review and optimization that a POSA would have engaged in. Therein, data from the DA VINCI DME clinical trial revealed that it was taking 5-6 months for patients to near a plateau of visual acuity gains:



(RGN-EYLEA-MYLAN-00585880 at -909). Contrast this with the results from the AMD phase 2 clinical trial using the same dosage (2 mg) and a similar loading dose scheme:



(Retina Society Meeting Presentation, 17). What is evident from these two sets of data is that DME appears more resistant to treatment than AMD, which also is consistent with observations I've made within my own practice. As a result, DME patients were taking longer to approach plateau. From this data, in my opinion, it is a matter of routine optimization to adjust upward the number of monthly loading doses if a patient is presenting with a more difficult to treat condition (e.g., DME), or taking longer to show a response to treatment. Thus, it is an obvious and routine matter to arrive at a particular number of loading doses.

321. In any event, Regeneron documents reveal that business/commercial concerns also were important in Regeneron's decision to implement 5 monthly loading doses for the treatment of DME. For example, a January 26, 2011 presentation of Bayer and Regeneron discusses their DME clinical plan and suggests that the selection of 5 loading doses for the DME trial was the result of "a compromise" between Regeneron and Bayer, deemed "acceptable from a commercial/market access perspective." (RGN-EYLEA-MYLAN-00513418 at 424).

322. Further, in my opinion, a person of ordinary skill in the art would have had a reasonable expectation of success at using 5 monthly loading doses in light of the positive phase 1 results seen with a single intravitreal dose of aflibercept. For example, Do 2009 reports that a single intravitreal dose of aflibercept resulted in an average of 9 letters in ETDRS score gained after one month. (Do 2009, 146). The reasonable expectation of success also would have come from the combination of highly relevant data that was in the public domain at the time showing that (1) aflibercept was effective at treating AMD after a series of monthly loading doses, followed by less frequent dosing (Dixon, 1576); (2) ranibizumab was effective at treating both AMD and DME (Rosenfeld 2006, 1426; Lalwani 2009b, 44-46). Indeed, as I discuss above, Regeneron itself

was deriving its DME clinical trial strategy from what already had been learned from the aflibercept AMD phase 2 results and ranibizumab DME results.

323. For at least the reasons discussed above, claim 10 is obvious in view of the 747 patent and the 9-14-2009 Regeneron Press Release alone or in combination with Do 2009, and the knowledge of a person of ordinary skill in the art.

b. Independent claim 10 is obvious in view of the 747 patent and the 9-14-2009 Regeneron Press Release alone, or in combination with the Lucentis art.

324. I was asked to review claims 10-12 and 15-17 of the 601 patent and compare them to the disclosures of the prior art, including the 747 patent, the 9-14-2009 Regeneron Press Release and the Lucentis art.

325. The 9-14-2009 Regeneron Press Release discloses VEGF Trap-Eye (aflibercept) as a drug intended for intravitreal administration. (9-14-2009 Regeneron Press Release, 1). The press release also discloses a phase 2 clinical trial in which aflibercept is administered to patients with diabetic macular edema (DME) in 2 mg doses for three monthly loading doses. (*Id.*, 2). After the monthly loading doses, patients are treated with fixed every-8-week injections or PRN (i.e., as needed) injections. (*Id.*).

326. The 747 patent discloses a method of treating eye disorders, including diabetic retinopathy ("DR"). (747 patent, Title, Abstract, 1:49-54, 2:9-35, 5:39-51, 6:8-24, 6:64 – 7:3). One of the complications associated with diabetic retinopathy is retinal edema (i.e., diabetic macular edema ("DME"). The 747 patent also discloses treatment with VEGFR1R2-FcΔC1(a)) (i.e., VEGF Trap-Eye or aflibercept). (747 patent at SEQ ID NO:6, 2:1-2, 2:9-35, 5:28-51, 7:5-63). The 747 patent further discloses intravitreal administration of the VEGF trap protein, and treatment with 25-4000 micrograms of the VEGF trap (i.e., 2 mg). (747 patent, 2:9-35; 7:5-63; 20:15-67; 21:1 – 22:42).

327. Shortly after Regeneron had initiated its phase 2 DME clinical trial, data emerged from Lucentis clinical trials in DME. The Lucentis clinical trial data revealed that patients treated with 0.5 mg on a monthly loading regimen achieved very similar BCVA scores as those observed in the Lucentis AMD trials. For example, in Lalwani 2009b, the author reported on data emerging from the clinical study Ranibizumab for Edema of the Macula in Diabetes 1 (READ 1). (Lalwani 2009b, 45). Lalwani 2009b discloses the design of the study, including the dosing regimen, which involved injections at baseline, and months 1, 2, 4, and 6 (i.e., 3 monthly loading doses followed by every-8-week dosing). (Lalwani 2009b, 45). The author further reports that at 12 months, the DME patients receiving ranibizumab had achieved, on average, a gain of 8 letters of visual acuity. (Lalwani 2009b, 45). The author further notes that the READ 2 program that followed READ 1 employed monthly dosing through 12 months, and the ranibizumab-only arm achieved mean gains of 6.46 letters. (Lalwani 2009b, 45-46 & Fig. 1).

328. In other words, Lucentis was showing that the treatment of AMD and DME can be accomplished to similar effect with similar regimens and the same amount of anti-VEGF agent.

329. However, a person of ordinary skill in the art also would have appreciated that the treatment of DME differed from AMD in at least one aspect.

330. For example, the author references the theory circulating among physicians at the time that VEGF was particularly elevated in DME compared to AMD, and thus may require more aggressive treatment. (Lalwani 2009b, 46). This also is consistent with the presentation of the RESOLVE trial data set forth in Lalwani 2009b, which showed a shallower curve to reach plateau levels of mean visual acuity than that observed with AMD in, for example, the MARINA and ANCHOR trials. (Lalwani 2009b, 46; *see also, e.g.*, Rosenfeld 2006, 1426). For example, one can compare the RESOLVE DME data in Lalwani 2009b:

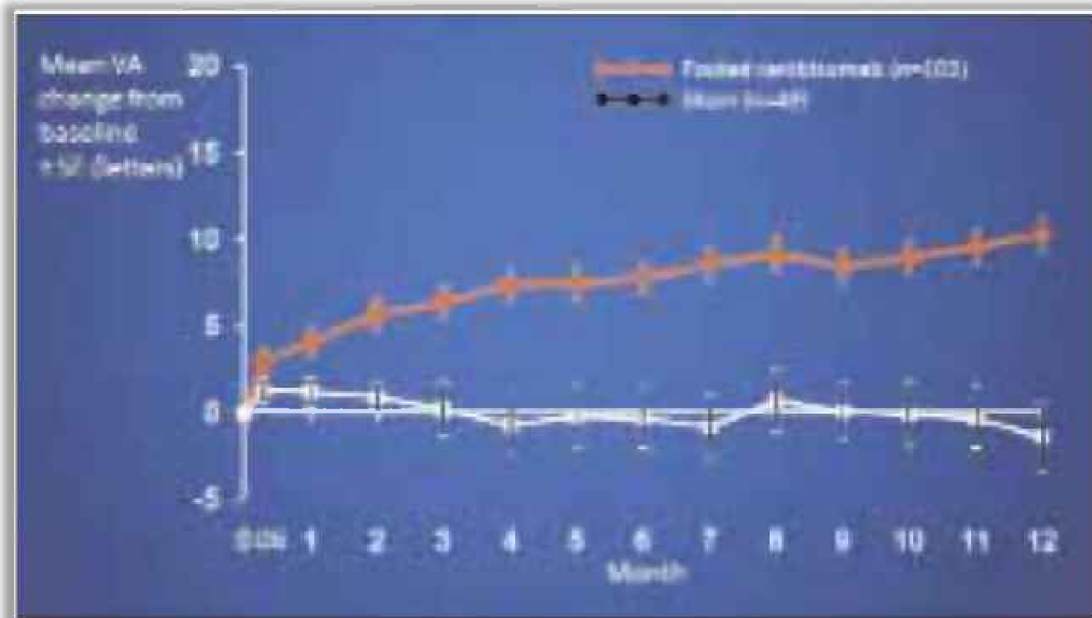
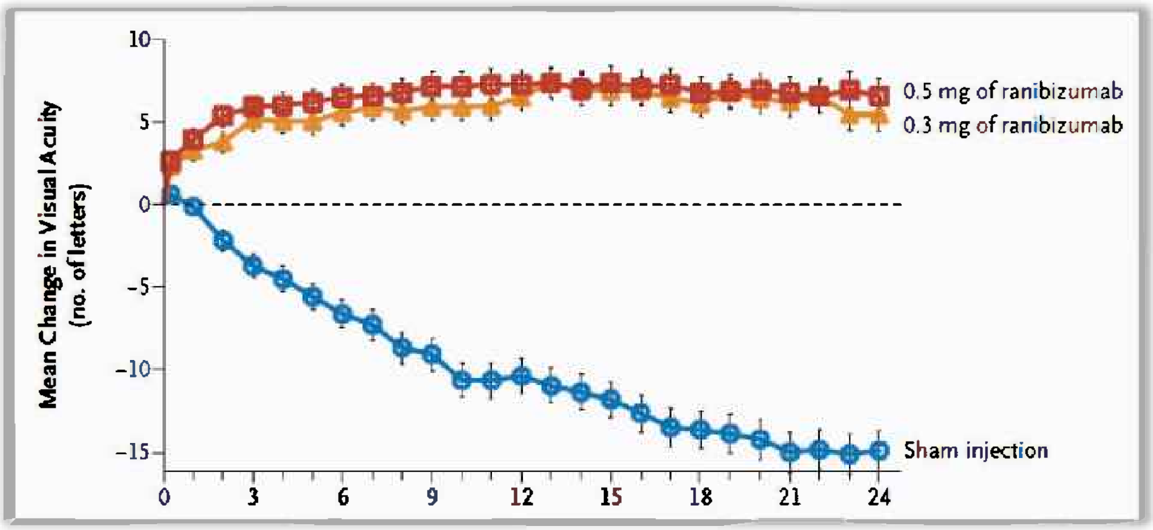


Figure 2. Visual acuity results at 1 year for the RESOLVE Trial.

(Lalwani 2009b, 46), with the data in Rosenfeld 2006 for AMD:



(Rosenfeld 2006, 1426). As discussed above, it is evident from these two sets of data that DME appears more resistant to treatment than AMD, which also is consistent with observations I've made within my own practice, and consistent with Lalwani 2009b's reference to the theory that VEGF is more elevated in DME patients. As a result of this resistance, DME patients in the

Lucentis trials were taking longer to approach plateau when compared to AMD patients. From this data, in my opinion, a person of ordinary skill in the art would have looked to increase the number of loading doses when treating DME patients with aflibercept. Based on the data above, 5 monthly loading is an obvious and reasonable number to incorporate, especially in view of the use of 3 and 4 loading doses in the aflibercept AMD clinical trials.

331. This also is consistent with internal Regeneron documents that indicated it was focusing its aflibercept DME program on no more than 3-6 monthly loading doses. (RGN-EYLEA-MYLAN-00631452 at -53; *see also* RGN-EYLEA-MYLAN-00495620 at -22 ("# loading doses (3 vs. 6 for 2q8)")). Regeneron also used the phase 2 AMD CLEAR-IT-2 clinical trial results to guide its design of the phase 3 DME trial, explaining to EU authorities that:

> Other intravitreal anti-VEGF therapies (Macugen, Avastin, Lucentis) that are commonly used for AMD have suggested efficacy of this therapeutic principle also in treating DME in Phase I/II studies and investigator initiated studies. This is further supported by Phase III studies recently initiated by Genentech for their product ranibizumab in DME patients. Most notably the doses employed in these studies (0.3 and 0.5 mg given monthly) are the same doses which are used in the AMD indication.

(RGN-EYLEA-MYLAN-00531609 at -614). Regeneron continues, stating that:

> Based on this experience we believe that the doses and dosing intervals for VEGF Trap-Eye for Phase III in DME can be selected based on the results of the Phase II study in patients with AMD (OD-0508, see Investigators Brochure, Vol. 14 , pg. 14) In this study, several doses of VEGF Trap-Eye have been assessed in 30 patients / treatment arm. The results suggested that 0.5mg VEGF Trap-Eye is effective in suppressing retinal edema if injected monthly and that 2mg are sufficient to suppress retinal edema for up to 8 weeks. We consider this Phase 2 study as providing an adequate basis for dose selection for the Phase 3 DME program and propose to use the 0.5mg dose in 4-weekly and the 2mg dose in 8-weekly intervals in the planned Phase 3 study (see outline of proposed Phase 3 studies in DME, Vol. 14 , pg. 14).

(RGN-EYLEA-MYLAN-00531609 at -614). In other words, Regeneron was relying on available data (which was publicly available) and selecting an every-8-week dosing regimen that was already in the public domain for its phase 3 DME clinical trials. The selection of the 5 monthly loading doses was a matter of routine optimization, which began with Regeneron confining itself,

as early as 2007/2008 to the use of 3-6 monthly loading doses. (*See, e.g.*, RGN-EYLEA-MYLAN-00631452 at -53; RGN-EYLEA-MYLAN-00531609 at -615 ("During an induction phase, VEGF Trap-Eye is administered by up to 6 intravitreal injections at intervals of 4 or 8 weeks until resolution of macular edema.")).

332. Further, in my opinion, a person of ordinary skill in the art would have had a reasonable expectation of success at using 5 monthly loading doses in light of the positive phase 1 results seen with a single intravitreal dose of aflibercept. For example, Do 2009 reports that a single intravitreal dose of aflibercept resulted in an average of 9 letters in ETDRS score gained after one month. (Do 2009, 146). The reasonable expectation of success also would have come from the combination of highly relevant data that was in the public domain at the time showing that (1) aflibercept was effective at treating AMD after a series of monthly loading doses, followed by less frequent dosing (Dixon, 1576); (2) ranibizumab was effective at treating both AMD and DME (Rosenfeld 2006, 1426; Lalwani 2009b, 45-46). Indeed, as I discuss above, Regeneron itself was deriving its DME clinical trial strategy from what already had been learned from the aflibercept AMD phase 2 results and ranibizumab DME results.

333. For at least the reasons discussed above, claim 10 is obvious in view of the 9-14-2009 Regeneron Press Release or the 747 patent alone, or in combination with the Lucentis art, including Lalwani 2009b, and the knowledge of a person of ordinary skill in the art.

c. Independent claim 10 is obvious in view of Dixon alone, or in combination with Lalwani 2009b.

334. I was asked to review claims 10-12 and 15-17 of the 601 patent and compare them to the disclosures of the prior art, including Dixon and Lalwani 2009b.

335. For example, Dixon discloses positive results from several aflibercept clinical trials, including several phase 1 trials in both AMD and DME, and the phase 2 CLEAR-IT-2 AMD

trial. (Dixon, 1575-76). Dixon reports that in the DME study, "[t]he single injection resulted in a median decrease of central macular thickness measured by OCT of 79 μm. BCVA increased by 9 letters at 4 weeks and regressed to a 3 letter improvement at 6 weeks." (Dixon, 1575).

336. Dixon also makes note of the "multifactorial nature of DME" and discloses that phase 2 clinical studies are underway with anti-VEGF agents, including aflibercept, for the treatment of DME. (Dixon, 1577-78).

337. Dixon also discloses that aflibercept/VEGF Trap-Eye is formulated in a 2 mg presentation and for intravitreal administration. (Dixon, 1575).

338. About this same time, data emerged from Lucentis clinical trials in DME. The Lucentis clinical trial data revealed that patients treated with 0.5 mg on a monthly loading regimen achieved very similar BCVA scores as those observed in the Lucentis AMD trials. For example, in Lalwani 2009b, the author reported on data emerging from the clinical study Ranibizumab for Edema of the Macula in Diabetes (READ 1). (Lalwani 2009b, 45). Lalwani 2009b discloses the design of the study, including the dosing regimen, which involved injections at baseline, and months 1, 2, 4, and 6 (i.e., 3 monthly loading doses followed by every 8 week dosing). (Lalwani 2009b, 45). The author further reports that at 12 months, the DME patients receiving ranibizumab had achieved, on average, a gain of 8 letters of visual acuity. (Lalwani 2009b, 45). The author further notes that the READ 2 program that followed READ 1 employed monthly dosing through 12 months, and the ranibizumab-only arm achieved mean gains of 6.46 letters. (Lalwani 2009b, 45-46 & Fig. 1).

339. In other words, Lucentis was showing that the treatment of AMD and DME can be accomplished to similar effect with similar regimens and the same amount of anti-VEGF agent.

340. However, a person of ordinary skill in the art also would have appreciated that the treatment of DME differed from AMD in at least one aspect.

341. For example, the author references the theory circulating among physicians at the time that VEGF was particularly elevated in DME compared to AMD, and thus may require more aggressive treatment. (Lalwani 2009b, 46). This also is consistent with the presentation of the RESOLVE trial data set forth in Lalwani 2009b, which showed a shallower curve to reach plateau levels of mean visual acuity than that observed with AMD in, for example, the MARINA and ANCHOR trials. (Lalwani 2009b, 46; *see also, e.g.*, Rosenfeld 2006, 1426). For example, one can compare the RESOLVE DME data in Lalwani 2009b:

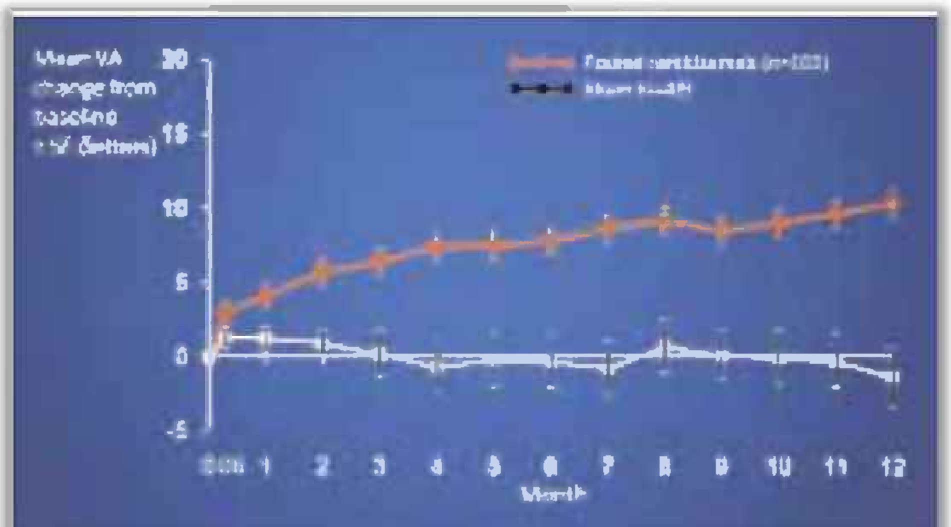
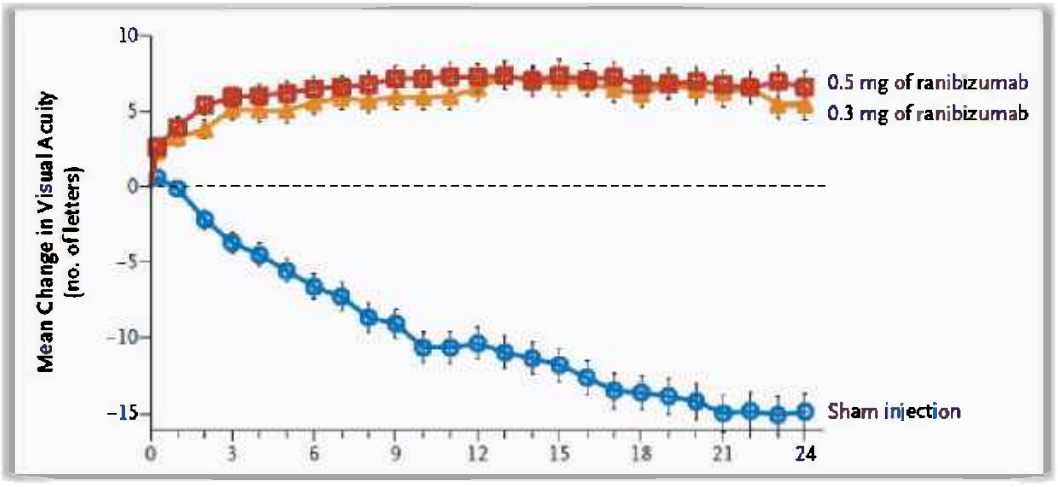


Figure 2. Visual acuity results at 1 year for the RESOLVE Trial.

(Lalwani 2009b, 46), with the data in Rosenfeld 2006 for AMD:



(Rosenfeld 2006, 1426). As discussed above, it is evident from these two sets of data that DME appears more resistant to treatment than AMD, which also is consistent with observations I've made within my own practice, and consistent with Lalwani 2009b's reference to the theory that VEGF is more elevated in DME patients. As a result of this resistance, DME patients in the Lucentis trials were taking longer to approach plateau when compared to AMD patients. From this data, in my opinion, a person of ordinary skill in the art would have looked to increase the number of loading doses when treating DME patients with aflibercept. Based on the data above, 5 monthly loading is an obvious and reasonable number to incorporate, especially in view of the use of 3 and 4 loading doses in the aflibercept AMD clinical trials.

342. This also is consistent with internal Regeneron documents that indicated it was focusing its aflibercept DME program on no more than 3-6 monthly loading doses. (RGN-EYLEA-MYLAN-00631452 at -53; *see also* RGN-EYLEA-MYLAN-00495620 at -22 ("# loading doses (3 vs. 6 for 2q8)")). Regeneron also used the phase 2 AMD CLEAR-IT-2 clinical trial results to guide its design of the phase 3 DME trial, explaining to EU authorities that:

> Other intravitreal anti-VEGF therapies (Macugen, Avastin, Lucentis) that are commonly used for AMD have suggested efficacy of this therapeutic principle also in treating DME in Phase I/II studies and investigator initiated studies. This is further supported by Phase III studies recently initiated by Genentech for their product ranibizumab in DME patients. Most notably the doses employed in these studies (0.3 and 0.5 mg given monthly) are the same doses which are used in the AMD indication.

(RGN-EYLEA-MYLAN-00531609 at -614). Regeneron continues, stating that:

> Based on this experience we believe that the doses and dosing intervals for VEGF Trap-Eye for Phase III in DME can be selected based on the results of the Phase II study in patients with AMD (OD-0508, see Investigators Brochure, Vol. 14 , pg. 14) In this study, several doses of VEGF Trap-Eye have been assessed in 30 patients / treatment arm. The results suggested that 0.5mg VEGF Trap-Eye is effective in suppressing retinal edema if injected monthly and that 2mg are sufficient to suppress retinal edema for up to 8 weeks. We consider this Phase 2 study as providing an adequate basis for dose selection for the Phase 3 DME program and propose to use the 0.5mg dose in 4-weekly and the 2mg dose in 8-weekly intervals in the planned Phase 3 study (see outline of proposed Phase 3 studies in DME, Vol. 14 , pg. 14).

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343. Further, in my opinion, a person of ordinary skill in the art would have had a reasonable expectation of success at using 5 monthly loading doses in light of the positive phase 1 results seen with a single intravitreal dose of aflibercept. For example, Do 2009 reports that a single intravitreal dose of aflibercept resulted in an average of 9 letters in ETDRS score gained after one month. (Do 2009, 146). The reasonable expectation of success also would have come from the combination of highly relevant data that was in the public domain at the time showing

that (1) aflibercept was effective at treating AMD after a series of monthly loading doses, followed by less frequent dosing (Dixon, 1576); (2) ranibizumab was effective at treating both AMD and DME (Rosenfeld 2006, 1426; Lalwani 2009b, 45-46). Indeed, as I discuss above, Regeneron itself was deriving its DME clinical trial strategy from what already had been learned from the aflibercept AMD phase 2 results and ranibizumab DME results.

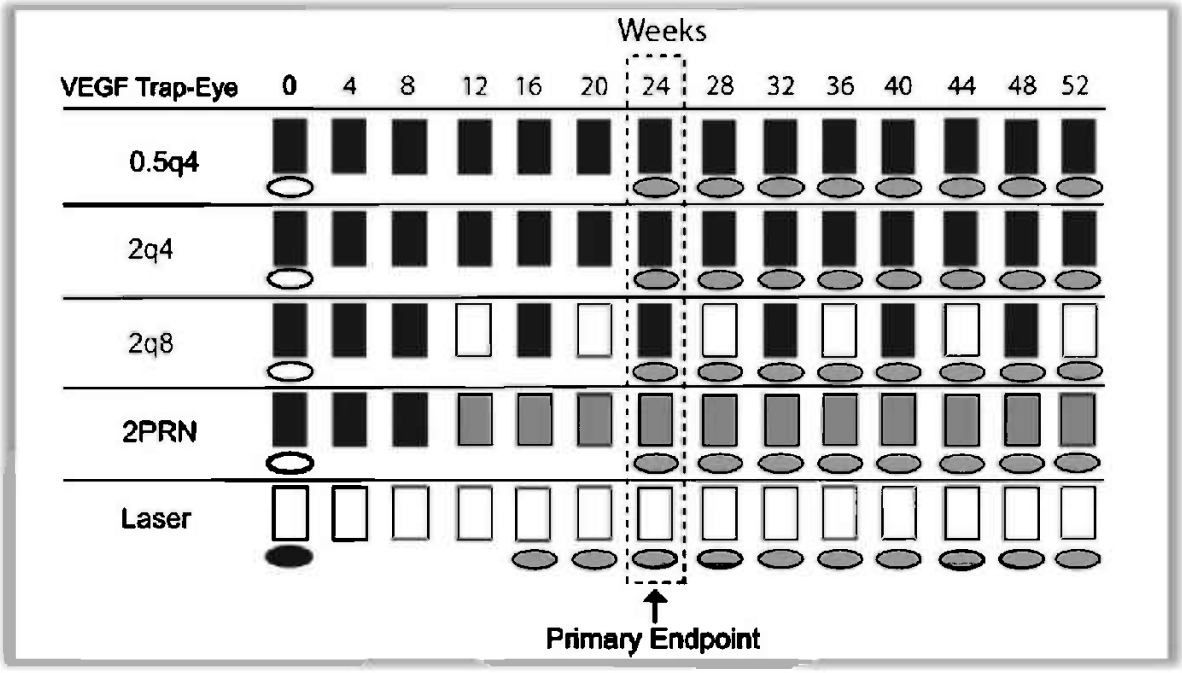
344. For at least the reasons discussed above, claim 10 is obvious in view of Dixon alone or in combination with Lalwani 2009b, and the knowledge of a person of ordinary skill in the art.

d. Independent claim 10 is obvious in view of Do 2012.

345. I was asked to review claims 10, 11, 12, 15, 16 and 17 of the 601 patent and compare them to the disclosures of the prior art, including Do 2012.[20]

346. Do 2012 discloses the treatment arms from the DA VINCI phase 2 clinical trials, with the filled black ovals indicating the visits in which injections were given:

[20] I understand that the 601 patent lists applications from 2010 and 2011 on the face of the patent. I also understand that Mylan does not believe that Plaintiff is entitled to rely upon the dates of those applications, and that Mylan contends that the earliest date that Plaintiff is entitled to rely upon is the date of the 370 application, filed July 12, 2013. I offer my opinions in this section based upon an assumption that the July 12, 2013 date applies.



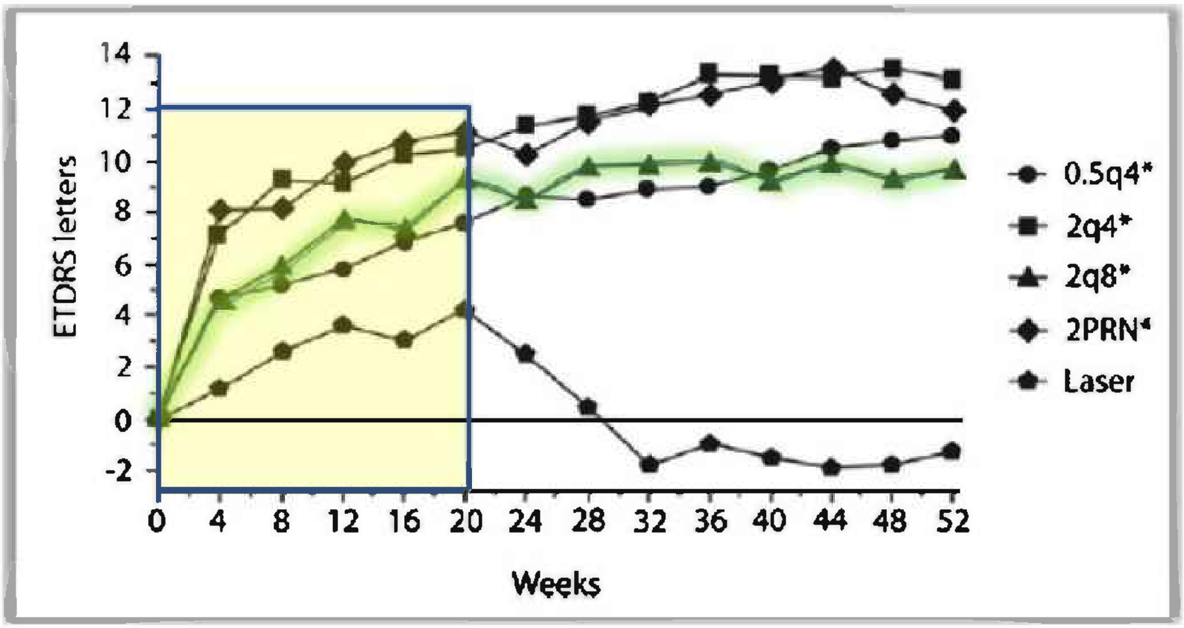
(Do 2012, 1660 & Fig. 1).

347. Do 2012 also discloses positive results from the phase 2 DME DA VINCI clinical trial. For example, Do 2012 disclosed that patients in the 2Q8 arm achieved gains of 8.5 and 9.7 BCVA letters at 24 and 52 weeks, respectively; patients in the 2Q4 arm achieved gains of 11.4 and 13.1 BCVA letters at 24 and 52 weeks, respectively; and patients in the 2PRN arm achieved gains of 10.3 and 12 BCVA letters at 24 and 52 weeks, respectively. (Do 2012, Abstract).

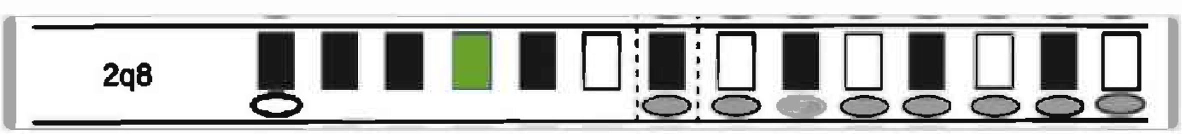
348. Further, a couple of additional data points emerged from the DA VINCI clinical trial that confirmed observations made in earlier ranibizumab trials. For example, Do 2012 reported that patients in the PRN arm received, on average, 7.4 injections over the course of the first year. (Do 2012, 1661 & Table 3). Compare this to the only 5.6 injections required in the PRN arm of the AMD phase 2 CLEAR-IT-2 trial. (Dixon, 1576). This reveals, like the earlier ranibizumab studies, that DME is typically a disease that tends to be more resistant to treatment, and thus usually requires more doses earlier in the treatment regimen.

349. A person of ordinary skill in the art would have been motivated to set a dosing regimen that would be optimal for the patient they are treating, and in the case of a typical DME patient, that regimen is one which would incorporate additional monthly loading doses.

350. A person of ordinary skill in the art would have looked to the DA VINCI arms and recognized that simply including one additional monthly dose would result in 5 straight monthly doses, which, based on the clinical trial results would get patients to or very near the plateau levels observed in DA VINCI patients in the 2Q8 arm (green line; 5 monthly loading doses in yellow shaded area):



(Do 2012, 1661 (emphasis added)). For example, adding an additional loading dose would have been as straightforward as adding a single injection in the middle of the first eight-week span in the 2Q8 arm:



(Do 2012, 1660 (emphasis added)). Such a regimen would have had the effect of ensuring that patients' DME was being treated with an aggressive initial pulse of aflibercept before transitioning to the extended dosing phase of the regimen, thus maximizing early therapeutic benefit.

351. This also is consistent with internal Regeneron documents that indicated it was focusing its aflibercept DME program on no more than 3-6 monthly loading doses. (RGN-EYLEA-MYLAN-00631452 at -53; *see also* RGN-EYLEA-MYLAN-00495620 at -22 ("# loading doses (3 vs. 6 for 2q8)")). Regeneron also used the phase 2 AMD CLEAR-IT-2 clinical trial results to guide its design of the phase 3 DME trial, explaining to EU authorities that:

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(RGN-EYLEA-MYLAN-00531609 at -614). Regeneron continues, stating that:

> Based on this experience we believe that the doses and dosing intervals for VEGF Trap-Eye for Phase III in DME can be selected based on the results of the Phase II study in patients with AMD (OD-0508, see Investigators Brochure, Vol. 14 , pg. 14) In this study, several doses of VEGF Trap-Eye have been assessed in 30 patients / treatment arm. The results suggested that 0.5mg VEGF Trap-Eye is effective in suppressing retinal edema if injected monthly and that 2mg are sufficient to suppress retinal edema for up to 8 weeks. We consider this Phase 2 study as providing an adequate basis for dose selection for the Phase 3 DME program and propose to use the 0.5mg dose in 4-weekly and the 2mg dose in 8-weekly intervals in the planned Phase 3 study (see outline of proposed Phase 3 studies in DME, Vol. 14 , pg. 14).

(RGN-EYLEA-MYLAN-00531609 at -614). In other words, Regeneron was relying on available data (which was publicly available) and selecting an every-8-week dosing regimen that was already in the public domain for its phase 3 DME clinical trials. The selection of the 5 monthly loading doses was a matter of routine optimization, which began with Regeneron confining itself, as early as 2007/2008 to the use of 3-6 monthly loading doses. (*See, e.g.*, RGN-EYLEA-MYLAN-00631452 at -53; RGN-EYLEA-MYLAN-00531609 at -615 ("During an induction phase, VEGF

Trap-Eye is administered by up to 6 intravitreal injections at intervals of 4 or 8 weeks until resolution of macular edema.")).

352. Further, a person of ordinary skill in the art would have had a reasonable expectation of success at using such a regimen given all of the positive DME data in the literature for both aflibercept and ranibizumab. (*See generally, e.g.*, Do 2012; Do 2009; Lalwani 2009b; Massin 2012). Indeed, as I discuss above, Regeneron itself was deriving its DME clinical trial strategy from what already had been learned from the aflibercept AMD phase 2 results and ranibizumab DME results.

353. For at least the reasons discussed above, claim 10 is obvious in view of Do 2012 in combination with the knowledge of a person of ordinary skill in the art.

e. Independent claim 10 is obvious in view of the 747 patent and the 9-14-2009 Regeneron Press Release.

354. I was asked to review claims 10, 11, 12, 15, 16 and 17 of the 601 patent and compare them to the disclosures of the prior art, including the 747 patent and the 9-14-2009 Regeneron Press Release.

355. As discussed above, the 9-14-2009 Regeneron Press Release discloses VEGF Trap-Eye (aflibercept) as a drug intended for intravitreal administration. (9-14-2009 Regeneron Press Release, 1).

356. The press release also discloses a phase 2 clinical trial in which aflibercept is administered to patients with diabetic macular edema (DME) in 2 mg doses on a monthly basis. (9-14-2009 Regeneron Press Release, 1).

357. The 747 patent discloses a method of treating eye disorders, including diabetic retinopathy ("DR"). (747 patent, Title, Abstract, 1:49-54, 2:9-35, 5:39-51, 6:8-24, 6:64 – 7:3). One of the complications associated with diabetic retinopathy is retinal edema (i.e., diabetic

macular edema ("DME"). The 747 patent also discloses treatment with VEGFR1R2-FcΔC1(a)) (i.e., VEGF Trap-Eye or aflibercept). (747 patent at SEQ ID NO:6, 2:1-2, 2:9-35, 5:28-51, 7:5-63). The 747 patent further discloses intravitreal administration of the VEGF trap protein, and treatment with 25-4000 micrograms of the VEGF trap (i.e., 2 mg). (747 patent, 2:9-35; 7:5-63; 20:15-67; 21:1 – 22:42).

358. Based on my read of dependent claim 12, that claim is essentially drawn to monthly dosing. I understand that dependent claims are understood to fall within the scope of the independent claim from which they depend. In other words, because claim 12 is drawn to monthly dosing, independent claim 10, from which it depends, also has monthly dosing within its scope. (601 patent, 22:40-52).

359. Because the prior art 9-14-2009 Regeneron Press Release recites the use of monthly dosing in treating DME patients, in my opinion, the monthly dosing disclosed in the 9-14-2009 Regeneron Press Release makes obvious claim 10. In addition, the 747 patent discloses treatment on a monthly basis, with a preferred embodiment including an initial treatment followed by subsequent treatments between 1-6 months apart (*see, e.g.*, 747 patent, 20:62-67), which a person of ordinary skill in the art would understand could encompass monthly treatment.

360. In addition, a person of ordinary skill in the art would have had a reasonable expectation of success in view of the positive results reported for aflibercept in treating DME in Do 2009, and the positive results reported for the use of ranibizumab in treating DME. For example, Do 2009 reports that a single intravitreal dose of aflibercept resulted in an average of 9 letters in ETDRS score gained after one month. (Do 2009, 146). In addition, Lalwani 2009b discloses that ranibizumab was effective at treating DME. (Lalwani 2009b, 45-46). The ranibizumab disclosures would have been informative because by 2009 aflibercept and

ranibizumab had already been shown to result in similar efficacy in treating AMD. Accordingly, a person of ordinary skill in the art would have expected the same to be true in DME.

361. For at least the reasons discussed above, claim 10 is obvious in view of the 747 patent and the 9-14-2009 Regeneron Press Release, and the knowledge of a person of ordinary skill in the art.

f. Dependent claim 11 is obvious.

362. I was asked to review claim 11 of the 601 patent and compare it to the disclosures of the prior art. Claim 11 purports to further limit the claimed dosing regimen of claim 10 to "wherein approximately every 4 weeks comprises approximately every 28 days or approximately monthly."

363. In my opinion, this added element of claim 11 does not add anything of interest to claim 10. A person of ordinary skill in the art would have viewed and understood "approximately every 4 weeks" to be equivalent to "approximately every 28 days" and "approximately monthly." In addition, Regeneron itself, as well as authors in the field, would use weeks and months interchangeably. (*See, e.g.*, 9-14-2009 Regeneron Press Release, 1 ("2 mg monthly" and "2 mg every eight weeks after three monthly loading doses"); Dixon, 1576 ("Two groups received monthly doses of either 0.5 or 2.0 mg for 12 weeks (at weeks 0, 4, 8 and 12)"); Do 2012, Figure 1 and legend (displaying every 4 week doses and monthly doses the same way and using the terms interchangeably ("3 initial monthly doses then every 8 weeks"))).

364. Thus, for these reasons, claim 11 is obvious in view of the art and combinations set forth above for claim 10.

g. Dependent claim 12 is obvious.

365. I was asked to review claim 12 of the 601 patent and compare it to the disclosures of the prior art. Claim 12 purports to further limit the claimed dosing regimen of claim 10 to

"further comprising, after 20 weeks, administering, via intravitreal injection, 2 mg of aflibercept once every 4 weeks."

366. I read claim 12 as being directed to monthly dosing after the first 5 monthly doses. This appears to conflict with claim 10, from which it depends, making claim 12 unclear. However, despite the lack of clarity, the prior art disclosed monthly dosing for the treatment of DME.

367. For example, Regeneron has represented to the public and the Patent Office that as of the relevant time period monthly dosing was the standard of care for angiogenic eye disorders. (*See, e.g.*, 338 PH, 9-11-2015 Applicant Remarks, 6). I disagree that monthly dosing was the standard of care. However, Regeneron also knew that monthly dosing, while not the majority practice, was nevertheless a long-practiced regimen. This is also evident from the 9-14-2009 Regeneron Press Release. (9-14-2009 Regeneron Press Release, 1 ("evaluat[ing] whether further improvements in vision and/or longer dosing intervals than *monthly* administration are possible.")).

368. Monthly dosing was an approved regimen for treating angiogenic eye disorders with the existing therapy (i.e., Lucentis), and in my experience, some doctors (though not many), were using fixed monthly dosing to treat these disorders prior to the filing of the 601 patent.

369. In addition, the 9-14-2009 Press Release discloses the administration of 2 mg of aflibercept, including at monthly intervals. (*See, e.g.*, 9-14-2009 Regeneron Press Release, 2 ("VEGF Trap-Eye dosed at … 2 mg monthly")). Other prior art also disclosed monthly dosing. (*See, e.g.*, 747 patent, 20:62-67; Lalwani 2009b, 45; Dixon, 1576; Do 2012, 1659).

370. Thus, in my opinion, monthly dosing with aflibercept for the treatment of an angiogenic eye disorder such as DME, and the use of 2 mg of aflibercept to do so, would have been obvious.

371. Thus, for these reasons, as well as at least the reasons discussed above for claim 10, claim 12 is obvious in view of the art and combinations set forth above for claim 10.

h. Dependent claims 15 and 16 are obvious.

372. I was asked to review claims 15 and 16 of the 601 patent and compare them to the disclosures of the prior art. Claim 15 purports to further limit the claimed dosing regimen of claim 10 to "wherein the patient gains at least 15 letters of Best Corrected Visual Acuity (BCVA) score," and claim 16 recites wherein the BCVA is according to the ETDRS letter score.

373. I have been informed that Mylan is taking the legal position that the visual acuity elements recited in claims 15 and 16 constitute statements of intended results of the claimed methods that do not result in a manipulative difference in the steps of the claim, and thus should be deemed non-limiting. Furthermore, in my opinion, the recited BCVA criteria are commonly used outcome measures in clinical trials assessing patients with angiogenic eye disorders who are receiving anti-VEGF treatment, and thus represent nothing more than the intended result of those trials, or the natural result flowing from those clinical trials. (*See, e.g.*, Nguyen 2009a, 2141-43, 2145-46; Dixon, 1575-76; Heier 2009A, 45; Brown 2006, 1433; Rosenfeld 2006, 1420, 1426). Indeed, there is nothing in the claims that instruct how to achieve the visual acuity measures recited in the claims. The claims merely recite a prior art dosing regimen, and then recite commonly used visual acuity metrics. But there are no modifications or adjustments to the dosing regimen included in the claims.

374. Regardless of whether the BCVA elements are considered in the patentability analysis, they are rendered obvious in view of the prior art. For example, the 9-14-2009 Regeneron Press Release discloses the use of ETDRS in assessing angiogenic eye disorders, which a person of ordinary skill in the art would have understood to be measuring BCVA. (9-14-2009 Regeneron

Press Release, 1; *see also, e.g.*, Do 2009, Abstract, 147 & Fig. 1 (assessing BCVA ETDRS in the aflibercept phase 1 DME trial)).

375. In addition, the results of the VIVID and VISTA phase 3 clinical trials, which utilized 5 monthly loading doses followed by every-8-week dosing, show that a significant fraction of the patient population experienced gains of at least 15 letters in visual acuity based on ETDRS score. (*See, e.g.*, Korobelnik 2014 DME, 2247). This result was not surprising in view of the earlier clinical trial results with aflibercept, and would have indicated to a person of ordinary skill in the art that a population of treated patients necessarily would have experienced such gains. Accordingly, in my opinion, the recited BCVA criteria are an inherent feature of the claimed dosing regimen. In addition, a person of ordinary skill in the art would have had a reasonable expectation of success at achieving such BCVA measures in view of the positive phase 1 DME results with aflibercept, showing a gain of 9 letters after just a single dose of aflibercept. (Do 2012, Abstract). A person of ordinary skill in the art also would have had a reasonable expectation of success in view of the data that was emerging from the ranibizumab DME clinical trials, as well as the reported primary outcome measure of the ranibizumab RISE and RIDE clinical studies and the reports from other clinical trials regarding "greater-than-15-letter gainers." (Lalwani 2009b, 46).

376. In the event that any of the 601 patent claims has a July 2013 priority date, as discussed above, a person of ordinary skill in the art also would have had a reasonable expectation of success in view of the phase 2 DA VINCI DME clinical trial data. (Do 2012, Abstract (reporting the proportion of patients gaining greater than 15 letters)).

377. Thus, for this reason, as well as the reasons discussed above for claim 10, it is my opinion that claims 15 and 16 of the 601 patent are obvious in view of the 9-14-2009 Regeneron Press Release alone, or if necessary, in combination with Do 2009, Do 2012, or Lalwani 2009b.

i. Dependent claim 17 of the 601 patent is obvious.

378. I was asked to review claim 17 of the 601 patent and compare it to the disclosures of the prior art. Claim 17 purports to further limit the claimed dosing regimen of claim 10 to "wherein exclusion criteria for the patient include (1) active intraocular inflammation; or (2) active ocular or periocular infection."

379. Claim 17 sets forth common criteria for excluding patients from clinical trials that involve the intravitreal administration of a drug. In fact, the phase 2 DME clinical trial included the application of these criteria, which would necessarily have been applied during the enrolment of patients in that trial. (*See, e.g.*, Do 2011, 1820 (disclosing ocular inflammation, and infectious blepharitis, keratitis, scleritis, or conjunctivitis as exclusion criteria in the phase 2 DME trial)).

380. Thus, in my opinion the conduct of the phase 2 DME trials described in the phase 2 DME references would have necessarily involved the application of one or both of the exclusion criteria listed in claim 17, and thus are an inherent aspect of that clinical trial.

381. Further, in my opinion the exclusion of patients with inflammation or infections would have been a routine and common practice given the risks of serious infection that can result from injecting eyes with signs of pre-existing ocular or periocular infections. The recited exclusion criteria also were commonly employed exclusion criteria in the clinical trials being conducted at the time. For example, Lucentis DME clinical trials included the claimed exclusion criteria. (*See, e.g.*, Chun 2006, 1707 ("ocular disorders that may confound interpretation of study results" and "ocular inflammation")). Further, the ranibizumab AMD MARINA and ANCHOR trials, involving monthly intravitreal administration of ranibizumab, employed exclusion criteria that

included, among other criteria, active intraocular inflammation in the study eye; history of idiopathic or autoimmune-associated uveitis in either eye; and infectious conjunctivitis, keratitis, scleritis, or endophthalmitis in either eye. (*See, e.g.*, Lucentis Medical Review, MYL-AFL0007147-49; Rosenfeld 2006, Appx., 2-3; NCT 836, 5-6; NCT 594, 5-6). The pegaptanib trials involving intravitreal administration in treating AMD likewise employed exclusion criteria that included, among other relevant criteria, choroiditis, and acute ocular or periocular infection. (*See, e.g.*, Macugen Medical Review, MYL-AFL0007406; Macugen Study Group, 1748).

382. Finally, it was known among those of ordinary skill in the art that intravitreal injections could be associated with serious side effects if proper, aseptic technique is not adhered to. Consequently, persons of ordinary skill in the art were aware of guidelines and other information in the literature about avoiding injecting eyes that are infected or show signs of infection (i.e., inflammation). (*See, e.g.*, Aiello 2004, S4, 6-8, 17; Jager 2004, 687-88; De Caro, 878; Heimann, 67, 74-77, 80-81, 85; CATT Study, 6-7; Regillo 2008, 248.e3; MACTEL Study, 4; Jaffe, 349-50; Lucentis PI 2006, 2, 5; Retinal Physician II, 2, 5; collectively, the cited references are referred to herein as the "injection guideline references").

383. Thus, for this reason, as well as the reasons discussed above for claim 10, it is my opinion that claim 17 of the 601 patent is obvious in view of the 9-14-2009 Regeneron Press Release alone, or if necessary, in combination with Chun 2006, the ranibizumab MARINA and ANCHOR references, the pegaptanib references, or the injection guideline references.

5. Claims 18-19, 21, and 23-25 of the 601 patent are obvious in view of the prior art.

a. Independent claim 18 is obvious in view of the 747 patent and the 9-14-2009 Regeneron Press Release alone, or in combination with Do 2009.

384. I was asked to review claims 18, 19, 21, and 23-25 of the 601 patent and compare them to the disclosures of the prior art, including the 747 patent, the 9-14-2009 Regeneron Press Release, and Do 2009.

385. The 9-14-2009 Regeneron Press Release discloses VEGF Trap-Eye (aflibercept) as a drug intended for intravitreal administration. (9-14-2009 Regeneron Press Release, 1).

386. The press release also discloses a phase 2 clinical trial in which aflibercept is administered to patients with diabetic macular edema (DME) in 2 mg doses for three monthly loading doses. After the monthly loading doses, patients are treated with fixed every-8-week injections or PRN (i.e., as needed) injections. In my opinion, persons of ordinary skill in the art understood by 2009 that DME was a complication of diabetic retinopathy (DR). This also is clear from the publications that report on the very phase 2 DME clinical trial that I discuss above and below. For example, Do 2011 states that "[d]iabetic macular edema (DME) is the most common vision-threatening manifestation of diabetic retinopathy." (Do 2011, 1819). Thus, a person of ordinary skill in the art, when treating DME, would have understood that they would also be treating DR, given that DME is a common manifestation of DR.

387. The 747 patent discloses a method of treating eye disorders, including diabetic retinopathy ("DR"). (747 patent, Title, Abstract, 1:49-54, 2:9-35, 5:39-51, 6:8-24, 6:64 – 7:3). One of the complications associated with diabetic retinopathy is retinal edema (i.e., diabetic macular edema ("DME"). The 747 patent also discloses treatment with VEGFR1R2-FcΔC1(a)) (i.e., VEGF Trap-Eye or aflibercept). (747 patent at SEQ ID NO:6, 2:1-2, 2:9-35, 5:28-51, 7:5-

63). The 747 patent further discloses intravitreal administration of the VEGF trap protein, and treatment with 25-4000 micrograms of the VEGF trap (i.e., 2 mg). (747 patent, 2:9-35; 7:5-63; 20:15-67; 21:1 – 22:42).

388. A regimen of 5 monthly loading doses would have been obvious in view of the phase 2 dosing regimens. For example, from the positive results of the phase 1 DME trial, and the disclosed dosing regimens of the phase 2 clinical trial, a person of ordinary skill in the art would have been motivated to identify an optimal dosing regimen for the treatment of DR patients. In my experience, identifying an optimum dosing regimen for a VEGF antagonist such as aflibercept is a matter of routine optimization. A person of ordinary skill in the art would have been motivated to try a range of monthly loading doses, especially since a series of monthly loading doses followed by extended PRN/treat-and-extend dosing was the industry standard and that was the approach being used, with success, by those in clinical practice. (*See, e.g.*, Retinal Physician 2007, MYL-AFL0090401; *id.*, MYL-AFL0090402-03; MYL-AFL0091273).

389. I am aware that Regeneron was experimenting with 1, 3, and 4 monthly loading doses in its aflibercept clinical trials. For example, Regeneron tried 1 and 4 monthly loading doses in its phase 2 AMD trials, (*see, e.g.*, Dixon, 1576; 9-14-2009 Regeneron Press Release, 2); and 3 monthly loading doses in its phase 2 DME and phase 3 VIEW trials, (*see, e.g.*, 9-14-2009 Regeneron Press Release, 1, 2).

390. This also is consistent with internal Regeneron documents that indicated it was focusing its aflibercept DME program on no more than 3-6 monthly loading doses. (RGN-EYLEA-MYLAN-00631452 at -53). Regeneron also used the phase 2 AMD CLEAR-IT-2 clinical trial results to guide its design of the phase 3 DME trial, explaining to EU authorities that:

> Other intravitreal anti-VEGF therapies (Macugen, Avastin, Lucentis) that are commonly used for AMD have suggested efficacy of this therapeutic principle also in treating DME in Phase I/II studies and investigator initiated studies. This is further supported by Phase III studies recently initiated by Genentech for their product ranibizumab in DME patients. Most notably the doses employed in these studies (0.3 and 0.5 mg given monthly) are the same doses which are used in the AMD indication.

(RGN-EYLEA-MYLAN-00531609 at -614). Regeneron continues, stating that:

> Based on this experience we believe that the doses and dosing intervals for VEGF Trap-Eye for Phase III in DME can be selected based on the results of the Phase II study in patients with AMD (OD-0508, see Investigators Brochure, Vol. 14 , pg. 14) In this study, several doses of VEGF Trap-Eye have been assessed in 30 patients / treatment arm. The results suggested that 0.5mg VEGF Trap-Eye is effective in suppressing retinal edema if injected monthly and that 2mg are sufficient to suppress retinal edema for up to 8 weeks. We consider this Phase 2 study as providing an adequate basis for dose selection for the Phase 3 DME program and propose to use the 0.5mg dose in 4-weekly and the 2mg dose in 8-weekly intervals in the planned Phase 3 study (see outline of proposed Phase 3 studies in DME, Vol. 14 , pg. 14).

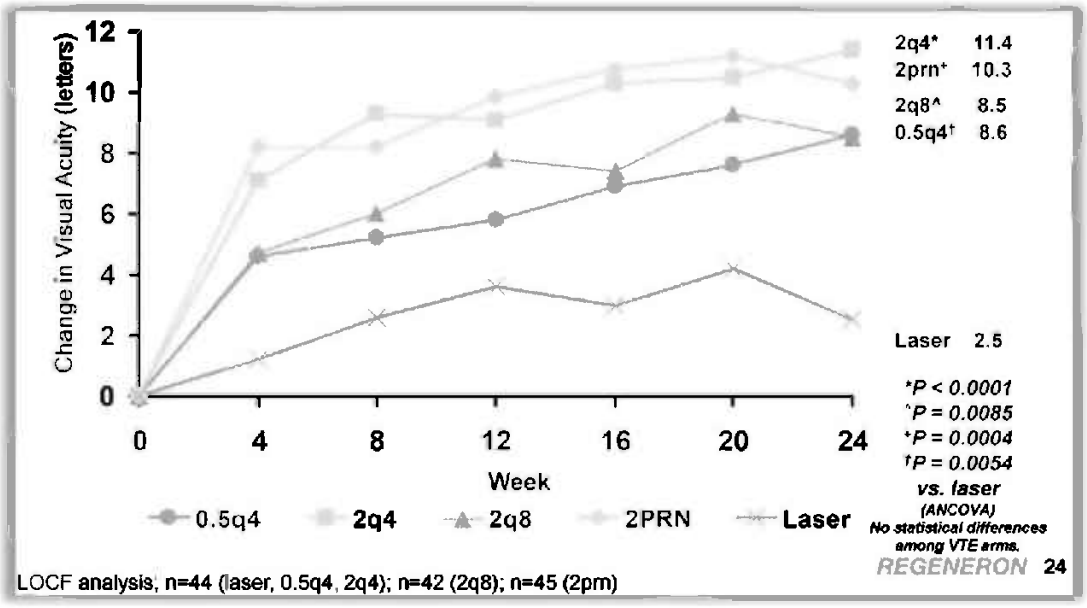
(RGN-EYLEA-MYLAN-00531609 at -614). In other words, Regeneron was relying on available data (which was publicly available) and selecting an every-8-week dosing regimen that was already in the public domain for its phase 3 DME clinical trials. The selection of the 5 monthly loading doses was a matter of routine optimization, which began with Regeneron confining itself, as early as 2007/2008 to the use of 3-6 monthly loading doses. (*See, e.g.*, RGN-EYLEA-MYLAN-00631452 at -53; RGN-EYLEA-MYLAN-00531609 at -615 ("During an induction phase, VEGF Trap-Eye is administered by up to 6 intravitreal injections at intervals of 4 or 8 weeks until resolution of macular edema.")).

391. Further, in my clinical experience, DME and DR patients tend to require more loading doses (compared to AMD patients) to achieve satisfactory retinal thickness and/or visual acuity measures.

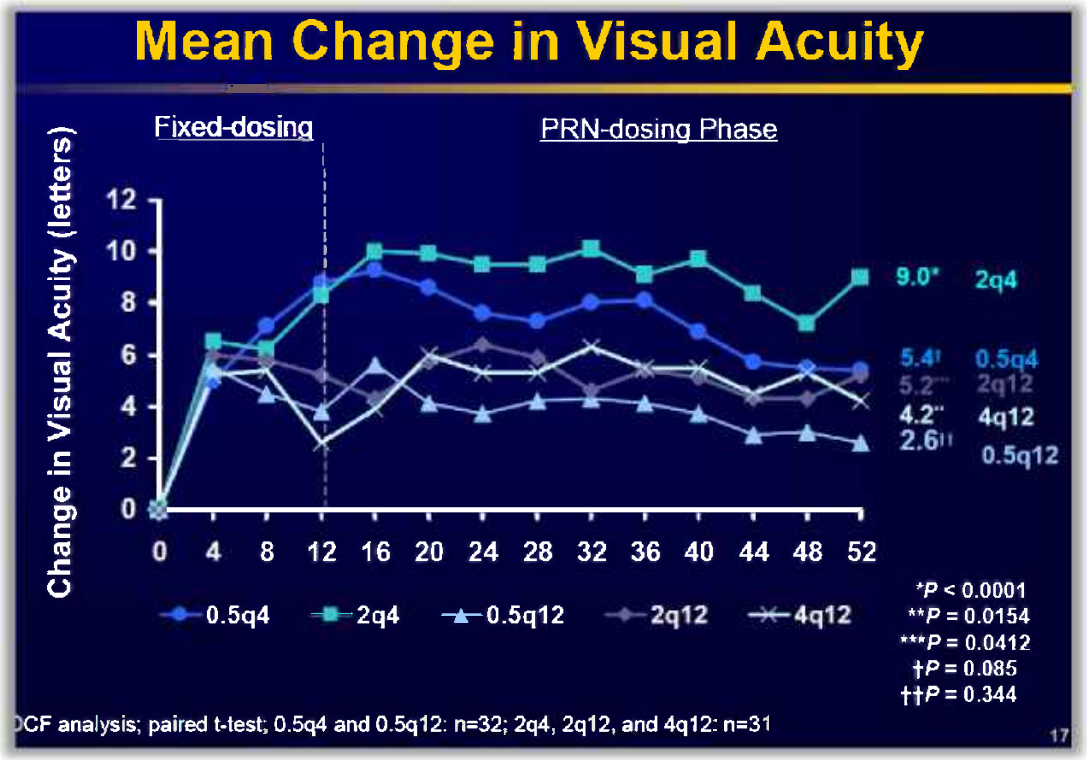
392. Thus, in my opinion, putting DME and DR patients on 4 or 5 monthly loading doses rather than three would have been obvious to try when conducting routine optimization of a loading

dose regimen for DR. This is confirmed by my review of the data that came out of the phase 2 DA VINCI DME clinical trial.

393. For example, as Regeneron was designing its VIVID and VISTA phase 3 clinical trial in DME in which 5 monthly loading doses were to be tested, they had available to them the data from the phase 2 DME DA VINCI trial. A person of ordinary skill in the art would have immediately noticed that the DA VINCI 2Q8 arm patient group exhibited a lengthier time to plateau than what would have been observed with AMD. For example, I reviewed information from a March 2010 slide presentation provided by Regeneron. Therein, data from the DA VINCI DME clinical trial revealed that it was taking 5-6 months for patients to near a plateau of visual acuity gains:



(RGN-EYLEA-MYLAN-00585880 at -909). Contrast this with the results from the AMD phase 2 clinical trial using the same dosage (2 mg) and a similar loading dose scheme:



(2008 Retina Society Slides, 17). What is evident from these two sets of data is that DME appears more resistant to treatment than AMD, which also is consistent with observations I've made within my own practice. As a result, DME patients were taking longer to approach plateau. From this data, in my opinion, it is a matter of routine optimization to adjust upward the number of monthly loading doses if a patient is presenting with a more difficult to treat condition (e.g., DME and DR), or taking longer to show a response to treatment. Thus, it is an obvious and routine matter to arrive at a particular number of loading doses.

394. In any event, internal Regeneron documents reveal that business/commercial concerns also were important in Regeneron's decision to implement 5 monthly loading doses for the treatment of DME. For example, a January 26, 2011 presentation of Bayer and Regeneron discusses their DME clinical plan and suggests that the selection of 5 loading doses for the DME

trial was the result of "a compromise" between Regeneron and Bayer, deemed "acceptable from a commercial/market access perspective." (RGN-EYLEA-MYLAN-00513418 at 424).

395. Further, in my opinion, a person of ordinary skill in the art would have had a reasonable expectation of success at using 5 monthly loading doses in light of the positive phase 1 results seen with a single intravitreal dose of aflibercept. For example, Do 2009 reports that a single intravitreal dose of aflibercept resulted in an average of 9 letters in ETDRS score gained after one month. (Do 2009, 146). The reasonable expectation of success also would have come from the combination of highly relevant data that was in the public domain at the time showing that (1) aflibercept was effective at treating AMD after a series of monthly loading doses, followed by less frequent dosing (Dixon, 1576); (2) ranibizumab was effective at treating both AMD and DME (Rosenfeld 2006, 1426; Lalwani 2009b, 45-46). Indeed, as I discuss above, Regeneron itself was deriving its DME clinical trial strategy from what already had been learned from the aflibercept AMD phase 2 results and ranibizumab DME results.

396. For at least the reasons discussed above, claim 18 is obvious in view of the 747 patent and 9-14-2009 Regeneron Press Release alone or in combination with Do 2009, and the knowledge of a person of ordinary skill in the art.

b. Independent claim 18 is obvious in view of the 747 patent and the 9-14-2009 Regeneron Press Release alone, or in combination with the Lucentis art.

397. I was asked to review claims 18, 19, 21, and 23-25 of the 601 patent and compare them to the disclosures of the prior art, including the 747 patent, the 9-14-2009 Regeneron Press Release and the Lucentis art.

398. The 9-14-2009 Regeneron Press Release discloses VEGF Trap-Eye (aflibercept) as a drug intended for intravitreal administration. (9-14-2009 Regeneron Press Release, 1).

399. The press release also discloses a phase 2 clinical trial in which aflibercept is administered to patients with diabetic macular edema (DME) in 2 mg doses for three monthly loading doses. (*Id.*, 2). After the monthly loading doses, patients are treated with fixed every-8-week injections or PRN (i.e., as needed) injections. (*Id.*). In my opinion, persons of ordinary skill in the art understood by 2009 that DME was a complication of diabetic retinopathy (DR). This also is clear from the publications that report on the very phase 2 DME clinical trial that I discuss above and below. For example, Do 2011 states that "[d]iabetic macular edema (DME) is the most common vision-threatening manifestation of diabetic retinopathy." (Do 2011, 1819). Thus, a person of ordinary skill in the art, when treating DME, would have understood that they would also be treating DR, given that DME is a common manifestation of DR.

400. The 747 patent discloses a method of treating eye disorders, including diabetic retinopathy ("DR"). (747 patent, Title, Abstract, 1:49-54, 2:9-35, 5:39-51, 6:8-24, 6:64 – 7:3). One of the complications associated with diabetic retinopathy is retinal edema (i.e., diabetic macular edema ("DME"). The 747 patent also discloses treatment with VEGFR1R2-FcΔC1(a)) (i.e., VEGF Trap-Eye or aflibercept). (747 patent, SEQ ID NO:6, 2:1-2, 2:9-35, 5:28-51, 7:5-63). The 747 patent further discloses intravitreal administration of the VEGF trap protein, and treatment with 25-4000 micrograms of the VEGF trap (i.e., 2 mg). (747 patent, 2:9-35; 7:5-63; 20:15-67; 21:1-22:42).

401. Shortly after Regeneron had initiated its phase 2 DME clinical trial, data emerged from Lucentis clinical trials in DME. The Lucentis clinical trial data revealed that patients treated with 0.5 mg on a monthly loading regimen achieved very similar BCVA scores as those observed in the Lucentis AMD trials. For example, in Lalwani 2009b, the author reported on data emerging from the clinical study Ranibizumab for Edema of the Macula in Diabetes (READ 1). (Lalwani

2009b, 45). Lalwani 2009b discloses the design of the study, including the dosing regimen, which involved injections at baseline, and months 1, 2, 4, and 6 (i.e., 3 monthly loading doses followed by every 8 week dosing). (Lalwani 2009b, 45). The author further reports that at 12 months, the DME patients receiving ranibizumab had achieved, on average, a gain of 8 letters of visual acuity. (*Id.*). The author further notes that the READ 2 program that followed READ 1 employed monthly dosing through 12 months, and the ranibizumab-only arm achieved mean gains of 6.46 letters. (*Id.*, 45-46).

402. In other words, Lucentis was showing that the treatment of AMD and DME (and DR) can be accomplished to similar effect with similar regimens and the same amount of anti-VEGF agent.

403. However, a person of ordinary skill in the art also would have appreciated that the treatment of DME and DR differed from AMD in at least one aspect.

404. For example, the author references the theory circulating among physicians at the time that VEGF was particularly elevated in DME compared to AMD, and thus may require more aggressive treatment. (Lalwani 2009b, 46). This also is consistent with the presentation of the RESOLVE trial data set forth in Lalwani 2009b, which showed a shallower curve to reach plateau levels of mean visual acuity than that observed with AMD in, for example, the MARINA and ANCHOR trials. (Lalwani 2009b, 46; *see also, e.g.*, Rosenfeld 2006, 1426). For example, one can compare the RESOLVE DME data in Lalwani 2009b:

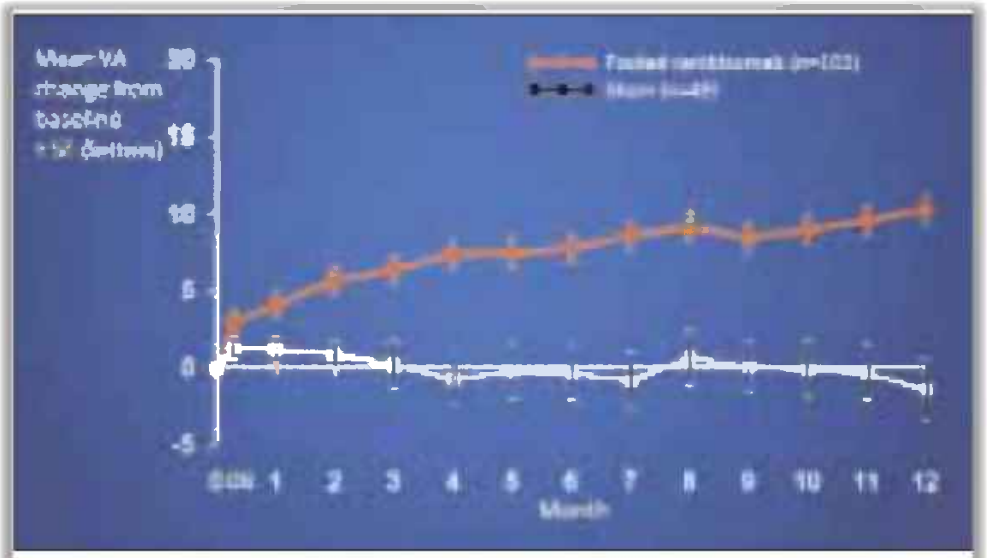
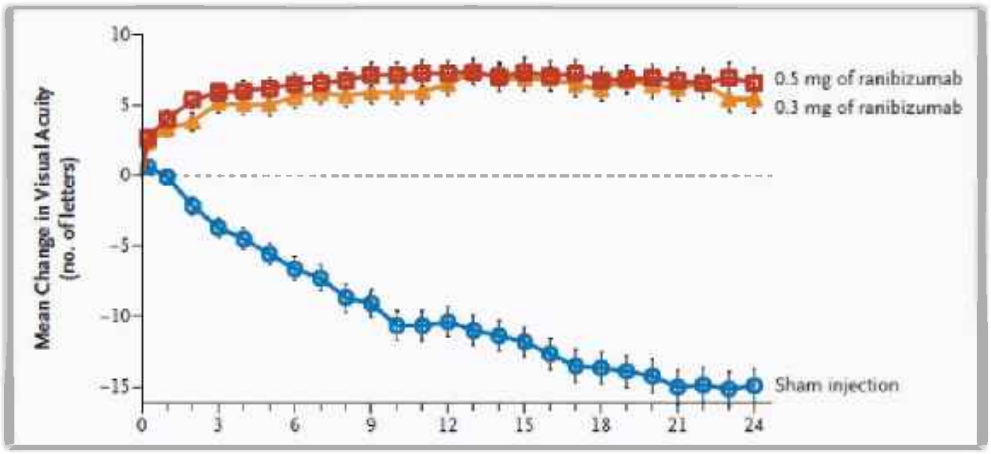


Figure 2. Visual acuity results at 1 year for the RESOLVE Trial.

(Lalwani 2009b, 46), with the data in Rosenfeld 2006 for AMD:



(Rosenfeld 2006, 1426). As discussed above, it is evident from these two sets of data that DME appears more resistant to treatment than AMD, which also is consistent with observations I've made within my own practice, and consistent with Lalwani 2009b's reference to the theory that VEGF is more elevated in DME patients. As a result of this resistance, DME patients in the Lucentis trials were taking longer to approach plateau when compared to AMD patients. From this data, in my opinion, a person of ordinary skill in the art would have looked to increase the

number of loading doses when treating DR patients with aflibercept. Based on the data above, 5 monthly loading is an obvious and reasonable number to incorporate, especially in view of the use of 3 and 4 loading doses in the aflibercept AMD clinical trials.

405. This also is consistent with internal Regeneron documents that indicated it was focusing its aflibercept DME program on no more than 3-6 monthly loading doses. (RGN-EYLEA-MYLAN-00631452 at -53; *see also* RGN-EYLEA-MYLAN-00495620 at -22 ("# loading doses (3 vs. 6 for 2q8)")). Regeneron also used the phase 2 AMD CLEAR-IT-2 clinical trial results to guide its design of the phase 3 DME trial, explaining to EU authorities that:

> Other intravitreal anti-VEGF therapies (Macugen, Avastin, Lucentis) that are commonly used for AMD have suggested efficacy of this therapeutic principle also in treating DME in Phase I/II studies and investigator initiated studies. This is further supported by Phase III studies recently initiated by Genentech for their product ranibizumab in DME patients. Most notably the doses employed in these studies (0.3 and 0.5 mg given monthly) are the same doses which are used in the AMD indication.

(RGN-EYLEA-MYLAN-00531609 at -614). Regeneron continues, stating that:

> Based on this experience we believe that the doses and dosing intervals for VEGF Trap-Eye for Phase III in DME can be selected based on the results of the Phase II study in patients with AMD (OD-0508, see Investigators Brochure, Vol. 14 , pg. 14) In this study, several doses of VEGF Trap-Eye have been assessed in 30 patients / treatment arm. The results suggested that 0.5mg VEGF Trap-Eye is effective in suppressing retinal edema if injected monthly and that 2mg are sufficient to suppress retinal edema for up to 8 weeks. We consider this Phase 2 study as providing an adequate basis for dose selection for the Phase 3 DME program and propose to use the 0.5mg dose in 4-weekly and the 2mg dose in 8-weekly intervals in the planned Phase 3 study (see outline of proposed Phase 3 studies in DME, Vol. 14 , pg. 14).

(RGN-EYLEA-MYLAN-00531609 at -614). In other words, Regeneron was relying on available data (which was publicly available) and selecting an every-8-week dosing regimen that was already in the public domain for its phase 3 DME clinical trials. The selection of the 5 monthly loading doses was a matter of routine optimization, which began with Regeneron confining itself, as early as 2007/2008 to the use of 3-6 monthly loading doses. (*See, e.g.*, RGN-EYLEA-MYLAN-00631452 at -53; RGN-EYLEA-MYLAN-00531609 at -615 ("During an induction phase, VEGF

Trap-Eye is administered by up to 6 intravitreal injections at intervals of 4 or 8 weeks until resolution of macular edema.")).

406. Further, in my opinion, a person of ordinary skill in the art would have had a reasonable expectation of success at using 5 monthly loading doses in light of the positive phase 1 results seen with a single intravitreal dose of aflibercept. For example, Do 2009 reports that a single intravitreal dose of aflibercept resulted in an average of 9 letters in ETDRS score gained after one month. (Do 2009, 146). The reasonable expectation of success also would have come from the combination of highly relevant data that was in the public domain at the time showing that (1) aflibercept was effective at treating AMD after a series of monthly loading doses, followed by less frequent dosing (Dixon, 1576); (2) ranibizumab was effective at treating both AMD and DME (Rosenfeld 2006, 1426; Lalwani 2009b, 45-46). Indeed, as I discuss above, Regeneron itself was deriving its DME clinical trial strategy from what already had been learned from the aflibercept AMD phase 2 results and ranibizumab DME results.

407. For at least the reasons discussed above, claim 18 is obvious in view of the 747 patent and the 9-14-2009 Regeneron Press Release alone or in combination with Lalwani 2009b, and the knowledge of a person of ordinary skill in the art.

c. Independent claim 18 is obvious in view of Dixon in combination with Lalwani 2009b.

408. I was asked to review claims 18, 19, 21, and 23-25 of the 601 patent and compare them to the disclosures of the prior art, including Dixon and Lalwani 2009b.

409. For example, Dixon discloses positive results from several aflibercept clinical trials, including several phase 1 trials in both AMD and DME, and the phase 2 CLEAR-IT-2 AMD trial. (Dixon, 1575-76). Dixon reports that in the DME study, "[t]he single injection resulted in a

median decrease of central macular thickness measured by OCT of 79 µm. BCVA increased by 9 letters at 4 weeks and regressed to a 3 letter improvement at 6 weeks." (Dixon, 1575).

410. Dixon also makes note of the "multifactorial nature of DME" and discloses that phase 2 clinical studies are underway with anti-VEGF agents, including aflibercept, for the treatment of DME. (Dixon, 1577-78). In my opinion, persons of ordinary skill in the art understood by 2009 that DME was a complication of diabetic retinopathy (DR). This also is clear from the publications that report on the very phase 2 DME clinical trial that I discuss above and below. For example, Do 2011 states that "[d]iabetic macular edema (DME) is the most common vision-threatening manifestation of diabetic retinopathy." (Do 2011, 1819). Thus, a person of ordinary skill in the art, when treating DME, would have understood that they would also be treating DR, given that DME is a common manifestation of DR.

411. Dixon also discloses that aflibercept/VEGF Trap-Eye is formulated in a 2 mg presentation and for intravitreal administration. (Dixon, 1575).

412. About this same time, data emerged from Lucentis clinical trials in DME. The Lucentis clinical trial data revealed that patients treated with 0.5 mg on a monthly loading regimen achieved very similar BCVA scores as those observed in the Lucentis AMD trials. For example, in Lalwani 2009b, the author reported on data emerging from the clinical study Ranibizumab for Edema of the Macula in Diabetes (READ 1). (Lalwani 2009b, 45). Lalwani 2009b discloses the design of the study, including the dosing regimen, which involved injections at baseline, and months 1, 2, 4, and 6 (i.e., 3 monthly loading doses followed by every-8-week dosing). (*Id.*, 45). The author further reports that at 12 months, the DME patients receiving ranibizumab had achieved, on average, a gain of 8 letters of visual acuity. (*Id.*). The author further notes that the

READ 2 program that followed READ 1 employed monthly dosing through 12 months, and the ranibizumab-only arm achieved mean gains of 6.46 letters. (*Id.*, 45-46).

413. In other words, Lucentis was showing that the treatment of AMD and DME (and DR) can be accomplished to similar effect with similar regimens and the same amount of anti-VEGF agent.

414. However, a person of ordinary skill in the art also would have appreciated that the treatment of DME (and DR) differed from AMD in at least one aspect.

415. For example, the author references the theory circulating among physicians at the time that VEGF was particularly elevated in DME compared to AMD, and thus may require more aggressive treatment. (Lalwani 2009b, 46). This also is consistent with the presentation of the RESOLVE trial data set forth in Lalwani 2009b, which showed a shallower curve to reach plateau levels of mean visual acuity than that observed with AMD in, for example, the MARINA and ANCHOR trials. (Lalwani 2009b, 46; *see also, e.g.*, Rosenfeld 2006, 1426). For example, one can compare the RESOLVE DME data in Lalwani 2009b:

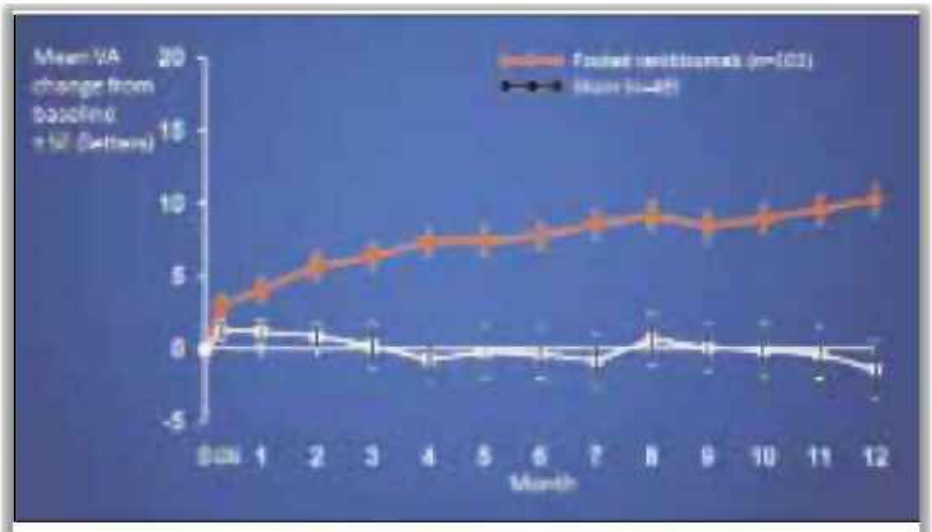
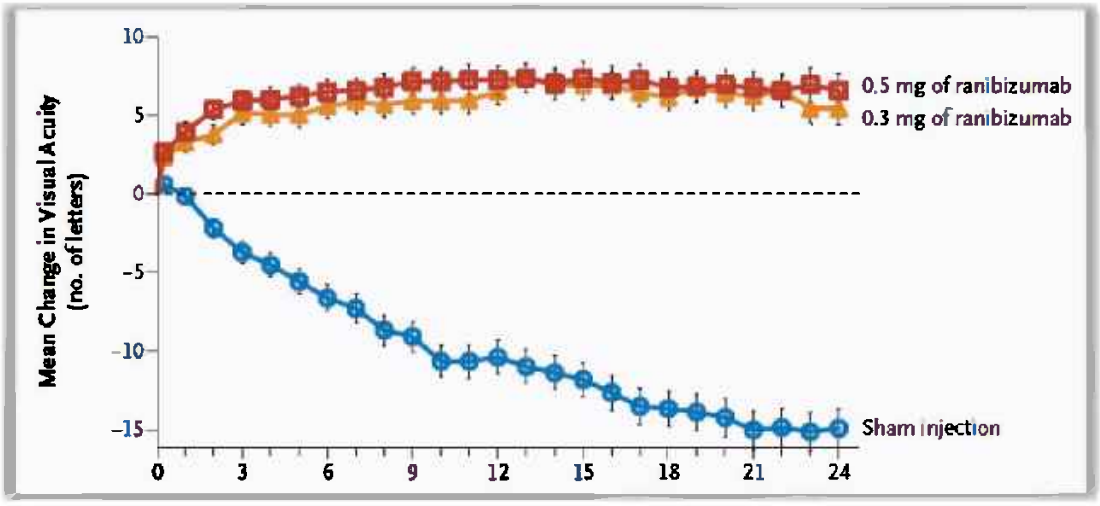


Figure 2. Visual acuity results at 1 year for the RESOLVE Trial.

(Lalwani 2009b, 46), with the data in Rosenfeld 2006 for AMD:



(Rosenfeld 2006, 1426). As discussed above, it is evident from these two sets of data that DME appears more resistant to treatment than AMD, which also is consistent with observations I've made within my own practice, and consistent with Lalwani 2009b's reference to the theory that VEGF is more elevated in DME patients. As a result of this resistance, DME patients in the Lucentis trials were taking longer to approach plateau when compared to AMD patients. From this data, in my opinion, a person of ordinary skill in the art would have looked to increase the number of loading doses when treating DR patients with aflibercept. Based on the data above, 5 monthly loading is an obvious and reasonable number to incorporate, especially in view of the use of 3 and 4 loading doses in the aflibercept AMD clinical trials.

416. This also is consistent with internal Regeneron documents that indicated it was focusing its aflibercept DME program on no more than 3-6 monthly loading doses. (RGN-EYLEA-MYLAN-00631452 at -53; *see also* RGN-EYLEA-MYLAN-00495620 at -22 ("# loading doses (3 vs. 6 for 2q8)")). Regeneron also used the phase 2 AMD CLEAR-IT-2 clinical trial results to guide its design of the phase 3 DME trial, explaining to EU authorities that:

> Other intravitreal anti-VEGF therapies (Macugen, Avastin, Lucentis) that are commonly used for AMD have suggested efficacy of this therapeutic principle also in treating DME in Phase I/II studies and investigator initiated studies. This is further supported by Phase III studies recently initiated by Genentech for their product ranibizumab in DME patients. Most notably the doses employed in these studies (0.3 and 0.5 mg given monthly) are the same doses which are used in the AMD indication.

(RGN-EYLEA-MYLAN-00531609 at -614). Regeneron continues, stating that:

> Based on this experience we believe that the doses and dosing intervals for VEGF Trap-Eye for Phase III in DME can be selected based on the results of the Phase II study in patients with AMD (OD-0508, see Investigators Brochure, Vol. 14 , pg. 14) In this study, several doses of VEGF Trap-Eye have been assessed in 30 patients / treatment arm. The results suggested that 0.5mg VEGF Trap-Eye is effective in suppressing retinal edema if injected monthly and that 2mg are sufficient to suppress retinal edema for up to 8 weeks. We consider this Phase 2 study as providing an adequate basis for dose selection for the Phase 3 DME program and propose to use the 0.5mg dose in 4-weekly and the 2mg dose in 8-weekly intervals in the planned Phase 3 study (see outline of proposed Phase 3 studies in DME, Vol. 14 , pg. 14).

(RGN-EYLEA-MYLAN-00531609 at -614). In other words, Regeneron was relying on available data (which was publicly available) and selecting an every-8-week dosing regimen that was already in the public domain for its phase 3 DME clinical trials. The selection of the 5 monthly loading doses was a matter of routine optimization, which began with Regeneron confining itself, as early as 2007/2008 to the use of 3-6 monthly loading doses. (*See, e.g.*, RGN-EYLEA-MYLAN-00631452 at -53; RGN-EYLEA-MYLAN-00531609 at -615 ("During an induction phase, VEGF Trap-Eye is administered by up to 6 intravitreal injections at intervals of 4 or 8 weeks until resolution of macular edema.")).

417. Further, in my opinion, a person of ordinary skill in the art would have had a reasonable expectation of success at using 5 monthly loading doses in light of the positive phase 1 results seen with a single intravitreal dose of aflibercept. For example, Do 2009 reports that a single intravitreal dose of aflibercept resulted in an average of 9 letters in ETDRS score gained after one month. (Do 2009, 146). The reasonable expectation of success also would have come from the combination of highly relevant data that was in the public domain at the time showing

that (1) aflibercept was effective at treating AMD after a series of monthly loading doses, followed by less frequent dosing (Dixon, 1576); (2) ranibizumab was effective at treating both AMD and DME (Rosenfeld 2006, 1426; Lalwani 2009b, 45-46). Indeed, as I discuss above, Regeneron itself was deriving its DME clinical trial strategy from what already had been learned from the aflibercept AMD phase 2 results and ranibizumab DME results.

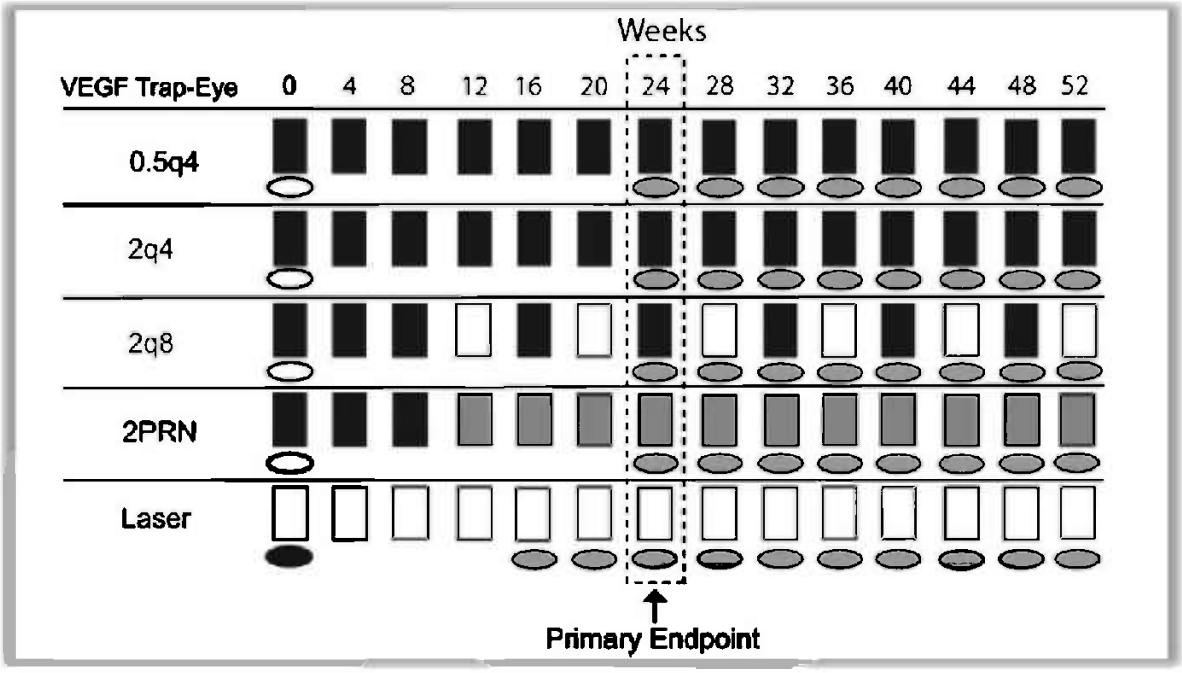
418. For at least the reasons discussed above, claim 18 is obvious in view of Dixon alone or in combination with Lalwani 2009b, and the knowledge of a person of ordinary skill in the art.

d. Independent claim 18 is obvious in view of Do 2012.

419. I was asked to review claims 18, 19, 21, and 23-25 of the 601 patent and compare them to the disclosures of the prior art, including Do 2012.[21]

420. Do 2012 discloses the treatment arms from the DA VINCI phase 2 clinical trials, with the filled black ovals indicating the visits in which injections were given:

[21] I understand that the 601 patent lists applications from 2010 and 2011 on the face of the patent. I also understand that Mylan does not believe that Regeneron is entitled to rely upon the dates of those applications, and that Mylan contends that the earliest date that Regeneron is entitled to rely upon is the date of the 370 application, filed July 12, 2013. I offer my opinions in this section based upon an assumption that the July 12, 2013 date applies.



(Do 2012, 1660 & Fig. 1).

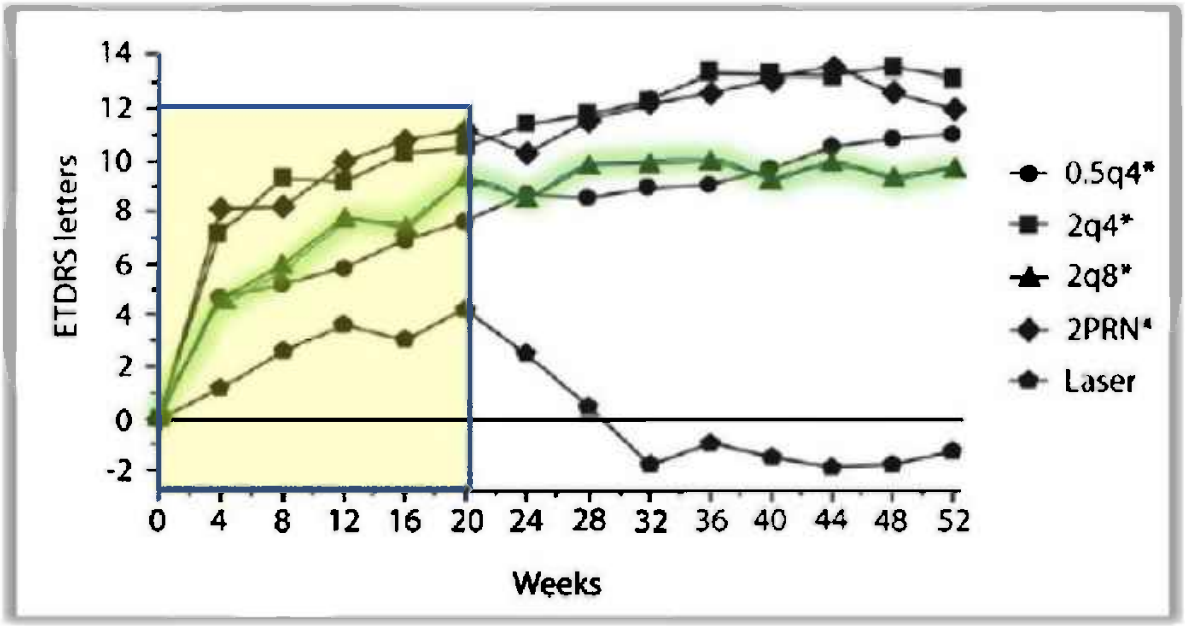
421. Do 2012 also discloses positive results from the phase 2 DME DA VINCI clinical trial. For example, Do 2012 disclosed that patients in the 2Q8 arm achieved gains of 8.5 and 9.7 BCVA letters at 24 and 52 weeks, respectively; patients in the 2Q4 arm achieved gains of 11.4 and 13.1 BCVA letters at 24 and 52 weeks, respectively; and patients in the 2PRN arm achieved gains of 10.3 and 12 BCVA letters at 24 and 52 weeks, respectively. (Do 2012, Abstract).

422. Further, a couple of additional data points emerged from the DA VINCI clinical trial that confirmed observations made in earlier ranibizumab trials. For example, Do 2012 reported that patients in the PRN arm received, on average, 7.4 injections over the course of the first year. (Do 2012, 1661 & Table 3). Compare this to the only 5.6 injections required in the PRN arm of the AMD phase 2 CLEAR-IT-2 trial. (Dixon, 1576). This reveals, like the earlier ranibizumab studies, that DME is typically a disease that tends to be more resistant to treatment, and thus usually requires more doses earlier in the treatment regimen. In my opinion, persons of ordinary skill in the art understood by 2009 that DME was a complication of diabetic retinopathy

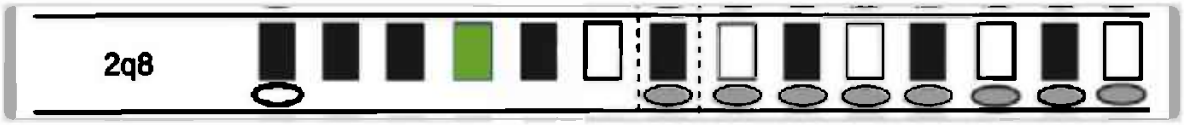
(DR). This also is clear from the publications that report on the very phase 2 DME clinical trial that I discuss above and below. For example, Do 2011 states that "[d]iabetic macular edema (DME) is the most common vision-threatening manifestation of diabetic retinopathy." (Do 2011, 1819). Thus, a person of ordinary skill in the art, when treating DME, would have understood that they would also be treating DR, given that DME is a common manifestation of DR.

423. A person of ordinary skill in the art would have been motivated to set a dosing regimen that would be optimal for the patient they are treating, and in the case of a typical DR patient, that regimen is one which would incorporate additional monthly loading doses.

424. A person of ordinary skill in the art would have looked to the DA VINCI arms and recognized that simply including one additional monthly dose would result in 5 straight monthly doses, which, based on the clinical trial results would get patients to or very near the plateau levels observed in DA VINCI patients in the 2Q8 arm (green line; 5 monthly loading doses in yellow shaded area).



(Do 2012, 1661 (emphasis added)). For example, adding an additional loading dose would have been as straightforward as adding a single injection in the middle of the first eight-week span in the 2Q8 arm:



(Do 2012, 1660 (emphasis added)). Such a regimen would have had the effect of ensuring that patients' DR was being treated with an aggressive initial pulse of aflibercept before transitioning to the extended dosing phase of the regimen, thus maximizing early therapeutic benefit.

425. This also is consistent with internal Regeneron documents that indicated it was focusing its aflibercept DME program on no more than 3-6 monthly loading doses. (RGN-EYLEA-MYLAN-00631452 at -53; *see also* RGN-EYLEA-MYLAN-00495620 at -22 ("# loading doses (3 vs. 6 for 2q8)")). Regeneron also used the phase 2 AMD CLEAR-IT-2 clinical trial results to guide its design of the phase 3 DME trial, explaining to EU authorities that:

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(RGN-EYLEA-MYLAN-00531609 at -614). Regeneron continues, stating that:

> Based on this experience we believe that the doses and dosing intervals for VEGF Trap-Eye for Phase III in DME can be selected based on the results of the Phase II study in patients with AMD (OD-0508, see Investigators Brochure, Vol. 14 , pg. 14) In this study, several doses of VEGF Trap-Eye have been assessed in 30 patients / treatment arm. The results suggested that 0.5mg VEGF Trap-Eye is effective in suppressing retinal edema if injected monthly and that 2mg are sufficient to suppress retinal edema for up to 8 weeks. We consider this Phase 2 study as providing an adequate basis for dose selection for the Phase 3 DME program and propose to use the 0.5mg dose in 4-weekly and the 2mg dose in 8-weekly intervals in the planned Phase 3 study (see outline of proposed Phase 3 studies in DME, Vol. 14 , pg. 14).

(RGN-EYLEA-MYLAN-00531609 at -614). In other words, Regeneron was relying on available data (which was publicly available) and selecting an every-8-week dosing regimen that was already in the public domain for its phase 3 DME clinical trials. The selection of the 5 monthly loading doses was a matter of routine optimization, which began with Regeneron confining itself, as early as 2007/2008 to the use of 3-6 monthly loading doses. (*See, e.g.*, RGN-EYLEA-MYLAN-00631452 at -53; and RGN-EYLEA-MYLAN-00531609 at -615 ("During an induction phase, VEGF Trap-Eye is administered by up to 6 intravitreal injections at intervals of 4 or 8 weeks until resolution of macular edema."))

426. Further, a person of ordinary skill in the art would have had a reasonable expectation of success at using such a regimen given all of the positive DME data in the literature for both aflibercept and ranibizumab. (*See generally, e.g.*, Do 2012; Do 2009; Lalwani 2009b; Massin 2012). Indeed, as I discuss above, Regeneron itself was deriving its DME clinical trial strategy from what already had been learned from the aflibercept AMD phase 2 results and ranibizumab DME results.

427. For at least the reasons discussed above, claim 18 is obvious in view of Do 2012 in combination with the knowledge of a person of ordinary skill in the art.

e. Independent claim 18 is obvious in view of the monthly disclosures in the 747 patent and the 9-14-2009 Regeneron Press Release.

428. As discussed above, the 9-14-2009 Regeneron Press Release discloses VEGF Trap-Eye (aflibercept) as a drug intended for intravitreal administration. (9-14-2009 Regeneron Press Release at 1).

429. The press release also discloses a phase 2 clinical trial in which aflibercept is administered to patients with diabetic macular edema (DME) in 2 mg doses on a monthly basis. (9-14-2009 Regeneron Press Release, 2). In my opinion, persons of ordinary skill in the art

understood by 2009 that DME was a complication of diabetic retinopathy (DR). This also is clear from the publications that report on the very phase 2 DME clinical trial that I discuss above and below. For example, Do 2011 states that "[d]iabetic macular edema (DME) is the most common vision-threatening manifestation of diabetic retinopathy." (Do 2011, 1819). Thus, a person of ordinary skill in the art, when treating DME, would have understood that they would also be treating DR, given that DME is a common manifestation of DR.

430. The 747 patent discloses a method of treating eye disorders, including diabetic retinopathy ("DR"). (747 patent, Title, Abstract, 1:49-54, 2:9-35, 5:39-51, 6:8-24, 6:64 – 7:3). One of the complications associated with diabetic retinopathy is retinal edema (i.e., diabetic macular edema ("DME"). The 747 patent also discloses treatment with VEGFR1R2-FcΔC1(a)) (i.e., VEGF Trap-Eye or aflibercept). (747 patent at SEQ ID NO:6, 2:1-2, 2:9-35, 5:28-51, 7:5-63). The 747 patent further discloses intravitreal administration of the VEGF trap protein, and treatment with 25-4000 micrograms of the VEGF trap (i.e., 2 mg). (747 patent, 2:9-35; 7:5-63; 20:15-67; 21:1-22:42).

431. Based on my read of dependent claim 21, that claim is essentially drawn to monthly dosing. I understand that dependent claims are understood to fall within the scope of the independent claim from which they depend. In other words, because claim 21 is drawn to monthly dosing, independent claim 18, from which it depends, also has monthly dosing within its scope. (601 patent, 23:1-15).

432. Because the prior art 9-14-2009 Regeneron Press Release recites the use of monthly dosing in treating DME patients, in my opinion, the monthly dosing disclosed in the 9-14-2009 Regeneron Press Release makes obvious claim 18.

433. In addition, the 747 patent discloses treatment on a monthly basis, with a preferred embodiment including an initial treatment followed by subsequent treatments between 1-6 months apart (*see, e.g.*, 747 patent, 20:62-67), which a person of ordinary skill in the art would understand could encompass monthly treatment.

434. In addition, a person of ordinary skill in the art would have had a reasonable expectation of success in view of the positive results reported for aflibercept in treating DME in Do 2009, and the positive results reported for the use of ranibizumab in treating DME. For example, Do 2009 reports that a single intravitreal dose of aflibercept resulted in an average of 9 letters in ETDRS score gained after one month. (Do 2009, 146). In addition, Lalwani 2009b discloses that ranibizumab was effective at treating DME. (Lalwani 2009b, 45-46). The ranibizumab would have been informative because by 2009 aflibercept and ranibizumab had already been shown to result in similar efficacy in treating AMD. Accordingly, a person of ordinary skill in the art would have expected the same to be true in DME and DR.

435. Thus, for at least these reasons, it is my opinion that claim 18 is obvious in view of the 747 patent and the 9-14-2009 Regeneron Press Release, in light of the knowledge of a person of ordinary skill in the art at the time.

f. Dependent claim 19 is obvious.

436. I was asked to review dependent claim 19 of the 601 patent and compare it to the disclosures of the prior art. Claim 19 purports to further limit the claimed dosing regimen of claim 18 to "wherein approximately every 4 weeks comprises approximately every 28 days or approximately monthly."

437. In my opinion, this added element of claim 19 does not add anything of interest to claim 18. A person of ordinary skill in the art would have viewed and understood "approximately every 4 weeks" to be equivalent to "approximately every 28 days" and "approximately monthly."

In addition, Regeneron itself, as well as authors in the field, would use weeks and months interchangeably. (*See, e.g.*, 9-14-2009 Regeneron Press Release, 2 ("2 mg monthly" and "2 mg every eight weeks after three monthly loading doses"); Dixon, 1576 ("Two groups received monthly doses of either 0.5 or 2.0 mg for 12 weeks (at weeks 0, 4, 8 and 12)"); Do 2012, Fig. 1 and legend (displaying every 4 week doses and monthly doses the same way and using the terms interchangeably ("3 initial monthly doses then every 8 weeks"))).

438. Thus, for at least these reasons, along with those discussed above for claim 18, it is my opinion that claim 19 is obvious in view of 747 patent and the 9-14-2009 Regeneron Press Release, in light of the knowledge of a person of ordinary skill in the art at the time.

g. Dependent claim 21 is obvious.

439. I was asked to review claim 21 of the 601 patent and compare it to the disclosures of the prior art. Claim 21 purports to further limit the claimed dosing regimen of claim 18 to "further comprising, after 20 weeks, administering, via intravitreal injection, 2 mg of aflibercept once every 4 weeks."

440. I read claim 21 as being directed to monthly dosing after the first 5 monthly doses. This appears to conflict with claim 18, from which it depends, making claim 21 unclear. However, despite the lack of clarity, the prior art disclosed monthly dosing for the treatment of DME.

441. For example, Regeneron has represented to the public and the Patent Office that as of the relevant time period monthly dosing was the standard of care for angiogenic eye disorders. (*See, e.g.*, 338 PH, 9-11-2015 Applicant Remarks, 6). I disagree that monthly dosing was the standard of care. However, Regeneron also knew that monthly dosing, while not the majority practice, was nevertheless a long-practiced regimen. This is also evident from the 9-14-2009 Regeneron Press Release. (9-14-2009 Regeneron Press Release, 1 ("evaluat[ing] whether further

improvements in vision and/or longer dosing intervals than *monthly* administration are possible.") (emphasis added)).

442. Monthly dosing was an approved regimen for treating angiogenic eye disorders with the existing therapy (i.e., Lucentis), and in my experience, some doctors (though not many), were using fixed monthly dosing to treat these disorders prior to the filing of the 601 patent.

443. In addition, the 9-14-2009 Regeneron Press Release discloses the administration of 2 mg of aflibercept, including at monthly intervals. (9-14-2009 Regeneron Press Release, 2 ("VEGF Trap-Eye dosed at … 2 mg monthly")). Other prior art also disclosed monthly dosing. (*See, e.g.*, 747 patent, 20:62-67; Lalwani 2009b, 45; Dixon, 1576; Do 2012, 1659).

444. Thus, in my opinion, monthly dosing with aflibercept for the treatment of an angiogenic eye disorder such as DR, and the use of 2 mg of aflibercept to do so, would have been obvious.

445. Thus, for at least these reasons, along with those discussed above for claim 18, it is my opinion that claim 21 is obvious in view of the 747 patent and the 9-14-2009 Regeneron Press Release, in combination with the references disclosing monthly dosing for DME, in light of the knowledge of a person of ordinary skill in the art at the time.

h. Dependent claim 23 is obvious.

446. I was asked to review claim 23 of the 601 patent and compare it to the disclosures of the prior art. Claim 23 purports to further limit the claimed dosing regimen of claim 18 to "wherein the patient gains at least 15 letters of Best Corrected Visual Acuity (BCVA) score."

447. I have been informed that Mylan is taking the legal position that the visual acuity elements recited in claim 23 constitutes statements of intended results of the claimed methods that do not result in a manipulative difference in the steps of the claim, and thus should be deemed non-limiting. Furthermore, in my opinion, the recited BCVA criteria are commonly used outcome

measures in clinical trials assessing patients with angiogenic eye disorders who are receiving anti-VEGF treatment, and thus represent nothing more than the intended result of those trials, or the natural result flowing from those clinical trials. (*See, e.g.*, Nguyen 2009a, 2141-43, 2145-46; Dixon, 1575-76; Heier 2009A, 45; Brown 2006, 1433; Rosenfeld 2006, 1420, 1426). Indeed, there is nothing in the claims that instruct how to achieve the visual acuity measures recited in the claims. The claims merely recite a prior art dosing regimen, and then recite commonly used visual acuity metrics. But there are no modifications or adjustments to the dosing regimen included in the claims.

448. Regardless of whether the BCVA criteria are considered in the patentability analysis, the added element of claim 23 is expressly disclosed in the prior art. For example, the 9-14-2009 Regeneron Press Release discloses the use of ETDRS in assessing visual acuity in the aflibercept Phase 3 VIEW trial, which a person of ordinary skill in the art would have understood to be measuring BCVA. (9-14-2009 Regeneron Press Release, 1 ("secondary endpoints include the mean change from baseline in visual acuity as measured by ETDRS and the proportion of patients who gained at least 15 letters"); *see also, e.g.*, Do 2009, Abstract, 147 & Fig. 1 (assessing BCVA ETDRS in the aflibercept phase 1 DME trial)).

449. In addition, the results of the VIVID and VISTA phase 3 clinical trials, which utilized 5 monthly loading doses followed by every-8-week dosing, show that a significant fraction of the patient population experienced gains of at least 15 letters in visual acuity. (*See, e.g.*, Korobelnik 2014 DME, 2247). This result was not surprising in view of the earlier clinical trial results with aflibercept, and would have indicated to a person of ordinary skill in the art that a population of treated patients necessarily would have experienced such gains. Accordingly, in my opinion, the recited BCVA criteria are an inherent feature of the claimed dosing regimen. In

addition, a person of ordinary skill in the art would have had a reasonable expectation of success at achieving such BCVA measures in view of the positive phase 1 DME results with aflibercept, showing a gain of 9 letters after just a single dose of aflibercept. (Do 2012, Abstract). A person of ordinary skill in the art also would have had a reasonable expectation of success in view of the data that was emerging from the ranibizumab DME clinical trials, as well as the reported primary outcome measure of the ranibizumab RISE and RIDE clinical studies and the reports from other clinical trials regarding "greater-than-15-letter gainers." (Lalwani 2009b, 45-46).

450. In the event that any of the 601 patent claims has a July 2013 priority date, as discussed above, a person of ordinary skill in the art also would have had a reasonable expectation of success in view of the phase 2 DA VINCI DME clinical trial data. (Do 2012, Abstract (reporting the proportion of patients gaining greater than 15 letters)).

451. Thus, for this reason, as well as the reasons discussed above for claim 18, it is my opinion that claim 23 of the 601 patent is obvious in view of the 9-14-2009 Regeneron Press Release alone, or if necessary, in combination with Do 2009, Do 2012, or Lalwani 2009b.

i. Dependent claim 25 is obvious.

452. I was asked to review claim 25 of the 601 patent and compare it to the disclosures of the prior art. Claim 25 purports to further limit the claimed dosing regimen of claim 18 to "wherein exclusion criteria for the patient include (1) active intraocular inflammation; or (2) active ocular or periocular infection."

453. As noted above, 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." (Dixon, 1577).[22]

454. Claim 25 sets forth common criteria for excluding patients from clinical trials that involve the intravitreal administration of a drug. In fact, the phase 2 DME clinical trial included the application of these criteria, which would necessarily have been applied during the enrolment of patients in that trial. (*See, e.g.*, Do 2011, 1820 (disclosing ocular inflammation, and infectious blepharitis, keratitis, scleritis, or conjunctivitis as exclusion criteria in the phase 2 DME trial)).

455. Thus, in my opinion the conduct of the phase 2 DME trials described in the phase 2 DME references would have necessarily involved the application of one or both of the exclusion criteria listed in claim 25, and thus are an inherent aspect of that clinical trial.

456. Further, in my opinion the exclusion of patients with inflammation or infections would have been a routine and common practice given the risks of serious infection that can result from injecting eyes with signs of pre-existing ocular or periocular infections. The recited exclusion criteria also were commonly employed exclusion criteria in the clinical trials being conducted at the time. For example, Lucentis DME clinical trials included the claimed exclusion criteria. (*See, e.g.*, Chun 2006, 1707 ("ocular disorders that may confound interpretation of study results" and "ocular inflammation")). Further, the ranibizumab AMD MARINA and ANCHOR trials, involving monthly intravitreal administration of ranibizumab, employed exclusion criteria that included, among other criteria, active intraocular inflammation in the study eye; history of idiopathic or autoimmune-associated uveitis in either eye; and infectious conjunctivitis, keratitis,

[22] It was well known and widely understood amongst skilled artisans at the time that patients with ocular or periocular infection and/or inflammation should be excluded from treatment methods involving direct injection of medication into the eye.

scleritis, or endophthalmitis in either eye. (*See, e.g.*, Lucentis Medical Review, MYL-AFL0007147-49; Rosenfeld 2006, Appx., 2-3; NCT 836, 5-6; NCT 594, 5-6). The pegaptanib trials involving intravitreal administration in treating AMD likewise employed exclusion criteria that included, among other relevant criteria, choroiditis, and acute ocular or periocular infection. (*See, e.g.*, Macugen Medical Review, MYL-AFL0007406; Macugen Study Group, 1748).

457. Finally, it was known among those of ordinary skill in the art that intravitreal injections could be associated with serious side effects if proper, aseptic technique is not adhered to. Consequently, persons of ordinary skill in the art were aware of guidelines and other information in the literature about avoiding injecting eyes that are infected or show signs of infection (i.e., inflammation). (*See, e.g.*, Aiello 2004, S4, 6-8, 17; Jager 2004, 687-88; De Caro, 878; Heimann, 67, 74-77, 80-81, 85; CATT Study, 6-7; Regillo 2008, 248.e3; MACTEL Study, 4; Jaffe, 349-50; Lucentis PI 2006, 2, 5; Retinal Physician II, 2, 5).

458. Thus, for at least these reasons, as well as the reasons discussed above for claim 18, it is my opinion that claim 25 of the 601 patent is obvious in view of the 9-14-2009 Regeneron Press Release alone (for the reasons set forth in my discussion of claim 18), or if necessary, in combination with Chun 2006, the ranibizumab MARINA and ANCHOR references, the pegaptanib references, or the injection guideline references, in view of the general knowledge of a person of ordinary skill in the art at the time.

6. Claims 26-28 and 31-33 of the 601 Patent are obvious in view of the prior art.

a. Independent claim 26 is obvious in view of the 9-14-2009 Regeneron Press Release alone, or in combination with Do 2009.

459. I was asked to review claims 26-28 and 31-33 of the 601 patent and compare them to the disclosures of the prior art, including the 9-14-2009 Regeneron Press Release and Do 2009.

460. The 9-14-2009 Regeneron Press Release discloses VEGF Trap-Eye (aflibercept) as a drug intended for intravitreal administration. (9-14-2009 Regeneron Press Release, 1).

461. The press release also discloses a phase 2 clinical trial in which aflibercept is administered to patients with diabetic macular edema (DME) in 2 mg doses for three monthly loading doses. (*Id.*, 2). After the monthly loading doses, patients are treated with fixed every-8-week injections or PRN (i.e., as needed) injections. (*Id.*). In my opinion, persons of ordinary skill in the art understood by 2009 that DME was a complication of DR. This also is clear from the publications that report on the very phase 2 DME clinical trial that I discuss above and below. For example, Do 2011 states that "[d]iabetic macular edema (DME) is the most common vision-threatening manifestation of diabetic retinopathy." (Do 2011, 1819). Thus, a person of ordinary skill in the art, when treating DME, would have understood that they would also be treating DR in a patient with DME, given that DME is a common manifestation of DR.

462. A regimen of 5 monthly loading doses would have been obvious in view of the phase 2 dosing regimens. For example, from the positive results of the phase 1 DME trial, and the disclosed dosing regimens of the phase 2 clinical trial, a person of ordinary skill in the art would have been motivated to identify an optimal dosing regimen for the treatment of DR in patients with DME. In my experience, identifying an optimum dosing regimen for a VEGF antagonist such as aflibercept is a matter of routine optimization. A person of ordinary skill in the art would have been motivated to try a range of monthly loading doses, especially since a series of monthly loading doses followed by extended PRN/treat-and-extend dosing was the industry standard and that was the approach being used, with success, by those in clinical practice. (*See, e.g.*, Retinal Physician 2007, MYL-AFL0090401; *id.*, MYL-AFL0090402-03; Regeneron Protected Material

Regeneron Protected Material

463. I am aware that Regeneron was experimenting with 1, 3, and 4 monthly loading doses in its aflibercept clinical trials. For example, Regeneron tried 1 and 4 monthly loading doses in its phase 2 AMD trials, (*see, e.g.*, Dixon, 1576; 9-14-2009 Regeneron Press Release, 2); and 3 monthly loading doses in its phase 2 DME and phase 3 VIEW trials, (*see, e.g.*, 9-14-2009 Regeneron Press Release, 1, 2).

464. This also is consistent with internal Regeneron documents that indicated it was focusing its aflibercept DME program on no more than 3-6 monthly loading doses. (RGN-EYLEA-MYLAN-00631452 at -53; *see also* RGN-EYLEA-MYLAN-00495620 at -22 ("# loading doses (3 vs. 6 for 2q8)")). Regeneron also used the phase 2 AMD CLEAR-IT-2 clinical trial results to guide its design of the phase 3 DME trial, explaining to EU authorities that:

> Other intravitreal anti-VEGF therapies (Macugen, Avastin, Lucentis) that are commonly used for AMD have suggested efficacy of this therapeutic principle also in treating DME in Phase I/II studies and investigator initiated studies. This is further supported by Phase III studies recently initiated by Genentech for their product ranibizumab in DME patients. Most notably the doses employed in these studies (0.3 and 0.5 mg given monthly) are the same doses which are used in the AMD indication.

(RGN-EYLEA-MYLAN-00531609 at -614). Regeneron continues, stating that:

> Based on this experience we believe that the doses and dosing intervals for VEGF Trap-Eye for Phase III in DME can be selected based on the results of the Phase II study in patients with AMD (OD-0508, see Investigators Brochure, Vol. 14 , pg. 14) In this study, several doses of VEGF Trap-Eye have been assessed in 30 patients / treatment arm. The results suggested that 0.5mg VEGF Trap-Eye is effective in suppressing retinal edema if injected monthly and that 2mg are sufficient to suppress retinal edema for up to 8 weeks. We consider this Phase 2 study as providing an adequate basis for dose selection for the Phase 3 DME program and propose to use the 0.5mg dose in 4-weekly and the 2mg dose in 8-weekly intervals in the planned Phase 3 study (see outline of proposed Phase 3 studies in DME, Vol. 14 , pg. 14).

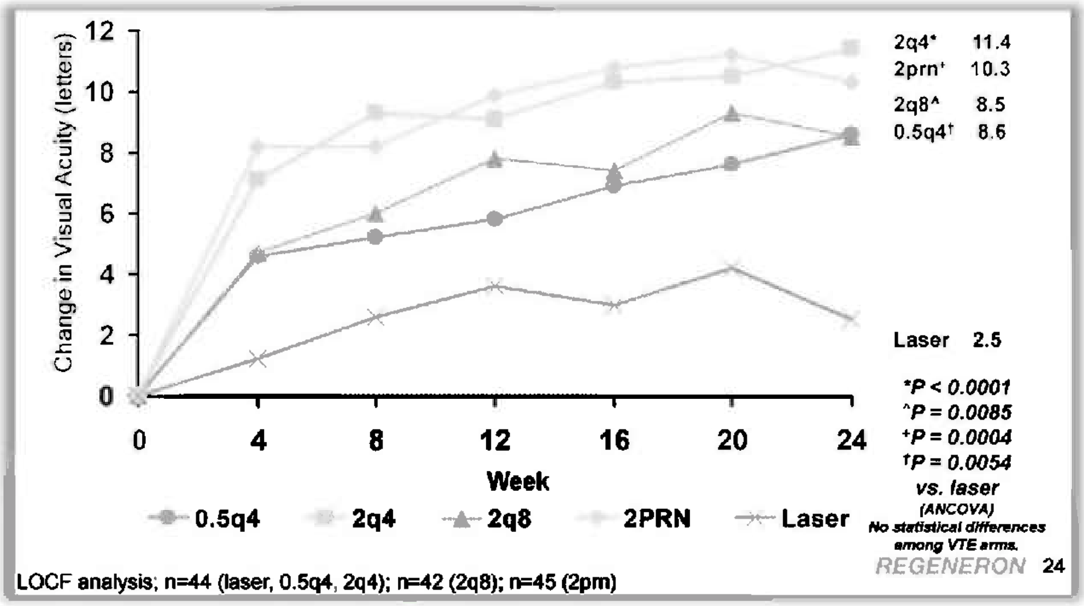
(RGN-EYLEA-MYLAN-00531609 at -614). In other words, Regeneron was relying on available data (which was publicly available) and selecting an every-8-week dosing regimen that was already in the public domain for its phase 3 DME clinical trials. The selection of the 5 monthly loading doses was a matter of routine optimization, which began with Regeneron confining itself,

as early as 2007/2008 to the use of 3-6 monthly loading doses. (*See, e.g.*, RGN-EYLEA-MYLAN-00631452 at -53; RGN-EYLEA-MYLAN-00531609 at -615 ("During an induction phase, VEGF Trap-Eye is administered by up to 6 intravitreal injections at intervals of 4 or 8 weeks until resolution of macular edema.")).

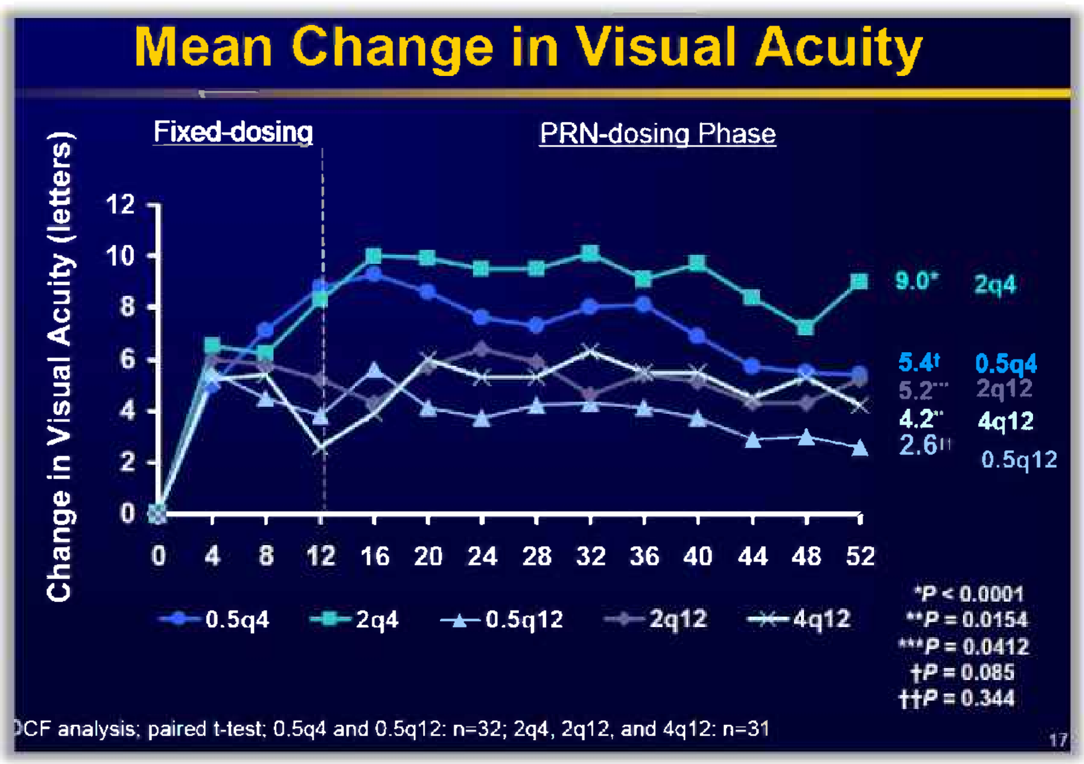
465. Further, in my clinical experience, DME and DR patients tend to require more loading doses (compared to AMD patients) to achieve satisfactory retinal thickness and/or visual acuity measures.

466. Thus, in my opinion, putting DR/DME patients on 4 or 5 monthly loading doses rather than three would have been obvious to try when conducting routine optimization of a loading dose regimen for treating DR in patients with DME. This is confirmed by my review of the data that came out of the phase 2 DA VINCI DME clinical trial.

467. For example, as Regeneron was designing its VIVID and VISTA phase 3 clinical trials in DME in which 5 monthly loading doses were to be tested, they had available to them the data from the phase 2 DME DA VINCI trial. A person of ordinary skill in the art would have immediately noticed that the DA VINCI 2Q8 arm patient group exhibited a lengthier time to plateau than what would have been observed with AMD. For example, I reviewed information from a March 2010 slide presentation provided by Regeneron. Therein, data from the DA VINCI DME clinical trial revealed that it was taking 5-6 months for patients to near a plateau of visual acuity gains:



(RGN-EYLEA-MYLAN-00585880 at -909). Contrast this with the results from the AMD phase 2 clinical trial using the same dosage (2 mg) and a similar loading dose scheme:



(2008 Retina Society Slides, 17). What is evident from these two sets of data is that DME appears more resistant to treatment than AMD, which also is consistent with observations I've made within my own practice. As a result, DME patients were taking longer to approach plateau. From this data, in my opinion, it is a matter of routine optimization to adjust upward the number of monthly loading doses if a patient is presenting with a more difficult to treat condition (e.g., DME and DR), or taking longer to show a response to treatment. Thus, it is an obvious and routine matter to arrive at a particular number of loading doses.

468. In any event, internal Regeneron documents reveal that business/commercial concerns also were important in Regeneron's decision to implement 5 monthly loading doses for the treatment of DME. For example, a January 26, 2011 presentation of Bayer and Regeneron discusses their DME clinical plan and suggests that the selection of 5 loading doses for the DME trial was the result of "a compromise" between Regeneron and Bayer, deemed "acceptable from a commercial/market access perspective." (RGN-EYLEA-MYLAN-00513418 at 424).

469. Further, in my opinion, a person of ordinary skill in the art would have had a reasonable expectation of success at using 5 monthly loading doses in light of the positive phase 1 results seen with a single intravitreal dose of aflibercept. For example, Do 2009 reports that a single intravitreal dose of aflibercept resulted in an average of 9 letters in ETDRS score gained after one month. (Do 2009, 146). The reasonable expectation of success also would have come from the combination of highly relevant data that was in the public domain at the time showing that (1) aflibercept was effective at treating AMD after a series of monthly loading doses, followed by less frequent dosing (Dixon, 1576); (2) ranibizumab was effective at treating both AMD and DME (Rosenfeld 2006 at 1426; Lalwani 2009 at 46). Indeed, as I discuss above, Regeneron itself

was deriving its DME clinical trial strategy from what already had been learned from the aflibercept AMD phase 2 results and ranibizumab DME results.

470. For at least the reasons discussed above, claim 26 is obvious in view of the 2009 Regeneron Press Release alone or in combination with Do 2009, and the knowledge of a person of ordinary skill in the art.

b. Independent claim 26 is obvious in view of the 9-14-2009 Regeneron Press Release alone, or in combination with the Lucentis art.

471. I was asked to review claims 26-28 and 31-33 of the 601 patent and compare them to the disclosures of the prior art, including the 9-14-2009 Regeneron Press Release.

472. The 9-14-2009 Regeneron Press Release discloses VEGF Trap-Eye (aflibercept) as a drug intended for intravitreal administration. (*See, e.g.*, 9-14-2009 Regeneron Press Release at 1).

473. The press release also discloses a phase 2 clinical trial in which aflibercept is administered to patients with diabetic macular edema (DME) in 2 mg doses for three monthly loading doses. After the monthly loading doses, patients are treated with fixed every-8-week injections or PRN (i.e., as needed) injections. In my opinion, persons of ordinary skill in the art understood by 2009 that DME was a complication of diabetic retinopathy (DR). This also is clear from the publications that report on the very phase 2 DME clinical trial that I discuss above and below. For example, Do 2011 states that "[d]iabetic macular edema (DME) is the most common vision-threatening manifestation of diabetic retinopathy." (Do 2011 at 1819). Thus, a person of ordinary skill in the art, when treating DME, would have understood that they would also be treating DR, given that DME is a common manifestation of DR.

474. Shortly after Regeneron had initiated its phase 2 DME clinical trial, data emerged from Lucentis clinical trials in DME. The Lucentis clinical trial data revealed that patients treated

with 0.5 mg on a monthly loading regimen achieved very similar BCVA scores as those observed in the Lucentis AMD trials. For example, in Lalwani 2009, the author reported on data emerging from the clinical study Ranibizumab for Edema of the Macula in Diabetes (READ 1). (Lalwani 2009 at 45). Lalwani 2009 discloses the design of the study, including the dosing regimen, which involved injections at baseline, and months 1, 2, 4, and 6 (i.e., 3 monthly loading doses followed by every 8 week dosing). (Lalwani 2009 at 45). The author further reports that at 12 months, the DME patients receiving ranibizumab had achieved, on average, a gain of 8 letters of visual acuity. (Lalwani 2009 at 45). The author further notes that the READ 2 program that followed READ 1 employed monthly dosing through 12 months, and the ranibizumab-only arm achieved mean gains of 6.46 letters. (Lalwani 2009 at 45-46).

475. In other words, Lucentis was showing that the treatment of AMD and DME can be accomplished to similar effect with similar regimens and the same amount of anti-VEGF agent.

476. However, a person of ordinary skill in the art also would have appreciated that the treatment of DME (and DR) differed from AMD in at least one aspect.

477. For example, the author references the theory circulating among physicians at the time that VEGF was particularly elevated in DME compared to AMD, and thus may require more aggressive treatment. (Lalwani 2009b, 46). This also is consistent with the presentation of the RESOLVE trial data set forth in Lalwani 2009b, which showed a shallower curve to reach plateau levels of mean visual acuity than that observed with AMD in, for example, the MARINA and ANCHOR trials. (Lalwani 2009b, 46; *see also, e.g.*, Rosenfeld 2006, 1426). For example, one can compare the RESOLVE DME data in Lalwani 2009b:

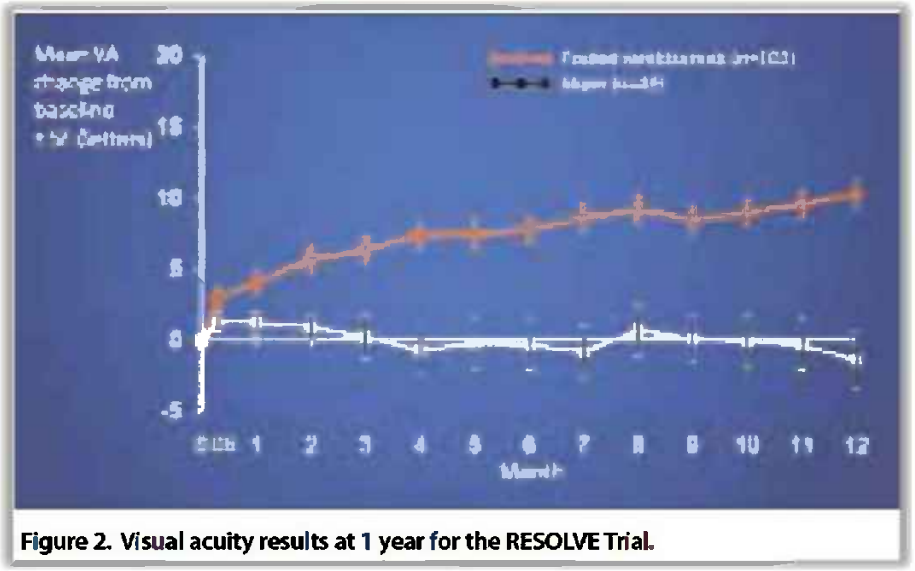
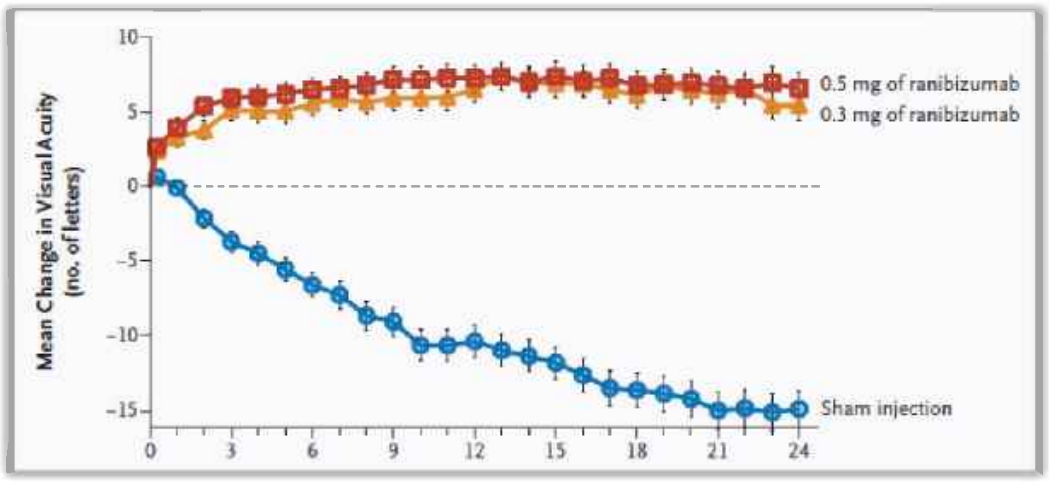


Figure 2. Visual acuity results at 1 year for the RESOLVE Trial.

(Lalwani 2009b, 46), with the data in Rosenfeld 2006 for AMD:



(Rosenfeld 2006, 1426). As discussed above, it is evident from these two sets of data that DME appears more resistant to treatment than AMD, which also is consistent with observations I've made within my own practice, and consistent with Lalwani 2009b's reference to the theory that VEGF is more elevated in DME patients. As a result of this resistance, DME patients in the Lucentis trials were taking longer to approach plateau when compared to AMD patients. From this data, in my opinion, a person of ordinary skill in the art would have looked to increase the number of loading doses when treating DR in DME patients with aflibercept. Based on the data

above, 5 monthly loading is an obvious and reasonable number to incorporate, especially in view of the use of 3 and 4 loading doses in the aflibercept AMD clinical trials.

478. This also is consistent with internal Regeneron documents that indicated it was focusing its aflibercept DME program on no more than 3-6 monthly loading doses. (RGN-EYLEA-MYLAN-00631452 at -53; *see also* RGN-EYLEA-MYLAN-00495620 at -22 ("# loading doses (3 vs. 6 for 2q8)")). Regeneron also used the phase 2 AMD CLEAR-IT-2 clinical trial results to guide its design of the phase 3 DME trial, explaining to EU authorities that:

> Other intravitreal anti-VEGF therapies (Macugen, Avastin, Lucentis) that are commonly used for AMD have suggested efficacy of this therapeutic principle also in treating DME in Phase I/II studies and investigator initiated studies. This is further supported by Phase III studies recently initiated by Genentech for their product ranibizumab in DME patients. Most notably the doses employed in these studies (0.3 and 0.5 mg given monthly) are the same doses which are used in the AMD indication.

(RGN-EYLEA-MYLAN-00531609 at -614). Regeneron continues, stating that:

> Based on this experience we believe that the doses and dosing intervals for VEGF Trap-Eye for Phase III in DME can be selected based on the results of the Phase II study in patients with AMD (OD-0508, see Investigators Brochure, Vol. 14 , pg. 14) In this study, several doses of VEGF Trap-Eye have been assessed in 30 patients / treatment arm. The results suggested that 0.5mg VEGF Trap-Eye is effective in suppressing retinal edema if injected monthly and that 2mg are sufficient to suppress retinal edema for up to 8 weeks. We consider this Phase 2 study as providing an adequate basis for dose selection for the Phase 3 DME program and propose to use the 0.5mg dose in 4-weekly and the 2mg dose in 8-weekly intervals in the planned Phase 3 study (see outline of proposed Phase 3 studies in DME, Vol. 14 , pg. 14).

(RGN-EYLEA-MYLAN-00531609 at -614). In other words, Regeneron was relying on available data (which was publicly available) and selecting an every-8-week dosing regimen that was already in the public domain for its phase 3 DME clinical trials. The selection of the 5 monthly loading doses was a matter of routine optimization, which began with Regeneron confining itself, as early as 2007/2008 to the use of 3-6 monthly loading doses. (*See, e.g.*, RGN-EYLEA-MYLAN-00631452 at -53; RGN-EYLEA-MYLAN-00531609 at -615 ("During an induction phase, VEGF

Trap-Eye is administered by up to 6 intravitreal injections at intervals of 4 or 8 weeks until resolution of macular edema.")).

479. Further, in my opinion, a person of ordinary skill in the art would have had a reasonable expectation of success at using 5 monthly loading doses in light of the positive phase 1 results seen with a single intravitreal dose of aflibercept. For example, Do 2009 reports that a single intravitreal dose of aflibercept resulted in an average of 9 letters in ETDRS score gained after one month. (Do 2009, 146). The reasonable expectation of success also would have come from the combination of highly relevant data that was in the public domain at the time showing that (1) aflibercept was effective at treating AMD after a series of monthly loading doses, followed by less frequent dosing (Dixon, 1576); (2) ranibizumab was effective at treating both AMD and DME (Rosenfeld 2006, 1426; Lalwani 2009b, 45-46). Indeed, as I discuss above, Regeneron itself was deriving its DME clinical trial strategy from what already had been learned from the aflibercept AMD phase 2 results and ranibizumab DME results.

480. For at least the reasons discussed above, claim 26 is obvious in view of the 2009 Regeneron Press Release alone or in combination with Lalwani 2009b, and the knowledge of a person of ordinary skill in the art.

c. Independent claim 26 is obvious in view of Dixon in combination with Lalwani 2009b.

481. I was asked to review claims 26-28 and 31-33 of the 601 patent and compare them to the disclosures of the prior art, including Dixon and Lalwani 2009b.

482. For example, Dixon discloses positive results from several aflibercept clinical trials, including several phase 1 trials in both AMD and DME, and the phase 2 CLEAR-IT-2 AMD trial. Dixon reports that in the DME study, "[t]he single injection resulted in a median decrease of

central macular thickness measured by OCT of 79 μm. BCVA increased by 9 letters at 4 weeks and regressed to a 3 letter improvement at 6 weeks." (Dixon, 1575).

483. Dixon also makes note of the "multifactorial nature of DME" and discloses that phase 2 clinical studies are underway with anti-VEGF agents, including aflibercept, for the treatment of DME. (Dixon, 1577-78). In my opinion, persons of ordinary skill in the art understood by 2009 that DME was a complication of diabetic retinopathy (DR). This also is clear from the publications that report on the very phase 2 DME clinical trial that I discuss above and below. For example, Do 2011 states that "[d]iabetic macular edema (DME) is the most common vision-threatening manifestation of diabetic retinopathy." (Do 2011, 1819). Thus, a person of ordinary skill in the art, when treating DME, would have understood that they would also be treating DR, given that DME is a common manifestation of DR.

484. Dixon also discloses that aflibercept/VEGF Trap-Eye is formulated in a 2 mg presentation and for intravitreal administration. (Dixon, 1575).

485. About this same time, data emerged from Lucentis clinical trials in DME. The Lucentis clinical trial data revealed that patients treated with 0.5 mg on a monthly loading regimen achieved very similar BCVA scores as those observed in the Lucentis AMD trials. For example, in Lalwani 2009b, the author reported on data emerging from the clinical study Ranibizumab for Edema of the Macula in Diabetes (READ 1). (Lalwani 2009b, 45). Lalwani 2009b discloses the design of the study, including the dosing regimen, which involved injections at baseline, and months 1, 2, 4, and 6 (i.e., 3 monthly loading doses followed by every 8 week dosing). (*Id.*). The author further reports that at 12 months, the DME patients receiving ranibizumab had achieved, on average, a gain of 8 letters of visual acuity. (*Id.*). The author further notes that the READ 2

program that followed READ 1 employed monthly dosing through 12 months, and the ranibizumab-only arm achieved mean gains of 6.46 letters. (*Id.*, 45-46).

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487. However, a person of ordinary skill in the art also would have appreciated that the treatment of DME differed from AMD in at least one aspect.

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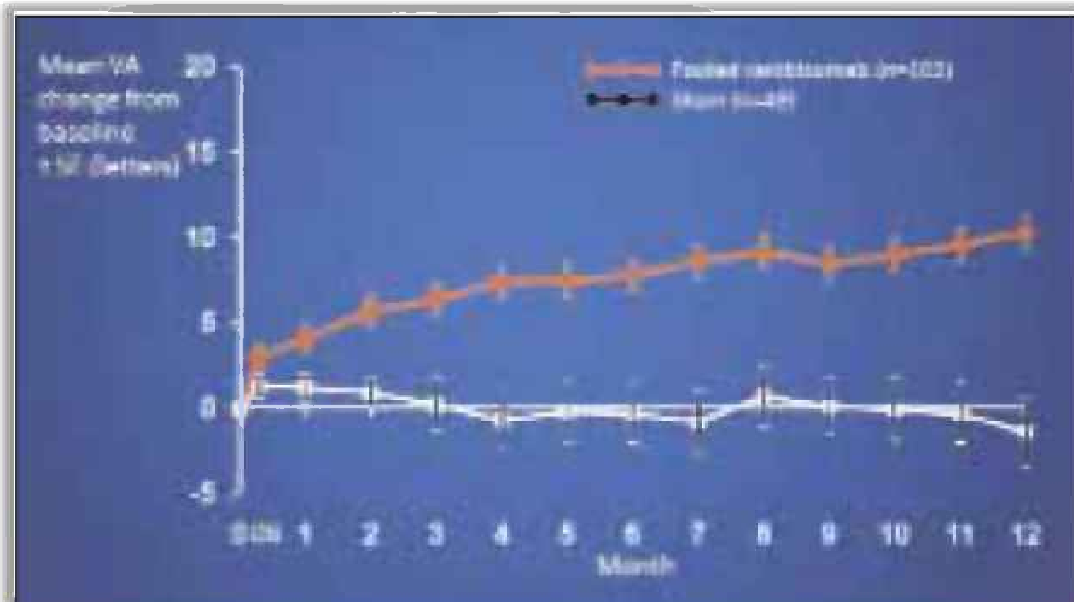

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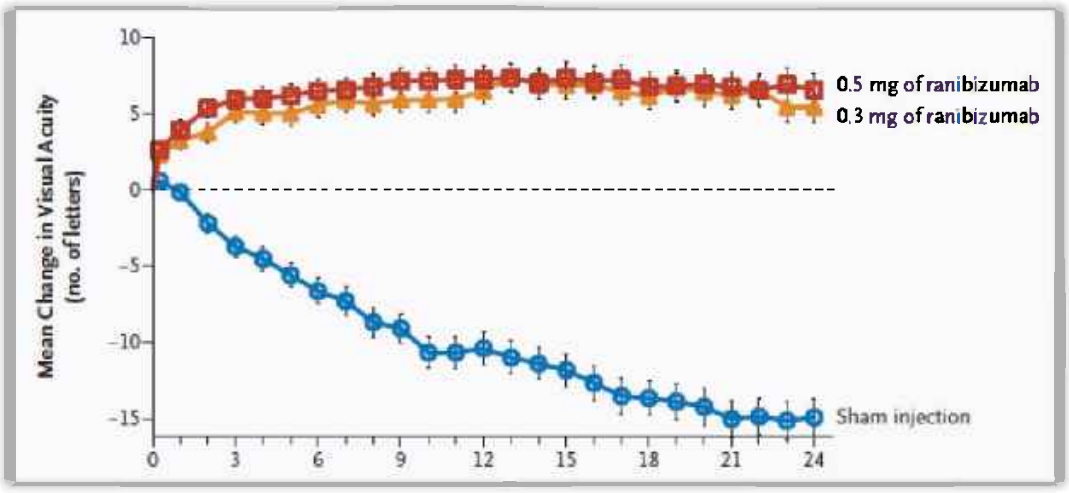

(Rosenfeld 2006 at 1426). As discussed above, it is evident from these two sets of data that DME appears more resistant to treatment than AMD, which also is consistent with observations I've made within my own practice, and consistent with Lalwani's reference to the theory that VEGF is more elevated in DME patients. As a result of this resistance, DME patients in the Lucentis trials were taking longer to approach plateau when compared to AMD patients. From this data, in my opinion, a person of ordinary skill in the art would have looked to increase the number of loading doses when treating DR in DME patients with aflibercept. Based on the data above, 5 monthly loading is an obvious and reasonable number to incorporate, especially in view of the use of 3 and 4 loading doses in the aflibercept AMD clinical trials.

489. This also is consistent with internal Regeneron documents that indicated it was focusing its aflibercept DME program on no more than 3-6 monthly loading doses. (RGN-EYLEA-MYLAN-00631452 at -53; *see also* RGN-EYLEA-MYLAN-00495620 at -22 ("# loading doses (3 vs. 6 for 2q8)")). Regeneron also used the phase 2 AMD CLEAR-IT-2 clinical trial results to guide its design of the phase 3 DME trial, explaining to EU authorities that:

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(RGN-EYLEA-MYLAN-00531609 at -614). Regeneron continues, stating that:

> Based on this experience we believe that the doses and dosing intervals for VEGF Trap-Eye for Phase III in DME can be selected based on the results of the Phase II study in patients with AMD (OD-0508, see Investigators Brochure, Vol. 14 , pg. 14) In this study, several doses of VEGF Trap-Eye have been assessed in 30 patients / treatment arm. The results suggested that 0.5mg VEGF Trap-Eye is effective in suppressing retinal edema if injected monthly and that 2mg are sufficient to suppress retinal edema for up to 8 weeks. We consider this Phase 2 study as providing an adequate basis for dose selection for the Phase 3 DME program and propose to use the 0.5mg dose in 4-weekly and the 2mg dose in 8-weekly intervals in the planned Phase 3 study (see outline of proposed Phase 3 studies in DME, Vol. 14 , pg. 14).

(RGN-EYLEA-MYLAN-00531609 at -614). In other words, Regeneron was relying on available data (which was publicly available) and selecting an every-8-week dosing regimen that was already in the public domain for its phase 3 DME clinical trials. The selection of the 5 monthly loading doses was a matter of routine optimization, which began with Regeneron confining itself, as early as 2007/2008 to the use of 3-6 monthly loading doses. (*See, e.g.*, RGN-EYLEA-MYLAN-00631452 at -53; RGN-EYLEA-MYLAN-00531609 at -615 ("During an induction phase, VEGF Trap-Eye is administered by up to 6 intravitreal injections at intervals of 4 or 8 weeks until resolution of macular edema.")).

490. Further, in my opinion, a person of ordinary skill in the art would have had a reasonable expectation of success at using 5 monthly loading doses in light of the positive phase 1 results seen with a single intravitreal dose of aflibercept. For example, Do 2009 reports that a single intravitreal dose of aflibercept resulted in an average of 9 letters in ETDRS score gained after one month. (Do 2009, 146). The reasonable expectation of success also would have come from the combination of highly relevant data that was in the public domain at the time showing

that (1) aflibercept was effective at treating AMD after a series of monthly loading doses, followed by less frequent dosing (Dixon, 1576); (2) ranibizumab was effective at treating both AMD and DME (Rosenfeld 2006, 1426; Lalwani 2009b, 45-46). Indeed, as I discuss above, Regeneron itself was deriving its DME clinical trial strategy from what already had been learned from the aflibercept AMD phase 2 results and ranibizumab DME results.

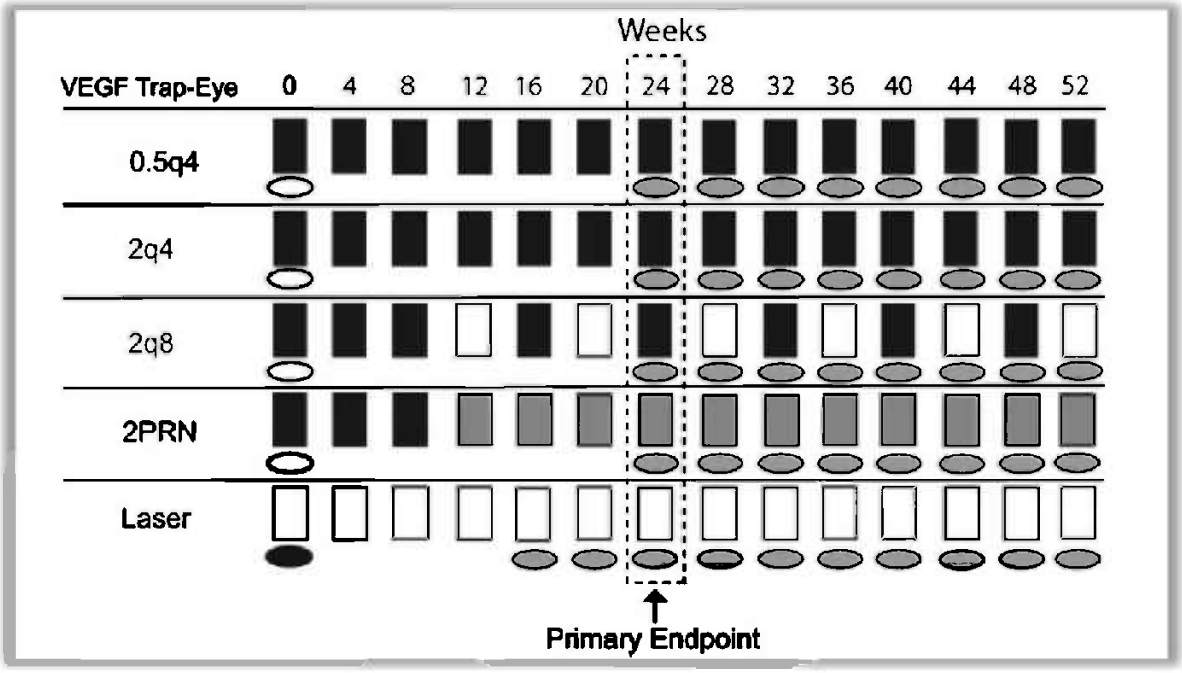
491. For at least the reasons discussed above, claim 26 is obvious in view of Dixon alone or in combination with Lalwani 2009b, and the knowledge of a person of ordinary skill in the art.

d. Independent claim 26 is obvious in view of Do 2012.

492. I was asked to review claims 26-28 and 31-33 of the 601 patent and compare them to the disclosures of the prior art, including Do 2012.[23]

493. Do 2012 discloses the treatment arms from the DA VINCI phase 2 clinical trials, with the filled black ovals indicating the visits in which injections were given:

[23] I understand that the 601 patent lists applications from 2010 and 2011 on the face of the patent. I also understand that Mylan does not believe that Regeneron is entitled to rely upon the dates of those applications, and that Mylan contends that the earliest date that Regeneron is entitled to rely upon is the date of the 370 application, filed July 12, 2013. I offer my opinions in this section based upon an assumption that the July 12, 2013 date applies.



(Do 2012, 1660).

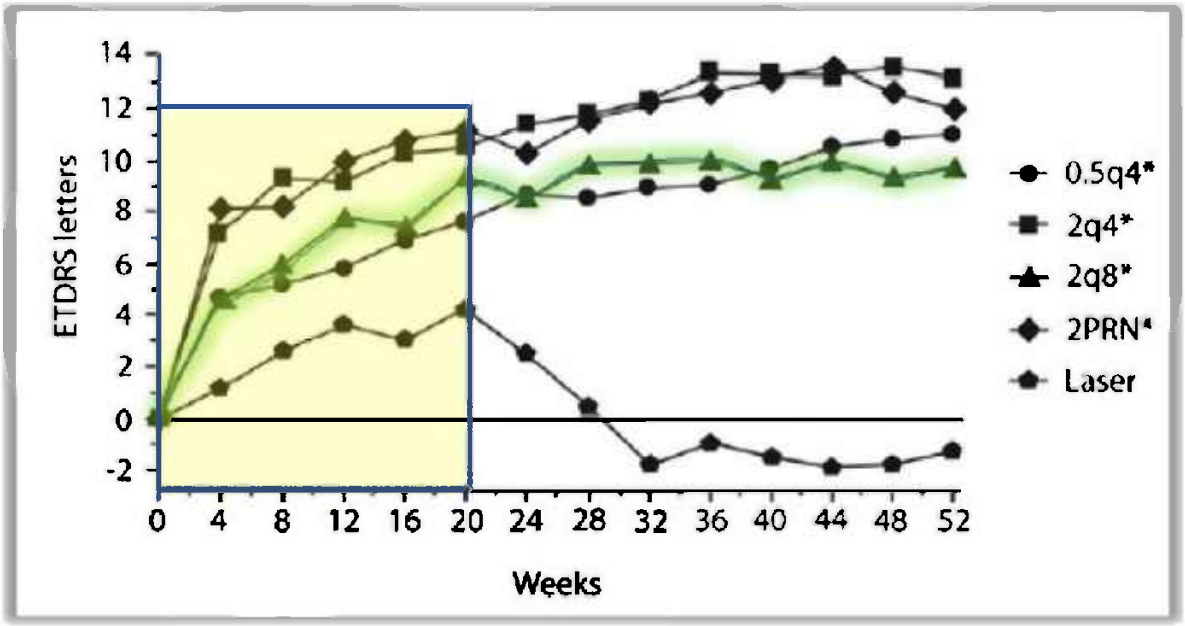
494. Do 2012 also discloses positive results from the phase 2 DME DA VINCI clinical trial. For example, Do 2012 disclosed that patients in the 2Q8 arm achieved gains of 8.5 and 9.7 BCVA letters at 24 and 52 weeks, respectively; patients in the 2Q4 arm achieved gains of 11.4 and 13.1 BCVA letters at 24 and 52 weeks, respectively; and patients in the 2PRN arm achieved gains of 10.3 and 12 BCVA letters at 24 and 52 weeks, respectively. (Do 2012, Abstract).

495. Further, a couple of additional data points emerged from the DA VINCI clinical trial that confirmed observations made in earlier ranibizumab trials. For example, Do 2012 reported that patients in the PRN arm received, on average, 7.4 injections over the course of the first year. (Do 2012 at Table 3). Compare this to the only 5.6 injections required in the PRN arm of the AMD phase 2 CLEAR-IT-2 trial. (Dixon, 1576). This reveals, like the earlier ranibizumab studies, that DME is typically a disease that tends to be more resistant to treatment, and thus usually requires more doses earlier in the treatment regimen. In my opinion, persons of ordinary skill in the art understood by 2009 that DME was a complication of diabetic retinopathy (DR). This also

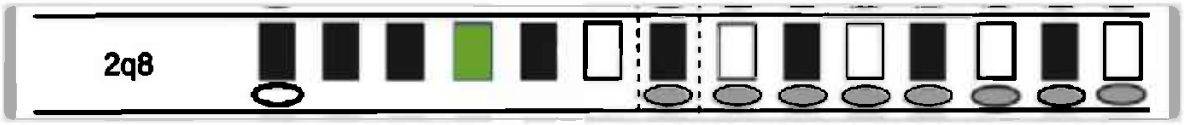
is clear from the publications that report on the very phase 2 DME clinical trial that I discuss above and below. For example, Do 2011 states that "[d]iabetic macular edema (DME) is the most common vision-threatening manifestation of diabetic retinopathy." (Do 2011, 1819). Thus, a person of ordinary skill in the art, when treating DME, would have understood that they would also be treating DR, given that DME is a common manifestation of DR.

496. A person of ordinary skill in the art would have been motivated to set a dosing regimen that would be optimal for the patient they are treating, and in the case of a typical DR patient, that regimen is one which would incorporate additional monthly loading doses.

497. A person of ordinary skill in the art would have looked to the DA VINCI arms and recognized that simply including one additional monthly dose would result in 5 straight monthly doses, which, based on the clinical trial results would get patients to or very near the plateau levels observed in DA VINCI patients in the 2Q8 arm (green line; 5 monthly loading doses in yellow shaded area).



(Do 2012, 1661 (emphasis added)). For example, adding an additional loading dose would have been as straightforward as adding a single injection in the middle of the first eight-week span in the 2Q8 arm:



(Do 2012, 1660 (emphasis added)). Such a regimen would have had the effect of ensuring that patients' DR was being treated with an aggressive initial pulse of aflibercept before transitioning to the extended dosing phase of the regimen, thus maximizing early therapeutic benefit.

498. This also is consistent with internal Regeneron documents that indicated it was focusing its aflibercept DME program on no more than 3-6 monthly loading doses. (RGN-EYLEA-MYLAN-00631452 at -53; *see also* RGN-EYLEA-MYLAN-00495620 at -22 ("# loading doses (3 vs. 6 for 2q8)")). Regeneron also used the phase 2 AMD CLEAR-IT-2 clinical trial results to guide its design of the phase 3 DME trial, explaining to EU authorities that:

> Other intravitreal anti-VEGF therapies (Macugen, Avastin, Lucentis) that are commonly used for AMD have suggested efficacy of this therapeutic principle also in treating DME in Phase I/II studies and investigator initiated studies. This is further supported by Phase III studies recently initiated by Genentech for their product ranibizumab in DME patients. Most notably the doses employed in these studies (0.3 and 0.5 mg given monthly) are the same doses which are used in the AMD indication.

(RGN-EYLEA-MYLAN-00531609 at -614). Regeneron continues, stating that:

> Based on this experience we believe that the doses and dosing intervals for VEGF Trap-Eye for Phase III in DME can be selected based on the results of the Phase II study in patients with AMD (OD-0508, see Investigators Brochure, Vol. 14 , pg. 14) In this study, several doses of VEGF Trap-Eye have been assessed in 30 patients / treatment arm. The results suggested that 0.5mg VEGF Trap-Eye is effective in suppressing retinal edema if injected monthly and that 2mg are sufficient to suppress retinal edema for up to 8 weeks. We consider this Phase 2 study as providing an adequate basis for dose selection for the Phase 3 DME program and propose to use the 0.5mg dose in 4-weekly and the 2mg dose in 8-weekly intervals in the planned Phase 3 study (see outline of proposed Phase 3 studies in DME, Vol. 14 , pg. 14).

(RGN-EYLEA-MYLAN-00531609 at -614). In other words, Regeneron was relying on available data (which was publicly available) and selecting an every-8-week dosing regimen that was already in the public domain for its phase 3 DME clinical trials. The selection of the 5 monthly loading doses was a matter of routine optimization, which began with Regeneron confining itself, as early as 2007/2008 to the use of 3-6 monthly loading doses. (*See, e.g.*, RGN-EYLEA-MYLAN-00631452 at -53; RGN-EYLEA-MYLAN-00531609 at -615 ("During an induction phase, VEGF Trap-Eye is administered by up to 6 intravitreal injections at intervals of 4 or 8 weeks until resolution of macular edema.")).

499. Further, a person of ordinary skill in the art would have had a reasonable expectation of success at using such a regimen given all of the positive DME data in the literature for both aflibercept and ranibizumab. (*See generally, e.g.*, Do 2012; Do 2009; Lalwani 2009; Massin 2012). Indeed, as I discuss above, Regeneron itself was deriving its DME clinical trial strategy from what already had been learned from the aflibercept AMD phase 2 results and ranibizumab DME results.

500. For at least the reasons discussed above, claim 26 is obvious in view of Do 2012 in combination with the knowledge of a person of ordinary skill in the art.

e. Independent claim 26 is obvious in view of the 9-14-2009 Regeneron Press Release.

501. I was asked to review claims 26-28 and 31-33 of the 601 patent and compare them to the disclosures of the prior art, including the 9-14-2009 Regeneron Press Release.

502. As discussed above, the 9-14-2009 Regeneron Press Release discloses VEGF Trap-Eye (aflibercept) as a drug intended for intravitreal administration. (9-14-2009 Regeneron Press Release, 1).

503. The press release also discloses a phase 2 clinical trial in which aflibercept is administered to patients with diabetic macular edema (DME) in 2 mg doses on a monthly basis. (*See, e.g.*, 9-14-2009 Regeneron Press Release, 1). In my opinion, persons of ordinary skill in the art understood by 2009 that DME was a complication of diabetic retinopathy (DR). This also is clear from the publications that report on the very phase 2 DME clinical trial that I discuss above and below. For example, Do 2011 states that "[d]iabetic macular edema (DME) is the most common vision-threatening manifestation of diabetic retinopathy." (Do 2011, 1819). Thus, a person of ordinary skill in the art, when treating DME, would have understood that they would also be treating DR, given that DME is a common manifestation of DR.

504. Based on my read of dependent claim 28, that claim is essentially drawn to monthly dosing. I understand that dependent claims are understood to fall within the scope of the independent claim from which they depend. In other words, because claim 28 is drawn to monthly dosing, independent claim 26, from which it depends, also has monthly dosing within its scope. (601 patent, 23:1-15).

505. Because the prior art 9-14-2009 Regeneron Press Release recites the use of monthly dosing in treating DME patients, in my opinion, the monthly dosing disclosed in the 9-14-2009 Regeneron Press Release makes obvious claim 26.

506. In addition, a person of ordinary skill in the art would have had a reasonable expectation of success in view of the positive results reported for aflibercept in treating DME in Do 2009, and the positive results reported for the use of ranibizumab in treating DME. For example, Do 2009 reports that a single intravitreal dose of aflibercept resulted in an average of 9 letters in ETDRS score gained after one month. (Do 2009, 146). In addition, Lalwani 2009b discloses that ranibizumab was effective at treating DME. (Lalwani 2009b, 46). The ranibizumab

would have been informative because by 2009 aflibercept and ranibizumab had already been shown to result in similar efficacy in treating AMD. Accordingly, a person of ordinary skill in the art would have expected the same to be true in treating DME and DR (including treating DR in patients with DME).

507. For at least the reasons discussed above, claim 26 is obvious in view of the 9-14-2009 Regeneron Press Release, in combination with the general knowledge and skill of a person of ordinary skill in the art.

f. Dependent claim 27 is obvious.

508. I was asked to review claim 27 of the 601 patent and compare it to the disclosures of the prior art. Claim 27 purports to further limit the claimed dosing regimen of claim 26 to "wherein approximately every 4 weeks comprises approximately every 28 days or approximately monthly."

509. In my opinion, this added element of claim 27 does not add anything of interest to claim 26. A person of ordinary skill in the art would have viewed and understood "approximately every 4 weeks to be equivalent to "approximately every 28 days," and "approximately monthly." In addition, Regeneron itself, as well as authors in the field, would use weeks and months interchangeably. (*See, e.g.*, 9-14-2009 Regeneron Press Release, 1 ("2 mg monthly" and "2 mg every eight weeks after three monthly loading doses"); Dixon, 1576 ("Two groups received monthly doses of either 0.5 or 2.0 mg for 12 weeks (at weeks 0, 4, 8 and 12)"; Do 2012, Figure 1 and legend (displaying every 4 week doses and monthly doses the same way and using the terms interchangeably ("3 initial monthly doses then every 8 weeks")).

510. Thus, for these reasons, as well as at least the reasons discussed above for claim 26, claim 27 is obvious in view of the art and combinations set forth above for claim 26.

g. Dependent claim 28 is obvious.

511. I was asked to review claim 28 of the 601 patent and compare it to the disclosures of the prior art. Claim 28 purports to further limit the claimed dosing regimen of claim 26 to "further comprising, after 20 weeks, administering, via intravitreal injection, 2 mg of aflibercept once every 4 weeks."

512. I read claim 28 as being directed to monthly dosing after the first 5 monthly doses. This appears to conflict with claim 26, from which it depends, making claim 26 unclear. However, despite the lack of clarity, the prior art disclosed monthly dosing for the treatment of DME.

513. For example, Regeneron has represented to the public and the Patent Office that as of the relevant time period monthly dosing was the standard of care for angiogenic eye disorders. (*See, e.g.*, 338 PH, 9-11-2015 Applicant Remarks, 6). I disagree that monthly dosing was the standard of care. However, Regeneron also knew that monthly dosing, while not the majority practice, was nevertheless a long-practiced regimen. This is also evident from the 9-14-2009 Regeneron Press Release. (9-14-2009 Regeneron Press Release, 1 ("evaluat[ing] whether further improvements in vision and/or longer dosing intervals than *monthly* administration are possible.")).

514. Monthly dosing was the approved regimen for treating angiogenic eye disorders with the existing therapy (i.e., Lucentis), and in my experience, some doctors (though not many), were using fixed monthly dosing to treat these disorders prior to the filing of the 601 patent.

515. In addition, the 9-14-2009 Regeneron Press Release discloses the administration of 2 mg of aflibercept, including at monthly intervals. (9-14-2009 Regeneron Press Release, 2 ("VEGF Trap-Eye dosed at … 2 mg monthly")). Other prior art also disclosed monthly dosing. (*See, e.g.*, 747 patent, 20:62-67; Lalwani 2009b, 45; Dixon, 1576; Do 2012, 1659).

516. Thus, in my opinion, monthly dosing with aflibercept for the treatment of an angiogenic eye disorder such as DR, and the use of 2 mg of aflibercept to do so, would have been obvious.

517. Thus, for these reasons, as well as at least the reasons discussed above for claim 26, claim 28 is obvious in view of the art and combinations set forth above for claim 26.

h. Dependent claim 31 is obvious.

518. I was asked to review claim 31 of the 601 patent and compare it to the disclosures of the prior art. Claim 31 purports to further limit the claimed dosing regimen of claim 26 to "wherein the patient gains at least 15 letters of Best Corrected Visual Acuity (BCVA) score."

519. I have been informed that Mylan is taking the legal position that the visual acuity elements recited in claim 31 constitutes statements of intended results of the claimed methods that do not result in a manipulative difference in the steps of the claim, and thus should be deemed non-limiting. Furthermore, in my opinion, the recited BCVA criteria are commonly used outcome measures in clinical trials assessing patients with angiogenic eye disorders who are receiving anti-VEGF treatment, and thus represent nothing more than the intended result of those trials, or the natural result flowing from those clinical trials. (*See, e.g.*, Nguyen 2009a, 2141-43, 2145-46; Dixon, 1575-76; Heier 2009A, 45; Brown 2006, 1433; Rosenfeld 2006, 1420 & Suppl. App'x). Indeed, there is nothing in the claims that instruct how to achieve the visual acuity measures recited in the claims. The claims merely recite a prior art dosing regimen, and then recite commonly used visual acuity metrics. But there are no modifications or adjustments to the dosing regimen included in the claims.

520. But regardless of whether the BCVA elements are considered in the patentability analysis, the prior art expressly discloses that BCVA criteria are commonly used clinical trial outcomes and measurements when assessing angiogenic eye disorder patients receiving anti-

VEGF therapy. For example, the results of the VIVID and VISTA phase 3 clinical trials, which utilized 5 monthly loading doses followed by every-8-week dosing, show that a significant fraction of the patient population experienced gains of at least 15 letters in visual acuity. (*See, e.g.*, Korobelnik 2014 DME, 2247). This result was not surprising in view of the earlier clinical trial results with aflibercept, and would have indicated to a person of ordinary skill in the art that a population of treated patients necessarily would have experienced such gains. Accordingly, in my opinion, the recited BCVA criteria are an inherent feature of the claimed dosing regimen. In addition, a person of ordinary skill in the art would have had a reasonable expectation of success at achieving such BCVA measures in view of the positive phase 1 DME results with aflibercept, showing a gain of 9 letters after just a single dose of aflibercept. (Do 2012, Abstract). A person of ordinary skill in the art also would have had a reasonable expectation of success in view of the data that was emerging from the ranibizumab DME clinical trials, as well as the reported primary outcome measure of the ranibizumab RISE and RIDE clinical studies and the reports from other clinical trials regarding "greater-than-15-letter gainers." (Lalwani 2009b, 46).

521. In the event that any of the 601 patent claims has a July 2013 priority date, as discussed above, a person of ordinary skill in the art also would have had a reasonable expectation of success in view of the phase 2 DA VINCI DME clinical trial data. (Do 2012, Abstract (reporting the proportion of patients gaining greater than 15 letters)).

522. Thus, for this reason, as well as the reasons discussed above for claim 26, it is my opinion that claim 31 of the 601 patent is obvious in view of the 9-14-2009 Regeneron Press Release alone, or if necessary, in combination with Do 2009, Do 2012, or Lalwani 2009b.

i. Dependent claim 32 is obvious.

523. I was asked to review claim 32 of the 601 patent and compare it to the disclosures of the prior art. Claim 32 purports to further limit the claimed dosing regimen of claim 31 to

"wherein Best Corrected Visual Acuity (BCVA) is according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score."

524. As with claim 31, above, I have been informed that the additional element of claim 32 constitutes a non-limiting statements of intended results, and thus is not entitled to patentable weight. But regardless of whether this element is limiting, it is made obvious in view of the prior art.

525. A person of ordinary skill in the art would have known, from their background knowledge, and from the prior art cited above, that BCVA scores were assessed using an ETDRS letter score. (*See, e.g.*, Do 2007 at 1; Do 2009 at Abstract; Chun 2006 at 1707-08, 1711).

526. Thus, for these reasons, as well as for the reasons discussed above for claims 10, 18, 26, and 31, it is my opinion that claim 32 is obvious in view of one or more of the references cited above.

j. Dependent claim 33 is obvious.

527. I was asked to review claim 33 of the 601 patent and compare it to the disclosures of the prior art. Claim 33 purports to further limit the claimed dosing regimen of claim 26 to "wherein exclusion criteria for the patient include (1) active intraocular inflammation; or (2) active ocular or periocular infection."

528. Claim 33 sets forth common criteria for excluding patients from clinical trials that involve the intravitreal administration of a drug. In fact, the phase 2 DME clinical trial included the application of these criteria, which would necessarily have been applied during the enrolment of patients in that trial. (*See, e.g.*, Do 2011, 1820 (disclosing ocular inflammation, and infectious blepharitis, keratitis, scleritis, or conjunctivitis as exclusion criteria in the phase 2 DME trial)).

529. Thus, in my opinion the conduct of the phase 2 DME trials described in the phase 2 DME references would have necessarily involved the application of one or both of the exclusion criteria listed in claim 33, and thus are an inherent aspect of that clinical trial.

530. Further, in my opinion the exclusion of patients with inflammation or infections would have been a routine and common practice given the risks of serious infection that can result from injecting eyes with signs of pre-existing ocular or periocular infections. The recited exclusion criteria also were commonly employed exclusion criteria in the clinical trials being conducted at the time. For example, Lucentis DME clinical trials included the claimed exclusion criteria. (*See, e.g.*, Chun 2006, 1707 ("ocular disorders that may confound interpretation of study results" and "ocular inflammation")). Further, the ranibizumab AMD MARINA and ANCHOR trials, involving monthly intravitreal administration of ranibizumab, employed exclusion criteria that included, among other criteria, active intraocular inflammation in the study eye; history of idiopathic or autoimmune-associated uveitis in either eye; and infectious conjunctivitis, keratitis, scleritis, or endophthalmitis in either eye. (*See, e.g.*, Lucentis Medical Review, MYL-AFL0007147-49; Rosenfeld 2006, Appx., 2-3; NCT 836, 5-6; NCT 594, 5-6). The pegaptanib trials involving intravitreal administration in treating AMD likewise employed exclusion criteria that included, among other relevant criteria, choroiditis, and acute ocular or periocular infection. (Macugen Medical Review, MYL-AFL0007406; Macugen Study Group, 1748).

531. Finally, it was known among those of ordinary skill in the art that intravitreal injections could be associated with serious side effects if proper, aseptic technique is not adhered to. Consequently, persons of ordinary skill in the art were aware of guidelines and other information in the literature about avoiding injecting eyes that are infected or show signs of infection (i.e., inflammation). (*See, e.g.*, Aiello 2004, S4, 6-8, 17; Jager 2004, 687-88; De Caro,

878; Heimann, 67, 74-77, 80-81, 85; CATT Study, 6-7; Regillo 2008, 248.e3; MACTEL Study, 4; Jaffe, 349-50; Lucentis PI 2006, 2, 5; Retinal Physician II, 2, 5).

532. Thus, for this reason, as well as the reasons discussed above for claim 26, it is my opinion that claim 33 of the 601 patent is obvious in view of the 9-14-2009 Regeneron Press Release alone, or if necessary, in combination with Chun 2006, the ranibizumab MARINA and ANCHOR references, the pegaptanib references, or the injection guideline references, along with the general knowledge of a person of ordinary skill in the art.

7. No Secondary Considerations of Non-Obviousness.

533. I understand Regeneron may assert one or more secondary considerations in support of the non-obviousness of 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 subsequent report.

IV. Opinions Regarding Invalidity of the 572 Patent Asserted Claims.

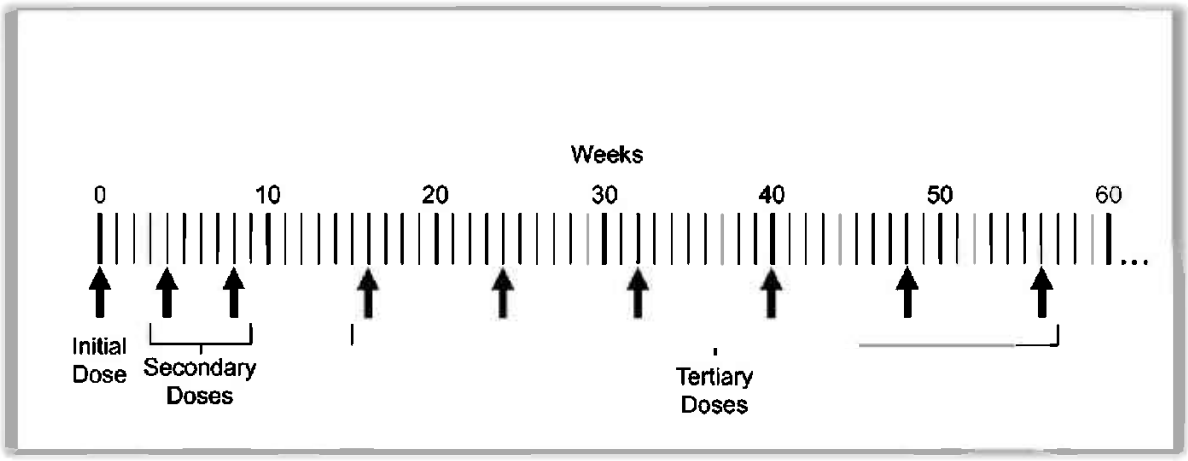
A. The Asserted Claims of the 572 Patent are Anticipated.

1. Claims 1-14 and 26-30 of the 572 Patent Are Anticipated by Several Prior Art References and Documents Disclosing the VIEW Clinical Trial, Including Dixon.

534. I was asked to review the Asserted Claims of the 572 patent and compare them to the disclosures of the prior art. It is my opinion that each of the below references discloses every element of the claimed method(s) and thus anticipates each of claims 1-14 and 26-30 of the 572 patent, either expressly or inherently.

535. First, Figure 1 of the 572 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."



(572 patent, Fig.1, 3:7-12).

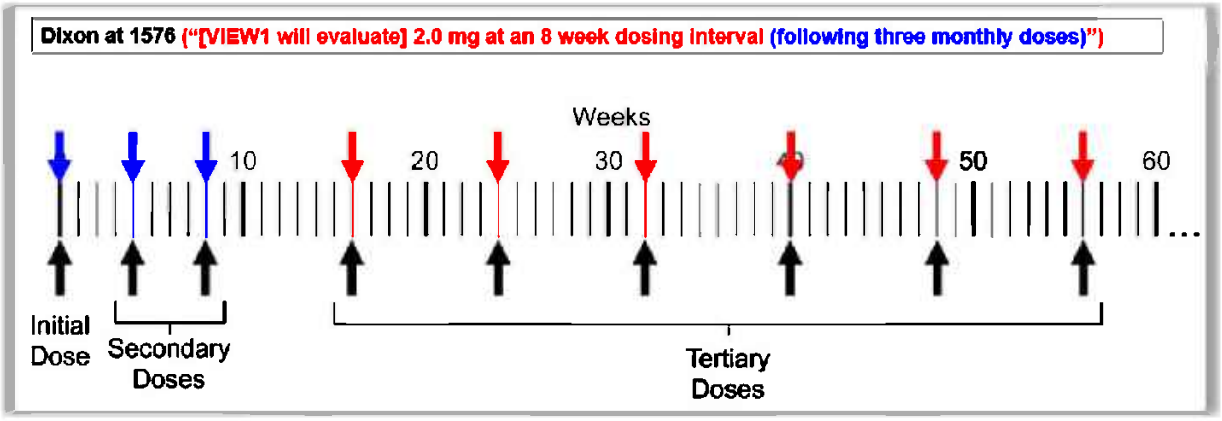
536. Based upon my reading of the patent specification, including Figure 1, and the claims of the 572 patent, it is my opinion that Figure 1 represents a dosing regimen that falls squarely within the scope of the challenged claims, including claim 1. For example, the 572 patent states that FIG. 1 "shows an exemplary dosing regimen of the present invention." (*Id.*, 3:6-7). In addition, the 572 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.*, 3:7-12). Because I will be using a modified version of Figure 1 of the 572 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 572 patent correspond to Figure 1 of the 572 patent:

Figure 1	Claims 1, 26, 29
"a single 'initial dose' of VEGF antagonist ('VEGFT') is administered at the beginning of the treatment regimen (i.e. at 'week 0')" (572 patent, 3:7-9).	"a single initial dose of 2 mg of aflibercept" (claim 1)
"two 'secondary doses' are administered at weeks 4 and 8, respectively" (*Id.*, 3:9-10).	"followed by one or more secondary doses of 2 mg of aflibercept . . . wherein each secondary dose is administered [to the patient] approximately 4 weeks following the immediately preceding dose" (claim 26)
"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.*, 3:10-12).	"followed by one or more tertiary doses of 2 mg of aflibercept . . . wherein each tertiary dose is administered [to the patient] approximately 8 weeks following the immediately preceding dose" (claim 29)

537. In addition, I note that dependent claim 5 purports to offer a narrower version of claim 1, specifying "wherein only two secondary doses are administered to the patient." Compare that to the Figure 1 legend: "two 'secondary doses' are administered at weeks 4 and 8, respectively." (*Id.*, 3:9-10). Therefore, in my opinion, claim 5 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 572 patent, and reproduced above.

538. Because the Figure 1 dosing regimen corresponds to the narrowest dosing regimen claim (claim 5), it also is representative of claim 1. I also note that this regimen comes straight from the VIEW1/VIEW2 Phase 3 studies. (*See, e.g.*, Dixon, 1576).

539. To illustrate why Dixon and the other VIEW references anticipate the claims, I have prepared the following *modified* version of Figure 1 from the 572 patent (set forth below), to show how Dixon (as just one example) discloses the exact dosing regimen set forth in Figure 1 of the 572 patent, as well as that which is claimed in the claims of the 572 patent:



(572 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. (Dixon, 1576). 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." (Dixon, 1576).

540. I note that the dosing regimen set forth in independent claims 1, 26, and 29 are similar, and thus the analysis is largely the same. Claims 26 and 29 only differ in the wording of the intended outcomes recited at the end of those claims. In my opinion, those recitations of intended outcome are just that – intended outcomes—and represent a natural result flowing from the operation of the claimed dosing regimen, which, as I have shown above and show below, was already set forth in the prior art and in public use well before the filing date of the 572 patent.

541. The dosing regimen steps otherwise remain the same. As a result, through Dixon's disclosure of VEGF Trap-Eye/aflibercept, Dixon discloses this aspect of claims 26 and 29 as well.

a. Independent claims 1, 26, and 29 are anticipated by Dixon and other references disclosing the VIEW clinical trials.

542. Below, I have constructed charts for the purpose of showing where each and every claim element from claim 1 is found in the Dixon and in other VIEW references:

Claim 1	Dixon
A method of treating an angiogenic eye disorder in a patient in need thereof, [Claims 26 and 29] A method of treating age related macular degeneration in a patient in need thereof	"VEGF Trap-Eye is a novel anti-VEGF therapy, with Phase I and II trial data indicating safety, tolerability and efficacy for the treatment of neovascular AMD." (Dixon, 1573; *see also id.*, 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." (*Id.*, 1576). "[P]atients . . . demonstrated stabilization of their vision that was similar to previous studies of ranibizumab at 1 year." (*Id.*, 1577). "Two Phase III studies in wet AMD, VIEW 1 and VIEW 2, are currently under way and seek to compare monthly ranibizumab to monthly or bimonthly VEGF Trap-Eye." (*Id.*, 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)." (*Id.*, 1576).
comprising sequentially administering to the patient by intravitreal injection	"[A]ll anti-VEGF agents for neovascular AMD are administered only by *intravitreal injection*." (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." (*Id.*, 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." (*Id.*, 1575). The VIEW1 and VIEW2 studies "will evaluate the safety and efficacy of intravitreal VEGF Trap-Eye." (*Id.*, 1576).

Claim 1	Dixon
a single initial dose of 2 mg of aflibercept, followed by one or more secondary doses of 2 mg of aflibercept, followed by one or more tertiary doses of 2 mg of aflibercept; wherein each secondary dose is administered approximately 4 weeks following the immediately preceding dose; and wherein each tertiary dose is administered approximately 8 weeks following the immediately preceding dose;	"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." (Dixon, 1573 (Background)). "VEGF Trap-Eye and aflibercept (the oncology product) have the same molecular structure." (*Id.*, 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." (*Id.*, 1575). "[Phase 3] will evaluate the safety and efficacy of . . . 2.0 mg at an 8 week dosing interval (*following three monthly doses*)." (Dixon, 1576 (emphasis added)).
wherein the patient achieves a gain in visual acuity within 52 weeks following the initial dose. [claim 26] wherein the method is as effective in achieving a gain in visual acuity as monthly administration of 0.5 mg of ranibizumab by intravitreal injection in human subjects with age-related macular degeneration at 52 weeks following the initial dose. [claim 29] wherein the method is as effective in maintaining visual acuity as monthly administration of 0.5 mg of ranibizumab by intravitreal injection in human subjects with age-related macular degeneration at 52	"In both [VIEW] trials, the primary outcome will be the proportion of patients who maintain vision at week 52 (defined as a loss of < 15 ETDRS letters)." (Dixon, 1576). 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." (Dixon, 1576). Patients in this arm also displayed mean decreases in retinal thickness of 143 µm compared to baseline. (*Id.*). Patients in the PRN arm of this phase 2 study received, on average, 1.6 injections after the initial 4 monthly injections, for a total of 5.6 injections. Patients in the VIEW clinical trials also inherently achieved the claimed visual acuity scores. (*See, e.g.*, Heier 2012, 2542, Table 2 (at week 52, 30.6% gaining ≥ 15 letters, and 95.1% losing < 15 letters)).

Claim 1	Dixon
weeks following the initial dose.	

Claim 1	Other VIEW References
A method of treating an angiogenic eye disorder in a patient in need thereof,	"Regeneron and Bayer inititiated [sic] a phase III trial of aflibercept in approximately 1200 patients with the neovascular form of wet AMD in August 2007." (Adis, 263). (*See also, e.g.*, NCT 795, 3-4; NCT 377, 3-5; 4-28-2008 Regeneron Press Release, 2; 5-8-2008 Regeneron Press Release, 1; 8-19-2008 Regeneron Press Release, 1; 9-28-2008 Regeneron Press Release, 1-2; 9-14-2009 Regeneron Press Release, 1; 11-22-2010 Regeneron Press Release, 2; 2009 Regeneron 10-K, 3; 3-31-2009 Regeneron 10-Q, 13; 6-30-2009 Regeneron 10-Q, 19; 9-30-2009 Regeneron 10-Q, 20; 3-31-2010 Regeneron 10-Q, 17; 6-30-2010 Regeneron 10-Q, 16; 9-30-2010 Regeneron 10-Q, 16; 5-8-2008 Bayer Press Release, 1-2; 8-19-2008 Bayer Press Release, 3-4).
comprising sequentially administering to the patient by intravitreal injection	"The noninferiority, VIEW 1 (VEGF Trap: Investigation of Efficacy and safety in Wet age-related macular degeneration) study will evaluate the safety and efficacy of ***intravitreal*** aflibercept…" (Adis, 263 (emphasis added)). (*See also, e.g.*, NCT 795, 3; NCT 377, 3-4; 4-28-2008 Regeneron Press Release, 1; 5-8-2008 Regeneron Press Release, 1; 8-19-2008 Regeneron Press Release, 1; 9-28-2008 Regeneron Press Release, 1; 9-14-2009 Regeneron Press Release, 1-2; 11-22-2010 Regeneron Press Release, 2; 2009 Regeneron 10-K, 3; 3-31-2009 Regeneron 10-Q, 13; 6-30-2009 Regeneron 10-Q, 19; 9-30-2009 Regeneron 10-Q, 20; 3-31-2010 Regeneron 10-Q, 16-17; 6-30-2010 Regeneron 10-Q, 16; 9-30-2010 Regeneron 10-Q, 16; 5-8-2008 Bayer Press Release, 1; 8-19-2008 Bayer Press Release, 3).
a single initial dose of 2 mg of aflibercept, followed by one or more secondary doses of 2 mg of aflibercept, followed by	"This study will evaluate the safety and efficacy of aflibercept at 0.5 mg and 2.0 mg administered at 4-week intervals and 2.0 mg at an 8-week dosing interval, including one additional 2.0 mg dose at week 4." (Adis, 263).

Claim 1	Other VIEW References
one or more tertiary doses of 2 mg of aflibercept; wherein each secondary dose is administered approximately 4 weeks following the immediately preceding dose; and wherein each tertiary dose is administered approximately 8 weeks following the immediately preceding dose;	(*See also, e.g.*, NCT 795, 6-8; NCT 377, 6; 4-28-2008 Regeneron Press Release, 2; 5-8-2008 Regeneron Press Release, 1; 8-19-2008 Regeneron Press Release, 1; 9-28-2008 Regeneron Press Release, 2; 9-14-2009 Regeneron Press Release, 1-2; 11-22-2010 Regeneron Press Release, 2; 2009 Regeneron 10-K, 3; 3-31-2009 Regeneron 10-Q, 13; 6-30-2009 Regeneron 10-Q, 19; 9-30-2009 Regeneron 10-Q, 20; 3-31-2010 Regeneron 10-Q, 17; 6-30-2010 Regeneron 10-Q, 16; 9-30-2010 Regeneron 10-Q, 16; 5-8-2008 Bayer Press Release, 1-2; 8-19-2008 Bayer Press Release, 2-3).
wherein the patient achieves a gain in visual acuity within 52 weeks following the initial dose. [claim 26] wherein the method is as effective in achieving a gain in visual acuity as monthly administration of 0.5 mg of ranibizumab by intravitreal injection in human subjects with age-related macular degeneration at 52 weeks following the initial dose. [claim 29] wherein the method is as effective in maintaining visual acuity as monthly administration of 0.5 mg of ranibizumab by intravitreal injection in human subjects with age-related macular degeneration at 52 weeks following the initial dose.	"The primary endpoint will be the proportion of patients treated with aflibercept who maintain vision at the end of 1 year compared with ranibizumab patients." (Adis, 263). "Key secondary endpoints 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." (5-8-2008 Regeneron Press Release, 1). (*See also, e.g.*, NCT 795, 9; NCT 377, 6-7; 4-28-2008 Regeneron Press Release, 1; 8-19-2008 Regeneron Press Release, 1; 9-28-2008 Regeneron Press Release, 1; 9-14-2009 Regeneron Press Release, 1; 11-22-2010 Regeneron Press Release, 1-2; 2009 Regeneron 10-K, 3-4; 3-31-2009 Regeneron 10-Q, 13-14; 6-30-2009 Regeneron 10-Q, 19-20; 9-30-2009 Regeneron 10-Q, 20-21; 3-31-2010 Regeneron 10-Q, 17; 6-30-2010 Regeneron 10-Q, 17; 9-30-2010 Regeneron 10-Q, 16; 5-8-2008 Bayer Press Release, 2; 8-19-2008 Bayer Press Release, 3-4).

As a result, Dixon, as well as each of the other VIEW references above, anticipate claims 1, 26, and 29 of the 572 patent.

b. Dependent claims 2-4 and 8-10 are anticipated by Dixon and the other VIEW references.

543. Claim 2 depends from claim 1 and further specifies that "the patient achieves a gain in Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score." Claims 3, 8, and 10 each depend from claim 2, which depends from claim 1. Claims 3, 8 and 10 each further require that the patient gain a specific number of letters according to the ETDRS letter score—specifically, requiring a gain of "at least 7 letters" (claim 3), "at least 8 letters" (claim 8), and "at least 9 letters" (claim 10). Dependent claims 4 and 9 further specify the timepoint—"within 24 weeks"—by which the patient must achieve the specific ETDRS letter score gain recited in claims 3 and 8.

544. I have been informed that Mylan is taking the legal position that the visual acuity elements recited in claims 2-4 and 8-10 constitute statements of intended results of the claimed methods that do not result in a manipulative difference in the steps of the claim, and thus should be deemed non-limiting. Indeed, there is nothing in the claims that instruct how to achieve the visual acuity measures recited in the claims. The claims merely recite a prior art dosing regimen, and then recite commonly used visual acuity metrics. But there are no modifications or adjustments to the dosing regimen included in the claims.

545. However, I also have been asked my opinion about the recited BCVA criteria in claims 2-4 and 8-10, in the event that the subject matter of those claims is later given patentable weight. Regardless of whether the BCVA elements are considered in the patentability analysis, they are anticipated.

546. In my opinion, the recited BCVA criteria are commonly used clinical trial measurements in trials assessing AMD patients who are receiving anti-VEGF treatment, including the primary outcome measure for the Phase III VIEW trials, and thus represent nothing more than

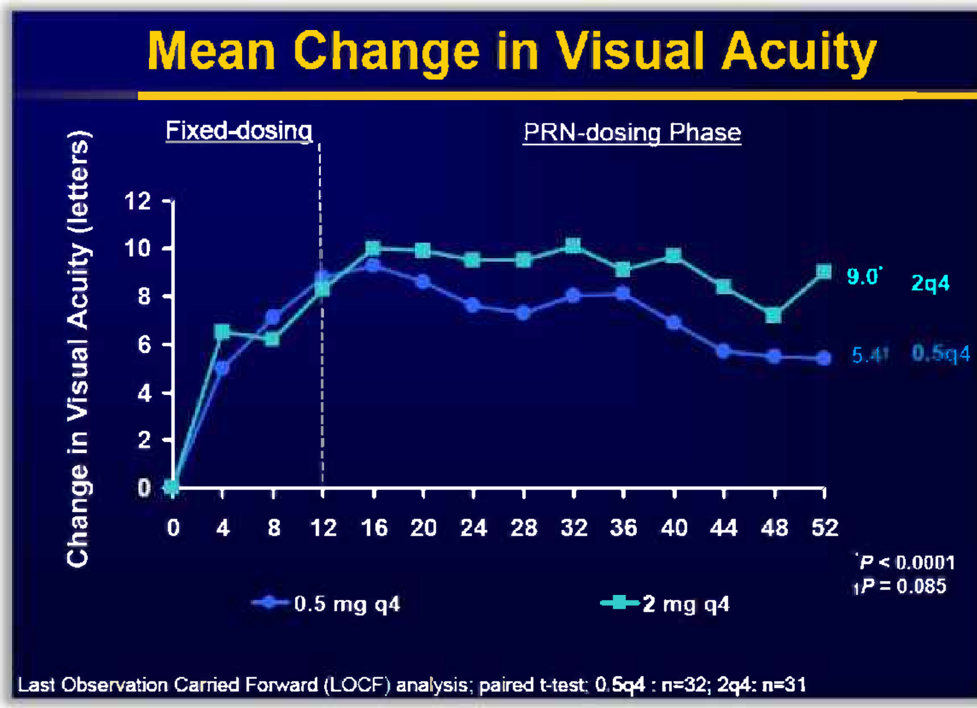
the intended result of those trials, or the natural result flowing from those clinical trials. (*See, e.g.*, Dixon, 1575-76; Nguyen 2009a, 2141-43, 2145-46; Heier 2009A, 45; Brown 2006, 1433, 1437-38; Rosenfeld 2006, 1420 & Suppl. App'x).

547. For example, Dixon discloses that in the aflibercept phase 2 clinical trial "[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." (Dixon, 1576; *see also, e.g.*, 5-8-2008 Regeneron Press Release, 1; 9-14-2009 Regeneron Press Release, 1; 5-8-2008 Bayer Press Release, 2). Dixon also discloses the use of the BCVA ETDRS criteria in connection with the assessment of AMD patients. (Dixon, 1575-76; *see also, e.g.*, Retina Society Meeting Presentation, 3; 11-22-2010 Regeneron Press Release, 1-2; 12-20-2010 Regeneron Press Release, 1-2; Heier 2012, 2538-39). Also, references such as NCT 377 and NCT 795 disclosed that the proportion of patients who gain at least 15 letters of vision at week 52 was an outcome measure of the VIEW clinical trials. (NCT 377, 6-7; NCT 795, 9; *see also, e.g.*, 5-8-2008 Regeneron Press Release, 1; 9-14-2009 Regeneron Press Release, 1; 5-8-2008 Bayer Press Release, 2). Accordingly, Dixon and the other VIEW references, including at least NCT 377 and NCT 795 disclose the added limitations, and thus anticipate this aspect of claims 2-4 and 8-10.

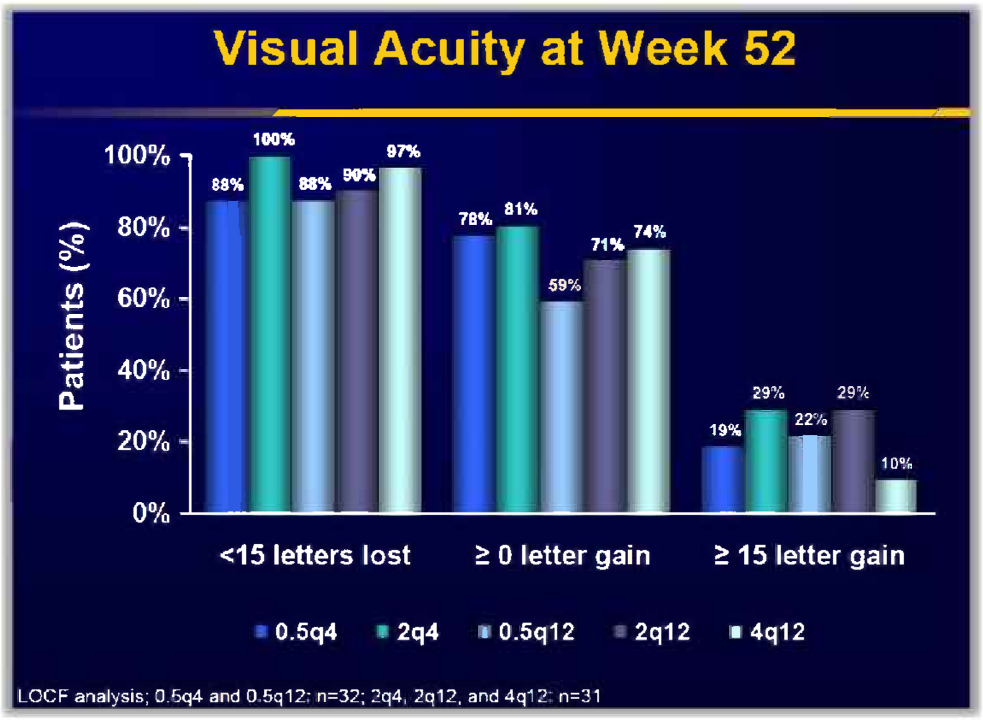
548. Further, Dixon and the other VIEW references disclosed the same VIEW clinical trial regimen with the same drug now claimed in claim 1 (from which claims 2-4 and 8-10 depend). In my opinion, the claimed visual acuity measures would have been a natural result flowing from the prior art Phase 3 regimen, 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 Dixon's

disclosure, and the other VIEW references' disclosures, of the dosing regimen used in the VIEW trials, Dixon and the other VIEW references anticipate this aspect of claims 2-4 and 8-10.

549. Also, a review of the data from the phase 2 AMD clinical trials reveals that a significant proportion of the patients receiving VEGF Trap-Eye would have experienced gains in visual acuity, including gains of 7, 8, or 9 BCVA letters. For example, as discussed above, Dixon reports that almost a third of the patients in the monthly loading dose arm achieved gains of ≥ 15 BCVA letters, and this was accomplished with, on average, only 1.6 additional injections in the PRN phase (i.e., between weeks 12 and 52). (Dixon, 1576). In addition, the 2008 Retina Society Meeting Presentation shows that significant gains were achieved after a single loading dose, and that visual acuity continued to improve throughout the loading dose phase in the 2 mg arm (aqua data points):



(Retina Society Meeting Presentation, 16). In addition, the phase 2 data showed that 81% of patients receiving monthly 2 mg loading doses, followed by PRN dosing, experienced ≥ 0 letters gained at week 52:



(Retina Society Meeting Presentation, 19). The above data also shows that 100% of patients treated with monthly loading doses followed by PRN treatment lost fewer than 15 letters. (*Id.*). Even among patients that received a single loading dose, followed by a dose 3 months later, followed by PRN dosing, 97% of those patients experienced fewer than 15 letters lost, and 74% experienced ≥ 0 letters gained. These data, using even fewer injections than the number used in the VIEW phase 3 trials,[24] support my opinion that the intended outcomes recited in claims 2-4

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[24] The VIEW regimen, which falls within the scope of the 572 patent claims 1, 26, and 29, included 3 loading doses plus 5 doses in the extended dosing phase = 8 injections in the first year. The relevant phase 2 regimen included 4 monthly loading doses plus 1.6 on average during the PRN phase = 5.6 injections in the first year.

and 8-10 would have been the natural results flowing from the operation of the claimed dosing regimen.

550. In addition, I have reviewed publications disclosing the results of the VIEW clinical trials. In Heier 2012, for example, the authors report that a substantial proportion of patients achieved the claimed visual acuity measures, providing additional evidence that such measures are a natural result of the dosing regimen set forth in claims 2-4 and 8-10. (*See* Heier 2012, 2542).

551. Thus, for these reasons, as well as for the reasons discussed above for claim 1, it is my opinion that claims 2-4 and 8-10 of the 572 patent are anticipated by Dixon, as well as each of the other VIEW references, including at least the Retina Society Meeting Presentation and Heier 2012.

c. Dependent claims 5, 11, and 27 are anticipated by Dixon and the other VIEW references.

552. Claims 5, 11, and 27 depend from claims 3, 10, and 26, respectively, and each recites "wherein only two secondary doses are administered to the patient."

553. As illustrated in my modified Figure 1 of the 572 patent above, which exemplifies a regimen falling within the scope of claims 1, 26, and 29, and the claims that depend therefrom, Dixon discloses the elements of claims 5, 11, and 27 through its disclosure of the VIEW phase 2 2Q8 treatment arm: "an 8 week dosing interval (following three monthly doses)," (i.e., an 8 week dosing interval after an initial dose and 2 "secondary" doses administered at monthly/4-week intervals. (Dixon, 1576). The other VIEW references likewise disclose the subject matter recited in claims 5, 11, and 27. (*See, e.g.*, Adis, 263; NCT 795, 8; NCT 377, 6; 4-28-2008 Regeneron Press Release, 1-2; 5-8-2008 Regeneron Press Release, 1; 9-28-2008 Regeneron Press Release, 1-2; 9-14-2009 Regeneron Press Release, 1; 11-22-2010 Regeneron Press Release, 1-2; 6-30-2009 Regeneron 10-Q, 19; 9-30-2009 Regeneron 10-Q, 20; 3-31-2010 Regeneron 10-Q, 17; 6-30-2010

Regeneron 10-Q, 16; 9-30-2010 Regeneron 10-Q, 16; 5-8-2008 Bayer Press Release, 1-2; 8-19-2008 Bayer Press Release, 3).

554. Thus, for these reasons, as well as for the reasons discussed above for claims 1, 26, and 29, it is my opinion that claims 5, 11, and 27 of the 572 patent is anticipated by Dixon, as well as each of the other VIEW references, including at least Adis and NCT 377.

d. Dependent claims 6-7 and 12-13 are anticipated by Dixon and the other VIEW references.

555. Dependent claims 6 and 12 recite "wherein the aflibercept is formulated as an isotonic solution" and dependent claims 7 and 13 recite "wherein the aflibercept is formulated with a nonionic surfactant."

556. In my opinion, the recitations in claims 6-7 and 12-13 do not distinguish the claims from the prior art. I have reviewed the opinions from Dr. Rabinow that the approved formulation of EYLEA is one that is isotonic and contains a non-ionic surfactant. Because I am not a protein formulator, I defer to Dr. Rabinow's opinion in this regard. I also understand that the approved formulation of EYLEA is described in the EYLEA label as a "preservative-free, sterile, aqueous solution in a single-use, glass vial designed to deliver 0.05 mL (50 microliters) of EYLEA (40 mg/mL in 10 mM sodium phosphate, 40 mM sodium chloride, 0.03% polysorbate 20, and 5% sucrose, pH 6.2)." (Eylea PI, 12). In my experience, the formulation described in the FDA approved label is the one used in a drug's phase 3 clinical trials. I also am not aware of any confidentiality restrictions that would have rendered the formulation used in the clinical trials confidential. Indeed, Dixon refers to aflibercept/VEGF Trap-Eye as being formulated in a manner that is "suitable for the comfortable, non-irritating, direct injection into the eye." (Dixon, 1575). Accordingly, in the absence of any evidence to the contrary, and deferring to Dr. Rabinow's opinions regarding isotonic and non-ionic surfactant, it is my opinion that the VIEW references'

disclosure of the VIEW clinical trial inherently disclosed the subject matter in claims 6-7 and 12-13.

557. Thus, for these reasons, as well as the reasons discussed above for claims 1-3 and 10, it is my opinion that claims 6-7 and 12-13 of the 572 patent are anticipated by Dixon and each of the other VIEW references.

e. Dependent claim 14 is anticipated by Dixon and the VIEW references.

558. Claim 14 depends from claim 1 and recites "wherein exclusion criteria for the patient include both of: (1) active ocular inflammation; and (2) active ocular or periocular infection."

559. 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 clinical trials involving administration of intraocular injections was known and published to POSAs well before the priority date of the 572 patent. (*See, e.g.*, Lucentis Medical Review, 32-33). Dixon also discloses, for example, that "[e]ach injection subjects patients to risks of cataract, intraocular inflammation, retinal detachment and endophthalmitis." (Dixon, 1577).[25]

560. Furthermore, the "exclusion criteria" listed in claim 14 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.*, Eylea® Medical Review, 112-14 (listing 37 exclusion

[25] 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.

criteria, including the two "exclusion criteria" listed in claim 14); Heier 2012, Appendix 2). The application of the "exclusion criteria" recited in claim 14, therefore, was a natural result flowing from the application of the VIEW trial study protocol. Thus, Dixon and each of the VIEW references disclosing the VIEW clinical trial and dosing regimen, inherently disclose this aspect of claim 14.

561. Lastly, the VIEW clinical trial references make clear that the VIEW clinical trials were being conducted at least as early as 2008. I am not aware of any confidentiality restrictions or obligations that would have been applicable to the exclusion criteria in that clinical trial, including at least because the exclusion criteria were largely carried over from the earlier-conducted ranibizumab studies. (*See, e.g.*, Heier 2012, 2540). Consequently, in my opinion, the subject matter of claim 14 would have been in public use or otherwise available to the public before 2010.

562. For these reasons, as well as for reasons discussed above for the claims from which claim 14 depends, it is my opinion that claim 14 is anticipated by Dixon and each of the other VIEW references disclosing the dosing regimen of the phase 3 VIEW clinical trial.

f. Dependent claim 28 is anticipated by Dixon and the VIEW references.

563. Claim 28 depends from claim 26 and recites "wherein the gain in visual acuity is measured using the Early Treatment Diabetic Retinopathy Study (ETDRS) letter score."

564. 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." (Dixon, 1576; *see also, e.g.*, 5-8-2008 Regeneron Press Release, 1-2; 9-14-2009 Regeneron Press Release, ; 5-8-2008 Bayer Press Release, 1). Dixon also discloses the use of the BCVA ETDRS criteria in connection with

the assessment of AMD patients in the phase 3 VIEW trials. (Dixon, 1575-76; *see also, e.g.*, Retina Society Meeting Presentation, 3; 11-22-2010 Regeneron Press Release, 1-2; 12-20-2010 Regeneron Press Release, 1-2; 1-18-2011 Regeneron Press Release, 2; Heier 2012, 2539). Additional references also disclose the use of ETDRS letter score in the assessment of patients in VEGF Trap-Eye clinical trials. (*See also, e.g.*, 5-8-2008 Press Release at 1; 9-14-2009 Regeneron Press Release).

565. Accordingly, Dixon and the other VIEW references, including at least various Regeneron press releases, disclose the added limitations, and thus anticipate this aspect of claim 28.

g. Dependent claim 30 is anticipated by Dixon and the VIEW references.

566. Claim 30 depends from claim 29 and recites "wherein maintenance of visual acuity means loss of less than 15 letters Best Corrected Visual Acuity (BCVA) as measured by using the Early Treatment Diabetic Retinopathy Study (ETDRS) letter score."

567. 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." (Dixon, 1576; *see also, e.g.*, 5-8-2008 Regeneron Press Release, 1; 9-14-2009 Regeneron Press Release, 2; 5-8-2008 Bayer Press Release, 1). Dixon also discloses the use of the BCVA ETDRS criteria in connection with the assessment of AMD patients in the phase 3 VIEW trials. (Dixon, 1575-76; *see also, e.g.*, Retina Society Meeting Presentation, 3; 11-22-2010 Regeneron Press Release, 1-2; 12-20-2010 Regeneron Press Release, 1-2; Heier 2012, 2538-39). Dixon further discloses that the primary outcome measure for the VIEW clinical trials was "the proportion of patients who maintain vision at week 52 (defined as a loss of < 15 ETDRS letters)." (Dixon, 1576; *see also* 5-8-2008 Bayer

Press Release, 2; 9-14-2009 Regeneron Press Release, 1; 11-22-2010 Regeneron Press Release, 1; 1-18-2011 Regeneron Press Release, 2; 2-9-2011 Regeneron Press Release, 1; 2-17-2011 Regeneron Press Release, 1; 2-22-2011 Regeneron Press Release, 1-2).

568. Accordingly, Dixon and the other VIEW references, including at least Regeneron's press releases disclose the added limitations, and thus anticipate this aspect of claim 30.

2. Claims 15-23 and 25 are anticipated by the 9-14-2009 Regeneron Press Release.

569. I have been asked to review claims 15-23 and 25 of the 572 patent and compare them to the disclosures of the prior art, including the 9-14-2009 Regeneron Press Release.

570. Independent claim 15 recites:

> A method of treating diabetic macular edema in a patient in need thereof comprising sequentially administering to the patient a single initial dose of 2 mg of aflibercept, followed by one or more secondary doses of 2 mg of aflibercept, followed by one or more tertiary doses of 2 mg of aflibercept;
>
> wherein each secondary dose is administered to the patient by intravitreal injection approximately 4 weeks following the immediately preceding dose; and
>
> wherein each tertiary dose is administered to the patient by intravitreal injection approximately 8 weeks following the immediately preceding dose.

571. Claims 16-23 and 25 each depend, either directly or indirectly, from independent claim 15.

a. Claim 15 is anticipated by the 9-14-2009 Regeneron Press Release.

572. It is my opinion that the 9-14-2009 Regeneron Press Release discloses every element of claim 15 and thus anticipates claim 15 of the 572 patent.

573. For example, the 9-14-2009 Regeneron Press Release discloses the phase 2 DME trial being conducted with VEGF Trap-Eye, and thus discloses "a method of treating diabetic

macular edema in a patient in need thereof." (*See* 9-14-2009 Regeneron Press Release, 2). The 9-14-2009 Regeneron Press Release also explains that the trial will involve dosing VEGF Trap-Eye at "2 mg every eight weeks after three monthly loading doses" (9-14-2009 Regeneron Press Release, 2), and thus discloses the recitation in claim 15:

> [S]equentially administering to the patient a single initial dose of 2 mg of aflibercept, followed by one or more secondary doses of 2 mg of aflibercept, followed by one or more tertiary doses of 2 mg of aflibercept; wherein each secondary dose is administered to the patient by intravitreal injection approximately 4 weeks following the immediately preceding dose; and wherein each tertiary dose is administered to the patient by intravitreal injection approximately 8 weeks following the immediately preceding dose.

(9-14-2009 Regeneron Press Release, 2). The 9-14-2009 Regeneron Press Release also discloses that VEGF Trap-Eye is a drug administered by intravitreal injection. (9-14-2009 Regeneron Press Release, 1).

574. In my opinion, claim 15 does not specify a particular level of efficacy, and I have been informed that claim preambles are presumed to be non-limiting. However, even if the preamble were a limitation, in my experience, any patient involved in a clinical study is, by definition, being treated. Further, the VEGF Trap-Eye phase 1 DME data showed treatment of DME, with just a single 4 mg dose of VEGF Trap-Eye. (*See, e.g.*, Do 2009, 144 (Results) (median improvement of 9 letters in BCVA at 4 weeks)). In addition, the phase 2 results using the every-8-week dosing regimen after three monthly loading doses confirm that the prior art regimens resulted in efficacious outcomes in patients with DME. (*See, e.g.*, Do 2011, Fig. 3 (93% of patients in the 2Q8 arm exhibiting $\geq$ 0 letter gain)). These data confirm that any efficacy, to the extent claim 15 requires it, was a result naturally flowing from the operation of the prior art dosing regimen.

575. Accordingly, for at least these reasons, it is my opinion that claim 15 is anticipated by the 9-14-2009 Regeneron Press Release.

b. Claims 16-17 and 20-21 are anticipated by the 9-14-2009 Regeneron Press Release.

576. Claims 16-17 and 20-21 depend, either directly or indirectly, from independent claim 15. Claims 16-17 and 20-21 recite various efficacy outcomes, including "wherein the patient achieves a gain in visual acuity within 52 weeks following the initial dose" (claim 16); "wherein the patient gains at least 9 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score" (claim 17); "wherein the patient achieves a gain in visual acuity within 24 weeks following the initial dose" (claim 20); and "wherein the patient gains at least 8 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score" (claim 22).

577. The VEGF Trap-Eye phase 1 DME data showed treatment of DME, with just a single 4 mg dose of VEGF Trap-Eye. (*See, e.g.*, Do 2009, 144 (Results) (median improvement of 9 letters in BCVA at 4 weeks)). In addition, the phase 2 results using the claimed every-8-week dosing regimen after three monthly loading doses confirm that the prior art regimens resulted in patients achieving the claimed outcomes in patients with DME. (*See, e.g.*, Do 2011, Fig. 3 (93% of patients in the 2Q8 arm exhibiting $\geq$ 0 letter gain); *see also, e.g.*, Do 2012, 1658 (Results)). These data confirm that the efficacy recited in claims 16-17 and 20-21 was a result naturally flowing from the operation of the prior art dosing regimen.

578. For example, Do 2012 shows that patients receiving the claimed dosing regimen achieved visual acuity gains by week 52. (Do 2012 at Fig. 2). Do 2012 further shows that almost all patients achieved $\geq$ 0 letters gained and almost half gained 10 or more letters. (Do 2012 at Fig.

4). Likewise, Do 2011 and Do 2012 both show visual acuity gains using a 2Q8 regimen by week 24. (Do 2011, Figs. 2 and 3; Do 2012, Figs. 2 and 4).

579. These data confirm that achieving "a gain in visual acuity," including a gain of 8 letters by week 24 or 9 letters by week 52, would have been a natural result flowing from the operation of the claimed dosing regimen, and an inherent aspect of the regimen.

580. Accordingly, for at least these reasons, along with those discussed above for claims 15, it is my opinion that claims 16-17 and 20-21 are anticipated by the 9-14-2009 Regeneron Press Release.

c. Dependent claims 18-19 and 22-23 are anticipated by the 9-14-2009 Regeneron Press Release.

581. Claims 18-19 depend from claim 17 and are drawn to "aflibercept formulated in an isotonic solution." Claims 19 and 23 depend from claim 21 and are drawn to "aflibercept formulated with a nonionic surfactant."

582. In my opinion, the recitations in claims 18-19 and 22-23 do not distinguish the claims from the prior art. I have reviewed the opinions from Dr. Rabinow that the approved formulation of EYLEA is one that is isotonic and contains a non-ionic surfactant. Because I am not a protein formulator, I defer to Dr. Rabinow's opinion in this regard. In my experience, the formulation described in the FDA approved label is the one used in a drug's clinical trials. I also am not aware of any confidentiality restrictions that would have rendered the formulation used in the clinical trials confidential. Accordingly, in the absence of any evidence to the contrary, and deferring to Dr. Rabinow's opinions regarding isotonic and non-ionic surfactant, it is my opinion that the 9-14-2009 Regeneron Press Release's disclosure of the DME clinical trial inherently disclosed the subject matter in claims 18-19 and 22-23.

583. Thus, for at least these reasons, along with those discussed above for claims 15-17 and 21, it is my opinion that claims 18-19 and 22-23 of the 572 patent are anticipated by the 9-14-2009 Regeneron Press Release.

d. Dependent claim 25 is anticipated by the 9-14-2009 Regeneron Press Release.

584. Claim 25 is drawn to the dosing regimen of claim 15, "wherein four secondary doses are administered to the patient."

585. The 9-14-2009 Regeneron Press Release discloses VEGF Trap-Eye (aflibercept) as a drug intended for intravitreal administration. (*See, e.g.*, 9-14-2009 Regeneron Press Release, 1). The press release also discloses a phase 2 clinical trial in which aflibercept is administered to patients with diabetic macular edema (DME) in 2 mg doses for three monthly loading doses. (*Id.* at 2). After the monthly loading doses, patients are treated with fixed every-8-week injections or PRN (i.e., as needed) injections. (*Id.*).

586. A person of ordinary skill in the art would immediately envision a regimen that involves 3 monthly loading doses followed by PRN dosing could easily result in patients receiving 5 total monthly injections and one or more injections that are 8 weeks apart.

587. In addition, claim 25, while reciting 4 secondary doses, does not provide an upper limit to the number of secondary doses. In other words, claim 25 could result in a regimen in which patients are administered monthly doses for an extended period of time. The 9-14-2009 Regeneron Press Release discloses treatment of DME with VEGF Trap-Eye dosed at "2 mg monthly." (*See, e.g.*, 9-14-2009 Regeneron Press Release, 2).

588. For at least the reasons discussed above, claim 25 is anticipated by the 9-14-2009 Regeneron Press Release.

3. Claims 1-14 and 26-30 of the 572 Patent Are Invalid for Being in Public Use or Otherwise Available to the Public.

589. For the reasons I discuss above, the public disclosures of the VIEW clinical trial design and dosing regimen disclose each and every aspect of claims 1-14 and 26-30, either expressly or inherently.

590. For the same reasons, the operation of the VIEW clinical trial also would have disclosed each and every aspect of claims 1-14 and 26-30. I am not aware of any confidentiality agreements or obligations relating to the VIEW clinical trial that would have extended to the dosing regimen, the exclusion criteria, or the outcome measures. According to Regeneron's own press releases, Regeneron began enrolling patients in the study in 2008, with enrollment completed in September 2009—enrollment necessarily would have entailed evaluating each enrolled patient for each of the exclusion criteria. (9-14-2009 Regeneron Press Release, 1). In addition, the press release notes that the one year data from VIEW will be available in the fourth quarter of 2010, meaning that dosing began in the fourth quarter of 2009 at the latest, over one year before the earliest filing dates of the 601 and 572 patents.

591. Accordingly, it is my opinion that the VIEW clinical trial, at least the aspects that appear in claims 1-14 and 26-30, would have been in public use or otherwise available to the public more than one year before the earliest filing date of the 572 patent.

B. The Asserted Claims of the 572 Patent are Obvious.

592. For at least each of the multiple reasons discussed in this report, it is my opinion that each of the Asserted Claims of the 572 patent would have been obvious to a person of ordinary skill in the art at the time of the alleged invention of the patent. I reserve the right to supplement or amend these reasons in light of ongoing discovery, as well as in rebuttal or response to any

opinions offered by any other expert, or in response to any claim construction orders entered by the Court.

593. At the time of the alleged invention of the 572 patent, a person of ordinary skill in the art would have been motivated to use the dosing regimens of the Asserted Claims of the 572 patent, and would have had a reasonable expectation of success in using such dosing regimens. Based on, among other things, my experience, the relevant prior art, and the reasons set forth herein, it is my opinion that the person of ordinary skill at the time would have been motivated to refine, and would have been able to successfully refine, dosing regimens falling within each of the Asserted Claims, and to use such regimens. In reaching my opinions, I did not use hindsight, but have performed my analysis from the perspective of one of ordinary skill in the art at the time of the alleged invention.[26]

1. The Scope and Content of the Prior Art Relevant to the Asserted Claims.

594. The scope of the prior art for the 572 patent relates to the use of a VEGF antagonist for intravitreal administration pursuant to various dosing regimens, including the administration of VEGF antagonists to treat eye disorders caused by or associated with angiogenesis, e.g., age related macular degeneration, diabetic retinopathy, and diabetic macular edema.

595. In forming my opinions, I relied on, among other things, my knowledge of, and years of experience in, treating angiogenic eye disorders, and took into consideration the specification and claims of the 572 patent, as well as the prosecution history of the patent, including the art cited by the examiner during prosecution, and the deposition of the alleged inventor.

[26] In Section III(B)(1), above, I set forth my opinions and observations regarding the prior art disclosures at the relevant time, as relevant to the 601 patent. These opinions and observations are equally relevant to the 572 patent, which shares a specification with, and claims the benefit of the same purported priority date as, the 601 patent. Thus, I incorporate that discussion here for purposes of my obviousness opinions relating to the 572 patent.

596. At a minimum, each of the prior art references and products discussed in this report, including in Appendix A to this report, falls within the scope of the prior art for the 572 patent and the Asserted Claims.

597. As discussed herein, if Plaintiff or any of its experts attempt to dispute that any reference discussed herein is properly considered "prior art" to the 572 patent under the law, based on an alleged invention date earlier than January 13, 2011, or for any other reason, I reserve the right to amend or supplement this report and my opinions set forth herein.

2. Comparison Between the Asserted Claims of the 572 Patent and the Prior Art.

598. The Asserted Claims of the 572 patent are generally directed to intravitreal administration of a VEGF antagonist and methods of treating angiogenic eye disorders by intravitreally administering the VEGF antagonist pursuant to dosing regimens that can generally be characterized as comprising sequential administration of multiple doses of the VEGF antagonist to a patient wherein the dosing regimen consists of an initial, monthly loading dose period, followed by a less frequent (every 8 week) maintenance period.

599. My opinions set forth herein include and are applicable to the references and products disclosed in Appendix A, which is attached as part of this report.

600. For the reasons disclosed herein, each of the following prior art references, products and combinations independently would have taught the person of ordinary skill at the time to administer VEGFT to angiogenic eye disorder patients pursuant to an every-8-week dosing regimen as set forth in the Asserted Claims. It is my opinion, for the reasons set forth below, that each and every Asserted Claim of the 572 patent, if not anticipated, as discussed above, is obvious in light of the relevant prior art.

3. Claims 1-14 and 26-30 of the 572 patent are obvious over the prior art.

601. I was asked to review claims 1-14 and 26-30 of the 572 patent, and compare them to the disclosures of the prior art, including Dixon.

602. As discussed above, it is my opinion that each of these Asserted Claims of the 572 patent is anticipated by the prior art. I incorporate my anticipation discussion, including my element-by-element claim analysis presented above, and I will refer to those discussions with respect to my opinions regarding the obviousness of those claims. In particular, it is my opinion that claims 1-14 and 26-30 of the 572 patent are obvious over Dixon (either alone or in combination with one or more prior art references) in light of the person of ordinary skill in the art's (i) clear motivation to use less frequent dosing; and (ii) reasonable expectation of success from the positive Phase 2 results.

a. Independent claims 1, 26, and 29 of the 572 patent are obvious over the prior art.

603. Independent claims 1, 26, and 29 of the 572 patent are obvious in view of Dixon, and, if necessary, in combination with one or more of the references cited herein as disclosing the Phase 2 CLEAR-IT-2 results.[27]

[27] While I have provided specific citations to Dixon to illustrate the obviousness of the Asserted Claims, I reserve the right to rely upon any of the art identified in this report and/or in Appendix A to this report. For instance, instead of, or in addition to, Dixon, I reserve the right to rely on any of the VIEW References that disclose the dosing regimen and VEGF Trap-Eye/aflibercept used in the VIEW trials, including Adis; NCT 795; NCT 377; 4-28-2008 Regeneron Press Release; 5-8-2008 Regeneron Press Release; 8-19-2008 Regeneron Press Release; 9-28-2008 Regeneron Press Release; 9-14-2009 Regeneron Press Release; 11-22-2010 Regeneron Press Release; 2009 Regeneron 10-K; 3-31-2009 Regeneron 10-Q; 6-30-2009 Regeneron 10-Q; 9-30-2009 Regeneron 10-Q; 3-31-2010 Regeneron 10-Q; 6-30-2010 Regeneron 10-Q; 9-30-2010 Regeneron 10-Q; 5-8-2008 Bayer Press Release; and 8-19-2008 Bayer Press Release.

604. As noted above, Dixon discloses each and every element of claims 1, 26, and 29 in the 572 patent. I incorporate and will refer to that discussion with respect to my obviousness opinions.

605. Dixon discloses that "VEGF Trap-Eye is a novel anti-VEGF drug currently in commercial development for the treatment of neovascular AMD." (Dixon, 1575). Dixon further discloses that "[o]ne 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." (Dixon, 1573). Prior to the earliest filing date of the 572 patent, the identity of aflibercept was already disclosed in the prior art, as confirmed by Dixon's disclosure that VEGF Trap-Eye and aflibercept, among others, are simply different names for the same active ingredient. (*See, e.g.*, Dixon, 1575 ("VEGF Trap-Eye and aflibercept (the oncology product) have the same molecular structure....")). Thus, in my opinion, the molecular structure of aflibercept was known to the skilled artisan.

606. Dixon also discloses that "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." (Dixon, 1573). Dixon teaches that the clinical trials sought to assess the improvements in visual acuity throughout the study period. (Dixon, 1576).

607. Dixon discloses the favorable results of the Phase 2 AMD clinical trial, where the patients achieved a gain in visual acuity within 52 weeks following the initial dose. (Dixon, 1576). Dixon also 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, and further disclosed that the Phase 2 patients required on average only 1.6 additional injections after the four monthly loading doses during the one-year study. (Dixon, 1576).

608. Following the favorable Phase 2 AMD trial results, Regeneron continued onto Phase 3 trials, referred to as VIEW1/VIEW 2, the details of which are also disclosed by Dixon. For example, Dixon discloses that "[t]wo 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." (Dixon, 1577-78).

609. In addition to monthly dosing arms, the VIEW1/VIEW2 studies also included a treatment arm dosing 2 mg every eight weeks after 3 initial monthly injections, (Dixon, 1576), which is the precise dosing regimen Regeneron claimed years later in the 572 patent (*see* 572 patent at Fig. 1; claims). (*See also* 572 patent at Example 4 (describing the same Phase 3 clinical trial described in Dixon, using aflibercept (referred to in the examples as VEGFT)). This choice to include a treatment arm of 3 monthly injections followed by dosing every 8 weeks was entirely consistent with the trend that had emerged in the treatment of patients with intravitreal VEGF blockers, and, indeed, consistent with Dixon's disclosure that "[t]he time and financial burden of monthly injections has led to the initiation of studies to examine the efficacy of alternative dosing schedules." (Dixon, 1574).

610. Although the final Phase 3 clinical trial data were not reported in the literature until after the priority date of the 572 patent, it is my opinion that Dixon's disclosure of the trial protocol and description of the claimed methods of treatment provided sufficient detail such that a POSA would be able to carry out the claimed methods.

611. ***Motivation to Explore Extended Dosing Regimens.*** The motivation to adopt the claimed dosing regimens for VEGF Trap-Eye comes from the references themselves, which persons of ordinary skill in the art would have appreciated set forth dosing regimens that allowed for dosing less frequently than monthly, as well as the understanding among those of ordinary skill

in the art that less frequent dosing is preferred given the risks and potential complications associated with intravitreal administration, among other things.

612. One of ordinary skill in the art would have been motivated to explore and 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. (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.*, 1577 ("Each injection subjects patients to risks of cataract, intraocular inflammation, retinal detachment and endophthalmitis.")).

613. One of ordinary skill in the art would have also observed in Dixon, and in the many other publicly available reports of the initiation of the VIEW Phase 3 trials, that a solution to the dosing frequency issue was presented therein in the form of the publicly disclosed VIEW regimens involving every-8-week dosing following three monthly loading doses. (*See* Dixon, 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.

614. ***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 dosing regimens for treating wet AMD, at least because of the widely publicized results of the Phase 2 CLEAR-IT-2 data, which demonstrate success at treating AMD patients using *even fewer doses*, on average, than in the VIEW every-8-week dosing regimen. (*See, e.g.*, Dixon, 1575-76; *see also* Heier 2009 at 45).

615. 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. (Dixon, 1576). Those patients also experienced a mean decrease in retinal thickness of 143 µm. (*Id.*). A comparison of the Phase 2 AMD trial results, to those 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 (CLEAR-IT-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

(*Id.*; Heier 2012, 2541-42).

616. As Dixon further notes, during the PRN dosing phase, which covered 40 weeks, patients only required, on average, 1.6 doses. (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, under the Phase 3 VIEW dosing regimen, a patient would receive 8 doses in the first year (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.

617. In my opinion, a person of ordinary skill in the art would have reasonably expected success in administering the claimed 8-week dosing regimens to AMD patients in light of the

[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, (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.*).

positive Phase 2 AMD trial results, as reported in Dixon, 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).

618. 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." (4-28-2008 Regeneron Press Release, 1). Additionally, Regeneron's President, and the 572 patent's named inventor, George Yancopoulos, publicly stated that the Phase 2 CLEAR-IT-2 "results further increase our confidence in the design of our Phase 3 clinical program for VEGF Trap-Eye in wet AMD." (4-28-2008 Regeneron Press Release, 1; *see also id.* (Phase 2 study's primary investigator quoted: "Due to its high affinity for all isoforms of VEGF-A and PIGF, potent mediators of blood vessel overgrowth in wet AMD, 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, especially on a chronic basis, without compromising visual acuity.")).

619. 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, Regeneron still made the decision to go ahead with the 2Q8 arm of the VIEW trial.

620. Notably, Regeneron's internal documents confirm that. (*See, e.g.*, RGN-EYLEA-MYLAN-00526316, -317 (explaining the rationale for the 2Q8 arm, noting that "any fixed dose regimen greater than every 4 weeks that doesn't require interim monitoring for visual acuity is seen as desirable among physicians"); *Id.*, -316 (noting that the 2Q8 arm's purpose was to "maximize efficacy"); RGN-EYLEA-MYLAN-00527017 (relaying an analyst's commentary that the 8-week regimen "seems reasonable"); RGN-EYLEA-MYLAN-00527040, -041 (commenting

on the market value of the "8q-weeks dosing"); RGN-EYLEA-MYLAN-00529944 ("The quarterly dosing arms seemed to sustain their effect on visual acuity out to eight weeks, providing the rationale for exploring an eight week dosing schedule in the Phase III program."); RGN-EYLEA-MYLAN-00532930 (discussing Phase 3 trial strategies after discussions with physicians and "Key Opinion Leaders" at the Association for Research in Vision and Ophthalmology)). 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.

621. 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." (CDER Statistical Reviews, 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 P1GF, 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")).

622. 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.

623. ***Visual Acuity Elements of Claims 1, 26 and 29.*** The final claim elements of each of claims 1, 26, and 29 of the 572 patent are as follows: "wherein the patient achieves a gain in visual acuity within 52 weeks following the initial dose," (claim 1), "wherein the method is as effective in achieving a gain in visual acuity as monthly administration of 0.5 mg of ranibizumab

by intravitreal injection in human subjects with age-related macular degeneration at 52 weeks following the initial dose," (claim 26), and "wherein the method is as effective in maintaining visual acuity as monthly administration of 0.5 mg of ranibizumab by intravitreal injection in human subjects with age-related macular degeneration at 52 weeks following the initial dose," (claim 29).

624. I have been informed that the "visual acuity" limitations of claims 1, 26, and 29 constitute non-limiting statements of intended results, and thus are not entitled to patentable weight. But regardless of whether limiting or not, the visual acuity elements are set forth in the prior art. For example, Dixon discusses the success in treatment of the Phase 1 trial, which resulted in visual acuity stability or improvement in 95% of patients, and the Phase 2 trial, which, for instance, evaluated a dosing regimen that resulted in a statistically significant reduction in retinal thickness (a primary indicator used in AMD treatment). (Dixon, 1575-76). Dixon states that Phase 2 patients "treated with 2.0 or 0.5 mg of VEGF Trap-Eye monthly achieved mean improvements of 9.0 ($p<0.0001$) and 5.4 ($p<0.085$) ETDRS letters with 29 and 19% gaining, respectively, $\geq$ 15 ETDRS letters at 52 weeks." (Dixon, 1576; *see also, e.g.*, Retina Society Meeting Presentation, 16-17). Thus, Dixon explains that "patients . . . demonstrated stabilization of their vision that was similar to previous studies of ranibizumab at 1 year." (Dixon, 1577).

* * *

625. Based on Dixon's description of the VEGF Trap-Eye/aflibercept Phase 3 AMD clinical trials (VIEW 1 and VIEW 2), and the positive results of the Phase 2 AMD trials (CLEAR-IT-2), a person of ordinary skill in the art would have known how to administer, what dosing schedule to follow, and how much aflibercept to administer to a patient to treat angiogenic eye disorders. Further, a person of ordinary skill in the art would have been aware of the efforts to reduce dosing frequency, and would have been aware of the promising results already observed in

the Phase 2 VEGF Trap-Eye trials. Thus, a person of ordinary skill in the art would have therefore been motivated to try—and would have had a reasonable of success in trying—treating an angiogenic eye disorder by administering VEGF Trap according to the claimed dosing regimen of three monthly loading doses, followed by every 8 week dosing.

626. For these reasons, it is my opinion that claims 1, 26, and 29 of the 572 patent are made obvious by Dixon and, if necessary, in combination with one or more references disclosing the AMD Phase 2 results.

b. Dependent claims 2-4, 8-10, and 28 are obvious over Dixon and the other VIEW references.

627. I have been informed that claims 2-4 and 8-10 can each be described as "dependent" on claim 1. Likewise, I have been informed that claim 28 can be described as "dependent" on claim 26. It is my understanding that a dependent claim incorporates the elements of the claims from which it depends.

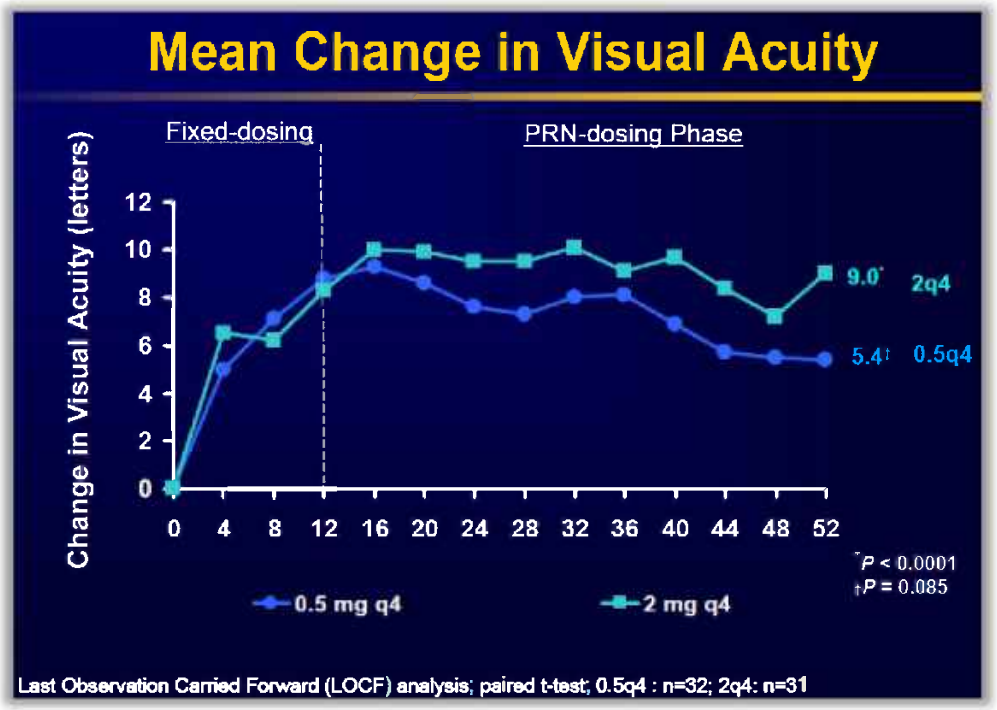
628. Claims 2 and 28 depend from claims 1 and 26, respectively, and each purportedly limit the "gain in visual acuity" as "measured [using the / according to] Early Treatment Diabetic Retinopathy Study (ETDRS) letter score." Claims 3, 8, and 10 each depend from claim 2, which itself depends from independent claim 1, and each further requires that the patient gain a specific number of letters according to the ETDRS letter score—specifically, requiring a gain of "at least 7 letters" (claim 3), "at least 8 letters" (claim 8), and "at least 9 letters" (claim 10). Dependent claims 4 and 9 further specify the timepoint—"within 24 weeks"—by which the patient must achieve the specific ETDRS letter score gain recited in claims 3 and 8.

629. I have been informed that the "visual acuity" limitations of claims 2-4, 8-10, and 28 constitute non-limiting statements of intended results, and thus are not entitled to patentable weight. But regardless of whether limiting or not, the visual acuity elements are set forth in the

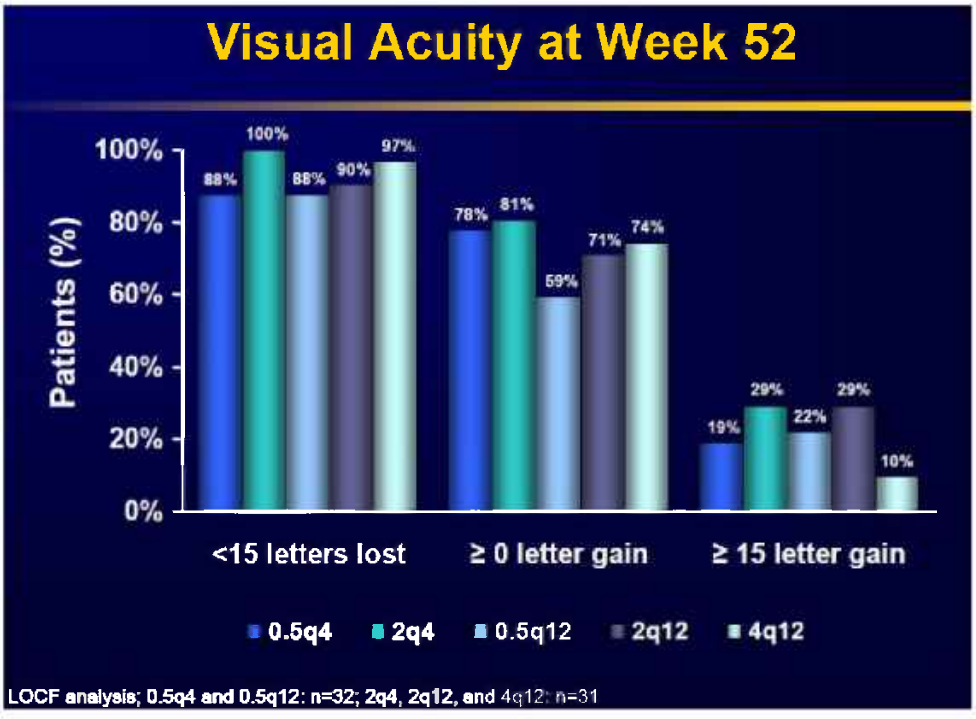
prior art. For example, Dixon discloses that in the aflibercept phase 2 clinical trial "[p]atients initially treated with 2.0 . . . mg of VEGF Trap-Eye monthly achieved mean improvements of 9.0 ($p < 0.0001$) . . . ETDRS [BCVA] letters with 29[%] . . . gaining . . . ≥ 15 ETDRS letters at 52 weeks." (Dixon, 1576; *see also, e.g.*, 5-8-2008 Regeneron Press Release, 1-2; 5-8-2008 Bayer Press Release, 1-3). Dixon also discloses the use of the BCVA ETDRS criteria in connection with the assessment of AMD patients. (Dixon, 1575-76; *see also, e.g.*, Retina Society Meeting Presentation, 3; 11-22-2010 Regeneron Press Release, 1-2; 12-20-2010 Regeneron Press Release, 1-2; Heier 2012, 2538-39). Also, references such as NCT-377 and NCT-795 disclosed that the proportion of patients who gain at least 15 letters of vision at week 52 was an outcome measure of the VIEW clinical trials. (NCT 377, 6-7; NCT 795, 9; *see also, e.g.*, 5-8-2008 Regeneron Press Release, 1; 9-14-2009 Regeneron Press Release, 1; 5-8-2008 Bayer Press Release, 2).

630. Accordingly, Dixon and the other VIEW references, including at least NCT-377 and NCT-795 disclose the additional element of claims 2-4, 8-10, and 28, thus rendering these claims obvious.

631. Further, a review of the data from the phase 2 AMD clinical trials reveals that a significant proportion of the patients would have experienced gains in visual acuity, including gains of 7, 8, or 9 BCVA letters. For example, as discussed above, Dixon reports that almost a third of the patients in the monthly loading dose arm achieved gains of ≥ 15 BCVA letters, and this was accomplished with, on average, only 1.6 additional injections in the PRN phase (i.e., between weeks 12 and 52). (Dixon, 1576). In addition, the 2008 Retina Society Meeting Presentation shows that significant gains were achieved in the Phase 2 AMD trial after a single loading dose, and that visual acuity continued to improve throughout the loading dose phase in the 2 mg arm (aqua data points):



(Retina Society Meeting Presentation, 16). In addition, the phase 2 data showed that 81% of patients receiving monthly 2 mg loading doses, followed by PRN dosing, experienced ≥ 0 letters gained at week 52:



(Retina Society Meeting Presentation, 19). The above data also shows that 100% of patients treated with monthly loading doses followed by PRN treatment lost fewer than 15 letters. (*Id.*). Even among patients that received a single loading dose, followed by a dose 3 months later, followed by PRN dosing, 97% of those patients experienced fewer than 15 letters lost and 74% experienced ≥ 0 letters gained. (*Id.*). These data, using even fewer injections than the number used in the VIEW phase 3 trials and set forth in the 572 patent claims,[29] support my opinion that the person of ordinary skill in the art would have reasonably expected success in achieving the intended outcomes recited in claims 2-4, 8-10, and 28 from the operation of the claimed dosing regimen.

632. In addition, I have reviewed publications disclosing the results of the VIEW Phase 3 clinical trials. In Heier 2012, for example, the authors report that a substantial proportion of patients achieved the claimed visual acuity measures, providing additional evidence that persons of ordinary skill in the art would have reasonably expected success with the dosing regimen set forth in claims 2-4, 8-10, and 28. (*See* Heier 2012, 2542-43).

633. Thus, for these reasons, as well as for the reasons discussed above for claims 1 and 26, it is my opinion that claims 2-4, 8-10, and 28 of the 572 patent are rendered obvious in view of Dixon and the other VIEW references.

c. Dependent claims 5, 11, and 27 are obvious over Dixon and the other VIEW references.

634. I was asked to review claims 5, 11 and 27 of the 572 patent and compare them to the disclosures of the prior art.

[29] The VIEW regimen, which falls within the scope of the 572 patent claims 1, 26, and 29, included 3 loading doses plus 5 doses in the extended dosing phase = 8 injections in the first year. The relevant phase 2 regimen included 4 monthly loading doses plus 1.6 on average during the PRN phase = 5.6 injections in the first year.

635. Dependent claims 5, 11, and 27 depend from claims 3, 10, and 26, respectively, and each recites "wherein only two secondary doses are administered to the patient."

636. As illustrated in my modified Figure 1 of the 572 patent above, which exemplifies a regimen falling within the scope of claims 1, 26, and 29, and the claims that depend therefrom, Dixon discloses the elements of claims 5, 11, and 27 through its disclosure of the VIEW Phase 3 2Q8 treatment arm: "an 8 week dosing interval (following three monthly doses)," (i.e., an 8 week dosing interval after an initial dose and 2 "secondary" doses administered at monthly/4-week intervals). (Dixon, 1576). The other VIEW references likewise disclose the subject matter recited in claims 5, 11, and 27. (*See, e.g.*, Adis, 263; NCT 795, 8; NCT 377, 6; 4-28-2008 Regeneron Press Release, 1; 5-8-2008 Regeneron Press Release, 1; 8-19-2008 Regeneron Press Release, 1; 9-28-2008 Regeneron Press Release, 1-2; 9-14-2009 Regeneron Press Release, 1; 11-22-2010 Regeneron Press Release, 1-2; 2009 Regeneron 10-K, 3; 3-31-2009 Regeneron 10-Q, 13; 6-30-2009 Regeneron 10-Q, 19; 9-30-2009 Regeneron 10-Q, 20; 3-31-2010 Regeneron 10-Q, 17; 6-30-2010 Regeneron 10-Q, 16; 9-30-2010 Regeneron 10-Q, 16; 5-8-2008 Bayer Press Release, 1-2; and 8-19-2008 Bayer Press Release, 3).

637. Thus, for these reasons, as well as for the reasons discussed above for claims 1, 26, and 29, it is my opinion that claims 5, 11, and 27 of the 572 patent are rendered obvious by Dixon alone and/or in combination with one or more of the other VIEW references, including at least Adis, NCT-377, and NCT-795.

d. Dependent claims 6-7 and 12-13 are obvious over Dixon and the other VIEW references.

638. I was asked to review claims 6-7 and 12-13 of the 572 patent and compare them to the disclosures of the prior art.

639. Dependent claims 6 and 12 depend from claims 3 and 10, respectively, and each requires that the "aflibercept is formulated as an isotonic solution." Dependent claims 7 and 13 depend from claims 3 and 10, respectively, and each requires that the "aflibercept is formulated with a nonionic surfactant."

640. As discussed above, each and every element of the claims upon which claims 6, 7, 12, and 13 depend is disclosed by Dixon and each of the other VIEW references. It is my opinion, including based upon the opinions I have reviewed by Dr. Rabinow, whose experience in this regard I defer to, that the added claim elements of using an isotonic formulation in the eye, and using a nonionic surfactant in the formulation, would have been obvious to a person of ordinary skill in the art in view of the prior art teachings on ophthalmic preparations.

641. As also noted above, it is my opinion that the recitations in claims 6-7 and 12-13 do not distinguish the claims from the prior art. Again, I defer to Dr. Rabinow and his opinions regarding, among other things, the LUCENTIS and EYLEA formulations, as well as the disclosures of Dixon, Hecht, and the 261 patent. Also, in my experience, the formulation described in the FDA approved label is the one used in a drug's phase 3 clinical trials. I also am not aware of any confidentiality restrictions that would have rendered the formulation used in the clinical trials confidential. Indeed, Dixon refers to aflibercept/VEGF Trap-Eye as being formulated in a manner that is "suitable for the comfortable, non-irritating, direct injection into the eye." (Dixon, 1575). Accordingly, and in the absence of any evidence to the contrary, it is my opinion that the VIEW references' disclosure of the VIEW clinical trial inherently disclosed the subject matter in claims 6-7 and 12-13.

642. Thus, a person of ordinary skill in the art would have been motivated to formulate aflibercept suitable for intravitreal injection, and I understand that Dr. Rabinow has described such formulations, and guidance in formulating such compositions, as existing in the prior art.

643. Thus, for these reasons, and relying on Dr. Rabinow's opinions regarding the formulation subject matter, as well as for the reasons discussed above, it is my opinion that claims 6-7 and 12-13 of the 572 patent are rendered obvious over Dixon alone, or in view of Hecht and/or the 261 patent.

e. Dependent claim 14 is obvious over Dixon and the other VIEW references.

644. Claim 14 depends from claim 1 and recites "wherein exclusion criteria for the patient include both of: (1) active ocular inflammation; and (2) active ocular or periocular infection."

645. I have set forth above the disclosures in Dixon that I believe anticipate and render obvious each of the asserted claims of the 572 patent, and I incorporate those disclosures herein. In my opinion, claim 14 of the 572 patent also is 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).

646. 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." (Dixon, 1577). Similarly, Heimann 2007 discloses that the "potentially sight-threatening complications of injections are intraocular inflammation." (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.

647. The exclusion of patients having infected and/or inflamed eyes in the LUCENTIS clinical trials (MARINA/ANCHOR) was expressly disclosed in Rosenfeld-2006. (Rosenfeld 2006, Appx., 2-3 (Table 1)). 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.*). Heimann 2007 similarly discloses the exclusion of "patients with suspected bacterial infections of the anterior segment (e.g., blepharitis conjunctivitis)" from intravitreal injections generally. (Heimann 2007, 85; *id.*, 69 ("Potentially sight-threatening complications of injections are intraocular inflammation….")).

648. 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). (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. (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)).

649. 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.

650. 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. (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***." (*Id.*, 1574 (emphasis added)).

651. 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. (Dixon, 1576). Consequently, a person of ordinary skill in the art 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.

652. Accordingly, it is my opinion that the disclosures of Dixon in combination with the disclosures of Rosenfeld 2006 or Heimann 2007, along with the knowledge of a person of ordinary skill in the art, make claim 14 obvious.

f. Dependent claim 30 is obvious over Dixon and the other VIEW references.

653. Claim 30 depends from claim 29 and thus incorporates the elements of claim 29. The reasons why claim 29 is obvious and/or anticipated are incorporated by reference. Claim 30 further requires that "wherein maintenance of visual acuity means loss of less than 15 letters Best Corrected Visual Acuity (BCVA) as measured by using the Early Treatment Diabetic Retinopathy Study (ETDRS) letter score."

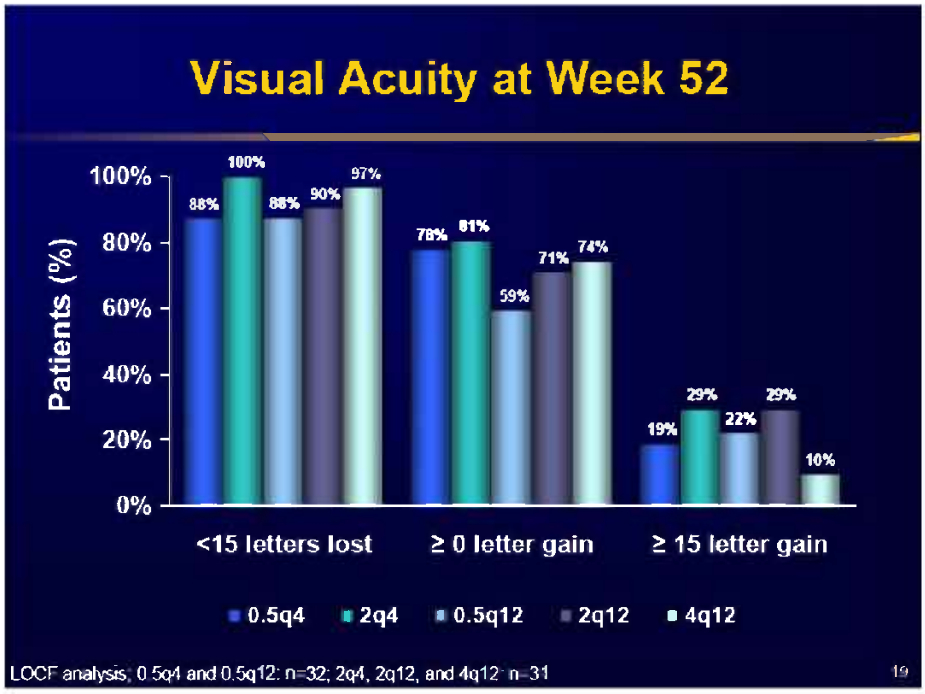
654. In my opinion, the recited BCVA criteria are commonly used outcome measures in clinical trials assessing patients with angiogenic eye disorders who are receiving anti-VEGF treatment, and thus represent nothing more than the intended result of those trials, or the natural result flowing from those clinical trials. (*See, e.g.*, Nguyen 2009a, 2141-43, 2145-46; Dixon, 1575-76; Heier 2009A, 45; Brown 2006, 1433; Rosenfeld 2006, 1420 & Suppl. App'x).

655. In addition, I have been informed that Mylan is taking the legal position that the claim elements directed to a gain in BCVA, including BCVA gains according to ETDRS letter score, constitute non-limiting statements of intended results, and thus are not entitled to patentable

weight. Indeed, there is nothing in the claims that instruct how to achieve the visual acuity measures recited in the claims. The claims merely recite a prior art dosing regimen, and then recite commonly used visual acuity metrics. But there are no modifications or adjustments to the dosing regimen included in the claims. However, I also have been asked my opinion about the recited BCVA criteria in claims 2-4 and 8-10, in the event that the subject matter of those claims is later given patentable weight. Regardless of whether the BCVA elements are considered in the patentability analysis, they are expressly set forth in the prior art.

656. For example, the VIEW References identify losing <15 ETDRS letters as a metric in assessing AMD treatment, including as a primary end point for the VIEW trials. (*See, e.g.*, NCT 377, 6 ("a subject is classified as maintaining vision if the subject has lost fewer than 15 letters on the ETDRS chart compared to baseline"); Heier 2012, 4 ("The primary end point analysis was noninferiority of the intravitreal aflibercept regimens to ranibizumab in the proportion of patients maintaining vision at week 52 (losing <15 ETDRS letters; per protocol data set) in each study"); 9-14-2009 Regeneron Press Release, 1 ("Maintenance of vision is defined as losing fewer than three lines (equivalent to 15 letters) on the ETDRS chart.")). Therefore, a person of ordinary skill in the art reading each of the VIEW References would have understood and been aware of the clinical trial endpoints identified for those trials.

657. A person of ordinary skill in the art would have had a reasonable expectation of success in achieving the claimed metric. The results of the VEGF Trap-Eye Phase 2 AMD trial show that 100% of the patients in the monthly loading dose/PRN arm exhibited fewer than 15 letters lost at week 52:



(Retina Society Meeting Presentation, 19). As such, a person of ordinary skill in the art would have had a reasonable expectation of success at meeting the BCVA criteria set forth in claim 30 when using the recited regimen, in light of the positive VEGF Trap-Eye Phase 1 and Phase 2 AMD trial results reported in the prior art. Moreover, Regeneron's experts in another venue have derided the loss of 15 or fewer letters metric as not indicative of an effective treatment, indicating that reaching such a threshold is not a high bar to meet, especially after the 2006 approval of Lucentis. (IPR Declaration of Dr. D. Brown, ¶¶ 41-42 [IPR2021-00881]).

658. Further, a person of ordinary skill in the art would have understood from the prior art that the best corrected visual acuity (or BCVA) letter measure is an obvious choice to use when assessing patients in clinical trials relating to angiogenic eye disorder treatments. (*See, e.g.*, Dixon, 1575-76; Heier 2009 at 45; Brown 2006 at 1433; Rosenfeld 2006 at 1420 & Suppl. App'x; *see generally* Nguyen 2009a).

659. Accordingly, for at least these reasons, along with those discussed above for claim 29, it is my opinion that claim 30 is obvious, in light of the knowledge of the person of ordinary skill in the art at the time.

4. Claims 15-23 and 25 of the 572 patent are obvious over the prior art.

660. I was asked to review claims 15-23 and 25 of the 572 patent, and compare them to the disclosures of the prior art.

661. As discussed above, it is my opinion that each of these Asserted Claims of the 572 patent is anticipated by the prior art. I incorporate my anticipation discussion, including my element-by-element claim analysis presented above, and I will refer to those discussions with respect to my opinions regarding the obviousness of those claims.

a. Independent claim 15 of the 572 patent is obvious in view of the 9-14-2009 Regeneron Press Release and optionally the Phase 1 and/or Phase 2 DME References.

662. I was asked to review claim 15 of the 572 patent and compare it to the disclosures of the prior art, including the 9-14-2009 Regeneron Press Release.

663. Independent claim 15 recites: "A method of treating diabetic macular edema in a patient in need thereof comprising sequentially administering to the patient a single initial dose of 2 mg of aflibercept, followed by one or more secondary doses of 2 mg of aflibercept, followed by one or more tertiary doses of 2 mg of aflibercept; wherein each secondary dose is administered to the patient by intravitreal injection approximately 4 weeks following the immediately preceding dose; and wherein each tertiary dose is administered to the patient by intravitreal injection approximately 8 weeks following the immediately preceding dose."

664. For the reasons discussed above, that discussion incorporated herein, it is my opinion that the 9-14-2009 Regeneron Press Release discloses every element of the claimed method(s) and thus anticipates claim 15 of the 572 patent. In addition, claim 15 is rendered

obvious by references disclosing the VEGF Trap-Eye Phase 2 DME clinical trial alone, or in combination with references disclosing the results of the VEGF Trap-Eye Phase 1 DME clinical trial, because the claimed regimen is nothing more than an obvious embodiment of the disclosed regimens.

665. The claimed regimen of sequentially administering to the patient a single initial dose of 2 mg of aflibercept, followed by one or more secondary doses of 2 mg of aflibercept in monthly intervals, followed by one or more tertiary doses of 2 mg of aflibercept in every-8-week intervals would have been obvious in view of the phase 2 dosing regimens disclosed in the 9-14-2009 Regeneron Press Release.

666. The 9-14-2009 Regeneron Press Release discloses that VEGF Trap-Eye (aflibercept) is a drug intended for intravitreal administration. (9-14-2009 Regeneron Press Release, 1). The press release also discloses a phase 2 clinical trial in which aflibercept is administered to patients with diabetic macular edema (DME) in 2 mg doses for three monthly loading doses. (*Id.*, 2). After the three monthly loading doses, patients are dosed with 2 mg monthly, 2 mg every-eight-weeks, or 2 mg on an as-needed (PRN) basis. (*Id.*).

667. A person of ordinary skill in the art would have been motivated to use the 2Q8 regimen disclosed for DME in the 9-14-2009 Regeneron Press Release in view of the desire among practicing physicians to reduce dosing frequency of anti-VEGF regimens, which the press release acknowledges. (9-14-2009 Regeneron Press Release, 1 ("monthly office visits and examinations [] are inconvenient for these often elderly patients")).

668. In addition, the person of ordinary skill in the art would have had a reasonable expectation of success in view of the results observed in the Phase 1 VEGF Trap-Eye DME trial, in which patients receiving a single intravitreal injection of VEGF Trap-Eye experienced

improvements in BCVA and retinal thickness. (*See, e.g.*, Do 2007, 1; Do 2009, 147-48; Lalwani 2009b, 46 (phase 1 DME study "resulted in a statistically significant reduction in central retinal thickness of approximately 100 μm by 2 weeks which was maintained through 6 weeks" and the "improvement in visual acuity ranged between 2.6 to 6.8 letters at the 6 week time point")). For example, Do 2007 discloses that a single intravitreal dose of VEGF Trap in DME patients resulted in improvements in BCVA, ranging from 6 to 10 letters, at 4 weeks post-injection. (Do 2007, 1; *see also* Do 2009, 148 ("This is the first report of the effects of VEGF Trap-Eye in patients with DMO and the results are consistent with expectations.")). A person of ordinary skill in the art also would have had a reasonable expectation of success based on the phase 2 AMD clinical trial results, which demonstrated successful blockade of VEGF in another angiogenic eye disorder, AMD. (Dixon, 1575-76; Heier 2009A, 45).

669. In the event that claim 15 has a July 2013 priority date, as discussed above, a person of ordinary skill in the art also would have had a reasonable expectation of success in view of the results observed in the Phase 2 VEGF Trap-Eye DME trial, in which patients experienced improvements in BCVA and retinal thickness. (*See, e.g.*, Do 2012, Abstract (reporting the proportion of patients gaining greater than 15 letters); Tolentino 2011, 1-2; 2-18-2010 Regeneron Press Release, 1).

670. For at least the reasons discussed above, claim 15 is obvious in view of the 9-14-2009 Regeneron Press Release alone or in combination with references disclosing the results of the VEGF Trap-Eye Phase 1 and/or Phase 2 DME clinical trials, and the knowledge of a person of ordinary skill in the art.

b. Dependent claims 16-17 and 20-21 are obvious.

671. I have been asked to review claims 16-17 and 20-21 of the 572 patent and compare them to the disclosures of the prior art, including the 9-14-2009 Regeneron Press Release.

672. Dependent claims 16-17 and 20-21 of the 572 patent recite various visual acuity outcomes, including the timepoint at which visual acuity is to be measured. Claims 17 and 21 each depend from claim 16, which itself depends from independent claim 15, and each of claims 17 and 21 further requires that the patient gain a specific number of letters according to the ETDRS letter score—specifically, requiring a gain of "at least 9 letters" (claim 17) and "at least 8 letters" (claim 21). Claim 16 depends from independent claim 15, a requires that the patient achieve any "gain in visual acuity within 52 weeks following the initial dose." Claim 20 depends from claim 17 and requires that the patient achieve a gain of at least 9 letters "within 24 weeks following the initial dose."

673. I have been informed that Mylan is taking the legal position that the visual acuity elements recited in claims 16-17 and 20-21 constitute statements of intended results of the claimed methods that do not result in a manipulative difference in the steps of the claim, and thus should be deemed non-limiting. Furthermore, in my opinion, the recited BCVA criteria are commonly used outcome measures in clinical trials assessing patients suffering from angiogenic eye disorders who are receiving anti-VEGF treatment, and thus represent nothing more than the intended result of those trials, or the natural result flowing from those clinical trials. (*See, e.g.*, Nguyen 2009a, 2141-43, 2145-46; Dixon, 1575-76; Heier 2009A, 45; Brown 2006, 1433; Rosenfeld 2006, 1420 & Suppl. App'x). Indeed, there is nothing in the claims that instruct how to achieve the visual acuity measures recited in the claims. The claims merely recite a prior art dosing regimen, and then recite commonly used visual acuity metrics. But there are no modifications or adjustments to the dosing regimen included in the claims.

674. I incorporate my arguments above that claims 16-17 and 20-21 are anticipated by prior art disclosing Regeneron's Phase 2 DME trial, including the 9-14-2009 Regeneron Press

Release. As noted above, achieving "a gain in visual acuity," including a gain of 8 letters by week 24, or 9 letters by week 52, would have been a natural result flowing from the operation of the claimed dosing regimen, and an inherent aspect of that regimen. (*See* 9-14-2009 Regeneron Press Release, 1; *see also, e.g.*, Do 2011, 1822 & Fig. 3 (93% of patients in the 2Q8 arm exhibiting ≥ 0 letter gain, thus confirming that the claimed visual acuity gains were a result naturally flowing from the operation of the prior art dosing regimen)). Because the therapeutic effect inherently resulted from operation of the prior art regimens, claims 16-17 and 20-21 are both anticipated and obvious over the prior art.

675. In addition, claims 16-17 and 20-21 are made obvious by the 9-14-2009 Regeneron Press Release alone, or in combination with references disclosing the results of the VEGF Trap-Eye DME Phase 1 and/or Phase 2 clinical trials. For example, Do 2009 reports that a single intravitreal dose of aflibercept resulted in an average of 9 letters in ETDRS score gained after one month. (Do 2009, 146; *see also id.*, 148 ("This is the first report of the effects of VEGF Trap-Eye in patients with DMO and the results are consistent with expectations.")). Thus, the person of ordinary skill in the art would have had a reasonable expectation of success in view of the results observed in the Phase 1 VEGF Trap-Eye DME trial, in which patients receiving a single intravitreal injection of VEGF Trap-Eye experienced improvements in BCVA and retinal thickness. A person of ordinary skill in the art also would have had a reasonable expectation of success based on the phase 2 AMD clinical trial results, which demonstrated successful blockade of VEGF in another angiogenic eye disorder, AMD. (Dixon, 1575-76; Heier 2009A, 45).

676. The reasonable expectation of success also would have come from the combination of highly relevant data that was in the public domain at the time showing that (1) aflibercept was effective at treating AMD after a series of monthly loading doses, followed by less frequent dosing

(Dixon, 1576); (2) ranibizumab was effective at treating both AMD and DME (Rosenfeld 2006, 1426; Lalwani 2009b, 45-46). For example, a person of ordinary skill in the art also would have had a reasonable expectation of success in view of the data that was emerging from the ranibizumab DME clinical trials, as well as the reported primary outcome measure of the ranibizumab RISE and RIDE clinical studies and the reports from other clinical trials regarding "greater-than-15-letter gainers." (Lalwani 2009b, 46).

677. Further, a person of ordinary skill in the art would have understood from the prior art that the BCVA letter measure is an obvious choice to use when assessing clinical trials relating to angiogenic eye disorder treatments. (*See, e.g.*, 9-14-2009 Regeneron Press Release; Dixon, 1575-76; Heier 2009, 45; Brown 2006, 1433; Rosenfeld 2006, 1420 & Suppl. App'x).

678. For at least these reasons, as well as those discussed above for claim 15, it is my opinion that claims 16-17 and 20-21 are obvious in view of the 9-14-2009 Regeneron Press Release alone, or in combination with Do 2009 and/or Dixon, in view of the knowledge of a person of ordinary skill in the art.

c. Dependent claims 18-19 and 22-23 are obvious.

679. I was asked to review claims 18-19 and 22-23 of the 572 patent and compare them to the disclosures of the prior art.

680. Claims 18-19 depend from claim 17, and claims 22-23 depend from claim 21. Dependent claims 18 and 22 each requires that the "aflibercept is formulated as an isotonic solution." Dependent claims 19 and 23 each requires that the "aflibercept is formulated with a nonionic surfactant."

681. As discussed above, each and every element of the claims upon which claims 18-19 and 22-23 depend is disclosed by Dixon and each of the other VIEW references. It is my opinion, including based upon the opinions I have reviewed by Dr. Rabinow, whose experience in

this regard I defer to, that the added claim elements of using an isotonic formulation in the eye, and using a nonionic surfactant in the formulation, would have been obvious to a person of ordinary skill in the art in view of the prior art teachings on ophthalmic preparations.

682. As also noted above, it is my opinion that the recitations in claims 18-19 and 22-23 do not distinguish the claims from the prior art. Again, I defer to Dr. Rabinow and his opinions regarding, among other things, the LUCENTIS and EYLEA formulations, as well as the disclosures of Dixon, Hecht, and the 261 patent. Also, in my experience, the formulation described in the FDA approved label is the one used in a drug's phase 3 clinical trials. I also am not aware of any confidentiality restrictions that would have rendered the formulation used in the clinical trials confidential. Indeed, Dixon refers to aflibercept/VEGF Trap-Eye as being formulated in a manner that is "suitable for the comfortable, non-irritating, direct injection into the eye." (Dixon, 1575). Accordingly, and in the absence of any evidence to the contrary, it is my opinion that the VIEW references' disclosure of the VIEW clinical trial inherently disclosed the subject matter in claims 18-19 and 22-23.

683. Thus, a person of ordinary skill in the art would have been motivated to formulate aflibercept suitable for intravitreal injection, and I understand that Dr. Rabinow has described such formulations, and guidance in formulating such compositions, as existing in the prior art.

684. Thus, for these reasons, and relying on Dr. Rabinow's opinions regarding the formulation subject matter, as well as for the reasons discussed above, it is my opinion that claims 18-19 and 22-23 of the 572 patent are rendered obvious over Dixon alone, or in view of Hecht and/or the 261 patent.

d. Dependent claim 25 is obvious in view of the 747 patent and 9-14-2009 Regeneron Press Release alone, or in combination with Do 2009.

685. Claim 25 is drawn to the dosing regimen of claim 15, "wherein four secondary doses are administered to the patient."

686. As noted above, the 9-14-2009 Regeneron Press Release discloses each and every element of claim 25 of the 572 patent. I incorporate and will refer to that discussion with respect to my obviousness opinions. In my opinion, in addition to being anticipated, claim 25 is also obvious over the prior art references and combinations discussed below.

687. In addition, the 747 patent discloses a method of treating eye disorders, including diabetic retinopathy ("DR"). (747 patent, Title, Abstract, 1:49-54, 2:9-35, 5:39-51, 6:8-24, 6:64 – 7:3). One of the complications associated with diabetic retinopathy is retinal edema (i.e., diabetic macular edema ("DME"). The 747 patent also discloses treatment with VEGFR1R2-FcΔC1(a)) (i.e., VEGF Trap-Eye or aflibercept). (747 patent, SEQ ID NO:6, 2:1-2, 2:9-35, 5:28-51, 7:5-63). The 747 patent further discloses intravitreal administration of the VEGF trap protein, and treatment with 25-4000 micrograms of the VEGF trap (i.e., 2 mg). (747 patent, 2:9-35; 7:5-63; 20:15-67; 21:1-22:42).

688. In my opinion, the additional element "wherein four secondary doses are administered to the patient" does not distinguish the claim from the prior art, which disclosed such regimens. For example, the 9-14-2009 Regeneron Press Release discloses VEGF Trap-Eye (aflibercept) as a drug intended for intravitreal administration. (9-14-2009 Regeneron Press Release, 1). The press release also discloses a phase 2 clinical trial in which aflibercept is administered to DME patients in 2 mg doses for 3 monthly loading doses. (*Id.*, 2). After the three monthly loading doses, patients are treated with fixed every-8-week injections or PRN (i.e., as needed) injections. (*Id.*).

689. A regimen of 5 monthly loading doses would have been obvious in view of the phase 2 dosing regimen. For example, from the positive results of the phase 1 DME trial, and the disclosed dosing regimens of the phase 2 clinical trial, a person of ordinary skill in the art would have been motivated to identify an optimal dosing regimen for the treatment of DME patients. In my experience, identifying an optimum dosing regimen for a VEGF antagonist such as aflibercept is a matter of routine optimization. A person of ordinary skill in the art would have been motivated to try a range of monthly loading doses, especially since a series of monthly loading doses followed by extended PRN/treat-and-extend dosing was the industry standard and that was the approach being used, with success, by those in clinical practice. (*See, e.g.*, Retinal Physician 2007, MYL-AFL0090401; *id.*, MYL-AFL0090402-03).

690. I am aware that Regeneron was experimenting with 1, 3, and 4 monthly loading doses in its aflibercept clinical trials. For example, Regeneron tried 1 and 4 monthly loading doses in its phase 2 AMD trials, (*see, e.g.*, Dixon, 1576; 9-14-2009 Regeneron Press Release, 2); and 3 monthly loading doses in its phase 2 DME and phase 3 VIEW trials, (*see, e.g.*, 9-14-2009 Regeneron Press Release, 1, 2).

691. This also is consistent with internal Regeneron documents that indicated it was focusing its aflibercept DME program on no more than 3-6 monthly loading doses. (RGN-EYLEA-MYLAN-00631452 at -53; *see also* RGN-EYLEA-MYLAN-00495620 at -22 ("# loading doses (3 vs. 6 for 2q8)")). Regeneron also used the phase 2 AMD CLEAR-IT-2 clinical trial results to guide its design of the phase 3 DME trial, explaining to EU authorities that:

> Other intravitreal anti-VEGF therapies (Macugen, Avastin, Lucentis) that are commonly used for AMD have suggested efficacy of this therapeutic principle also in treating DME in Phase I/II studies and investigator initiated studies. This is further supported by Phase III studies recently initiated by Genentech for their product ranibizumab in DME patients. Most notably the doses employed in these studies (0.3 and 0.5 mg given monthly) are the same doses which are used in the AMD indication.

(RGN-EYLEA-MYLAN-00531609 at -614). Regeneron continues, stating that:

> Based on this experience we believe that the doses and dosing intervals for VEGF Trap-Eye for Phase III in DME can be selected based on the results of the Phase II study in patients with AMD (OD-0508, see Investigators Brochure, Vol. 14 , pg. 14) In this study, several doses of VEGF Trap-Eye have been assessed in 30 patients / treatment arm. The results suggested that 0.5mg VEGF Trap-Eye is effective in suppressing retinal edema if injected monthly and that 2mg are sufficient to suppress retinal edema for up to 8 weeks. We consider this Phase 2 study as providing an adequate basis for dose selection for the Phase 3 DME program and propose to use the 0.5mg dose in 4-weekly and the 2mg dose in 8-weekly intervals in the planned Phase 3 study (see outline of proposed Phase 3 studies in DME, Vol. 14 , pg. 14).

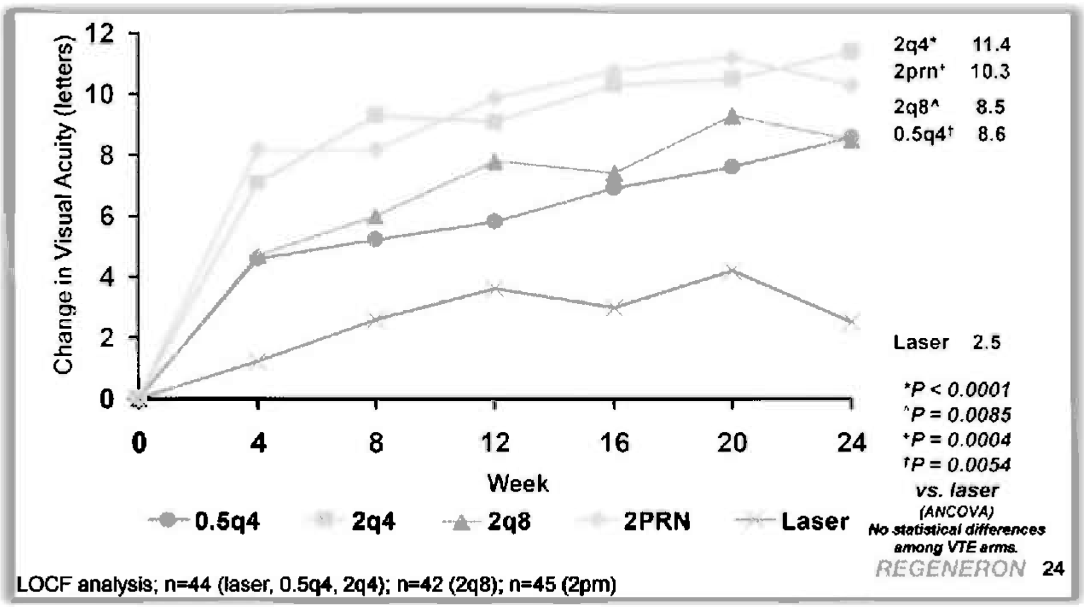
(RGN-EYLEA-MYLAN-00531609 at -614). In other words, Regeneron was relying on publicly available data and selecting an every-8-week dosing regimen that was already in the public domain for its phase 3 DME clinical trials. The selection of the 5 monthly loading doses was a matter of routine optimization, which began with Regeneron confining itself, as early as 2007/2008 to the use of 3-6 monthly loading doses. (*See, e.g.*, RGN-EYLEA-MYLAN-00631452 at -53; RGN-EYLEA-MYLAN-00531609 at -615 ("During an induction phase, VEGF Trap-Eye is administered by up to 6 intravitreal injections at intervals of 4 or 8 weeks until resolution of macular edema.")).

692. Further, in my clinical experience, DME patients tend to require more loading doses (compared to AMD patients) to achieve satisfactory retinal thickness and/or visual acuity measures.

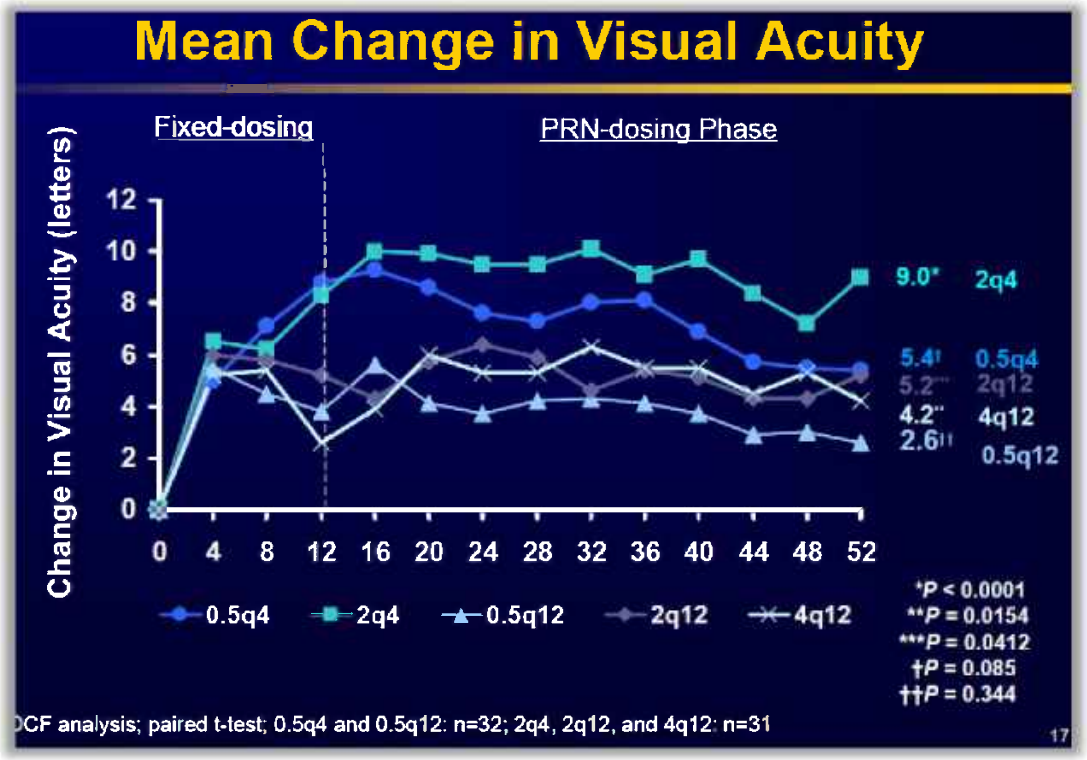
693. Thus, in my opinion, putting DME patients on 4 or 5 monthly loading doses rather than 3 would have been obvious to try when conducting routine optimization of a loading dose regimen for DME. This is confirmed by my review of the data that came out of the phase 2 DA VINCI DME clinical trial.

694. For example, as Regeneron was designing its VIVID and VISTA phase 3 clinical trials in DME in which 5 monthly loading doses were to be tested, they had available to them the

data from the phase 2 DME DA VINCI trial. A person of ordinary skill in the art would have immediately noticed that the DA VINCI 2Q8 arm patient group exhibited a lengthier time to plateau than what would have been observed with AMD. For example, I reviewed information from a March 2010 slide presentation provided by Regeneron. Therein, data from the DA VINCI DME clinical trial revealed that it was taking 5-6 months for patients to near a plateau of visual acuity gains:



(RGN-EYLEA-MYLAN-00585880 at -909). Contrast this with the results from the AMD phase 2 clinical trial using the same dosage (2 mg) and a similar loading dose scheme:



(Retina Society Meeting Presentation, 17). What is evident from these two sets of data is that DME appears more resistant to treatment than AMD, which also is consistent with observations I've made within my own practice. As a result, DME patients were taking longer to approach plateau. From this data, in my opinion, it is a matter of routine optimization to adjust upward the number of monthly loading doses if a patient is presenting with a more difficult to treat condition (e.g., DME), or taking longer to show a response to treatment. Thus, it is an obvious and routine matter to arrive at a particular number of loading doses.

695. In any event, Regeneron documents reveal that business/commercial concerns also were important in Regeneron's decision to implement 5 monthly loading doses for the treatment of DME. For example, a January 26, 2011 presentation of Bayer and Regeneron discusses their DME clinical plan and suggests that the selection of 5 loading doses for the DME trial was the

result of "a compromise" between Regeneron and Bayer, deemed "acceptable from a commercial/market access perspective." (RGN-EYLEA-MYLAN-00513418 at 424).

696. Further, in my opinion, a person of ordinary skill in the art would have had a reasonable expectation of success at using 5 monthly loading doses in light of the positive phase 1 DME clinical trial results seen with a single intravitreal dose of aflibercept. For example, Do 2009 reports that a single intravitreal dose of aflibercept resulted in an average of 9 letters in ETDRS score gained after one month. (Do 2009, 146). The reasonable expectation of success also would have come from the combination of highly relevant data that was in the public domain at the time showing that (1) aflibercept was effective at treating AMD after a series of monthly loading doses, followed by less frequent dosing (Dixon, 1576); (2) ranibizumab was effective at treating both AMD and DME (Rosenfeld 2006, 1426; Lalwani 2009b, 45-46). Indeed, as I discuss above, Regeneron itself was deriving its DME clinical trial strategy from what already had been learned from the aflibercept AMD phase 2 results and ranibizumab DME results.

697. For at least the reasons discussed above, claim 25 is obvious in view of the 747 patent and 9-14-2009 Regeneron Press Release alone or in combination with Do 2009, and the knowledge of a person of ordinary skill in the art.

e. Dependent claim 25 is obvious in view of the 9-14-2009 Regeneron Press Release alone, or in combination with the Lucentis art.

698. I was asked to review claim 25 of the 572 patent and compare it to the disclosures of the prior art, including the 9-14-2009 Regeneron Press Release and the Lucentis art.

699. For example, the 9-14-2009 Regeneron Press Release discloses VEGF Trap-Eye (aflibercept) as a drug intended for intravitreal administration. (9-14-2009 Regeneron Press Release, 1). The press release also discloses a phase 2 clinical trial in which aflibercept is administered to patients with diabetic macular edema (DME) in 2 mg doses for three monthly

loading doses. (*Id.*, 2). After the monthly loading doses, patients are treated with fixed every-8-week injections or PRN (i.e., as needed) injections. (*Id.*).

700. Shortly after Regeneron had initiated its phase 2 DME clinical trial, data emerged from Lucentis clinical trials in DME. The Lucentis clinical trial data revealed that patients treated with 0.5 mg on a monthly loading regimen achieved very similar BCVA scores as those observed in the Lucentis AMD trials. For example, in Lalwani 2009b, the author reported on data emerging from the clinical study Ranibizumab for Edema of the Macula in Diabetes (READ 1). (Lalwani 2009b, 45). Lalwani 2009b discloses the design of the study, including the dosing regimen, which involved injections at baseline, and months 1, 2, 4, and 6 (i.e., 3 monthly loading doses followed by every 8 week dosing). (Lalwani 2009b, 45). The author further reports that at 12 months, the DME patients receiving ranibizumab had achieved, on average, a gain of 8 letters of visual acuity. (Lalwani 2009b, 45). The author further notes that the READ 2 program that followed READ 1 employed monthly dosing through 12 months, and the ranibizumab-only arm achieved mean gains of 6.46 letters. (Lalwani 2009b, 45-46).

701. In other words, Lucentis was showing that the treatment of AMD and DME can be accomplished to similar effect with similar regimens and the same amount of anti-VEGF agent.

702. However, a person of ordinary skill in the art also would have appreciated that the treatment of DME differed from AMD in at least one aspect.

703. For example, the author references the theory circulating among physicians at the time that VEGF was particularly elevated in DME compared to AMD, and thus may require more aggressive treatment. (Lalwani 2009b, 46). This also is consistent with the presentation of the RESOLVE trial data set forth in Lalwani 2009b, which showed a shallower curve to reach plateau levels of mean visual acuity than that observed with AMD in, for example, the MARINA and

ANCHOR trials. (Lalwani 2009b, 46; *see also, e.g.*, Rosenfeld 2006, 1426). For example, one can compare the RESOLVE DME data in Lalwani 2009b:

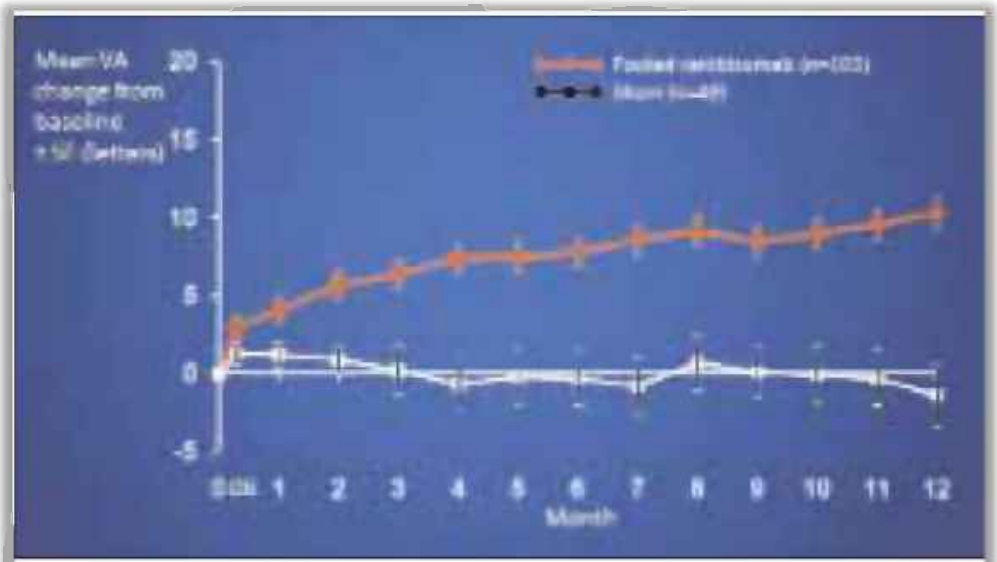
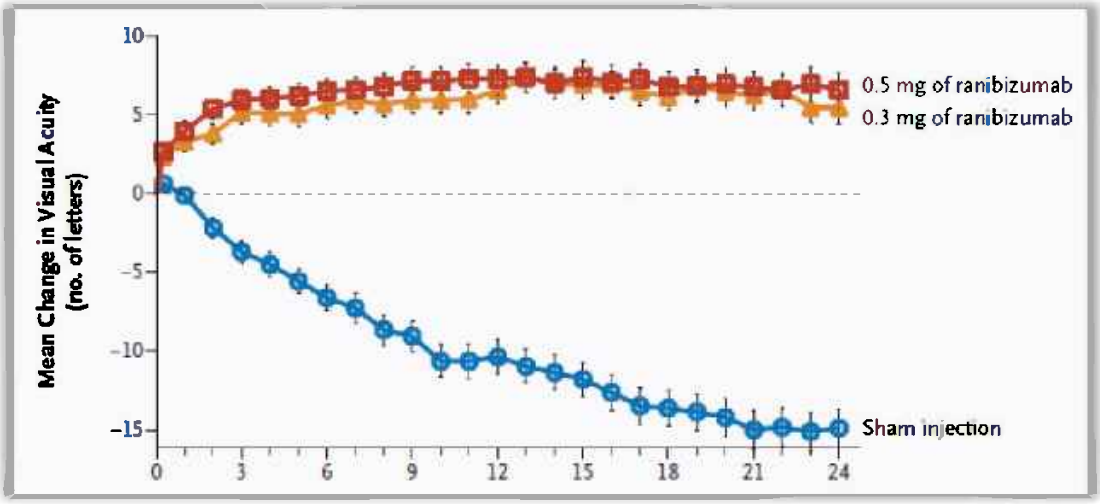


Figure 2. Visual acuity results at 1 year for the RESOLVE Trial.

(Lalwani 2009b, 46), with the data in Rosenfeld 2006 for AMD:



(Rosenfeld 2006, 1426). As discussed above, it is evident from these two sets of data that DME appears more resistant to treatment than AMD, which also is consistent with observations I've made within my own practice, and consistent with Lalwani 2009b's reference to the theory that VEGF is more elevated in DME patients. As a result of this resistance, DME patients in the

Lucentis trials were taking longer to approach plateau when compared to AMD patients. From this data, in my opinion, a person of ordinary skill in the art would have looked to increase the number of loading doses when treating DME patients with aflibercept. Based on the data above, 5 monthly loading is an obvious and reasonable number to incorporate, especially in view of the use of 3 and 4 loading doses in the aflibercept AMD clinical trials.

704. This also is consistent with internal Regeneron documents that indicated it was focusing its aflibercept DME program on no more than 3-6 monthly loading doses. (RGN-EYLEA-MYLAN-00631452 at -53). Regeneron also used the phase 2 AMD CLEAR-IT-2 clinical trial results to guide its design of the phase 3 DME trial, explaining to EU authorities that:

> Other intravitreal anti-VEGF therapies (Macugen, Avastin, Lucentis) that are commonly used for AMD have suggested efficacy of this therapeutic principle also in treating DME in Phase I/II studies and investigator initiated studies. This is further supported by Phase III studies recently initiated by Genentech for their product ranibizumab in DME patients. Most notably the doses employed in these studies (0.3 and 0.5 mg given monthly) are the same doses which are used in the AMD indication.

(RGN-EYLEA-MYLAN-00531609 at -614). Regeneron continues, stating that:

> Based on this experience we believe that the doses and dosing intervals for VEGF Trap-Eye for Phase III in DME can be selected based on the results of the Phase II study in patients with AMD (OD-0508, see Investigators Brochure, Vol. 14 , pg. 14) In this study, several doses of VEGF Trap-Eye have been assessed in 30 patients / treatment arm. The results suggested that 0.5mg VEGF Trap-Eye is effective in suppressing retinal edema if injected monthly and that 2mg are sufficient to suppress retinal edema for up to 8 weeks. We consider this Phase 2 study as providing an adequate basis for dose selection for the Phase 3 DME program and propose to use the 0.5mg dose in 4-weekly and the 2mg dose in 8-weekly intervals in the planned Phase 3 study (see outline of proposed Phase 3 studies in DME, Vol. 14 , pg. 14).

(RGN-EYLEA-MYLAN-00531609 at -614). In other words, Regeneron was relying on available data (which was publicly available) and selecting an every-8-week dosing regimen that was already in the public domain for its phase 3 DME clinical trials. The selection of the 5 monthly loading doses was a matter of routine optimization, which began with Regeneron confining itself, as early as 2007/2008 to the use of 3-6 monthly loading doses. (*See, e.g.*, RGN-EYLEA-MYLAN-

00631452 at -53; RGN-EYLEA-MYLAN-00531609 at -615 ("During an induction phase, VEGF Trap-Eye is administered by up to 6 intravitreal injections at intervals of 4 or 8 weeks until resolution of macular edema.")).

705. Further, in my opinion, a person of ordinary skill in the art would have had a reasonable expectation of success at using 5 monthly loading doses in light of the positive DME phase 1 results seen with a single intravitreal dose of aflibercept. For example, Do 2009 reports that a single intravitreal dose of aflibercept resulted in an average of 9 letters in ETDRS score gained after one month. (Do 2009, 146). The reasonable expectation of success also would have come from the combination of highly relevant data that was in the public domain at the time showing that (1) aflibercept was effective at treating AMD after a series of monthly loading doses, followed by less frequent dosing (Dixon, 1576); (2) ranibizumab was effective at treating both AMD and DME (Rosenfeld 2006, 1426; Lalwani 2009b, 45-46). Indeed, as I discuss above, Regeneron itself was deriving its DME clinical trial strategy from what already had been learned from the aflibercept AMD phase 2 results and ranibizumab DME results.

706. Accordingly, for at least these reasons, along with those discussed above for claim 15, it is my opinion that claim 25 is obvious in view of the 9-14-2009 Regeneron Press Release alone or in combination with the Lucentis art, in light of the knowledge of a person of ordinary skill in the art at the time

f. Dependent claim 25 is obvious in view of Dixon in combination with Lalwani 2009b.

707. I was asked to review claim 25 of the 572 patent and compare it to the disclosures of the prior art, including Dixon and Lalwani 2009b.

708. For example, Dixon discloses positive results from several aflibercept clinical trials, including several phase 1 trials in both AMD and DME, and the phase 2 CLEAR-IT-2 AMD

trial. Dixon reports that in the DME study, "[t]he single injection resulted in a median decrease of central macular thickness measured by OCT of 79 μm. BCVA increased by 9 letters at 4 weeks and regressed to a 3 letter improvement at 6 weeks." (Dixon, 1575).

709. Dixon also makes note of the "multifactorial nature of DME" and discloses that phase 2 clinical studies are underway with anti-VEGF agents, including aflibercept, for the treatment of DME. (Dixon, 1577-78).

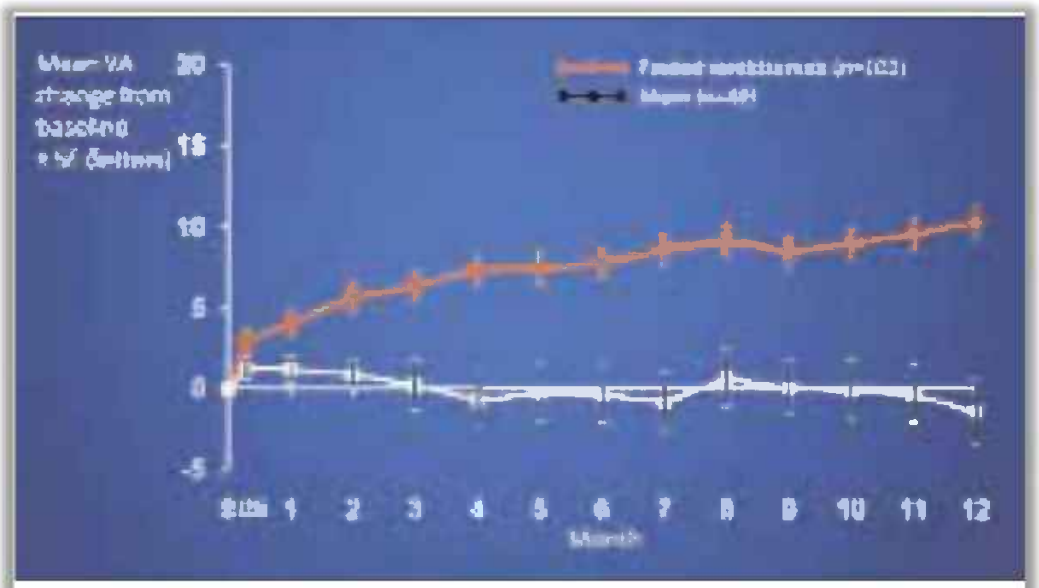
710. Dixon also discloses that aflibercept/VEGF Trap-Eye is formulated in a 2 mg presentation and for intravitreal administration. (Dixon, 1575).

711. About this same time, data emerged from Lucentis clinical trials in DME. The Lucentis clinical trial data revealed that patients treated with 0.5 mg on a monthly loading regimen achieved very similar BCVA scores as those observed in the Lucentis AMD trials. For example, in Lalwani 2009b, the author reported on data emerging from the clinical study Ranibizumab for Edema of the Macula in Diabetes (READ 1). (Lalwani 2009b, 45). Lalwani 2009 discloses the design of the study, including the dosing regimen, which involved injections at baseline, and months 1, 2, 4, and 6 (i.e., 3 monthly loading doses followed by every 8 week dosing). (*Id.*). The author further reports that at 12 months, the DME patients receiving ranibizumab had achieved, on average, a gain of 8 letters of visual acuity. (*Id.*). The author further notes that the READ 2 program that followed READ 1 employed monthly dosing through 12 months, and the ranibizumab-only arm achieved mean gains of 6.46 letters. (*Id.*, 45-46).

712. In other words, Lucentis was showing that the treatment of AMD and DME can be accomplished to similar effect with similar regimens and the same amount of anti-VEGF agent.

713. However, a person of ordinary skill in the art also would have appreciated that the treatment of DME differed from AMD in at least one aspect.

714. For example, the author references the theory circulating among physicians at the time that VEGF was particularly elevated in DME compared to AMD, and thus may require more aggressive treatment. (Lalwani 2009b, 46). This also is consistent with the presentation of the RESOLVE trial data set forth in Lalwani 2009b, which showed a shallower curve to reach plateau levels of mean visual acuity than that observed with AMD in, for example, the MARINA and ANCHOR trials. (Lalwani 2009b, 46; *see also, e.g.*, Rosenfeld 2006, 1426). For example, one can compare the RESOLVE DME data in Lalwani 2009b:



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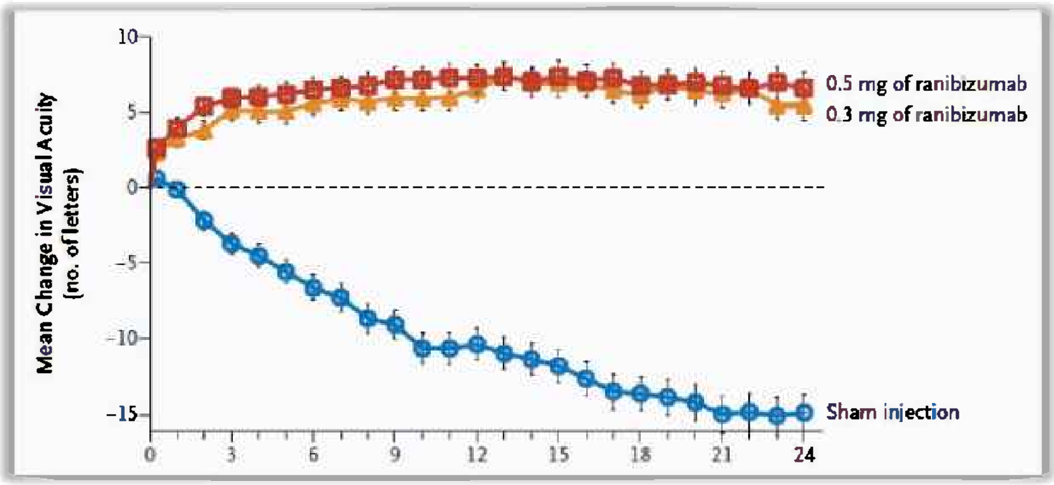


(Rosenfeld 2006, 1426). As discussed above, it is evident from these two sets of data that DME appears more resistant to treatment than AMD, which also is consistent with observations I've made within my own practice, and consistent with Lalwani 2009b's reference to the theory that VEGF is more elevated in DME patients. As a result of this resistance, DME patients in the Lucentis trials were taking longer to approach plateau when compared to AMD patients. From this data, in my opinion, a person of ordinary skill in the art would have looked to increase the number of loading doses when treating DME patients with aflibercept. Based on the data above, 5 monthly loading is an obvious and reasonable number to incorporate, especially in view of the use of 3 and 4 loading doses in the aflibercept AMD clinical trials.

715. This also is consistent with internal Regeneron documents that indicated it was focusing its aflibercept DME program on no more than 3-6 monthly loading doses. (RGN-EYLEA-MYLAN-00631452 at -53). Regeneron also used the phase 2 AMD CLEAR-IT-2 clinical trial results to guide its design of the phase 3 DME trial, explaining to EU authorities that:

> Other intravitreal anti-VEGF therapies (Macugen, Avastin, Lucentis) that are commonly used for AMD have suggested efficacy of this therapeutic principle also in treating DME in Phase I/II studies and investigator initiated studies. This is further supported by Phase III studies recently initiated by Genentech for their product ranibizumab in DME patients. Most notably the doses employed in these studies (0.3 and 0.5 mg given monthly) are the same doses which are used in the AMD indication.

(RGN-EYLEA-MYLAN-00531609 at -614). Regeneron continues, stating that:

> Based on this experience we believe that the doses and dosing intervals for VEGF Trap-Eye for Phase III in DME can be selected based on the results of the Phase II study in patients with AMD (OD-0508, see Investigators Brochure, Vol. 14 , pg. 14) In this study, several doses of VEGF Trap-Eye have been assessed in 30 patients / treatment arm. The results suggested that 0.5mg VEGF Trap-Eye is effective in suppressing retinal edema if injected monthly and that 2mg are sufficient to suppress retinal edema for up to 8 weeks. We consider this Phase 2 study as providing an adequate basis for dose selection for the Phase 3 DME program and propose to use the 0.5mg dose in 4-weekly and the 2mg dose in 8-weekly intervals in the planned Phase 3 study (see outline of proposed Phase 3 studies in DME, Vol. 14 , pg. 14).

(RGN-EYLEA-MYLAN-00531609 at -614). In other words, Regeneron was relying on available data (which was publicly available) and selecting an every-8-week dosing regimen that was already in the public domain for its phase 3 DME clinical trials. The selection of the 5 monthly loading doses was a matter of routine optimization, which began with Regeneron confining itself, as early as 2007/2008 to the use of 3-6 monthly loading doses. (*See, e.g.*, RGN-EYLEA-MYLAN-00631452 at -53; RGN-EYLEA-MYLAN-00531609 at -615 ("During an induction phase, VEGF Trap-Eye is administered by up to 6 intravitreal injections at intervals of 4 or 8 weeks until resolution of macular edema.")).

716. Further, in my opinion, a person of ordinary skill in the art would have had a reasonable expectation of success at using 5 monthly loading doses in light of the positive phase 1 results seen with a single intravitreal dose of aflibercept. For example, Do 2009 reports that a single intravitreal dose of aflibercept resulted in an average of 9 letters in ETDRS score gained after one month. (Do 2009, 146). The reasonable expectation of success also would have come from the combination of highly relevant data that was in the public domain at the time showing that (1) aflibercept was effective at treating AMD after a series of monthly loading doses, followed by less frequent dosing (Dixon, 1576); (2) ranibizumab was effective at treating both AMD and DME (Rosenfeld 2006, 1426; Lalwani 2009b, 45-46). Indeed, as I discuss above, Regeneron itself

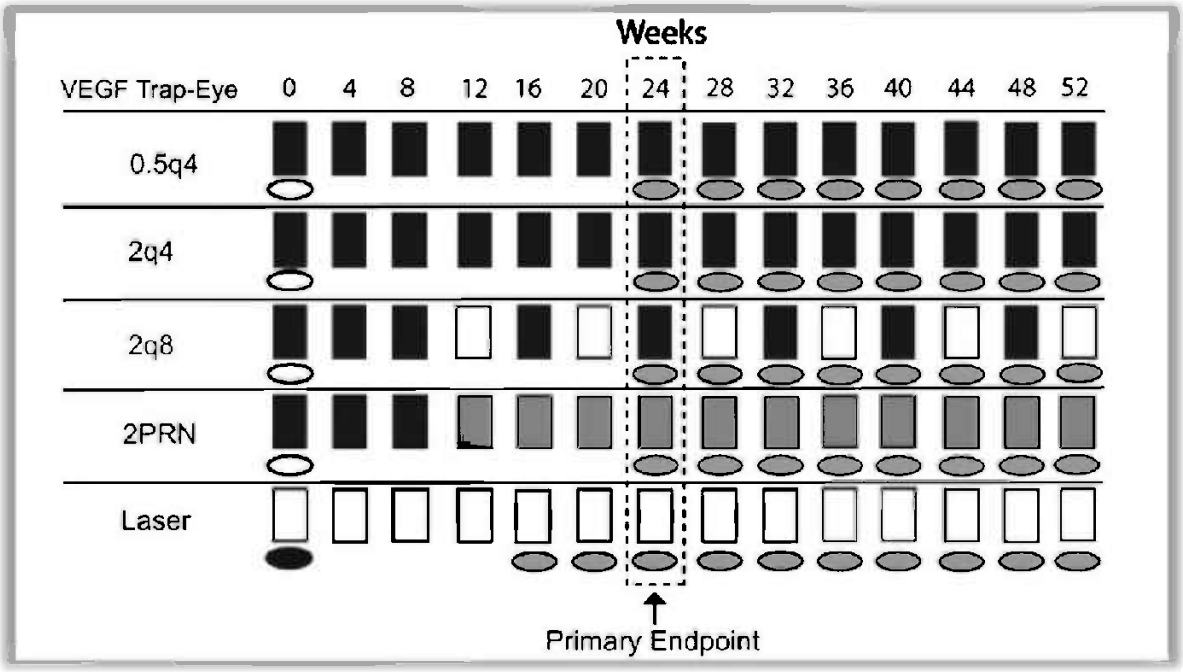
was deriving its DME clinical trial strategy from what already had been learned from the aflibercept AMD phase 2 results and ranibizumab DME results.

717. For at least these reasons, along with those discussed above for claim 15, it is my opinion that claim 25 is obvious in view of Dixon alone or in combination with Lalwani 2009b, in light of the knowledge of a person of ordinary skill in the art at the time.

g. Dependent claim 25 is obvious in view of Do 2012.

718. I was asked to review claim 25 of the 572 patent and compare it to the disclosures of the prior art, including Do 2012.[30]

719. Do 2012 discloses the treatment arms from the DA VINCI phase 2 clinical trials, with the filled black ovals indicating the visits in which injections were given:



[30] I understand that the 572 patent lists applications from 2010 and 2011 on the face of the patent. I also understand that Mylan does not believe that Regeneron is entitled to rely upon the dates of those applications, and that Mylan contends that the earliest date that Regeneron is entitled to rely upon is the date of the 370 application, filed July 12, 2013. I offer my opinions in this section based upon an assumption that the July 12, 2013 date applies.

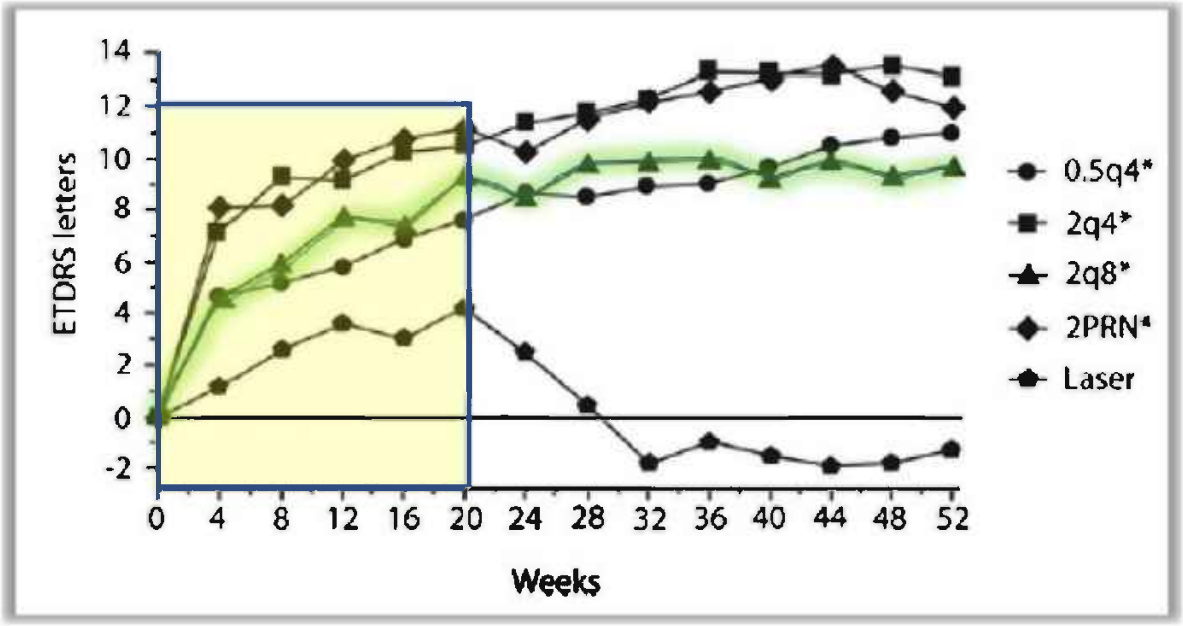
(Do 2012, 1660).

720. Do 2012 also discloses positive results from the phase 2 DME DA VINCI clinical trial. For example, Do 2012 disclosed that patients in the 2Q8 arm achieved gains of 8.5 and 9.7 BCVA letters at 24 and 52 weeks, respectively; patients in the 2Q4 arm achieved gains of 11.4 and 13.1 BCVA letters at 24 and 52 weeks, respectively; and patients in the 2PRN arm achieved gains of 10.3 and 12 BCVA letters at 24 and 52 weeks, respectively. (Do 2012, Abstract).

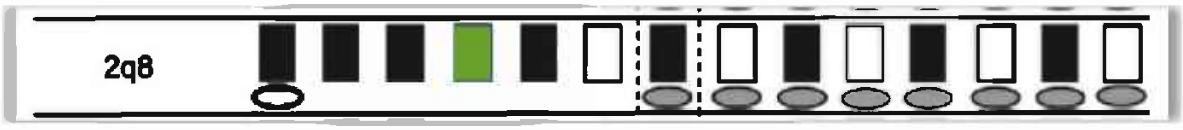
721. Further, a couple of additional data points emerged from the DA VINCI clinical trial that confirmed observations made in earlier ranibizumab trials. For example, Do 2012 reported that patients in the PRN arm received, on average, 7.4 injections over the course of the first year. (Do 2012, Table 3). Compare this to the only 5.6 injections required in the PRN arm of the AMD phase 2 CLEAR-IT-2 trial. (Dixon, 1576). This reveals, like the earlier ranibizumab studies, that DME is typically a disease that tends to be more resistant to treatment, and thus usually requires more doses earlier in the treatment regimen.

722. A person of ordinary skill in the art would have been motivated to set a dosing regimen that would be optimal for the patient they are treating, and in the case of a typical DME patient, that regimen is one which would incorporate additional monthly loading doses.

723. A person of ordinary skill in the art would have looked to the DA VINCI arms and recognized that simply including one additional monthly dose would result in 5 straight monthly doses, which, based on the clinical trial results would get patients to or very near the plateau levels observed in DA VINCI patients in the 2Q8 arm (green line; 5 monthly loading doses in yellow shaded area).



(Do 2012, 1661 (emphasis added)). For example, adding an additional loading dose would have been as straightforward as adding a single injection in the middle of the first eight-week span in the 2Q8 arm:



(Do 2012, 1660 (emphasis added)). Such a regimen would have had the effect of ensuring that patients' DME was being treated with an aggressive initial pulse of aflibercept before transitioning to the extended dosing phase of the regimen, thus maximizing early therapeutic benefit.

724. This also is consistent with internal Regeneron documents that indicated it was focusing its aflibercept DME program on no more than 3-6 monthly loading doses. (RGN-EYLEA-MYLAN-00631452 at -53). Regeneron also used the phase 2 AMD CLEAR-IT-2 clinical trial results to guide its design of the phase 3 DME trial, explaining to EU authorities that:

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(RGN-EYLEA-MYLAN-00531609 at -614). Regeneron continues, stating that:

> Based on this experience we believe that the doses and dosing intervals for VEGF Trap-Eye for Phase III in DME can be selected based on the results of the Phase II study in patients with AMD (OD-0508, see Investigators Brochure, Vol. 14 , pg. 14) In this study, several doses of VEGF Trap-Eye have been assessed in 30 patients / treatment arm. The results suggested that 0.5mg VEGF Trap-Eye is effective in suppressing retinal edema if injected monthly and that 2mg are sufficient to suppress retinal edema for up to 8 weeks. We consider this Phase 2 study as providing an adequate basis for dose selection for the Phase 3 DME program and propose to use the 0.5mg dose in 4-weekly and the 2mg dose in 8-weekly intervals in the planned Phase 3 study (see outline of proposed Phase 3 studies in DME, Vol. 14 , pg. 14).

(RGN-EYLEA-MYLAN-00531609 at -614). In other words, Regeneron was relying on available data (which was publicly available) and selecting an every-8-week dosing regimen that was already in the public domain for its phase 3 DME clinical trials. The selection of the 5 monthly loading doses was a matter of routine optimization, which began with Regeneron confining itself, as early as 2007/2008 to the use of 3-6 monthly loading doses. (*See, e.g.*, RGN-EYLEA-MYLAN-00631452 at -53; RGN-EYLEA-MYLAN-00531609 at -615 ("During an induction phase, VEGF Trap-Eye is administered by up to 6 intravitreal injections at intervals of 4 or 8 weeks until resolution of macular edema.")).

725. Further, a person of ordinary skill in the art would have had a reasonable expectation of success at using such a regimen given all of the positive DME data in the literature for both aflibercept and ranibizumab. (*See generally, e.g.*, Do 2012; Do 2009; Lalwani 2009; Massin 2012). Indeed, as I discuss above, Regeneron itself was deriving its DME clinical trial strategy from what already had been learned from the aflibercept AMD phase 2 results and ranibizumab DME results.

726. For at least these reasons, along with those discussed above claim 15, it is my opinion that claim 25 is obvious in view of Do 2012, in light of the knowledge of the person of ordinary skill in the art at that time.

5. No Secondary Considerations of Non-Obviousness.

727. I understand Regeneron may assert one or more secondary considerations in support of the non-obviousness of the 572 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 subsequent report.

V. INEQUITABLE CONDUCT.

728. I have been informed that an individual associated with the filing and prosecution of a patent application commits inequitable conduct when he or she:

(i) makes an affirmative misrepresentation of a material fact, fails to disclose material information, or submits false material information to the PTO;

(ii) with the specific intent to deceive the PTO.

729. I am further informed that the materiality required to establish inequitable conduct is but-for materiality—in other words, prior art is but-for material if the PTO would not have allowed a claim had it been aware of the undisclosed prior art.

730. I further understand that when assessing the materiality of a withheld reference, the court must determine whether the PTO would have allowed the claim if it had been aware of the undisclosed reference.

731. I am further informed that when the patentee has engaged in affirmative acts of egregious misconduct, such as the filing of an unmistakably false affidavit, the misconduct is material.

VI. THE PROSECUTION HISTORY OF THE PATENTS-IN-SUIT AND RELATED APPLICATIONS.

732. I have reviewed the prosecution history of the patents-in-suit, the 601 and 572 patents, as well as portions of the prosecution history of their parent application, which issued as the 338 patent. In the following paragraphs, I address important aspects of those prosecution histories, as well as certain representations Regeneron made to the examiner.

A. The Prosecution History of the 338 Patent.

733. I have reviewed the prosecution history of the 338 patent, and summarize certain events below.

1. July 12, 2013: Filing of Application No. 13/940,370 ("370 application").

734. The 370 application was filed on July 12, 2013 with the following claims:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

(338 patent PH, 7/12/2013 Original Application, 22-23).

2. October 18, 2013: IDS.

735. On October 18, 2013, the applicants filed an IDS identifying at least 19 references. (338 patent PH, 10/18/2013 IDS). The applicants only included one submission that provided information about the VIEW dosing regimen, and it was a Thomson Reuters bearing a copyright of 2012, which appears to be a summary of an earlier Regeneron press release. (338 patent PH at

RGN-EYLEA-MYLAN-00013630-39). The 2012 date on the Thomson Reuters document is the same date as the Heier 2012 article that Regeneron raises with the examiner later in prosecution, and discussed below. Regeneron did not submit any of the actual prior art Regeneron press releases, which George Yancopoulos and Regeneron had knowledge and possession of. (*See, e.g.*, RGN-EYLEA-MYLAN-00539067-68).

3. November 8, 2013 Oath and Declaration.

736. On November 8, 2013, George Yancopoulos, the lone named inventor, submitted a declaration attesting that the "application was made or authorized to be made by" George Yancopoulos, that he believes himself to be the original inventor, and that he understands the repercussions of making intentionally false statements. (338 patent PH, 11/8/2013 Declaration).

4. March 17, 2015: IDS.

737. On March 17, 2015, the applicants filed an IDS identifying one additional reference, which did not contain information regarding the VIEW clinical trial dosing regimen. (338 patent PH, 3/17/2015 IDS).

5. June 23, 2015: Office Action.

738. On June 23, 2015, the Examiner issued an Office Action rejecting all pending claims. Among other things, the Examiner made a rejection based on the ground of nonstatutory obviousness-type double patenting over claims of U.S. Patent Nos. 7,303,746, 7,303,747, 7,306,799, and 7,521,049. (338 patent PH, 6/23/2015 Office Action, 6-9).

739. The Examiner stated that "Although the conflicting claims are not identical, they are not patentably distinct from each other" because the earlier patents disclose the same eye disorders, and arriving at the dosing regimens is nothing more than "routine experimentation." (338 patent PH, 6/23/2015 Office Action, 6-9).

6. September 11, 2015: Reply.

740. On September 11, 2015, the applicants filed a Reply to the June 23, 2015 Office Action with the following claim amendments to claim 1:

> 1. (**Currently Amended**) A method for treating an angiogenic eye disorder in a patient, said method comprising sequentially administering to the patient a single initial dose of a VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonist;
>
> wherein each secondary dose is administered 2 to 4 weeks after the immediately preceding dose; and
>
> wherein each tertiary dose is administered at least 8 weeks after the immediately preceding dose;
>
> **wherein the VEGF receptor-based chimeric molecule comprises (1) a VEGFR1 component comprising amino acids 27 to 129 of SEQ ID NO:2; (2) a VEGFR2 component comprising amino acids 130-231 of SEQ ID NO:2; and (3) a multimerization component comprising amino acids 232-457 of SEQ ID NO:2.**

(338 patent PH, 9/11/2015, Reply at 2). The applicants also added the following new claims:

> 21. (**New**) A method for treating an angiogenic eye disorder in a patient, said method comprising sequentially administering to the patient a single initial dose of a VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonist;
>
> wherein each secondary dose is administered 2 to 4 weeks after the immediately preceding dose; and
>
> wherein each tertiary dose is administered at least 8 weeks after the immediately preceding dose;
>
> wherein the VEGF receptor-based chimeric molecule comprises VEGFR1R2-FcΔC1(a) encoded by the nucleic acid sequence of SEQ ID NO:1.
>
> 22. (**New**) The method of claim 21, wherein only a single secondary dose is administered to the patient, and wherein the single secondary dose is administered 4 weeks after the initial dose of the

23. (**New**) The method of claim 21, wherein only two secondary doses are administered to the patient, and wherein each secondary dose is administered 4 weeks after the immediately preceding dose.

24. (**New**) The method of claim 23, wherein each tertiary dose is administered 8 weeks after the immediately preceding dose.

25. (**New**) The method of claim 21, wherein at least 5 tertiary doses of the VEGF antagonist are administered to the patient, and wherein the first four tertiary doses are administered 8 weeks after the immediately preceding dose, and wherein each subsequent tertiary dose is administered 8 or 12 weeks after the immediately preceding dose.

26. (**New**) The method of claim 21, wherein the angiogenic eye disorder is selected from the group consisting of: age related macular degeneration, diabetic retinopathy, diabetic macular edema, central retinal vein occlusion, branch retinal vein occlusion, and corneal neovascularization.

27. (**New**) The method of claim 24, wherein the angiogenic eye disorder is age related macular degeneration.

28. (**New**) The method of claim 21, wherein all doses of the VEGF antagonist are administered to the patient by topical administration or by intraocular administration.

29. (**New**) The method of claim 28, wherein all doses of the VEGF antagonist are administered to the patient by intraocular administration.

30. (**New**) The method of claim 29, wherein the intraocular administration is intravitreal administration.

31. (**New**) The method of claim 30, wherein all doses of the VEGF antagonist comprise from about 0.5 mg to about 2 mg of the VEGF antagonist.

32. (**New**) The method of claim 31, wherein all doses of the VEGF antagonist comprise 0.5 mg of the VEGF antagonist.

33. (**New**) The method of claim 31, wherein all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist.

(338 patent PH, 9/11/2015, Reply at 3-4).

741. The applicants also submitted arguments to the Patent Office regarding the obviousness-type double patenting rejections asserted by the Examiner in the June 23, 2015 Office Action. Specifically, the applicants made statements about the standard of care, and argued as follows:

At the time of the invention the well accepted standard of care for the treatment of the neovascular (or wet) form of age-related macular degeneration (AMD) was to administer an antibody formulation (ranibizumab) by injection to the eye once per month (see the attached Heier et al. paper).

This treatment protocol is (1) expensive; (2) painful to the patient; (3) inconvenient for the patient as well as the patient's family; (4) psychologically and physically traumatic to the patient; and (5) subjects the patient to potential adverse effects such as infection with each treatment event.

Due to all the above factors (1-5) there was a need in the art for alternative treatment protocols whereby the treatment would be carried out with less inconvenience and reduced safety risks to the patient. However, until the present invention once a month treatment remained the standard of care.

There are virtually an infinite number of different treatment protocols that could be tested. A drug could be administered more frequently, or less frequently, relative to the accepted standard of care. Further, different variations in timing between dosing events are possible. Due to the virtually infinite number of combinations, applicants do not believe that the claimed treatment protocol is *prima facie* obvious in view of the prior art standard of care which is administration of the drug once per month. However, notwithstanding that position, any *prima facie* case of obviousness is overcome by the showing of improved unexpected results. Thus, while the rejection is citing case law which supports the

position that where the general conditions of a claim are disclosed within the prior art, it is not inventive to discover optimal ranges, the Examiner is aware that this case law is not applicable to situations where improved unexpected results are shown. Such results have been obtained and are described in the working examples of the present application and in the attached publication, portions of which are referred to below.

The attached Heier et al. paper published in December of 2012, and as such is not prior art with respect to the present application filed on January 11, 2012 and claiming priority to November 21, 2011.

The Heier et al. paper shows results of a treatment protocol of the type claimed on over 2,400 patients. The studies summarized in the Heier *et al.* paper correspond to the clinical trials disclosed in Example 4 of the present application which involve the use of the VEGF receptor-based chimeric molecule known as aflibercept or "VEGF Trap."[1] The results clearly show that by administering the VEGF antagonist in accordance with a dosage regimen as claimed in independent claims 1 and 21, it is possible to treat angiogenic eye disorders such as AMD while administering doses on a less frequent basis than previously thought possible. This provides enormous benefits to patients, reduces health care cost, reduces the pain and suffering of the patient, as well as the inconvenience to the patient and their family, and as such provides a major step forward in the treatment of patients suffering from angiogenic eye disorders, which is worthy of patent protection.

The attached Heier et al. article is a peer reviewed article published in "Ophthalmology" which describes the aforementioned clinical trial as follows;

> "Patients were randomized in a 1:1:1:1 ratio to the following regimens: 0.5 mg aflibercept every 4 weeks (0.5q4); 2 mg aflibercept every 4 weeks (2q4); 2mg aflibercept every 8 weeks (2q8) after 3 injections at week 0, 4 and 8 (to maintain masking, sham injections were given at the interim 4-week visits after week 8); or 0.5mg ranibizumab every 4 weeks (Rq4). Consecutively enrolled patients were assigned to treatment groups on the basis of predetermined central randomization scheme with balanced allocation, managed by an interactive voice response system. "

In the "primary end point analysis" section of the paper, it is indicated that the proportion of

patients maintaining vision was similar among all treatment groups and this is dramatically shown within Figure 2. Thus, the results show that the treatment groups which were compared with the monthly treatment groups surprisingly did not obtain an inferior result. As such, the treatment protocol as encompassed by the presently pending independent claims 1 and 21 achieves results which are as good or better than the results obtained with monthly treatment.

Within the "Discussion" section of the Heier et al. paper, it is noted that the treatment group treated every two months achieved a visual acuity score within 0.3 letters of the group treated on a monthly basis. See also the results summarized in Table 1, page 15, of the present application. Thus, it is indicated that the treatment group which received the drug far less frequently than the monthly dosing arm achieved remarkably similar improvements without requiring the monthly monitoring and visits to the health care provider.

Similar remarkable results are shown in Example 5 of the present application, which illustrates an administration regimen encompassed by claims 1 and 21 (*i.e.*, 3 initial doses of VEGF Trap administered once every four weeks, followed by additional doses administered once every 8 weeks) for the effective treatment of diabetic macular edema (DME). As noted at paragraph [0065] of the present specification: "the administration of VEGFT to patients suffering from angiogenic eye disorders (*e.g.*, AMD and DME) at a frequency of once every 8 weeks, following a single initial dose and two secondary doses administered four weeks apart, resulted in significant prevention of moderate or severe vision loss or improvements in visual acuity."

An acknowledgement of the unexpected results of the administration regimen of the present invention is echoed in the Heier et al. paper, which points out that less frequent injections should also provide an ocular safety benefit, and that using fewer injections may substantially decrease the cumulative population risk of certain adverse events which can have a considerable impact considering the millions of injections given each year. For example, Heier et al. states on page 2546, middle left colum that:

> "The demonstration that monthly aflibercept provides similar efficacy and safety as the current approved standard of monthly ranibizumab is important, but the finding that remarkably similar improvement in vision and anatomic measures can be achieved with less than monthly intravitreal aflibercept injections and without requiring monthly monitoring visits provides an important advance for both patients and their treating physicians."

Moreover, the final paragraph of the Heier et al. paper reads as follows:

"In conclusion, intravitreal aflibercept dosed monthly or every 2 months after 3 initial monthly doses resulted in similar visual and anatomic outcomes as ranibizumab dosed monthly, as well as similar safety and tolerability. Intravitreal aflibercept dosed every 2 months has the potential to provide patients, their families and clinicians the opportunity for the optimal vision gains and anatomic disease control they have come to expect from monthly ranibizumab, with a substantially decreased treatment and compliance burden, and a lower cumulative risk of injection-related adverse events."

Based on the above, it is clear that the claimed treatment protocol provides enormous advantages to patients. Further, in view of the disadvantages of carrying out the treatment on a once per month basis, there was a need in the art for alternative treatment protocols. However, this did not occur until the present invention and as such, the claimed treatment protocol is inventive above and beyond the inventions claimed within the patents cited in the obviousness type double patenting rejection. In view of such, those rejections should be reconsidered and withdrawn.

Applicants do not acquiesce to the *prima facie* obviousness of the claimed invention over the invention claimed within the cited patents. This is because there are virtually an infinite number of different possible treatment protocols. However, notwithstanding any *prima facie* case of obviousness, applicants have demonstrated improved and unexpected results, and based on such, the rejections should be reconsidered and withdrawn.

(338 patent PH, 12/16/2021 Reply, 6-9). Regeneron did not inform the Examiner at any point in this submission that the 2Q8 VIEW dosing regimen was disclosed in a number of prior art references, including those publicly released by Regeneron itself, and of which George Yancopoulos was aware. For example, the May 8, 2008 Press Release quotes George Yancopoulos and discloses the VIEW 2Q8 dosing regimen. (5-8-2008 Regeneron Press Release, 1). Neither this press release, nor others like it, were submitted to the Patent Office and the Examiner.

7. October 19, 2015: Notice of Allowance.

742. Shortly after Regeneron's above arguments and submission, the Examiner withdrew the obviousness-type double patenting rejections and allowed the claims. (338 patent PH, 10/19/2015 Notice of Allowance).

8. January 20, 2016: 338 Patent Issuance.

743. On January 20, 2016, the 370 application issued as U.S. Patent No. 9,254,338.

B. The Prosecution History of the 601 Patent.

744. I have reviewed the prosecution history of the 601 patent, and summarize certain events below.

1. April 29, 2019: Filing of Application No. 16/397,267 ("267 application").

745. The 267 application was filed on April 29, 2019, with the following claims:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

(601 patent PH, 4/29/2019 Original Application at 22-23).

2. April 29, 2019: Preliminary Amendment.

746. On April 29, 2019, the applicants filed a Preliminary Amendment in which claims 1-20 were canceled, and new claims 21-49 were added as follows:

21. (New) A method for treating age related macular degeneration in a patient, comprising administering, to said patient, by intravitreal injection, 2 mg aflibercept approximately every 4 weeks for the first 3 months, followed by 2 mg aflibercept approximately once every 8 weeks or once every 2 months.

22. (New) The method of claim 21, wherein the age-related macular degeneration is neovascular (wet).

23. (New) The method of claim 21, wherein approximately every 4 weeks comprises approximately every 28 days or approximately monthly.

24. (New) The method of claim 23, wherein the age-related macular degeneration is neovascular (wet).

25. (New) The method of claim 22 wherein the patient loses less than 15 letters of Best Corrected Visual Acuity (BCVA) score.

26. (New) The method of claim 25 wherein Best Corrected Visual Acuity (BCVA) is measured by Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

27. (New) The method of claim 22 wherein the patient gains at least 15 letters of Best Corrected Visual Acuity (BCVA) score.

28. (New) The method of claim 27 wherein Best Corrected Visual Acuity (BCVA) is measured by Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

29. (New) A method for treating diabetic macular edema in a patient, comprising administering, to said patient, by intravitreal injection, 2 mg aflibercept approximately every 4 weeks for the first 5 injections followed by 2 mg aflibercept approximately once every 8 weeks or once every 2 months.

30. (New) The method of claim 29, wherein approximately every 4 weeks comprises approximately every 28 days or approximately monthly.

31. (New) The method of claim 29, further comprising, after 20 weeks, administering, via intravitreal injection, 2 mg of aflibercept once every 4 weeks.

32. (New) The method of claim 29 wherein the patient loses less than 15 letters of Best Corrected Visual Acuity (BCVA) score.

33. (New) The method of claim 32 wherein Best Corrected Visual Acuity (BCVA) is measured by Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

34. (New) The method of claim 29 wherein the patient gains at least 15 letters of Best Corrected Visual Acuity (BCVA) score.

35. (New) The method of claim 34 wherein Best Corrected Visual Acuity (BCVA) is measured by Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

36. (New) A method for treating diabetic retinopathy in a patient, comprising administering, to said patient, by intravitreal injection, 2 mg aflibercept approximately every 4 weeks for the first 5 injections followed by 2 mg aflibercept approximately once every 8 weeks or 2 months.

37. (New) The method of claim 36, wherein approximately every 4 weeks comprises approximately every 28 days or approximately monthly.

38. (New) The method of claim 36, further comprising after 20 weeks, administering via intravitreal injection 2 mg of aflibercept once every 4 weeks

39. (New) The method of claim 36 wherein the patient loses less than 15 letters of Best Corrected Visual Acuity (BCVA) score.

40. (New) The method of claim 37 wherein Best Corrected Visual Acuity (BCVA) is measured by Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

41. (New) The method of claim 36 wherein the patient gains at least 15 letters of Best Corrected Visual Acuity (BCVA) score.

42. (New) The method of claim 41 wherein Best Corrected Visual Acuity (BCVA) is measured by Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

43. (New) A method for treating diabetic retinopathy in a patient with diabetic macular edema, comprising administering, to said patient, by intravitreal injection, 2 mg aflibercept approximately every 4 weeks for the first 5 injections followed by 2 mg aflibercept approximately once every 8 weeks or 2 months.

44. (New) The method of claim 43, wherein approximately every 4 weeks comprises approximately every 28 days or approximately monthly.

45. (New) The method of claim 43, further comprising after 20 weeks, administering via intravitreal injection 2 mg of aflibercept once every 4 weeks

46. (New) The method of claim 43 wherein the patient loses less than 15 letters of Best Corrected Visual Acuity (BCVA) score.

47. (New) The method of claim 46 wherein Best Corrected Visual Acuity (BCVA) is measured by Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

48. (New) The method of claim 43 wherein the patient gains at least 15 letters of Best Corrected Visual Acuity (BCVA) score.

49. (New) The method of claim 48 wherein Best Corrected Visual Acuity (BCVA) is measured by Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

(601 patent PH, 4/29/2019 Preliminary Amendment, 2-5).

3. June 19, 2019: IDS.

747. On June 19, 2019, the applicants filed an IDS identifying 78 references, totaling approximately 1,524 pages. (601 patent PH, 6/19/2019 IDS).

4. August 14, 2019: Preliminary Amendment.

748. On August 14, 2019, the applicants filed a Preliminary Amendment with claims 21-49 as previously presented, and new claims 50-63 as follows:

> 50. (New) A method for treating an angiogenic eye disorder in a patient, said method comprising sequentially administering to the patient
>
> a single initial dose of a VEGF antagonist, followed by
>
> one or more secondary doses of the VEGF antagonist, followed by
>
> one or more tertiary doses of the VEGF antagonist;
>
> wherein each secondary dose is administered 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 immunoglobin-like (Ig) domain 2 of a first VEGF receptor and Ig domain 3 of a second VEGF receptor, and a multimerizing component.
>
> 51. (New) The method of claim 50 wherein the first VEGF receptor is Flt1 and the second VEGF receptor is Flk1.
>
> 52. (New) The method of claim 50 wherein the VEGF antagonist is aflibercept.
>
> 53. (New) The method of claim 51, wherein all doses of the VEGF antagonist are administered to the patient by intraocular administration.
>
> 54. (New) The method of claim 53, wherein the intraocular administration is intravitreal administration.
>
> 55. (New) The method of claim 54, wherein all doses of the VEGF antagonist comprise from about 0.5 mg to about 2 mg of the VEGF antagonist.

56. (New) The method of claim 55, wherein all doses of the VEGF antagonist comprise 0.5 mg of the VEGF antagonist.

57. (New) The method of claim 55, wherein all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist.

58. (New) The method of claim 51, wherein the angiogenic eye disorder is selected from the group consisting of: age related macular degeneration, diabetic retinopathy, diabetic macular edema, central retinal vein occlusion, branch retinal vein occlusion, and corneal neovascularization.

59. (New) The method of claim 51 wherein the angiogenic eye disorder is age related macular degeneration.

60. (New) The method of claim 51 wherein the angiogenic eye disorder is diabetic retinopathy.

61. (New) The method of claim 51, wherein the angiogenic eye disorder is diabetic macular edema.

62. (New) The method of claim 59 wherein all doses of VEGF antagonist comprise 0.5 mg of the VEGF antagonist.

63. (New) The method of claim 59 wherein all doses of VEGF antagonist comprise 2.0 mg of the VEGF antagonist.

(601 patent PH, 8/14/2019 Preliminary Amendment, 2-6).

5. September 18, 2019: IDS.

749. On September 18, 2019, the applicants filed an IDS identifying 42 references, totaling 414 pages. (601 patent PH, 9/18/2019 IDS).

6. January 7, 2020: Preliminary Amendment.

750. On January 7, 2020, the applicants filed a Preliminary Amendment amending claims 21, 29, 36, 38, 43, 45, and 50 as follows:

21. **(Currently amended)** A method for treating age related macular degeneration in a patient, comprising **intravitreally** administering, to said patient, ~~by intravitreal injection,~~ **an effective amount of aflibercept which is** 2 mg ~~aflibercept~~ approximately every 4 weeks for the first 3 months, followed by 2 mg ~~aflibercept~~ approximately once every 8 weeks or once every 2 months.

29. **(Currently amended)** A method for treating diabetic macular edema in a patient, comprising **intravitreally** administering, to said patient~~, by intravitreal injection~~, **an effective amount of aflibercept which is** 2 mg ~~aflibercept~~ approximately every 4 weeks for the first 5 injections followed by 2 mg ~~aflibercept~~ approximately once every 8 weeks or once every 2 months.

36. **(Currently amended)** A method for treating diabetic retinopathy in a patient, comprising **intravitreally** administering, to said patient, ~~by intravitreal injection,~~ **an effective amount of aflibercept which is** 2 mg ~~aflibercept~~ approximately every 4 weeks for the first 5 injections followed by 2 mg ~~aflibercept~~ approximately once every 8 weeks or 2 months.

38. **(Currently amended)** The method of claim 36, further comprising**,** after 20 weeks, administering**,** via intravitreal injection**,** 2 mg of aflibercept once every 4 weeks**.**

43. **(Currently amended)** A method for treating diabetic retinopathy in a patient with diabetic macular edema, comprising **intravitreally** administering, to said patient, ~~by intravitreal injection,~~ **an effective amount of aflibercept which is** 2 mg ~~aflibercept~~ approximately every 4 weeks for the first 5 injections followed by 2 mg ~~aflibercept~~ approximately once every 8 weeks or 2 months.

45. **(Currently amended)** The method of claim 43, further comprising**,** after 20 weeks, administering**,** via intravitreal injection**,** 2 mg of aflibercept once every 4 weeks**.**

50. **(Currently Amended)** A method for treating an angiogenic eye disorder in a patient, said method comprising ~~sequentially~~ 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 immunoglobin-like (Ig) domain 2 of a first VEGF receptor and Ig domain 3 of a second VEGF receptor, and a multimerizing component.

(601 patent PH, 1/7/2020 Preliminary Amendment, 2-6).

7. January 27, 2020: IDS.

751. On January 27, 2020, the applicants filed an IDS identifying 20 references, totaling approximately 158 pages. (601 patent PH, 1/27/2020 IDS).

8. February 21, 2020: IDS.

752. On February 21, 2020, the applicants filed an IDS identifying 23 references, totaling 386 pages. (601 patent PH, 2/21/2020 IDS).

9. March 31, 2020: IDS.

753. On March 31, 2020, the applicants filed an IDS identifying 27 references, totaling approximately 351 pages. (601 patent PH, 3/31/2020 IDS).

10. May 12, 2020: Office Action.

754. On May 12, 2020, the Examiner issued an Office Action rejecting all pending claims on the ground of nonstatutory obviousness-type double patenting over claims of U.S. Patent Nos. 9,254,338, 9,669,069, 10,130,681, and provisionally over claims of U.S. Application No. 16/159,282. (601 patent PH, 5/12/2020 Office Action, 3-6).

11. June 30, 2020: IDS.

755. On June 30, 2020, the applicants filed an IDS identifying 24 references, totaling 68 pages. (601 patent PH, 6/30/2020 IDS).

12. July 16, 2020: IDS.

756. On July 16, 2020, the applicants filed an IDS identifying 76 references, totaling approximately 4,561 pages. (601 patent PH, 7/16/2020 IDS).

13. October 21, 2020: Amendment Under 37 C.F.R. § 1.111.

757. On October 21, 2020, the applicants filed an Amendment in which claim 51 was canceled, claims 21, 26, 28, 29, 33, 35, 36, 40, 42, 43, 47, 49, 50, 53 were amended, and new claims 64-68 were added as follows:

21. **(Currently Amended)** 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.

22. **(Previously Presented)** The method of claim 21, wherein the age-related macular degeneration is neovascular (wet).

23. **(Previously Presented)** The method of claim 21, wherein approximately every 4 weeks comprises approximately every 28 days or approximately monthly.

24. **(Previously Presented)** The method of claim 23, wherein the age-related macular degeneration is neovascular (wet).

25. **(Previously Presented)** The method of claim 22 wherein the patient loses less than 15 letters of Best Corrected Visual Acuity (BCVA) score.

26. **(Currently Amended)** The method of claim 25 wherein Best Corrected Visual Acuity (BCVA) is ~~measured by~~ **according to** Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

27. **(Previously Presented)** The method of claim 22 wherein the patient gains at least 15 letters of Best Corrected Visual Acuity (BCVA) score.

28. **(Currently Amended)** The method of claim 27 wherein Best Corrected Visual Acuity (BCVA) is ~~measured by~~ **according to** Early Treatment Diabetic Retinopathy Study (ETDRS) letter

score.

29. **(Currently Amended)** A method for treating diabetic macular edema in a patient **in need thereof**, comprising intravitreally administering, to said patient, an effective amount of aflibercep which is 2 mg approximately every 4 weeks for the first 5 injections followed by 2 mg approximately once every 8 weeks or once every 2 months.

30. **(Previously Presented)** The method of claim 29, wherein approximately every 4 weeks comprises approximately every 28 days or approximately monthly.

31. **(Previously presented)** The method of claim 29, further comprising, after 20 weeks, administering, via intravitreal injection, 2 mg of aflibercept once every 4 weeks.

32. **(Previously Presented)** The method of claim 29 wherein the patient loses less than 15 letters of Best Corrected Visual Acuity (BCVA) score.

33. **(Currently Amended)** The method of claim 32 wherein Best Corrected Visual Acuity (BCVA) is ~~measured by~~ **according to** Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

34. **(Previously Presented)** The method of claim 29 wherein the patient gains at least 15 letters of Best Corrected Visual Acuity (BCVA) score.

35. **(Currently Amended)** The method of claim 34 wherein Best Corrected Visual Acuity (BCVA) is ~~measured by~~ **according to** Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

36. **(Currently Amended)** A method for treating diabetic retinopathy 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 5 injections followed by 2 mg approximately once every 8 weeks or 2 months.

37. (Previously Presented) The method of claim 36, wherein approximately every 4 weeks comprises approximately every 28 days or approximately monthly.

38. (Previously Presented) The method of claim 36, further comprising, after 20 weeks, administering, via intravitreal injection, 2 mg of aflibercept once every 4 weeks.

39. (Previously Presented) The method of claim 36 wherein the patient loses less than 15 letters of Best Corrected Visual Acuity (BCVA) score.

40. (Currently Amended) The method of claim 37 wherein Best Corrected Visual Acuity (BCVA) is ~~measured by~~ according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

41. (Previously Presented) The method of claim 36 wherein the patient gains at least 15 letters of Best Corrected Visual Acuity (BCVA) score.

42. (Currently Amended) The method of claim 41 wherein Best Corrected Visual Acuity (BCVA) is ~~measured by~~ according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

43. (Currently Amended) A method for treating diabetic retinopathy in a patient with diabetic macular edema, who is in need of such treatment, comprising intravitreally administering, to said patient, an effective amount of aflibercept which is 2 mg approximately every 4 weeks for the first 5 injections followed by 2 mg approximately once every 8 weeks or 2 months.

44. (Previously Presented) The method of claim 43, wherein approximately every 4 weeks comprises approximately every 28 days or approximately monthly.

45. (Previously Presented) The method of claim 43, further comprising, after 20 weeks, administering, via intravitreal injection, 2 mg of aflibercept once every 4 weeks.

46. (Previously Presented) The method of claim 43 wherein the patient loses less than 15 letters of Best Corrected Visual Acuity (BCVA) score.

47. **(Currently Amended)** The method of claim 46 wherein Best Corrected Visual Acuity (BCVA) is ~~**measured by**~~ **according to** Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

48. (Previously Presented) The method of claim 43 wherein the patient gains at least 15 letters of Best Corrected Visual Acuity (BCVA) score.

49. **(Currently Amended)** The method of claim 48 wherein Best Corrected Visual Acuity (BCVA) is ~~**measured by**~~ **according to** Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

50. **(Currently Amended)** 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 immunoglobin-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.

51. **(Cancelled)**

52. (Previously Presented) The method of claim 50 wherein the VEGF antagonist is aflibercept.

53. **(Currently Amended)** The method of claim **50** ~~**51**~~, wherein all doses of the VEGF

antagonist are administered to the patient by intraocular administration.

54. (Previously Presented) The method of claim 53, wherein the intraocular administration is intravitreal administration.

55. (Previously Presented) The method of claim 54, wherein all doses of the VEGF antagonist comprise from about 0.5 mg to about 2 mg of the VEGF antagonist.

56. (Previously Presented) The method of claim 55, wherein all doses of the VEGF antagonist comprise 0.5 mg of the VEGF antagonist.

57. (Previously Presented) The method of claim 55, wherein all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist.

58. (**Currently Amended**) The method of claim 50 ~~54~~, wherein the angiogenic eye disorder is selected from the group consisting of: age related macular degeneration, diabetic retinopathy, diabetic macular edema, central retinal vein occlusion, branch retinal vein occlusion, and corneal neovascularization.

59. (**Currently Amended**) The method of claim 50 ~~51~~ wherein the angiogenic eye disorder is age related macular degeneration.

60. (**Currently Amended**) The method of claim 50 ~~51~~ wherein the angiogenic eye disorder is diabetic retinopathy.

61. (**Currently Amended**) The method of claim 50 ~~51~~, wherein the angiogenic eye disorder is diabetic macular edema.

62. (Previously Presented) The method of claim 59 wherein all doses of VEGF antagonist comprise 0.5 mg of the VEGF antagonist.

63. (Previously Presented) The method of claim 59 wherein all doses of VEGF antagonist comprise 2.0 mg of the VEGF antagonist.

64. (New) The method of claim 24 wherein exclusion criteria for the patient include (1) active intraocular inflammation; or (2) active ocular or periocular infection.

65. (New) The method of claim 29 wherein exclusion criteria for the patient include (1) active intraocular inflammation; or (2) active ocular or periocular infection.

66. (New) The method of claim 36 wherein exclusion criteria for the patient include (1) active intraocular inflammation; or (2) active ocular or periocular infection.

67. (New) The method of claim 43 wherein exclusion criteria for the patient include (1) active intraocular inflammation; or (2) active ocular or periocular infection.

68. (New) The method of claim 52 wherein exclusion criteria for the patient include (1) active intraocular inflammation; or (2) active ocular or periocular infection.

(601 patent PH, 10/21/2020 Amendment, 2-7). The applicants also filed Terminal Disclaimers in response to the obviousness-type double patenting rejections and argued that the rejections were rendered moot. (*Id.*, 9; *see also* 10/21/2020 Terminal Disclaimers; *see also* 601 patent PH, 10/21/2020 Terminal Disclaimer of Issued Patents, 1; 601 patent PH, 10/21/2020 Terminal Disclaimer of Provisional Application).

14. November 12, 2020: Notice of Allowance.

758. On November 12, 2020, the Examiner issued a Notice of Allowance. (601 patent PH, 11/12/2020 Notice of Allowance). The Examiner withdrew the obviousness-type double patenting rejections in view of the Terminal Disclaimers and allowed all pending claims. (*Id.*, 2-3).

15. January 12, 2021: 601 Patent Issuance.

759. On January 12, 2021, the 267 application issued as U.S. Patent No. 10,888,601.

C. The Prosecution History of the 572 Patent.

760. I have reviewed the prosecution history of the 572 patent, and summarize certain events below.

1. June 21, 2021: Filing of Application No. 17/352,892 ("892 application").

761. The 892 application was filed on June 21, 2021, with the following claims:

> 1. A method for treating an angiogenic eye disorder in a patient, said method comprising sequentially administering to the patient a single initial dose of a VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonist;
>
> wherein each secondary dose is administered 2 to 4 weeks after the immediately preceding dose; and
>
> wherein each tertiary dose is administered at least 8 weeks after the immediately preceding dose.
>
> 2. The method of claim 1, wherein only a single secondary dose is administered to the patient, and wherein the single secondary dose is administered 4 weeks after the initial dose of the VEGF antagonist.
>
> 3. The method of claim 1, wherein only two secondary doses are administered to the patient, and wherein each secondary dose is administered 4 weeks after the immediately preceding dose.
>
> 4. The method of claim 3, wherein each tertiary dose is administered 8 weeks after the immediately preceding dose.
>
> 5. The method of claim 1, wherein at least 5 tertiary doses of the VEGF antagonist are administered to the patient, and wherein the first four tertiary doses are administered 8 weeks after the immediately preceding dose, and wherein each subsequent tertiary dose is administered 8 or 12 weeks after the immediately preceding dose.
>
> 6. The method of claim 1, wherein the angiogenic eye disorder is selected from the group consisting of: age related macular degeneration, diabetic retinopathy, diabetic macular edema, central retinal vein occlusion, branch retinal vein occlusion, and corneal neovascularization.
>
> 7. The method of claim 6, wherein the angiogenic eye disorder is age related macular degeneration.
>
> 8. The method of claim 1, wherein the VEGF antagonist is an anti-VEGF antibody or fragment thereof, an anti-VEGF receptor antibody or fragment thereof, or a VEGF receptor-based chimeric molecule.

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

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

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

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

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

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

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

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

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

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

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

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

(572 patent PH, 6/21/2021 Original Application, 23-24).

2. June 21, 2021: Preliminary Amendment.

762. On June 21, 2021, the applicants filed a Preliminary Amendment in which claims 1-20 were canceled, and new claims 21-50 were added as follows:

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

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

wherein each secondary dose is administered approximately 4 weeks following the immediately preceding dose; and

wherein each tertiary dose is administered approximately 8 weeks following the immediately preceding dose;

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

22. **(New)** The method of claim 21 wherein the patient achieves a gain in Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

23. **(New)** The method of claim 22 wherein the patient gains at least 7 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

24. **(New)** The method of claim 23 wherein the patient achieves the gain in visual acuity within 24 weeks following the initial dose.

25. **(New)** The method of claim 23 wherein only two secondary doses are administered to the patient.

26. (New) The method of claim 23 wherein the aflibercept is formulated as an isotonic solution.

27. (New) The method of claim 23 wherein the aflibercept is formulated with a non-ionic surfactant.

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

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

30. (New) The method of claim 22 wherein the patient gains at least 9 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

31. (New) The method of claim 30 wherein only two secondary doses are administered to the patient.

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

33. (New) The method of claim 30 wherein the aflibercept is formulated with a non-ionic surfactant.

34. (New) The method of claim 21 wherein exclusion criteria for the patient include both of:

(1)active ocular inflammation; and

(2) active ocular or periocular infection.

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

wherein each secondary dose is administered to the patient by intravitreal injection approximately 4 weeks following the immediately preceding dose; and

wherein each tertiary dose is administered to the patient by intravitreal injection approximately 8 weeks following the immediately preceding dose.

36. (New) The method of claim 35 wherein the patient achieves a gain in visual acuity within 52 weeks following the initial dose.

37. (New) The method of claim 36 wherein the patient gains at least 9 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

38. (New) The method of claim 37 wherein the aflibercept is formulated as an isotonic solution.

39. (New) The method of claim 37 wherein the aflibercept is formulated with a non-ionic surfactant.

40. (New) The method of claim 37 wherein the patient achieves a gain in visual acuity within 24 weeks following the initial dose.

41. (New) The method of claim 36 wherein the patient gains at least 8 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

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

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

44. (New) The method of claim 35 wherein only two secondary doses are administered to the patient.

45. (New) The method of claim 35 wherein four secondary doses are administered to the patient.

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

wherein each secondary dose is administered to the patient by intravitreal injection approximately 4 weeks following the immediately preceding dose; and

wherein each tertiary dose is administered to the patient by intravitreal injection approximately 8 weeks following the immediately preceding dose;

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

47. (New) The method of claim 46 wherein only two secondary doses are administered to the patient.

48. (New) The method of claim 46 wherein the gain in visual acuity is measured using the Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

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

wherein each secondary dose is administered to the patient by intravitreal injection approximately 4 weeks following the immediately preceding dose; and

wherein each tertiary dose is administered to the patient by intravitreal injection approximately 8 weeks following the immediately preceding dose;

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

50. (New) The method of claim 49 wherein maintenance of visual acuity means loss of less than 15 letters Best Corrected Visual Acuity (BCVA) as measured by using the Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

(572 patent PH, 6/21/2021 Preliminary Amendment, 2-6).

3. June 21, 2021: IDS.

763. On June 21, 2021, the applicants filed an IDS identifying 274 references, totaling approximately 13,858 pages. (572 patent PH, 6/21/2021 IDS).

4. July 9, 2021: IDS.

764. On July 9, 2021, the applicants filed an IDS identifying 93 references, totaling approximately 2,243 pages. (572 patent PH, 7/9/2021 IDS).

5. September 3, 2021: IDS.

765. On September 3, 2021, the applicants filed an IDS identifying 23 references, totaling 1,123 pages. (572 patent PH, 9/3/2021 IDS).

6. October 28, 2021: Office Action.

766. On October 28, 2021, the Examiner issued an Office Action rejecting all pending claims on the ground of nonstatutory obviousness-type double patenting over claims of U.S. Patent

Nos. 9,254,338, 9,669,069, 10,130,681, 10,828,345, and 10,888,601 (572 patent PH, 10/28/2021 Office Action, 3-6).

7. November 24, 2021: IDS.

767. On November 24, 2021, the applicants filed an IDS identifying 144 references, totaling approximately 3,798 pages. (572 patent PH, 11/24/2021 IDS).

8. December 7, 2021: Reply Under 37 C.F.R. § 1.111.

768. On December 7, 2021, the applicants filed a Reply with no claim amendments. (572 patent PH, 12/7/2021 Reply, 7). The applicants also filed Terminal Disclaimers in response to the obviousness-type double patenting rejections and stated that "the application is believed to be in condition for allowance." (*Id.*; *see also* 12/7/2021 Terminal Disclaimers).

9. December 16, 2021: IDS.

769. On December 16, 2021, the applicants filed an IDS identifying one reference, totaling 54 pages. (572 patent PH, 12/16/2021 IDS).

10. December 22, 2021: Notice of Allowance.

770. On December 22, 2021, the Examiner issued a Notice of Allowance. (572 patent PH, 12/22/2021 Notice of Allowance). The Examiner withdrew the obviousness-type double patenting rejections in view of the Terminal Disclaimers and allowed all pending claims. (*Id.*, 2).

11. February 22, 2022: 572 Patent Issuance.

771. On February 22, 2022, the 892 application issued as U.S. Patent No. 11,253,572.

VII. UNENFORCEABILITY / INEQUITABLE CONDUCT OPINIONS.

A. Inequitable Conduct For Knowingly Misrepresenting the Standard of Care and the State of the Art.

772. I address below my opinions regarding some of the representations and omissions that Regeneron made during prosecution of the 338 patent, as well as Regeneron's actions during the prosecution of the 601 and 572 patents.

773. First, during the prosecution of the 338 patent, the applicants admitted to the examiner that the VIEW1/2 every-8-week dosing regimen falls squarely within the scope of the claims of the 338 patent. This is the same regimen that was disclosed and disseminated before the filing date of the 338 patent, as I discuss at length above. (*See, e.g.*, Dixon, 1576; Adis, 263; 5-8-2008 Regeneron Press Release, 1; NCT 795, 8; NCT 377, 6; and the detailed discussion above of the disclosures of the VIEW1 and/or VIEW2 studies in each of these references). This also is the same 2Q8 regimen that is found in the 601 and 572 patent. (*See, e.g.*, 601 patent, claim 1; 572 patent, claim 1).

774. Second, during prosecution of the 338 patent, Regeneron relied on the Heier 2012 publication for its disclosure of the 2Q8 dosing regimen and the results of the VIEW clinical trial. (338 patent PH, 12/16/2021 Reply, 6-9). Regeneron did not inform the examiner that the 2Q8 regimen disclosed in the Heier 2012 presentation of the VIEW clinical trial was the same 2Q8 VIEW regimen disclosed in multiple earlier publications and Regeneron public statements. (338 patent PH, 12/16/2021 Reply, 6-9). Regeneron also failed to inform the Examiner of the positive phase 2 CLEAR-IT-2 results that were already published and available to the public prior to the filing of the 338 patent. (*See, e.g.*, RGN-EYLEA-MYLAN-00539067- 00539068).

775. Third, Regeneron stated to the Patent Office and the Examiner, that monthly administration was the standard of care at the time of the invention. (338 FH, 9/11/2015 Remarks,

6). Regeneron further characterizes the results reported in Heier 2012 as surprising, dramatic, and unexpected since the every-eight-week dosing group exhibited outcomes similar to those receiving monthly injections. The crux of Regeneron's argument is that the 2Q8 regimen was an unexpected and surprising departure from monthly dosing. However, in my experience and that of a person of ordinary skill in the art, as of 2009/2010, monthly dosing was not the regimen used by most in standard clinical practice. By that time, 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 and employ extended dosing regimens. 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 regular visits to assess visual acuity and retinal swelling and only administer injections on those visits where there appeared to be loss in visual acuity or increase in retinal swelling. We referred to this treatment practice as PRN, or treat-and-extend, which is a type of PRN dosing that extends intervals between office visits.

776. Based on documents I have reviewed I understand that Regeneron and George Yancopoulos also were aware that extended dosing schemes, including PRN dosing schemes were the standard of care. (*See, e.g.*, DX228 to the Deposition of K. Chu (April 4, 2007 Email from G. Yancopoulos stating that PRN approaches "are being widely adopted as current standard of care.")). In my opinion, George Yancopoulos' knowledge of the current standard of care is inconsistent with his and Regeneron's representations to the Patent Office in their 9/11/2015 Reply.

777. In addition, by 2012, George Yancopoulos and Regeneron were aware of peer skepticism regarding their claims of surprising and unexpected outcomes compared to Lucentis. For example, they were aware that the New England Journal of Medicine ("NEJM") had turned down Regeneron's manuscript reporting the VIEW results, a manuscript on which George Yancopoulos was a listed author. They also were aware of criticism from reviewers at the NEJM, including statements that "the argument for increased patient safety is overstated, particularly relative to ranibizumab PRN," and that the "outcomes are essentially the same as ranibizumab," and thus "not a major conceptual advance." (RGN-EYLEA-MYLAN-00501236 at -241-242). The reviewers went on to say that the results "are not surprising" given that ranibizumab has the same mechanism of action, molecular target, and delivery method and in light of "numerous prior antiVEGF studies." (*Id.* at -242). Yet another reviewer commented that the manuscript was too "heavy-handed" when it came to touting the 2Q8 regimen and results, and "comes off as the beginning of a marketing campaign." (*Id.* at -242). Despite this skepticism from peer reviewers, Regeneron and George Yancopoulos touted unexpected and surprising results to the Examiner during prosecution of patent claims directed to the 2Q8 dosing regimen.

778. Fourth, in addition to as-needed dosing schemes 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.*, Mitchell, 6-7, 9-13 (summarizing the following studies: 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); Mitchell, 6-7 (providing a summary of each of the above studies). From these studies, authors concluded that while fixed quarterly dosing may be inferior to monthly dosing (though still more effective than placebo), the individualized PrONTO regimens could achieve outcomes similar to that observed for monthly dosing. (*See, e.g.*, Mitchell, 6-7; *id.*, 12-13 ("Although small and open label, [PrONTO] suggests that flexible OCT guided re-treatment could sustain visual gain with fewer injections.")).

779. Because of Regeneron's interest in the angiogenic eye disorder market, and its focus on establishing non-inferiority of aflibercept to ranibizumab, Regeneron would have been aware of the PrONTO study and other extended dosing regimens being investigated by Genentech. (*See, e.g.*, Nguyen 2007, available at https://iovs.arvojournals.org/article.aspx?articleid=2385580 (Regeneron authors Chu and Ingerman referencing the PrONTO study); *see also, e.g.*, RGN-EYLEA-MYLAN-00537180 (April 2009 email chain among individuals at Regeneron, including George Yancopoulos, discussing the 2-year results of the PrONTO trial)). In addition, Regeneron knew by 2007 that ranibizumab was approved in the EU for PRN dosing, and that ranibizumab was being administered on a basis less than frequent than monthly. (*See, e.g.*, RGN-EYLEA-MYLAN-00526134 at -135 (March 29, 2007 email and attachment noting that "in the EU, a PRN dosing schedule is allowed after the initial first 3 months of dosing."); *see also, e.g.*, RGN-EYLEA-MYLAN-00525081 (2007 email discussing the ranibizumab EU PRN dosing instructions). Internal notes further state that "Genentech estimates that the average patient will receive 5 to 7 Lucentis injections per year per eye." (RGN-EYLEA-MYLAN-00526134 at -135). This injection

frequency works out to far less than monthly dosing, and is very close to what the frequency would be on a 2Q8 dosing scheme.

780. Fifth, in my opinion, the results reported in Heier 2012, and which Regeneron relies upon in their remarks to the Patent Office, were not unexpected in light of the positive results reported for Regeneron's Phase 2 study of VEGF Trap-Eye in AMD. In that study, Regeneron used two treatment arms: (1) quarterly dosing for 12 weeks followed by PRN dosing; and (2) fixed monthly dosing for 12 weeks followed by PRN dosing. The latter group, when dosed with 2 mg, achieved on average a gain in visual acuity of 9 letters and a mean decrease in retinal thickness of 143 µm. (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. (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." (4-28-2008 Regeneron Press Release, 1; *see also id.* ("Due to its high affinity for all isoforms of VEGF-A and PIGF . . . as well as its long residence time in the eye, it is anticipated that VEGF Trap-Eye may be able to be dosed at a frequency less than once monthly . . . . These emerging Phase 2 clinical data seem to support the concept of durability of VEGF Trap-Eye.")). However, in their 9/11/2015 Reply to the Patent Office, Regeneron and George Yancopoulos did not inform the examiner of the phase 2 AMD CLEAR-IT-2 data, despite touting to investors that the phase 2 data was "encouraging." (RGN-EYLEA-MYLAN-00585881 at -903).

781. In my opinion, had Regeneron and George Yancopoulos not misrepresented the standard of care, had they informed the Examiner of the prior art publication and dissemination of

the 2Q8 VIEW dosing regimen, and had they informed the Examiner of the successful phase 2 CLEAR-IT-2 results, the Examiner would have used the prior art VIEW regimen disclosures to reject the claims that eventually issued as the 338 patent, and likewise would have used the prior art VIEW regimen disclosures to reject the 2Q8 claims that later issued in the 601 and 571 patents.

B. Inequitable Conduct Arising From Regeneron's Efforts to Obscure the VIEW Prior Art Disclosures from the Examiner.

1. The 338 patent.

782. The prosecution history of the 338 patent is described above.

783. As I discuss in that section, Regeneron and George Yancopoulos, the named inventor, did not submit Dixon to the Examiner during prosecution of the 338 patent. In addition, Regeneron and George Yancopoulos did not submit any of the pre-2010 Regeneron press releases and SEC documents that they were aware of that publicly disclosed the 2Q8 VIEW dosing regimen to the Patent Office or the Examiner. George Yancopoulos and Regeneron were aware of these press releases. (*See, e.g.*, RGN-EYLEA-MYLAN-00539067-68).

784. As I discuss above, these prior art references, including Dixon, the press releases I discuss above, including at least the May 8, 2008 press release, and particular SEC forms, all disclose each and every element of the claims of the 338 patent.

785. I also understand that the Patent Trial and Appeal Board ("PTAB") recently invalidated the claims of the 338 patent that were challenged by Mylan. That proceeding is the same one in which I provided a declaration in support of Mylan's petition.

786. In the PTAB's Final Written Decision ("FWD"), the panel of three judges agreed with Mylan, and wrote that Dixon inherently discloses the claimed VEGF antagonist recited in the 338 patent claims (FWD at 29-40), and that Dixon discloses the treatment regimen set forth in the 338 patent claims (FWD at 41-45).

787. Accordingly, it is my opinion that the Dixon reference, as well as the other prior art VIEW dosing regimen disclosures are material with respect to claims directed to 2Q8 dosing, as confirmed by the PTAB's recent FWDs with regard to the 338 patent claims. Further, because the AMD-related claims in the 601 and 572 patents are drawn to the same 2Q8 dosing regimen, the references are material to those claims as well.

788. In my opinion, the most reasonable inference to be drawn from Regeneron's and George Yancopoulos' omissions of the prior art during the prosecution of the 338 patent is that the omissions were made with the intention to mislead and deceive the Examiner. In addition, I believe the omissions and misstatements were material, because if the Examiner would have had all of the facts discussed above, he would have rejected the claims on the same bases that Mylan challenged the 338 patent claims in IPR and on the same bases that the Patent Office invalidated those same claims in its FWD.

2. The 601 and 572 patents.

789. In addition, I have reviewed the prosecution histories of the 601 and 572 patents. There, I understand that Regeneron and George Yancopoulos (the lone named inventor on the 601 and 572 patents) did submit the Dixon reference and select press releases and SEC forms to the Examiner, but did so among hundreds of other references and almost 24,000 pages of material. (*See* Sections VI.B and VI.C).

790. Based on this production in the more recent applications, it is clear that Regeneron and George Yancopoulos were aware of these references and could have submitted them during prosecution of the 338 patent. (*See, e.g.*, RGN-EYLEA-MYLAN-00539067-68).

791. As such, I believe Regeneron's omissions in the earlier 338 patent prosecution, and its subsequent submissions of the VIEW clinical trial prior art disclosures among hundreds of other references, were made with the intent to deceive, and that they were material, because if the

Examiner would have been provided with the VIEW clinical trial dosing regimen prior art, he would have rejected the claims on the same bases that the PTAB recently invalidated the every-8-week dosing claims.

* * *

For at least the reasons set forth herein, it is my opinion that the Asserted Claims of the 601 and 572 patents are unenforceable for inequitable conduct.

VIII. FUTURE OPINIONS.

792. I reserve the right to supplement or amend this report based on additional information made available to me, including in light of the ongoing discovery, or in order to clarify the information provided herein. I specifically reserve the right to supplement or amend this report in response to any arguments made by Plaintiff or any expert for Plaintiff or any other party, and expect to supplement or amend this report in response to, at the very least, arguments made by one or more experts for Plaintiff. I also reserve the right to supplement or amend this report in light of any relevant Orders entered by the Court, including claim construction rulings.

IX. TRIAL EXHIBITS/TUTORIAL.

793. If I testify at trial in this case, I may rely on exhibits and/or visual aids to demonstrate the basis for my opinions. I have not yet prepared any such exhibits or visual aids, but expect that I may do so. I also reserve the right to provide a tutorial relating to the general topics contained in this report, including a discussion of the prior art references and products discussed herein.

X. INFORMATION CONSIDERED IN FORMING OPINIONS.

794. In forming the opinions set forth in this report, I considered and relied upon my education, background, and years of experience in the field of vitreoretinal disorders and the

treatment of the same. I also reviewed and considered the documents cited in this report and/or listed as part of this report in **Appendix A** and **Exhibit 2**.

XI. COMPENSATION.

795. Mylan, through its attorneys, has agreed to compensate me for my time spent working on this case at a rate of $750 per hour and $1,000 per hour for deposition testimony, and to reimburse me for reasonable expenses. My compensation is not at all dependent upon the substance of my opinions or testimony, or the outcome of this case.

XII. PRIOR TESTIMONY.

796. According to my records, I have testified as an expert by deposition in the following proceedings within the preceding four years:

- *Mylan Pharmaceuticals Inc. v. Regeneron Pharmaceuticals, Inc.*, IPR2021-00880 (P.T.A.B.); and
- *Mylan Pharmaceuticals Inc. v. Regeneron Pharmaceuticals, Inc.*, IPR2021-00881 (P.T.A.B.).

Dated: February 2, 2023

Dr. Thomas A. Albini