

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MYLAN PHARMACEUTICALS INC., CELLTRION, INC.,
and APOTEX INC.,
Petitioners

v.

REGENERON PHARMACEUTICALS, INC.
Patent Owner

Case IPR2021-00880¹
Patent 9,669,069 B2

Case IPR2021-00881
Patent 9,254,338 B2

EXPERT DECLARATION OF DAVID M. BROWN, M.D.

¹ IPR2022-00257, IPR2022-00258, IPR2022-00298, and IPR2022-00301 have been joined with this proceeding.

Exhibit 2050
Page 01 of 92

Mylan v. Regeneron IPR2021-00881 U.S. Pat. 9,254,338 Exhibit 2050
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TABLE OF CONTENTS

	Page No.
Contents	
I. Introduction.....	1
II. Qualifications and Experience.....	2
III. Summary of Opinions.....	4
IV. The Person of Ordinary Skill in the Art	5
V. Legal Standards	6
A. Burden of Proof.....	6
B. Obviousness.....	6
C. Anticipation	8
VI. The State Of The Art	8
A. The Prior Art Treatment of Angiogenic Eye Disorders with Anti-VEGF Therapies.....	8
B. The Need for an Extended Dosing Regimen.....	17
C. Extended Dosing Failures in the Prior Art.....	18
VII. Clinical Testing And Approval Of Eylea®	32
A. CLEAR-IT 2	34
B. VIEW 1 and VIEW 2	35
C. Approval of Eylea®	43
VIII. The '338 Patent	44
A. The Claimed Invention.....	44
B. Claim Construction	46
1. “A method for treating an angiogenic eye disorder in a patient”	46
2. “tertiary dose”	47

IX.	The '069 Patent.....	47
X.	'338 Patent, Ground 6: The Challenged claims are not Obvious Based on Dixon.....	49
A.	The POSA Would Not Have Had a Reasonable Expectation of Success That the Claimed Q8 Dosing Regimen Would Be Effective Until After Regeneron's VIEW Trials.	49
1.	Failures to Achieve an Extended Dosing Regimen in the Art Would Have Led the POSA to Be Skeptical About the Disclosed Q8 Dosing Regimen.	50
2.	The Fact That Regeneron Initiated Phase 3 Testing Would Not Have Provided the POSA with a Reasonable Expectation of Success.	51
3.	The Results of CLEAR-IT 2 Would Not Have Provided the POSA With a Reasonable Expectation of Success.....	55
4.	Dixon Cautioned That the Most Effective Dosing Regimen Was Not Established.	61
XI.	'069 Patent, Ground 4: The Challenged Claims Are not anticipated or obvious Based on VIEW 1/VIEW 2 as Disclosed In Dixon.....	62
A.	The VIEW 8-Week Dosing Regimen is Fixed, Not As-Needed / <i>Pro Re Nata</i> (PRN).....	62
B.	The POSA Would Not Have Been Motivated to Replace VIEW's 8-Week Fixed Dosing Regimen with PRN Dosing.	62
XII.	'069 Patent, Ground 5: The Challenged Claims Are not obvious Based on HEIER-2009 In View Of Mitchell Or Dixon.	67
XIII.	Objective Indicia Of Non-Obviousness.....	74
A.	Long-Felt Need for an Extended Dosing Regimen.....	74
B.	Satisfaction of a Long-Felt Need	77
C.	Failure of Others to Achieve an Extended Dosing Regimen	79
1.	Lucentis (ranibizumab)	79
2.	Macugen.....	81
3.	Conbercept	83

D.	Unexpected Benefits	84
E.	Industry Praise and Recognition	86

I, Dr. David Brown, declare as follows:

I. INTRODUCTION

1. I have been retained by counsel for Regeneron Pharmaceuticals, Inc. (“Regeneron”) as a technical expert in connection with the above-captioned proceeding. I have been asked to provide my opinions and views on the materials I have reviewed in relation to the Petition for *Inter Partes* review of U.S. Patent No. 9,254,338 (“the ’338 Patent”) (Ex. 1001)² and the Petition for *Inter Partes* review of U.S. Patent No. 9,669,069 (“the ’069 Patent”) (Ex. 1019). In particular, I have been asked to comment on the state of the art as of the earliest filing date (“priority date”) of the ’338 and ’069 Patents and to respond to the opinion and views of Petitioner’s declarant, Thomas A. Albini, M.D. I submit this declaration in support of Regeneron’s Patent Owner Responses (“PORs”).

2. I am being paid at my usual and customary rate for my work on this matter. I have no personal or financial stake in, or affiliation with, the petitioner, real-parties-in-interest, or the patent owner. My compensation is not dependent upon the outcome of, or my testimony in, the present proceeding.

² Unless otherwise noted, all citations to exhibits refer to exhibits filed in IPR2021-00881, and all pin cites refer to the stamped exhibit page.

II. QUALIFICATIONS AND EXPERIENCE

3. I am the Director of the Greater Houston Retina Research Center, where I have been a Physician Partner and Researcher since 1995. I also have a series of academic appointments: Clinical Professor of Ophthalmology, Cullen Eye Institute at Baylor College of Medicine; Vice-Chair of Ophthalmology for Research and Associate Clinical Professor of Ophthalmology at the Methodist Hospital, Weill Cornell College of Medicine in Houston, Texas; and the NASA Research and Clinical Advisory Panel—Space Associated Neuro-Ophthalmic Syndrome at NASA Johnson Space Center in Houston, Texas.

4. I graduated from Baylor College of Medicine with highest honors in 1988. I completed a medical/surgical internship at Baylor College of Medicine from 1989-1990. From 1990-1995, I completed ophthalmology and retina training at the University of Iowa where I was a Thomas Heed Fellow, a Hermann Knapp Fellow, and was awarded the Ron Michels Fellowship award presented to the top retinal surgery fellow in the United States in 1994.

5. I have served on the Board of Directors of the American Society of Retina Specialists since 2014; the Macula Society Credentials Committee since 2013; and the Retina Society Finance Committee since 2018. I have served in numerous additional leadership roles in professional organizations and societies in the retina and ophthalmology field over the past three decades. I have also been a peer

reviewer for the journals in these fields, including OPHTHALMOLOGY, RETINA, and the New England Journal of Medicine,

6. I maintain an active medical and surgical practice focused on treatment of retinal diseases and have continuously been elected as one of the “Best Doctors in America” from 2007-2021 and “Texas Super Docs” from 2009-2021. I am also an elected member of the Macula Society, the Retina Society, and the Club Jules Gonin. My honors include the American Academy of Ophthalmology Honor Award (2000), the American Society of Retina Specialists Honor Award (2008), the ASRS Senior Honor Award (2010), the AAO Senior Honor Award (2014), and Retina Hall of Fame inaugural inductee (2017).

7. My research and clinical trial experience has led to my recognition as an international thought leader on treatments and current standards of care for age related macular degeneration, retinal vein occlusion, and diabetic retinopathy. I have written and published over 400 national meeting presentations, abstracts, and scientific papers including many of the primary papers establishing the safety and efficacy of use of anti-vascular endothelial growth factor (“anti-VEGF”) agents for wet age-related macular degeneration (“wAMD”), retinal vein occlusion, and diabetic retinopathy.

8. I have served as a key investigator on the seminal Phase III clinical trials establishing the efficacy of anti-VEGF agents ranibizumab (Genentech’s

Lucentis) and aflibercept (Regeneron's Eylea) in wAMD, diabetic macular edema and diabetic retinopathy, and retinal vein occlusions. For example, I was a lead investigator on Genentech's Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-related Macular Degeneration (ANCHOR) Study, the Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular AMD (MARINA) Study, and Regeneron's VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD (VIEW1) Study. My research efforts have contributed to a transformation in the nature of treatments and outcomes for angiogenic eye disorders. A current copy of my curriculum vitae is filed herewith as Ex. 2083.

III. SUMMARY OF OPINIONS

9. My opinions and views set forth in this declaration are based on my education, training, research, and clinical experience in ophthalmology, specifically in researching and treating retinal diseases, as well as the materials I reviewed in preparing this declaration and the state of scientific knowledge in the art pertaining to the subject matter of the '338 patent at the time of its earliest priority application.

10. In forming my opinions, I have reviewed the following materials: (a) the Petition for *Inter Partes* Review of U.S. Patent No. 9,254,338 B2, IPR2021-00881, including all cited exhibits; (b) the Petition for *Inter Partes* review of U.S. Patent No. 9,669,069 B2, IPR2021-00880, including all cited exhibits; (c) all other

documents and references herein; and (d) the Patent Owner's Response to which my declaration relates.

IV. THE PERSON OF ORDINARY SKILL IN THE ART

11. I am informed that the person of ordinary skill in the art is a hypothetical person who is presumed to have access to, and be aware of, all of the relevant prior art at the time of the invention. At times I will refer to such person as the "POSA."

12. In forming my opinions, I have been asked to consider the level of ordinary skill in the art as it relates to the earliest effective filing date of the '338 Patent and '069 Patents. I understand that the application that led to the '338 Patent was filed on July 12, 2013. I understand that the application that led to the '069 Patent was filed on December 17, 2015. I further understand that both applications claim priority to provisional applications filed on January 13, 2011, January 21, 2011, and November 21, 2011. I have been informed and understand that the earliest filing date of the '338 Patent and the '069 Patent is January 13, 2011.

13. I understand that Petitioner contends that a person of ordinary skill in the art of the '338 and '069 Patents 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.

14. I understand that Patent Owner contends that the skilled artisan is an ophthalmologist with experience in treating angiogenic eye disorders, including through the use of VEGF antagonists.

15. My opinions set forth in this declaration remain the same under either Petitioner's or Patent Owner's definition.

V. LEGAL STANDARDS

16. I am not an expert in the law. The legal standards I have applied were explained to me by counsel for Patent Owner.

A. Burden of Proof

17. I have been informed that each claim of an issued patent is presumed to be valid. To overcome that presumption of validity, the party challenging the claim's validity must establish unpatentability by a preponderance of the evidence.

B. Obviousness

18. I have been informed that a patent challenger may contend that a patent claim is invalid by arguing that it would have been obvious to a person of ordinary skill in the art at the time of the claimed invention.

19. I have been informed that a patent claim is obvious in view of the prior art if the differences between the patented claims and the prior art are such that, at the time of the invention, the subject matter as a whole would have been obvious to a POSA.

20. I have been informed that the factors to be considered in analyzing whether a claim was obvious are (i) the scope and content of the prior art; (ii) the differences between the prior art and the claims; (iii) the level of ordinary skill in the art; and (iv) any asserted objective indicia of non-obviousness.

21. I have been further informed that objective indicia of non-obviousness are considered when assessing whether an invention would have been obvious at the time of the invention, as a check against “hindsight bias”—the inclination after a problem has been solved to see the solution as obvious or predictable when it was not.

22. I have been informed that objective indicia of non-obviousness may include satisfying a long-standing problem or long-felt need, failure of other, unexpected benefits or results, industry skepticism, and praise for the invention.

23. I have been informed that the objective indicia of non-obviousness should have a “nexus” to the claimed invention, that is, a link to the claimed invention. I am informed that such a “nexus” may exist when the objective indicia

are tied to a product that embodies the claimed invention or a product whose use embodies the claimed invention.

C. Anticipation

24. I have been informed that for a patent to be valid, the invention claimed must be novel (*i.e.*, new). A claimed invention that is not novel is said to be “anticipated.”

25. I have also been informed that for a claim to be anticipated, every limitation of the claimed invention must be found in a single prior art reference, either expressly or inherently. I understand that the words of a prior art reference do not have to be in the same words as the claim but that all limitations must be present.

VI. THE STATE OF THE ART

A. The Prior Art Treatment of Angiogenic Eye Disorders with Anti-VEGF Therapies

26. Angiogenic eye disorders, characterized by pathologic growth of abnormal blood vessels and vascular leakage from damaged blood vessels in the retina, present significant risks to patients’ vision absent treatment. Angiogenic eye disorders, or neovascular eye diseases, include conditions such as iris neovascularization, retinal vein occlusion, diabetic retinopathy, diabetic macular edema, neovascular glaucoma, wAMD, and retinopathy of prematurity. Ex. 2084 at

5.³ A shared feature of angiogenic eye disorders is the presence of elevated ocular levels of VEGF, a molecule that plays a critical role in the pathology of angiogenesis and vascular permeability.

27. By 2005, it was recognized by the POSA that treating patients with certain anti-VEGF agents, which reduce ocular VEGF levels, could reduce the incidence of pathologic angiogenesis and vascular permeability, and prevent loss of vision and even, in many cases, improve vision. Before the use of anti-VEGF agents, treatments for angiogenic eye disorders included methods such as laser ablation and photodynamic therapy (“PDT”). These treatments generally did not improve vision in a clinically significant manner and often carried risks of further vision loss through, for example, irreversible scarring of the retina and choroid at the site targeted by the treatment.

28. Of the angiogenic eye disorders, wAMD had a particularly poor prognosis, as vision loss in these patients could be sudden, severe, and irreversible. Laser and PDT treatments generally could only slow eventual vision loss or mitigate the extent of the area of central total vision loss. Unlike certain other angiogenic eye disorders such as diabetic macular edema and retinal vein occlusion, wAMD is less

³ Anthony P. Adamis, *Ocular Angiogenesis: Vascular Endothelial Growth Factor and Other Factors*, in *Retinal Pharmacotherapy* 23 (Quan Dong Nguyen et al. eds., 2010).

forgiving if patients wait too long to receive initial treatment or are not treated at sufficiently regular intervals. With wAMD, irreversible vision loss stems from a combination of retinal pigment epithelium (“RPE”) rips, subretinal hemorrhages, and atrophy of the photoreceptors overlying the RPE, as well as fibrosis secondary to long-standing retinal and subretinal edema.

29. Early investigation of anti-VEGF agents to treat wAMD included the use of pegaptanib (Macugen[®]) and investigation of the use of off-label injections of Genentech’s VEGF antibody drug bevacizumab (Avastin[®]).

30. Macugen[®] was the first anti-VEGF agent approved for treatment of angiogenic eye disorders, specifically wAMD. Ex. 2117.⁴ Macugen was approved in 2004 for administration once every six weeks based on two pivotal Phase 3 studies. Ex. 2038 at 3-5, 7.⁵ The primary efficacy endpoint for Macugen trials was the proportion of patients losing less than 15 letters of visual acuity. *Id.* at 4 (“On average, Macugen 0.3 mg treated patients and sham treated patients ***continued to experience vision loss***. However, the rate of vision decline in the Macugen treated group was slower than the rate in the patients who received sham treatment.” (emphasis added)).

⁴ Letter from Jonca C. Bull, Dir., Office of Drug Evaluation V, CDER, to Loni da Silva, Vice President, Glob. Regulatory Affairs, Eyetech Pharms., Inc. (Dec. 17, 2004).

⁵ Macugen Label (2004).

31. The major clinical experimentation that established for the retinal community the efficacy of anti-VEGF therapy, however, came with Genentech's drug, ranibizumab (Lucentis[®]), a VEGF antibody fragment designed to be injected intravitreally into the patient's eye at regular intervals.

32. In 2003, before the approval of Macugen, Genentech began two large-scale, randomized Phase III clinical trials to test monthly ranibizumab injections in subjects with wAMD—MARINA and ANCHOR. I served as a principal investigator for both of these studies and was the first author on the NEJM primary manuscript for ANCHOR, Ex. 2118,⁶ and second author on the NEJM primary manuscript for MARINA, Ex. 2119.⁷

33. The MARINA trial ran from March of 2003 to December 2005 and enrolled 716 subjects with wAMD, with either minimally classic or occult choroidal neovascularization ("CNV"), were randomly assigned to received 24 monthly intravitreal injections of Lucentis (either 0.3 mg or 0.5 mg) or sham injections. Ex. 2119 (MARINA) at 2-3. The primary endpoint of the study was the proportion of subjects losing fewer than 15 letters from baseline visual acuity at 12 months. *Id.* at 2.

⁶ David M. Brown et al., *Ranibizumab Versus Verteporfin for Neovascular Age-Related Macular Degeneration*, 355 N. Eng. J. Med. 1432 (2006).

⁷ Philip J. Rosenfeld, David M. Brown et al., *Ranibizumab for Neovascular Age-Related Macular Degeneration*, 355 N. Eng. J. Med. 1419 (2006).

34. One-year results of the MARINA trial were presented by Genentech in July of 2005. Ex. 2120 at 4.⁸ The results showed that nearly ninety-five percent of subjects treated with Lucentis[®] maintained or improved vision at 12 months. *Id.* The two-year results of the MARINA trial were then published in the New England Journal of Medicine on October 5, 2006. Ex. 2119 (MARINA). The mean improvements in vision demonstrated in the first 12 months of the study were sustained through the second years of study. *Id.* at 11. Mean increases in visual acuity were +6.5 letters in the 0.3 mg group and +7.2 letters in the 0.5 mg groups, compared with a decrease of -10.5 letters in the sham-injection group. Ex. 2120 (Dec. 30, 2005, Genentech Press Release) at 4. Impressively, visual acuity improved by 15 or more letters in 24.8% of the 0.3 mg group and 33.8% of the 0.5 mg group. *Id.*

35. The unmasking of the one-year results of the MARINA study prompted discussion with the data and safety monitoring committee, and it was determined in October 2005, 2 months before the end of the patient's final study visit at 24 months, that all subjects still in the sham arm could be offered ranibizumab injections.

⁸ Press Release, *Genentech, Inc. Submits Biologics License Application for FDA Review of Lucentis^(TM) In Wet Age-Related Macular Degeneration* (Dec. 30, 2005), <https://www.biospace.com/article/releases/genentech-inc-submits-biologics-license-application-for-fda-review-of-lucentis-tm-in-wet-age-related-macular-degeneration-/>.

Monthly ranibizumab injections were determined by this point to be a critical tool to not only arrest vision loss in wAMD patients, but to offer hope for sustained improvements in visual acuity.

36. The MARINA results were supplemented by the outcomes from the ANCHOR trial. The ANCHOR trial ran from May of 2003 to September of 2006 and enrolled 423 subjects with predominantly classic choroidal neovascularization in wAMD. Ex. 2118 (ANCHOR) at 1. Study subjects were randomized to receive monthly intravitreal Lucentis (0.3 mg or 0.5 mg) plus sham photodynamic verteporfin therapy or monthly sham injections plus active verteporfin therapy. *Id.* As in MARINA, the primary endpoint of the study was also the proportion of patients losing fewer than 15 letters from baseline visual acuity at 12 months. *Id.*

37. One-year results of the ANCHOR trial were presented by Genentech in November of 2005. Ex. 2120 (Dec. 30, 2005, Genentech Press Release) at 2-3. Preliminary one-year data showed that approximately 94 percent of subjects treated with 0.3 mg of Lucentis and 96 percent of those treated with 0.5 mg of Lucentis maintained or improved vision compared to approximately 64 percent of those treated with PDT alone. *Id.* The one-year results were published in the New England Journal of Medicine on October 5, 2006, a paper on which I served as the first author. Ex. 2118 (ANCHOR). The two-year results of ANCHOR were then published in

January 2009 in Ophthalmology. Ex. 2085.⁹ In the ANCHOR study, visual acuity improved from baseline, on average, by +8.1 to +10.7 letters, versus a mean decline of -9.8 letters in the verteporfin photodynamic group. *Id.* at 1. Impressively, visual acuity improved by 15 or more letters in 35.7% of the 0.3-mg group and 40.3% of the 0.5-mg group at Month 12. *Id.* at 4.

38. ANCHOR, while confirming the effectiveness of a monthly intravitreal ranibizumab treatment regimen, also represented a “major breakthrough in the treatment of predominantly classic CNV secondary to AMD” by showing this treatment was “superior to verteporfin PDT” treatment. Ex. 2085 (ANCHOR 2009) at 7. “The VA benefit from ranibizumab was both rapid and sustained: The superiority of ranibizumab to PDT was evident by 1 month after starting treatment, increased to a plateau by the end of the first year, and then persisted through month 24.” *Id.* Like the MARINA study, the positive results demonstrated in the ranibizumab treatment arms resulted in a protocol amendment that allowed subjects in the PDT-alone arm of the study to cross over to ranibizumab injections during the latter part of the study. *Id.* at 4.

⁹ David M. Brown et al., *Ranibizumab Versus Verteporfin Photodynamic Therapy for Neovascular Age-Related Macular Degeneration: Two-Year Results of the ANCHOR Study*, 116 Ophthalmology 57 (2009).

39. To put this in perspective if a patient were to come to me with 20/80 vision, which was the average vision at study initiation of subjects in Regeneron's VIEW 1 trial, Ex. 1018, tbl.1,¹⁰ they would no longer be able to have a driver's license in any state in the United States. If I could treat that patient's underlying angiogenic eye disorder and the patient were to gain between 8-10 letters from anti-VEGF therapy, that would translate into vision better than 20/63, putting that patient well within the guidelines for a daytime driver's license. Thus, a gain of letters can translate into a meaningful real-world difference for patients. Once a therapy was available that could deliver visual acuity gains, physicians and their patients were no longer content to simply slow disease progression.

40. Based on this data from MARINA and ANCHOR, Lucentis received FDA approval for the treatment of wAMD in June 2006. Ex. 2121 at 2.¹¹ By this point in time, it was well established in the retinal community that standard of care had moved beyond observation and monitoring or destructive therapies (MPS photocoagulation-style laser or PDT with verteporfin) for wAMD to frequent intravitreal injections of ranibizumab (or off-label Avastin), which demonstrated the ability to improve vision , and maintain those gains over the course of treatment.

¹⁰ Jeffrey S. Heier, David M. Brown et al., *Intravitreal Aflibercept (VEGF Trap-Eye) in Wet Age-Related Macular Degeneration*, 119 *Ophthalmology* 2537 (2012).

¹¹ Press Release, Genentech, *FDA Approves Lucentis for the Treatment of Wet Age-Related Macular Degeneration* (June 30, 2006).

41. After Lucentis approval, the POSA would not have viewed “loss of less than 15 letters on ETDRS best corrected visual acuity” as an effective treatment for an angiogenic eye disorder.

42. Indeed, Macugen use, which was approved based on a primary endpoint of “loss of less than 15 letters on ETDRS best corrected visual acuity,” all but disappeared once Lucentis was approved. Ex. 2038 (Macugen 2004 label) at 3-4. Even though Macugen was indicated for injection every 6 weeks, as compared to Lucentis’ recommended dosing regimen of once every 4 weeks, retina doctors promptly stopped using Macugen in favor of Lucentis or off-label Avastin. Simply put, Lucentis moved the goal post and *visual acuity gains* became the new standard-of-care in treating wAMD. The slow decline of vision loss was no longer viewed as effective treatment of angiogenic eye disorders once there was an approved therapy that could significantly improve vision in the average patient even if this meant that patients needed more frequent visits and injections.

43. In fact, clinical trials conducted *after* Lucentis’ approval typically measured efficacy in terms of visual acuity gains, not losses, for example:

- **RISE/RIDE** (Genentech, Inc.): percentage of patients who gained ≥ 15 letters in BCVA at month 24 (Exs. 2122 and 2123);
- **BRAVO/CRUISE** (Genentech, Inc.): mean change from baseline in BCVA score at 6 months (Exs. 2124 and 2125); and

- **COPERNICUS/GALILEO** (Bayer/Regeneron): percentage of participants who gained at least 15 letters in BCVA as measured by ETDRS Letter Score at week 24 (Exs. 2126 and 2127).

44. Indeed, Regeneron's clinical trials of VEGF Trap-Eye (that were not designed as non-inferiority trials), used mean change in visual acuity from baseline (Phase II DME Study, Example 5) and proportion of patients who gained ≥ 15 letters in BCVA at month 24 (Phase III Study in CRVO, Example 6) as primary endpoint measures of efficacy. *See* Ex. 1001 ('338 Patent) at 13:50-14:26, 14:35-15:8.

B. The Need for an Extended Dosing Regimen

45. While MARINA and ANCHOR changed the treatment paradigm for wAMD, a persistent goal of the retinal community was to find a treatment regimen that required less than monthly visits to an ophthalmologist. Intravitreal injections, while generally safe, present the risk of rare but serious adverse events such as endophthalmitis, severe intraocular inflammation, and retinal detachment. Further, monthly visits for injections are costly and burdensome to patients, their caregivers, and physician practices. Even simple monthly monitoring, while reducing risk from IVT injections themselves, is burdensome, as patients with wAMD are typically elderly and in-person visits present a challenge for the patient and their caretakers. *See* Ex. 1018 (Heier 2012) at 9 ("Because of the large treatment burden, extensive efforts have been devoted toward developing an optimized treatment paradigm that avoids the need for monthly injections or monitoring visits.").

C. Extended Dosing Failures in the Prior Art

46. Dr. Albin notes that after ANCHOR and MARINA, Genentech also conducted a number of studies with Lucentis in an effort to explore less frequent dosing, including SUSTAIN, EXCITE, PrONTO, SAILOR, and PIER. Ex. 1002 (Albin Decl.) at ¶ 60, citing Ex. 1030 (Mitchell) at 6-7. Yet, each of these prior art studies with Lucentis demonstrated inferior results to the fixed monthly dosing regimen of ANCHOR and MARINA.

47. In 2004, Genentech initiated the PIER Study, which ran from August 2004 to March 2007, and was designed to compare three monthly loading doses followed by fixed quarterly dosing of 0.3 mg and 0.5 mg Lucentis against sham control over 24 months in 184 patients. Ex. 2086 at 2, 4.¹² I participated as a clinical investigator, was part of the PIER Study Group, and was also involved in the presentation and publication of the Year One data from PIER. As explained below, the PIER Study revealed that fixed quarterly intravitreal injections of ranibizumab over an extended treatment period was not an effective method of treatment.

48. As one of the lead clinical investigators on the PIER trial, I received the first read-out of the one-year data from the study from Genentech in early 2006, and was the first to present on this data at the Retinal Physician Symposium held in the

¹² Carl D. Regillo, David M. Brown et al., *Randomized, Double-masked, Sham-controlled Trial of Ranibizumab for Neovascular Age-related Macular Degeneration: PIER Study Year 1*, 145 Am. J. Ophthalmology 239 (2008).

Bahamas from May 31-June 3, 2006. The data was highly disappointing to say the least. While patients saw an initial gain in visual acuity during the three monthly loading doses, these gains were entirely lost once quarterly dosing began. Ex. 2086 (PIER 2008) at 7 (“On average, there was 4.5-letter decline in VA between month three and month 12 for both ranibizumab dose groups.”). By month twelve, the 0.3 mg study arm saw a -1.6 letter difference from baseline visual acuity, and the 0.5 mg study arm saw a -0.2 letter difference from baseline. *Id.* at 5 fig.1.

49. Optical coherence tomography (“OCT”)-assessed anatomic outcomes in the Year One data also confirmed ranibizumab’s failure to maintain efficacy over the quarterly dosing period. The maximal decrease in foveal center point thickness was seen at months two and three for both ranibizumab groups. Ex. 2086 (PIER 2008) at 7. During assessments made at months five and eight, the foveal center point thickness was on average greater than at months two and three, and was also greater than at month twelve, which had followed a ranibizumab dose at month eleven. *Id.* This suggested that, on average, ranibizumab’s therapeutic effectiveness in a patient would wane between injections, pointing to recurrent neovascular activity and associated exudation occurring between injections. Ex. 2042 at 4.¹³

¹³ Jonathan P. Levine et al., *Macular Hemorrhage in Neovascular Age-Related Macular Degeneration After Stabilization with Antiangiogenic Therapy*, 29 Retina 1074 (2009).

50. Over the course of the PIER study, the study sponsor (Genentech) implemented two key protocol amendments. First, the protocol was amended on February 27, 2006, to provide sham injection patients the opportunity to cross over to receive 0.5 mg ranibizumab quarterly after completing the month-12 visit (i.e., the assessment time point for the primary analysis). Ex. 2087 at 2.¹⁴ As explained above, the 12-month data from MARINA and ANCHOR had established to the retinal community that it would be in the best interest of subjects in the sham cohorts to be treated with ranibizumab, rather than be put further at risk for severe, irreversible vision loss under an observation-only or PDT scheme.

51. The second protocol amendment was the direct result of the review of the 12-month PIER data and the disappointing lack of efficacy of subjects in the treatment arms. On August 21, 2006, the study was amended to provide all patients remaining in the study the opportunity to roll over to receive 0.5 mg ranibizumab monthly for the remainder of the study. Ex. 2087 (Abraham 2010) at 2. The second year of the PIER study was functionally designed to be confirmatory of fixed quarterly dosing's efficacy, and given the disappointing lack of efficacy observed in the PIER quarterly treatment regimen, the study sponsor initiated a rollover at this

¹⁴ Prema Abraham et al., *Randomized, Double-Masked, Sham-Controlled Trial of Ranibizumab for Neovascular Age-Related Macular Degeneration: PIER Study Year 2*, 150 Am. J. Ophthalmology 315 (2010).

point to mitigate against future visual acuity losses, which would be expected on continued quarterly dosing.

52. The year-two results from PIER confirmed the disappointing lack of efficacy of the dosing regimen. The 0.3 mg ranibizumab group saw a mean loss of -2.2 letters as compared to baseline, and the 0.5 mg ranibizumab arm saw a mean loss of -2.3 letters as compared to baseline. Ex. 2087 (Abraham 2010) at 5 tbl.3. This stood in stark contrast to MARINA and ANCHOR. *Id.* at 8 (“In those studies, patients who received monthly injections of ranibizumab experienced a gain of 5 to 11 letters from baseline at month 24 compared to a loss of approximately 2 letters with the PIER dosing regimen.”). After approval of Lucentis, and certainly by 2011, the goal of any treatment regimen for age-related macular degeneration was to improve vision and maintain those gains and prevent blindness.

53. Post-hoc analyses of the study data from MARINA, ANCHOR, and PIER also demonstrated that while patients on monthly ranibizumab were significantly less likely to develop macular hemorrhages as compared to sham control, patients in the treatment arm of PIER saw no benefit in the incidence of

macular hemorrhage as compared to sham control and, indeed, incidence rates were numerically higher. Ex. 2088 at 3, 7.¹⁵

54. Importantly, macular hemorrhages are a hallmark of active wAMD and are considered to be a definitive sign of disease progression. “[W]hen occupying larger areas or located in the subfoveal region, they are usually associated with a poor visual prognosis in a majority of cases.” Ex. 2088 (Barbazetto 2010) at 1. It was a serious concern, therefore, that quarterly dosing did not decrease the incidence of macular hemorrhage as compared to sham and it was recognized that “switching from monthly to quarterly injection intervals may not have the same beneficial effect and could put the patient at an increased risk for vision threatening complications.” *Id.* at 9.

55. As a result, my conclusion from the PIER Study results was that “we cannot just mandatorily treat on a quarterly basis and maintain the visual gains seen with the first three monthly injections.” Ex. 2089 at 1¹⁶; *id.* at 2 (“You can’t just do mandatory quarterly injections.”). My expressed concerns with fixed quarterly

¹⁵ Irene Barbazetto et al., *Dosing Regimen and the Frequency of Macular Hemorrhages in Neovascular Age-Related Macular Degeneration Treated with Ranibizumab*, 30 Retina 1376 (2010).

¹⁶ Daniele Cruz, *PIER Data Suggest a Need for Tailored Injection Schedule*, Ocular Surgery News, (Sept. 1, 2006), <https://www.healio.com/news/ophthalmology/20120331/pier-data-suggest-a-need-for-tailored-injection-schedule>.

injections were shared across the retina community at the time. *E.g.*, Ex. 2042 (Levine 2009) at 4-5 (“A recent analysis of the ANCHOR, MARINA, and PIER data demonstrated that monthly intravitreal ranibizumab dosing significantly reduced the frequency of macular hemorrhages compared with the sham controls or photodynamic therapy-treated patients regardless of lesion type. ***The effect was lost when patients were switched from monthly to quarterly dosing in the PIER study. Reducing the frequency of injections should, therefore, be done with caution.***”) (emphasis added); Ex. 2090 at 2¹⁷ (“The PIER data have led Genentech to recommend that patients receive either monthly injections of ranibizumab, or have their retreatment schedules determined through individualized testing.”).

56. These concerns were also reflected in the FDA’s labeling when Lucentis was approved for wAMD treatment in June 2006, as PIER’s year-one results were included in the FDA’s review. Ex. 2121 (Genentech June 30, 2006, press release) at 2. The label explains: “Although less effective, treatment may be reduced to one injection every three months after the first four injections if monthly injections are not feasible. Compared to continued monthly dosing, dosing every 3 months will lead to an approximate 5-letter (1-line) loss of visual acuity benefit, on

¹⁷ *Retinal Physician Symposium Covers Broad Range of Topics*, Retinal Physician (Sept. 1, 2006), <https://www.retinalphysician.com/issues/2006/september-2006/retinal-physician-symposium-covers-broad-range-of>.

average, over the following 9 months. Patients should be evaluated regularly.” Ex. 2091 at 2.¹⁸

57. Dr. Albini proposes that this language in the FDA label would indicate that the PIER regimen “suggested a regimen of less frequent dosing following four monthly intravitreal injections.” Ex. 1002 (Albini Decl.) ¶¶ 58, 60. I disagree with Dr. Albini and note that he does not address the label’s explicit caution that this is a “less effective” regimen than fixed monthly, and that it “will lead” to a “loss of visual acuity benefit.” Ex. 2091 (Lucentis 2006 label) at 2.

58. It is my understanding that FDA would present a comprehensive look at the clinical data submitted when issuing approval guidelines, and indeed the clinical studies section of the Lucentis label (at §§ 14.1 and 14.2) plainly shows the drastic disparity between the study results from ANCHOR and MARINA and those of PIER. Ex. 2091 (Lucentis 2006 label) at 6-7. Figure 1 shows that the Lucentis 0.5 mg arm in Study 1 (MARINA) had a mean change in visual acuity of +6.6 letters at 24 months, and the Lucentis 0.5 mg arm in Study 2 (ANCHOR) had a +11.3 letters mean change at 24 months, while Figure 2 shows the Lucentis 0.5 mg arm in Study 3 (PIER) had a mean change of -0.2 letters at 12 months. *Id.* at 7. The import of

¹⁸ CDER Approved Labeling for BLA Application 125156 (Lucentis®) (2006).

these Figures would be clear to the POSA: The fixed quarterly dosing regimen of PIER carries a high risk for permanent vision loss.

59. In my opinion, FDA’s review and consideration of the PIER results, and this language in the label, would not suggest to the person of ordinary skill that quarterly maintenance dosing was an effective or acceptable option for a treatment regimen for a patient with an angiogenic eye disorder, such as wAMD. Indeed, I am not aware of any retina doctor who, after the results of PIER were published, would treat a wAMD patient on a Q12 maintenance dosing regimen of ranibizumab or would view such a dosing regimen as acceptable treatment for an angiogenic eye disorder.

60. I also disagree with Dr. Albini’s suggestion that the EXCITE study demonstrated that fixed quarterly dosing “could achieve outcomes similar to that observed for monthly dosing.” Ex. 1002 (Albini Decl.) ¶¶ 60, 408. The EXCITE study, which ran from December 2005 to January 2008, was designed to demonstrate the noninferiority of a quarterly treatment regimen to a monthly regimen of ranibizumab in patients with subfoveal CNV secondary to wAMD. Ex. 2092 at 2, 7.¹⁹ The study authors concluded that “noninferiority of a quarterly regimen was not

¹⁹ Ursula Schmidt-Erfurth et al., *Efficacy and Safety of Monthly Versus Quarterly Ranibizumab Treatment in Neovascular Age-related Macular Degeneration: The EXCITE Study*, 118 *Ophthalmology* 831 (2011).

achieved with reference to 5.0 letters.” *Id.* at 1. Like PIER, the treatment arms of EXCITE were administered as three monthly loading doses prior to fixed quarterly doses of ranibizumab, and also like PIER, EXCITE demonstrated losses of initial visual acuity gains after patients moved to quarterly injections. *Id.* at 5. The study group concluded: “The direct comparative analysis between monthly and quarterly treatment regimens of the EXCITE study is consistent with the clinical guidance on ranibizumab treatment, which recommends rigorous monthly monitoring with timely retreatment of patients with recurrent disease activity to achieve the best treatment outcomes for patients.” *Id.* at 8.

61. The SAILOR trial, while a quarterly PRN dosing regimen, further confirmed the problems with a quarterly treatment regimen. After 3 monthly loading doses, subjects had monitoring visits on a quarterly basis and were retreated on the basis of optical coherence tomography (OCT) or visual acuity (VA) criteria. Not surprisingly, by month 12, subjects had lost much of the visual acuity gains they achieved after three monthly loading doses. Ex. 2032 at 5-6 & fig.5.²⁰ In addition, because such a large number of study subjects discontinued in one of the SAILOR

²⁰ David S. Boyer, David M. Brown et al., *A Phase IIIb Study to Evaluate the Safety of Ranibizumab in Subjects with Neovascular Age-related Macular Degeneration*, 116 *Ophthalmology* 1731 (2009).

cohorts, the authors concluded that they could not accurately assess the results. *Id.* at 4 & tbl.3.

62. Indeed, Mitchell (Ex. 1030²¹), on which Dr. Albini relies, concludes, with respect to PIER, that “quarterly treatment is, on average, inferior to monthly treatment and that more frequent monitoring is needed.” Ex. 1030 at 8. Similarly, with respect to SAILOR, Mitchell notes that “quarterly visits were insufficient to monitor and capture disease progression.” *Id.* at 7.

63. Dr. Albini relies heavily on the PrONTO study to suggest that the POSA would have understood that similar visual acuity outcomes could be obtained with PRN treatment as compared with a monthly dosing regimen. Ex 1002 (Albini Decl.) ¶¶ 58, 62 (citing Ex. 1050²²); *see also* IPR2021-00880 Ex. 1002 (Albini Decl.) ¶ 194. I disagree.

64. PrONTO was a 40 patient, open-label, single center, non-randomized study that reported a 9.3 letter improvement in visual acuity at 12 months with an average of 5.6 injections and a median of 5 injections (as compared to 13 injections during the same period for the MARINA and ANCHOR studies, which saw 7.2-

²¹ P. Mitchell et al., *Ranibizumab (Lucentis) in Neovascular Age-related Macular Degeneration: Evidence from Clinical Trials*, 94 *Brit. J. Ophthalmology* 2 (2010).

²² Ursula Schmidt-Erfurth, *Current Concepts in the Management of Diabetic Macular Edema*, 7 *Johns Hopkins Advanced Stud. in Ophthalmology* 52 (2010).

letter and 11.3-letter improvements in visual acuity, respectively). Ex. 1034 at 14.²³ Importantly, there was significant selection bias in the study subject population, an unusually high number of visits mandated by the study protocol, and no control arm in the PrONTO study, so it is impossible to say how the treatment protocol would have compared with monthly dosing.

65. The PrONTO protocol mandated *24 dilated clinical visits with OCT testing and photography in the first 12 months*—i.e., 24 visits lasts approximately 3 hours each for a total of 72 in office hours annually. Ex. 1034 (PrONTO) at 3 (“Eligible patients underwent visual acuity testing and ophthalmoscopic examinations at baseline, day 14, day 30, day 46, day 60, and monthly thereafter. Fundus photography and OCT imaging were performed at baseline and on days one, two, four, seven, 14, and 30 after the first two monthly injections, and monthly thereafter. Fluorescein angiography was performed at baseline, month 1, month 2, month 3, and every three months thereafter.”). Thus, the PrONTO trial in no way decreased the burden of monthly treatment. Rather, it required patients to be seen

²³ Anne E. Fung et al., *An Optical Coherence Tomography-Guided, Variable Dosing Regimen with Intravitreal Ranibizumab (Lucentis) for Neovascular Age-related Macular Degeneration*, 143 Am. J. Ophthalmology 566 (2007). Notably, even the PrONTO study paper recognized that the PIER trial was unsuccessful: “The most likely explanation for these disappointing outcomes from the PIER trial is the need for more frequent retreatment in some patients as shown from the results of the PrONTO study.” *Id.* at 16.

much more frequently than once a month. In a bit of an understatement, Lalwani notes: “The PrONTO Study was designed to minimize the number of retreatments but not the number of visits.” Ex. 1035 at 14.²⁴ Even so, patients developed vision-threatening complications during PrONTO. Post-hoc analysis from PrONTO showed that PRN treatment with ranibizumab was not as effective as monthly treatment and, worse yet, led to significant and irreversible vision complications. See Ex. 2093 at 3²⁵ (“When treating patients on an ‘as-needed’ basis with either anti-VEGF monotherapy or combination approaches, we observed a subset of patients who experienced recurrent exudation with submacular hemorrhage shortly after a stable eye examination in which the Stratus OCT (Carl Zeiss Meditec) did not detect fluid before the event.”); see also Ex. 2042 (Levine 2009) at 4-5 (discussing the PrONTO, ANCHOR, MARINA, and PIER data and noting “monthly intravitreal ranibizumab dosing significantly reduced the frequency of macular hemorrhages ... *[but t]he effect was lost when patients were switched from monthly to quarterly dosing in the PIER study. Reducing the frequency of injections should, therefore, be done with caution.*”) (emphasis added).

²⁴ Geeta A. Lalwani et al., *A Variable-dosing Regimen with Intravitreal Ranibizumab for Neovascular Age-related Macular Degeneration: Year 2 of the PrONTO Study*, 148 Am. J. Ophthalmology 43 (2009).

²⁵ Ron Margolis & K. Bailey Freund, *Hemorrhagic Recurrence of Neovascular Age-Related Macular Degeneration Not Predicted by Spectral Domain Optical Coherence Tomography*, 4 Retinal Cases & Brief Rep. 1 (2010)

66. Lalwani reports on two-year data from PrONTO. Ex. 1035 (Lalwani 2009). Lalwani notes that the PrONTO protocol was amended in the second year to incorporate qualitative changes into the treatment criteria because of clinical observations, including at least one study subject who developed macular hemorrhage. *Id.* at 14.

67. While the results of PrONTO may seem promising, several important differences were noted as between PrONTO, on one hand, and MARINA and ANCHOR on the other, that would have limited the ability of the POSA to extrapolate results from PrONTO. Whereas MARINA and ANCHOR were large, double-masked, randomized, controlled Phase III clinical trials, PrONTO was a much smaller, open-label, unmasked study that enrolled a heterogeneous population of neovascular lesions with prior therapy permitted and selected primarily by the presence of macular fluid as detected using OCT. Ex. 1035 (Lalwani 2009) at 2-3, 14. Dr. Albini also relies on SUSTAIN to suggest that PRN dosing regimens in the art were able to deliver “outcomes similar to monthly dosing regimens of MARINA/ANCHOR.” Ex. 1002 (Albini Decl.) ¶¶ 60, 408; *see also* IPR2021-00880 Ex. 1002 (Albini Decl.) ¶ 107. The 12-month SUSTAIN results, although slightly better than those from SAILOR, were still not nearly as good as monthly treatment with Lucentis. The authors noted that “[o]ther relatively large studies using a traditional PRN approach” have “highlight[ed] an important trend: the best visual

acuity results come from the study with the greatest mean number of treatments and closest follow up, whereas the poorest outcomes were observed in the study with the lowest mean number of treatments and office visits.” Ex. 2030 at 4.²⁶ Indeed, Mitchell notes that visual acuity loss occurred after month 3 in SUSTAIN, whereas further visual acuity improvement was seen during the maintenance phase with fixed, monthly dosing. Ex. 1030 (Mitchell 2010) at 7 fig.1F, 9.

68. These trials—PIER, PrONTO, SAILOR, EXCITE, and SUSTAIN—confirmed either inferior results with quarterly dosing, as opposed to monthly dosing (ANCHOR and MARINA), of ranibizumab or loss of visual acuity coupled with severe vision-threatening complications with PRN dosing as compared to monthly dosing with ranibizumab. Ex. 2031 at 2²⁷ (“So giving patients a reduced number of injections—a therapy not based on objective factors of need—appeared to result in a less favorable outcome.”). As a result of these poor clinical outcomes, fixed quarterly dosing of ranibizumab was never adopted in clinical practice.

69. By 2011, the field continued to investigate extended dosing regimens to treat angiogenic eye disorders. As Jeffrey Heier, M.D., a colleague and co-investigator in the Regeneron Phase III wAMD trials (VIEW 1/2) noted: “Because

²⁶Young Gun Park et al., *New Approach of Anti-VEGF Agents for Age-related Macular Degeneration*, J. Ophthalmology (2012).

²⁷ Richard Spaide, *Ranibizumab According to Need: A Treatment for Age-related Macular Degeneration*, 143 Am. J. Ophthalmology 679 (2007).

of the large treatment burden, extensive efforts have been devoted toward developing an optimized treatment paradigm that avoids the need for monthly injections or monitoring visits.” Ex. 1018 (Heier 2012) at 9. Despite these efforts, before 2011, studies showed “fixed quarterly or ‘as needed’ (pro re nata [PRN]) dosing regimens, without requiring monthly monitoring visits, were not effective at maintaining vision.” *Id.* at 1 (alteration in original).

VII. CLINICAL TESTING AND APPROVAL OF EYLEA®

70. I served as a key investigator on the Phase II and III clinical trials establishing the efficacy of VEGF Trap-Eye (Regeneron’s Eylea) in wAMD, diabetic macular edema and diabetic retinopathy, and retinal vein occlusions. With respect to wAMD, I was a lead investigator on Regeneron’s Phase II Clinical Evaluation of Anti-angiogenesis in the Retina Intravitreal Trial (CLEAR-IT 2) and the Phase III VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD (VIEW 1 and VIEW 2) trials. I am the lead author of “Primary Endpoint Results of a Phase II Study of Vascular Endothelial Growth Factor Trap-Eye in Wet Age-related Macular Degeneration,” 118 Ophthalmology 1089 (2011) (Ex. 2094); a co-author with Jeff Heier on “The 1-year Results of CLEAR-IT 2, a Phase 2 Study of Vascular Endothelial Growth Factor Trap-Eye Dosed As-needed After 12-week Fixed Dosing,” 118 Ophthalmology 1099 (2011) (Ex. 2095); and a co-author with

Jeff Heier on “Intravitreal Aflibercept (VEGF Trap-Eye) in Wet Age-related Macular Degeneration.” 119 Ophthalmology 2537 (2012) (Ex. 1018).

71. In each of these clinical trials, Regeneron required its clinical investigators to sign a confidentiality agreement and clinical trial agreement that limited disclosure of information regarding its investigational drug, VEGF Trap-Eye. For example, my institution, Vitreoretinal Consultants of Houston, signed a Clinical Study Agreement to conduct a clinical study entitled “A Randomized, Double Masked, Active Controlled Phase III Study of the Efficacy, Safety, and Tolerability of Repeated Doses of Intravitreal VEGF Trap in Subjects with Neovascular Age-Related Macular Degeneration” concerning Protocol number VGFT-OD-0605, which required my institution/practice to maintain information disclosed by Regeneron or generated as a result of the study in confidence and also limited our use of such information only for the purposes of the study. Ex. 2096 ¶ 6.²⁸ In addition to the clinical study agreement, when our group/institution was provided the protocol for the VIEW trial, the document was clearly marked with a confidentiality legend and required that the clinical investigator sign the protocol and agree to be bound by its limitations on use and disclosure. Ex. 2128.²⁹

²⁸ Clinical Study Agreement Between Vitreoretinal Consultants and Regeneron Pharmaceuticals, Inc. (July 31, 2007).

²⁹ VGFT-OD-0605 (VIEW 1 Trial) Protocol Signature Page.

72. In addition, my institution was only authorized to provide the investigational drug, VEGF Trap-Eye, to study subjects who were enrolled in a Regeneron clinical trial and randomized to receive the drug as part of the conduct of the ongoing study. As part of the conduct of the clinical study, an unmasked auditor was assigned to ensure that all investigational product was accounted for, and at the end of the study, all remaining investigational product, in this case VEGF Trap-Eye, was returned to the Sponsor. I did not and was not authorized to provide Regeneron's study drug to any of my patients outside of the clinical study. Until it was FDA approved, there was no mechanism to get VEGF Trap-Eye to patients outside of an ongoing clinical trial. This is consistent with my experience in conducting other therapeutic clinical trials, including trials of ranibizumab. In my experience, VEGF Trap-Eye was not publicly available (or even available to my patients outside of clinical testing) until after it was approved by FDA.

A. CLEAR-IT 2

73. The CLEAR-IT 2 Study was designed to compare the effects of VEGF Trap-Eye administered in doses of 0.5 or 2 mg every 4 weeks, (0.5Q4 or 2Q4) on day 1 and at weeks 4, 8, and 12 for a total of 4 treatments or 0.5, 2, or 4 mg every 12 weeks (0.5Q12, 2Q12, or 4Q12) on day 1 and week 12 for a total of 2 treatments. Ex. 2094 (Brown 2011) at 2; *see also* Ex. 2095 (Heier 2011) at 2. The PRN dosing phase began at week 16 and continued through week 52. *Id.*

74. As discussed more fully in Section IX.A.3 below, the 12-week primary endpoint data from CLEAR-IT 2 indicated that fluid began to reaccumulate on the retina between the week-4 and week-8 in the quarterly dosing arm. The only dosing arms that were successful in sustaining therapeutic efficacy were the monthly treatment dosing arms (i.e., 0.5Q4 and 2Q4). *See* Section IX.A.3 *infra*. In addition, CLEAR-IT 2 demonstrated the importance of the monthly loading doses because, even after PRN dosing was available, the quarterly arms were never able to “catch-up” to the visual acuity gains of the treatment arms that had monthly loading doses in the first 12 weeks of treatment.

B. VIEW 1 and VIEW 2

75. Regeneron conducted two Phase 3 studies designed to test the use of VEGF Trap-Eye to treat wAMD as compared to ranibizumab (Lucentis): VIEW 1 and VIEW 2. Ex. 1018 (Heier 2012). The VIEW trials compared three different dosing arms of aflibercept to monthly administration of 0.5 mg of ranibizumab. *Id.* at 3-4.³⁰ At the conclusion of study enrollment, patients were randomized in a 1:1:1:1 ratio to the following four dosing regimens: 2 mg aflibercept every 4 weeks (2Q4); 0.5 mg aflibercept every 4 weeks (0.5Q4); 2 mg aflibercept every 8 weeks (2Q8) after 3 injections at week 0, 4, and 8 (to maintain masking, sham injections

³⁰ In the seminal publication on the VIEW trials, published in 2012, the study authors note intravitreal aflibercept injection had previously been called “VEGF Trap-Eye” in the literature. *Id.* at 3.

were given at the interim 4-week visits after week 8); or 0.5 mg ranibizumab every 4 weeks (RQ4). *Id.* at 4.

76. “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.” Ex. 1018 (Heier 2012) at 4. Prespecified secondary endpoints included “52-week data regarding mean change in BCVA; gaining ≥ 15 letters; change in total National Eye Institute 25-Item Visual Function Questionnaire (NEI VFQ-25) score; and change in CNV area on fluorescein angiography.” *Id.*

77. A non-inferiority study is often used when it would not be ethical to use a placebo because there is an existing effective treatment for the indicated condition. Ex. 2097 at 10.³¹ As discussed above, once ranibizumab was approved, it set a new bar for the effective treatment of angiogenic eye disorders. Consequently, Regeneron ran its VIEW 1 and VIEW 2 Phase III trials as noninferiority studies with Lucentis as an active comparator. A non-inferiority study also makes practical sense since clinicians and patients would not want to use an inferior treatment if a better treatment already existed.

³¹ FDA, Non-Inferiority Clinical Trials to Establish Effectiveness: Guidance for Industry (Nov. 2016).

78. A non-inferiority study seeks to show the amount (or margin) by which the test drug is inferior (or not) to the active control. In designing a non-inferiority study, FDA estimates this margin based on the past performance of the active control (here, Lucentis) and applies a “constancy assumption”—*i.e.*, that the non-inferiority study is sufficiently similar in study design (such as study endpoints, dose of active control, characteristics of patient population) to past studies with the active control that it is appropriate to use the historical studies to estimate the effect of the active control in the non-inferiority study. Ex. 2097 (FDA Guidance: Non-Inferiority Clinical Trials) at 11, 15-16. Thus, Regeneron’s VIEW trials used “loss of less than 15 letters on ETDRS best corrected visual acuity” as a primary endpoint because that was Genentech’s primary endpoint in its pivotal trials of Lucentis.

79. Multiplicity arising from the comparison of each of the three VEGF Trap-Eye regimens to ranibizumab was controlled using a conditional sequence of confidence intervals (CIs) for the statistical evaluation of non-inferiority of VEGF Trap-Eye to 0.5 mg ranibizumab. The treatments arms were ranked hierarchically in the following conditional sequence:

(1) 2 mg aflibercept every 4 weeks (2Q4) versus 0.5 mg ranibizumab given every 4 weeks (RQ4);

(2) 0.5 mg aflibercept every 4 weeks (0.5Q4) versus 0.5 mg ranibizumab given every 4 weeks (RQ4); and

(3) 2 mg aflibercept every 8 weeks (2q8) versus 0.5 mg ranibizumab given every 4 weeks (RQ4).

Ex. 2098 at 17.³² Based on my clinical trial experience, if Regeneron had an expectation that an 8-week maintenance dosing would be successful, it would have had a strong incentive to eliminate the 4-week VEGF Trap-Eye dosing arms given the additional time and expense required to test additional treatment arms, and Regeneron's size and financial condition at the time.

80. The primary end point analysis in VIEW showed that all VEGF Trap-Eye groups, including the group receiving 2q8 treatment, "achieved statistical noninferiority compared with monthly ranibizumab." Ex. 1018 (Heier 2012) at 5. "Regardless of whether the analysis was by LOCF, by multiple imputations, by assessing completers, or by using actual observed data, intravitreal aflibercept dosed every 2 months achieved a mean visual acuity score within 0.3 letters of monthly

³² CDER, Statistical Review for Application Number 125387 (Nov. 18, 2011).

ranibizumab in the integrated analysis, with a CI of less than 2 letters.” *Id.* at 6.

Figure 3 is reproduced below:

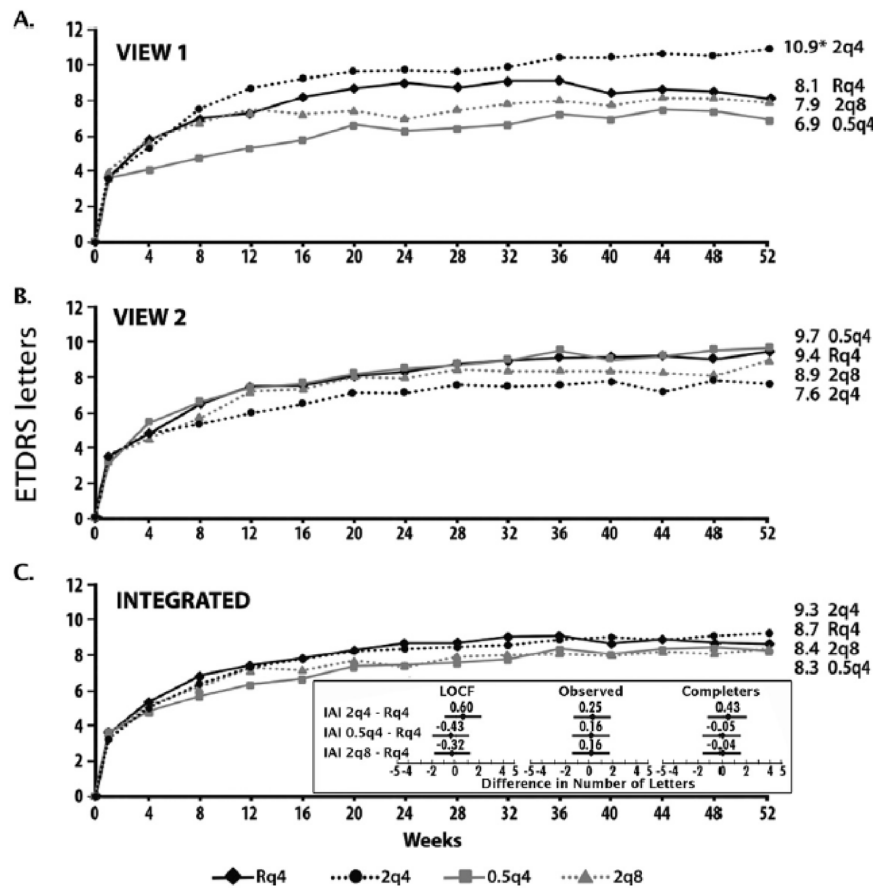


Figure 3. Mean change in best-corrected visual acuity (BCVA) from baseline to week 52 in the individual VIEW studies and in the integrated analysis. Values in the line graphs refer to mean changes in the number of letters from baseline at week 52. Only the intravitreal aflibercept 2q4 arm in VIEW 1 was significantly different from ranibizumab (*P = 0.005 for the difference). The panel inset (integrated analysis) shows the difference in visual acuity between each intravitreal aflibercept arm and ranibizumab (least-square mean with 95% confidence interval [CI]) at week 52, using 3 different analyses: by last observation carried forward (LOCF), using observed case data, and by assessing completers. Rq4 = 0.5 mg ranibizumab monthly; 0.5q4 = 0.5 mg IAI monthly; 2q4 = 2 mg IAI monthly; 2q8 = 2 mg IAI every 2 months after 3 initial monthly doses; ETDRS = Early Treatment Diabetic Retinopathy Study; IAI = intravitreal aflibercept injection.

Id. at 8.

81. Based on the observed clinical outcomes, we concluded that “all 3 aflibercept treatment regimens (*including the every-2-month regimen after 3 initial monthly loading doses*) were statistically noninferior to monthly ranibizumab in preventing moderate visual acuity loss at 1 year, meeting the primary outcome of the trials.” Ex. 2018 (Heier 2012) at 9 (emphasis added). While 94.4% of patients who received active control (0.5 mg ranibizumab Q4) met the primary endpoint, a larger proportion of patients in each VEGF Trap-Eye treatment arm also met this primary endpoint. VIEW trials 1 and 2 reported that, respectively, 95.1% and 95.6% of patients dosed 2q8 met this same endpoint. *Id.* at 5 tbl.1 and 6-7 tbl.2. We also observed “aflibercept dosed every 2 months achieved a visual acuity score within 0.3 letters of monthly ranibizumab, with a CI of less than 2 letters, regardless of the analysis set used.” *Id.* at 9.

82. We further noted “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.” Ex. 1080 (Heier 2012) at 10. As noted in the study, by halving the need for monthly visits, the every-2-month regimen of aflibercept markedly decreases the treatment burden experienced by patients and their families, and less frequent injections can provide

an ocular safety benefit. *Id.*; *see also id.* at 11 (“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.”).

83. The 52-week results from VIEW 1 and VIEW 2 are also set forth in the '338 Patent at Example 4. Ex. 1001 at 9:10-13:48. Based on review of the clinical trial data in the '338 Patent, the POSA would have understood that VEGF Trap-Eye was noninferior to standard-of-care Lucentis based on both a similar proportion of patients achieving the primary endpoint, as well as secondary endpoint data that showed similar mean visual acuity gains between the VEGF Trap-Eye dosing arms and the Lucentis active control arm. The POSA would not have considered the '338 patent specification to suggest that it was enough for some subjects to achieve the primary endpoint of “loss of less than 15 letters on ETDRS best corrected visual acuity” for VEGF Trap-Eye to demonstrate that it was noninferior to standard-of-care Lucentis. In addition, by 2011, average retinal specialist would not have thought that simply achieving “loss of less than 15 letters on ETDRS best corrected visual acuity” in a patient would be effective treatment of

an angiogenic eye disorder, nor would it show that VEGF Trap-Eye was noninferior to standard of care Lucentis (or off-label Avastin).

84. Based on these findings, Regeneron sought and received approval of VEGF Trap-Eye (later known as Eylea® or aflibercept)³³ for the treatment of wAMD—administration of 2 mg (0.05 mL) of Eylea® every 4 weeks (approximately every 28 days, monthly) for the first 3 months, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months) for the treatment of wAMD. Ex. 1091 (Eylea label) at § 2.2; *see also* Ex. 2116³⁴ at 1. This represented a major breakthrough in the treatment of wAMD and was the first approved treatment that permitted regular, fixed dosing at 8-week intervals.

85. It is worth noting that a retrospective analysis of VIEW, published in 2016, showed that for a subpopulation of patients with early persistent fluid, about 20% of the subjects in the VIEW trials, 8-week dosing was significantly less effective than monthly dosing. Ex. 2018 at 6³⁵ (“[W]hen early persistent fluid was

³³ “Intravitreal aflibercept injection (IAI) (previously known in the scientific literature as VEGF Trap-Eye, Regeneron, Tarrytown, NY, and Bayer HealthCare, Berlin, Germany) is a soluble decoy receptor fusion protein that is specifically purified and formulated for intraocular injection.” Ex. 1018 (Heier 2012) at 3.

³⁴ Press Release, Regeneron, *Regeneron Announces FDA Approval of Eylea® (Aflibercept) Injection for the Treatment of Wet Age-Related Macular Degeneration* (Nov. 18, 2011).

³⁵ Glenn J. Jaffe et al., *Differential Response to Anti-VEGF Regimens in Age-Related Macular Degeneration Patients with Early Persistent Retinal Fluid*, 123 *Ophthalmology* 1856 (2016).

present after the initial 3 injections (a finding present in approximately 20% of eyes initially treated with IAI and in 30% of eyes with Rq4), there may be a benefit to monthly IAI compared with the other regimens”). Consequently, in 2016, EYLEA®’s label was amended to specify that “[s]ome patients may need every 4 week (monthly) dosing after the first 12 weeks (3 months).” Ex. 2019 (Eylea 2016 label) at 1; *see also id.* (“[A]dditional efficacy was not demonstrated in most patients when EYLEA was dosed every 4 weeks compared to every 8 weeks.”).

C. Approval of Eylea®

86. Eylea® is a vascular endothelial growth factor (VEGF) antagonist that is indicated for, among other things, “the treatment of patients with: Neovascular (Wet) Age-Related Macular Degeneration (AMD).” Ex. 1091 (Eylea label) at § 1.1.

87. The active ingredient in Eylea® is the recombinant fusion protein VEGF Trap-Eye, which consists of “portions of human VEGF receptors 1 and 2 extracellular domains fused to the Fc portion of human IgG1.” Ex. 1091 (Eylea label) at § 11. Eylea® is believed to treat wAMD by binding to “VEGF-A and PlGF,” resulting in the inhibition of “binding and activation of [the] VEGF receptors.” *Id.* § 12.1.

88. Eylea® is “formulated as an iso-osmotic solution for intravitreal administration.” Ex. 1091 (Eylea label) § 11.

89. The Eylea[®] label instructs intravitreal injection of 2 mg (0.05 mL) of Eylea[®] every 4 weeks (approximately every 28 days, monthly) for the first 3 months, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months) for the treatment of wAMD. Ex. 1091 (Eylea label) § 2.2.

90. Eylea[®] was approved by FDA for the treatment of wAMD on November 18, 2011. Ex. 2075 (Eylea Approval Letter). Eylea[®] was not available to clinicians prior to its approval on November 18, 2011.

VIII. THE '338 PATENT

A. The Claimed Invention

91. The '338 Patent provides methods for treating angiogenic eye disorders, including wet age-related macular degeneration (wAMD), by the administration of a specific VEGF antagonist in a specified dosing regimen. Ex. 1001. I understand that Petitioner has challenged claims 1, 3-11, 13-14, 16-24, and 26 of the '338 Patent.

92. The '338 Patent has two independent claims, claim 1 and 14. Claim 1, reproduced below, is representative:

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

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

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

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

Ex. 1001 at 23:1-18.

93. The dosing regimen of Claim 1 is directed to the treatment of angiogenic eye disorders with a VEGF antagonist that has a particular amino acid sequence—i.e., VEGF Trap-Eye.

94. The dosing regimen of Claim 1 requires treatment of an angiogenic eye disorder by administration of an initial dose of the claimed VEGF antagonist followed by one or more “secondary” doses administered two to four weeks after the preceding dose, and then one or more “tertiary” doses that are administered at least eight weeks following the preceding dose.

95. Claim 14 differs from Claim 1 only with respect to the last “wherein clause” specifying the nucleic acid sequence of SEQ ID NO:1. I understand that SEQ ID NO:2 is the amino acid sequence that corresponds to the nucleic acid sequence SEQ ID NO:1.

96. Challenged Claims 3-11 and 13 depend from Claim 1, and further limit the timing between dosage administration, the specific angiogenic eye disorder to be treated, route of administration, and dosage amount. Similarly, Challenged Claims 16-24 and 26 depend from Claim 14, and further limit the timing between dosage administration, the specific angiogenic eye disorder to be treated, route of administration, and dosage amount.

B. Claim Construction

1. “A method for treating an angiogenic eye disorder in a patient”

97. I understand that the parties dispute the meaning of the term “a method for treating an angiogenic eye disorder in a patient.”

98. I have been informed that the Board has preliminarily found that the phrase “a method for treating an angiogenic eye disorder in a patient” is limiting because it “sets forth the essences of the invention” and prescribes the “specific purpose of treating an angiogenic eye disorder.” Paper 21 at 19.

99. I understand that Dr. Do has offered the opinion that the claim term “method for treating” in Claims 1 and 14 of the ’338 Patent requires highly effective treatment that was noninferior to the standard of care by the time the patent was filed in 2011.

100. I have reviewed Dr. Do’s declaration and agree with her conclusion that “method of treating” requires an effective treatment and, further, that by 2011, the

POSA would have understood an effective treatment was one that was at least noninferior to the standard of care, *i.e.*, Lucentis.

101. Moreover, in my role as a key opinion leader in the treatments for angiogenic eye disorders, as well as an active clinician and clinical instructor, I am very familiar with the standards for how retina specialists are trained, best clinical practices, and how in fact retina doctors treat patients. As discussed above, by the time that Lucentis received FDA approval it was well established in the retinal community that standard of care had moved beyond observation and monitoring or destructive therapies (laser or PDT) for wAMD to frequent intravitreal injections of ranibizumab (or off-label Avastin) to improve vision and, often, maintain those visual acuity gains over the course of treatment. *See supra* Section VI.A.

2. “tertiary dose”

102. I also understand that Dr. Do has offered the opinion that the claim term “tertiary dose” means “dose(s), administered after the initial and secondary doses, that maintain(s) the efficacy gain achieved after the initial and secondary doses.”

103. I have reviewed Dr. Do’s declaration and agree with her conclusion.

IX. THE ’069 PATENT

104. The ’069 Patent is titled “Use of a VEGF Antagonist to Treat Angiogenic Eye Disorders.” I understand that Petitioner has challenged claims 1 and 8-12 of the ’069 Patent.

105. Claim 1 of the '069 Patent, the only independent claim, is reproduced

below:

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 on an as-needed/pro re nata (PRN) basis, based on visual and/or anatomical outcomes as assessed by a physician or other qualified medical professional;

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

Ex. 1019 at 21:40-60.

106. A POSA would understand that claim 1 is directed to the treatment of angiogenic eye disorders with a VEGF antagonist that has a particular amino acid sequence—namely, SEQ ID NO:2.

107. Claim 8 depends from claim 1 and recites “wherein only two secondary doses are administered to the patient, and wherein each secondary dose is administered 4 weeks after the immediately preceding dose.” Ex. 1019 at 22:49-52.

108. Claims 9-12 depend from claim 1 and further limit the types of angiogenic eye disorders, administration route, and the nucleic acid sequence of the VEGF antagonist.

X. '338 PATENT, GROUND 6: THE CHALLENGED CLAIMS ARE NOT OBVIOUS BASED ON DIXON

A. The POSA Would Not Have Had a Reasonable Expectation of Success That the Claimed Q8 Dosing Regimen Would Be Effective Until After Regeneron's VIEW Trials.

109. The POSA would not have had a reasonable expectation of successfully achieving the Q8 dosing regimen claimed by the '338 Patent until after Regeneron conducted its VIEW 1/VIEW 2 trials. As discussed in Sections VI.C, the prior art was littered with failed efforts to develop an extended dosing regimen for the treatment of wAMD. Many of those failures were only recognized after the trial was completed or upon post-hoc analysis, which would have contributed to a general skepticism by the POSA regarding whether a prospective extended dosing regimen would be successful until the results were recognized. In addition, here, the Phase 2 results of VEGF Trap-Eye in CLEAR-IT 2 would have created uncertainty that VEGF Trap-Eye could be effective if dosed on a Q8 regimen. That same skepticism is reflected in Regeneron's design of its Phase 3 VIEW Studies, which ranked a Q8 dosing regimen as the least likely of the tested regimens to succeed. Taken together, the POSA would not have had any "expectation of success using the VIEW regimens to treat wAMD." Ex. 1002 (Albini Decl.) ¶ 367.

1. Failures to Achieve an Extended Dosing Regimen in the Art Would Have Led the POSA to Be Skeptical About the Disclosed Q8 Dosing Regimen.

110. As discussed in Section VI.C above, the extensive failure in the art to achieve an extended dosing regimen with ranibizumab would have led the POSA to have misgivings and no reasonable expectation that the extended fixed dosing regimen of VIEW 1/2 would be successful until results were obtained.

111. Dr. Albini suggests that PIER, PrONTO, SAILOR, EXCITE, and SUSTAIN taught the POSA that extended dosing regimens could be achieved. Ex. 1002 (Albini Decl.) ¶¶ 60, 408. This is incorrect. As discussed above, these studies confirmed the opposite—*i.e.*, demonstrating either inferior results with quarterly dosing of ranibizumab or loss of visual acuity gains with PRN dosing as compared to monthly dosing with ranibizumab. *See* Section VI.C *supra*; Ex. 2029 (Bhisitkul 2010) at 3-6.

112. Indeed, the seminal publication of the one-year results from the VIEW 1 and 2 studies noted that previously reported “fixed quarterly or ‘as needed’ (pro re nata [PRN]) dosing regimens without requiring monthly monitoring visits, were not effective at maintaining vision.” Ex. 1018 at 1 (alteration in original) (citing EXCITE (Ex. 2092 (Schmidt-Erfurth 2011)), HORIZON (Ex. 2029 (Bhisitkul 2010) at 4-5), PIER (Ex 2086 (Regillo 2008)), SAILOR (Ex. 2032 (Boyer 2009))).

113. Thus, prior art failures to achieve an effective extended dosing regimen demonstrate that there was great uncertainty as to whether Regeneron's fixed extended dosing regimen (with ≥ 8 weeks maintenance dosing) would work until the results of the VIEW 1/2 studies were reported.

2. The Fact That Regeneron Initiated Phase 3 Testing Would Not Have Provided the POSA with a Reasonable Expectation of Success.

114. Dr. Albini contends that the POSA would have a "reasonable expectation of success based on the Phase 2 data" from CLEAR-IT 2. Ex. 1002 ¶ 367. Dr. Albini posits that because Regeneron reported promising clinical results in CLEAR-IT 2, the POSA would have expected success in the VIEW 1/2 trials. *Id.* ¶ 367–68. I strongly disagree with Dr. Albini.

115. Dr. Albini's assertion that promising Phase 2 results provide a reasonable expectation of success in subsequent Phase 3 studies is incorrect.

116. As a general matter, large scale clinical trials routinely fail, even when phase 2 results show promise. *See* Ex. 2099³⁶ (describing 22 case studies where promising experimental therapies demonstrated lack of efficacy and/or safety in Phase 3 trials). Failed Phase 3 studies for investigational wAMD treatments have been common. For example, Phase 3 clinical trials for lampalizumab, Conbercept,

³⁶ FDA, *22 Case Studies Where Phase 2 and Phase 3 Trials Had Divergent Results* (Jan. 2017).

and Fovista all failed despite showing promising results in Phase 2 studies. Ex. 2020 (SPECTRI) at 1-2,³⁷ Ex. 2021 (CHROMA) at 1-2³⁸ (lampalizumab Phase 3 clinical trials, enrolling 975 and 906 patients respectively, that failed to meet primary endpoints); Ex. 2023 (PANDA-1) at 1-2,³⁹ Ex. 2022 (PANDA-2) at 1-2⁴⁰ (Conbercept Phase 3 clinical trials, enrolling 1,157 and 1,157 patients respectively, that failed to meet primary endpoints); Ex. 2024 at 1-2,⁴¹ Ex. 2025 at 1-2⁴² (Fovista Phase 3 clinical trials, enrolling 619 and 627 patients, that failed to meet primary endpoints). Thus, far from indicating expectation of success, Regeneron's

³⁷ A Study Investigating the Efficacy and Safety of Lampalizumab Intravitreal Injections in Participants With Geographic Atrophy Secondary to Age-Related Macular Degeneration (CHROMA), ClinicalTrials.gov, <https://clinicaltrials.gov/ct2/show/NCT02247479>.

³⁸ A Study Investigating the Safety and Efficacy of Lampalizumab Intravitreal Injections in Participants With Geographic Atrophy Secondary to Age-Related Macular Degeneration (SPECTRI), ClinicalTrials.gov, <https://clinicaltrials.gov/ct2/show/NCT02247531>.

³⁹ Efficacy and Safety Trial of Conbercept Intravitreal Injection for Neovascular AMD (PANDA-1), ClinicalTrials.gov, <https://clinicaltrials.gov/ct2/show/NCT03577899>.

⁴⁰ Efficacy and Safety Trial of Conbercept Intravitreal Injection for Neovascular AMD (PANDA-2), ClinicalTrials.gov, <https://clinicaltrials.gov/ct2/show/NCT03630952>.

⁴¹ A Phase 3 Safety and Efficacy Study of Fovista® (E10030) Intravitreal Administration in Combination With Lucentis® Compared to Lucentis® Monotherapy, ClinicalTrials.gov, <https://clinicaltrials.gov/ct2/show/NCT01944839>.

⁴² A Phase 3 Safety and Efficacy Study of Fovista® (E10030) Intravitreal Administration in Combination With Lucentis® Compared to Lucentis® Monotherapy, ClinicalTrials.gov, <https://clinicaltrials.gov/ct2/show/NCT01940900>.

commencement of the Phase 3 VIEW 1/2 studies merely indicates that it had sufficient data to hope that the trial could be successful.

117. Moreover, Regeneron's VIEW 1/2 study design confirms that there was great uncertainty as to whether an extended dosing regimen could be successful. Specifically, the VIEW trials included study arms with 2 mg and 0.5 mg administered on a 4-week dosing regimen (2Q4 and 0.5Q4), in addition to the 2Q8 study arm. *See* Section VII.B *supra*. These additional study arms increased the number of patients and time needed to conduct the clinical trial as well as the cost of the studies. At the time Regeneron was designing its Phase 3 trials, it needed to seek a collaboration partner in order to help fund the trials. If Regeneron had been able to save on the time and expense of recruiting for and running additional study arms (in other words, if it had been reasonably certain that Q8 maintenance dosing would work), it would have had every incentive to drop the 4-week VEGF Trap-Eye dosing arms from the VIEW studies.

118. Moreover, as discussed above, in the VIEW studies, Regeneron hierarchically ranked its treatment arms to demonstrate non-inferiority and it ranked the 2Q8 treatment arm third out of the three dosing arms in conditional sequence:

Multiplicity arising from the comparison of each of the three VEGF Trap-Eye regimens to ranibizumab was controlled using a conditional sequence of confidence intervals (CIs) for the statistical evaluations of non-inferiority of VEGF Trap-Eye to 0.5 mg ranibizumab. The conditional sequence was as follows:

- 1. 2 mg VEGF given every 4 weeks (2Q4) versus 0.5 mg ranibizumab given every 4 weeks (RQ4).**
- 2. 0.5 mg VEGF given every 4 weeks (0.5Q4) versus 0.5 mg ranibizumab given every 4 weeks (RQ4).**
- 3. 2 mg VEGF given every 8 weeks (2Q8) versus 0.5 mg ranibizumab given every 4 weeks (RQ4).**

Ex. 2098 (CDER Statistical Review for Application Number 125387) at 17.

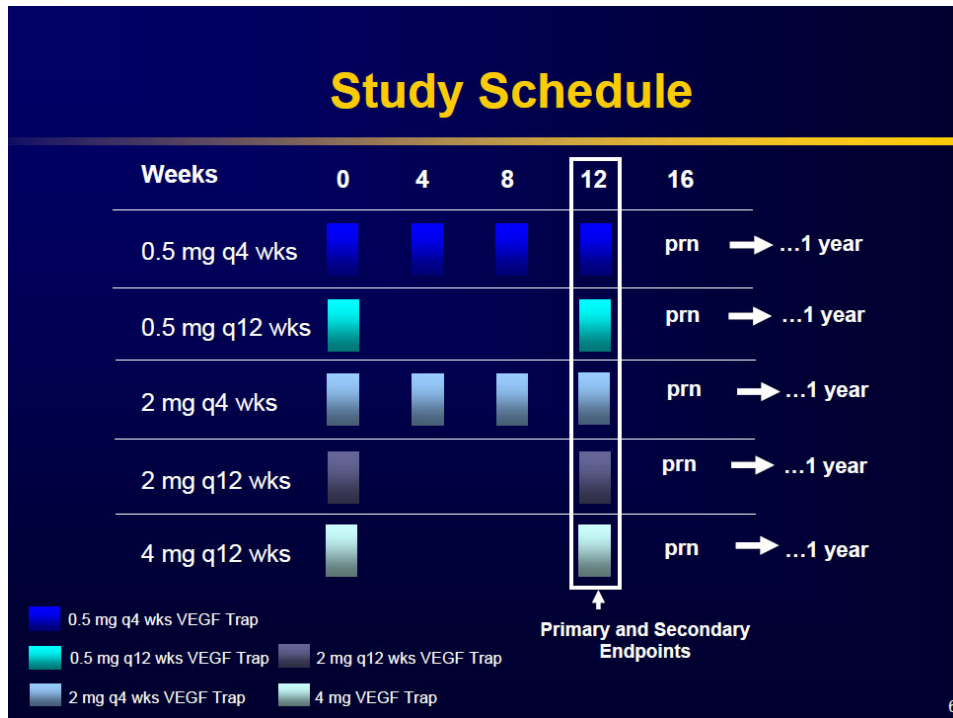
119. Hierarchical ranking of endpoints requires that each preceding endpoint show statistical significance in order for the next successive endpoint to show statistical significance. EX. 2098 (CDER Statistical Review for Application Number 125387) at 17. Given this conditional or hierarchical ranking, the 2Q8 VEGF Trap-Eye dosing arm could only demonstrate non-inferiority to ranibizumab if both the 2Q4 and 0.5Q4 dosing arms had successfully done so. This means that Regeneron was the least confident in 2Q8 than in any of its other dosing arms, including 0.5 mg monthly. The POSA would have understood Regeneron's inclusion of two Q4 dosing arms in the VIEW 1/2 studies and the hierarchical ranking of the Q8 dosing arm to indicate that even Regeneron had significant uncertainty as to whether the Q8 regimen would be successful until it was tested.

3. The Results of CLEAR-IT 2 Would Not Have Provided the POSA With a Reasonable Expectation of Success.

120. Dr. Albini contends that the Phase 2 results of CLEAR-IT 2, as disclosed in Dixon, would have provided the POSA with a reasonable expectation of success that the VIEW dosing regimen would be successful. Ex. 1002 ¶¶ 367, 409. However, Dr. Albini fails to consider all that CLEAR-IT 2 taught the POSA and, further, fails to account for the significant differences between the CLEAR-IT 2 dosing regimens and the VIEW 1/2 dosing regimens.

121. The CLEAR-IT 2 Study, for which I was a principal investigator, was designed to compare the effects of patients receiving an intravitreal injection of VEGF Trap-Eye 0.5 or 2 mg every 4 weeks (0.5Q4 or 2Q4) on day 1 and at weeks 4, 8, and 12 for a total of 4 treatments *or* 0.5, 2, or 4 mg every 12 weeks (0.5Q12, 2Q12, or 4Q12) on day 1 and week 12 for a total of 2 treatments. Ex. 2094 (Brown 2011) at 2 & 3 fig.1; *see also* Ex. 2095 (Heier 2011) at 2 & 3 fig.2. The PRN dosing

phase began at week 16 and continued through week 52. *Id.* A diagram of the study schedule is reproduced below:

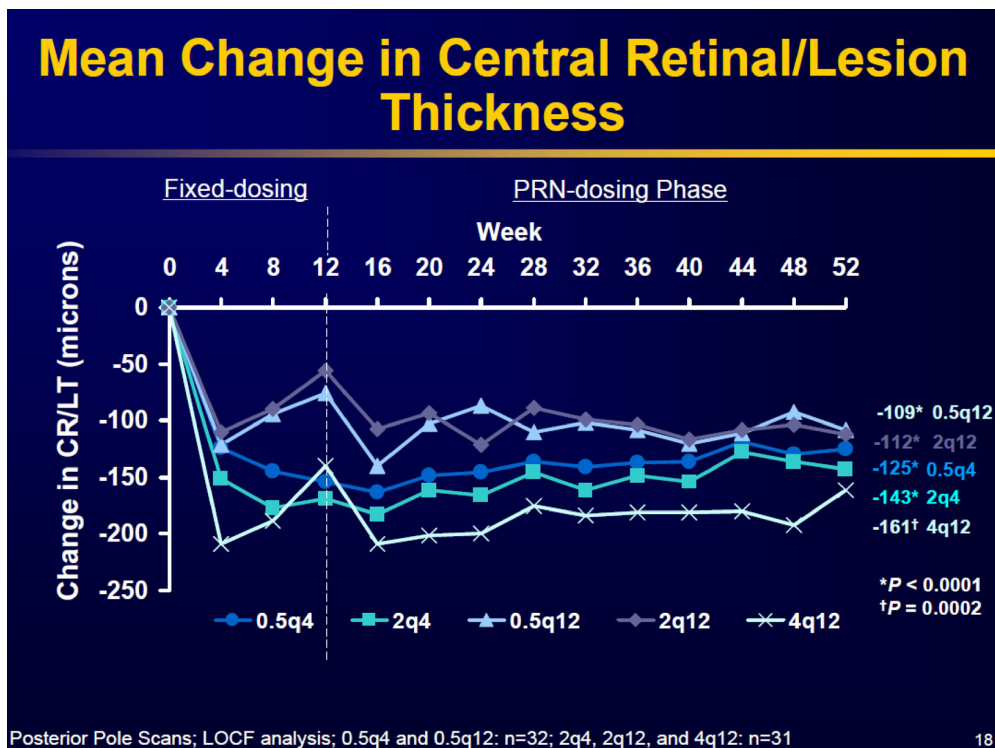


Ex. 1055 at 6.⁴³

122. The results from CLEAR-IT 2 showed that the therapeutic effect of VEGF Trap-eye was began to wear off between week-4 and week-8. The slide below reports on central retinal/lesion thickness. A decrease in central retinal thickness (CRT) corresponds to drying of the macula and the fluid that is created by the angiogenic process for wet-AMD. In contrast, an increase in CRT corresponds

⁴³ *VEGF Trap-Eye in Wet AMD, CLEAR-IT 2: Summary of One-Year Key Results*, 2008 Retina Society Meeting (Sept. 28, 2008).

to fluid re-accumulation on the retina and indicates a need for retreatment. As shown in the slide below, there is re-accumulation of fluid between week-4 and week-8 in the quarterly dosing arms (curves for arms 0.5Q12, 2Q12, and 4Q12 trend upwards), which continues through week 12. In fact, the only treatment arms that were successful in sustaining effective treatment were the monthly dosing arms (i.e., 0.5Q4 and 2Q4):

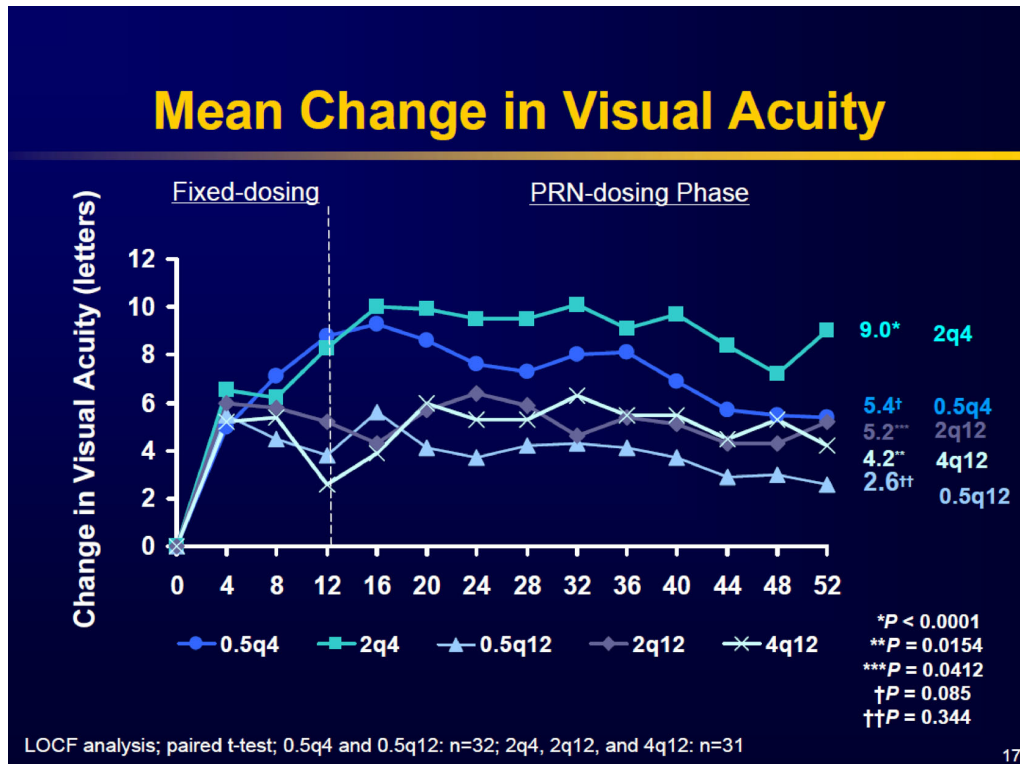


Ex. 1055 (Sept. 28, 2008, Retina Society Meeting Presentation) at 18. In addition, the CRT data at week 16 shows that study subjects who received monthly loading doses continued to experience reductions in CRT with the fourth monthly loading dose, corresponding to further drying of the retina.

123. The POSA would have understood that fluid re-accumulation between week-4 and week-8 on CRT would strongly suggest that VEGF Trap-Eye would not be effective on an 8-week dosing interval. Similarly, in the slide below (at 17), the POSA would have understood that the visual acuity decreased at week-8 in the 0.5Q12 and 2Q12 arms relative to visual acuity at week-4, suggesting that VEGF Trap-Eye's effect was waning sometime between week-4 and week-8.

124. Thus, rather than providing an expectation of success for a Q8 dosing regimen as suggested by Dr. Albini, the Phase 2 clinical trial results would have provided a basis to doubt that VEGF Trap-Eye would be successful on an 8-week dosing schedule. In addition, the CLEAR-IT 2 results showed the importance of four monthly loading doses. Even though all treatment arms were able to switch to PRN dosing after 12 weeks, no amount of "as needed" treatment thereafter allowed

patients who received initial quarterly dosing to catch-up to the patients who had received monthly loading doses:



Ex. 1055 (Sept. 28, 2008, Retina Society Meeting Presentation) at 17. The data at week 16 also shows that the two monthly loading dosing arms (2Q4 and 0.5Q4) continue to see improvements in visual acuity outcomes based on the fourth loading dose.

125. Therefore, the POSA would have understood that the four monthly loading doses of CLEAR-IT 2 were important to maximize initial visual acuity gains and to the overall success of the therapy. Said another way, CLEAR-IT 2 (4 monthly loading doses followed by PRN) would not have provided a reasonable expectation

of success that three monthly intravitreal injections of VEGF Trap-Eye followed by fixed Q8 or longer dosing would be an effective method of treatment. CLEAR-IT 2 merely suggested that additional studies with VEGF Trap-Eye were warranted.

126. In fact, I recall discussing the design of Regeneron's Phase 3 VIEW trials with co-investigator Jeff Heier before the initiation of the VIEW trials. At the time, we only had preliminary Phase 2 data from CLEAR-IT 2, and I recall that, looking at the rise in mean CRT, we both thought that VEGF Trap-Eye might last six weeks, but had great skepticism that it would be noninferior to Lucentis on an 8-week fixed dosing regimen. While we thought monthly dosing of VEGF Trap-Eye would likely work (*i.e.*, be noninferior to Lucentis monthly dosing), we viewed the Q8 arm as a long shot. Indeed, as discussed above, when Regeneron ranked its dosing regimens for statistical reporting, it ranked the 2Q8 arm below both the 2Q4 and the 0.5Q4 dosing arms, indicating that Regeneron believed both Q4 dosing arms were more likely than the Q8 dosing arm to hit their primary endpoints.

127. The published results of CLEAR-IT 2 and the clinical trial design for VIEW 1/2 demonstrate that there was great uncertainty as to whether Regeneron's extended fixed dosing regimen (with ≥ 8 weeks maintenance dosing) after only three monthly loading doses would be successful, until the results of the VIEW 1/2 study were completed.

4. Dixon Cautioned That the Most Effective Dosing Regimen Was Not Established.

128. Dr. Albini is also wrong that the Dixon reference would have provided the POSA with a reasonable expectation of success in achieving the extended dosing regimen. Dixon actually supports the uncertainty as to whether an extended dosing regimen could be successful and provides no teaching that would indicate that VIEW 1/2 was likely to work.

129. Indeed, Dixon confirmed that PIER and PrONTO studies “seem to indicate that quarterly dosing is associated with poorer outcomes but it may be possible to extend the time between injections if the patient is frequently monitored.” Ex. 1006 at 2⁴⁴; see also *id.* at 4-5. Dixon also cautioned against overinterpreting Phase 2 results as “[t]he most effective dosing regimen and monitoring program for anti-VEGF therapy has yet to be firmly established.” *Id.* at 5. Dixon further notes that the durability of VEGF Trap-Eye and its adoption in clinical practice will only be known after Regeneron’s Phase 3 clinical trial results are reported. *Id.* at 5 (“Its adoption into clinical practice will depend on efficacy at 4 and 8 week intervals.”)

130. Thus, Dixon confirms there was uncertainty as to whether Regeneron’s extended fixed dosing regimen (with ≥ 8 weeks maintenance dosing) would work until the results of the VIEW 1/2 study were reported.

⁴⁴ *James A. Dixon et al., VEGF Trap-Eye for the Treatment of Neovascular Age-related Macular Degeneration*, 18 *Expert Op. Investigational Drugs* 1573 (2009).

XI. '069 PATENT, GROUND 4: THE CHALLENGED CLAIMS ARE NOT ANTICIPATED OR OBVIOUS BASED ON VIEW 1/VIEW 2 AS DISCLOSED IN DIXON.

A. The VIEW 8-Week Dosing Regimen is Fixed, Not As-Needed / *Pro Re Nata* (PRN).

131. The VIEW trials, as described in Dixon, included three VEGF Trap-Eye dosing arms: 0.5 mg every four weeks (0.5Q4), 2 mg Q4 (2Q4), and 2 mg Q8 (2Q8) following three monthly injections. Ex. 1006 (Dixon 2009) at 4. In the 8-week dosing arm, study subjects would receive a 2 mg dose of aflibercept every 8 weeks (after three monthly loading doses) regardless of an assessment of the patient's visual acuity or anatomic features, *e.g.*, based on OCT, etc. Ex. 1018 (Heier 2012) at 4 ("For the 2q8 treatment group, no treatment decisions were made at the interim monthly visits."). In contrast, when treating a patient on an as-needed basis or *pro re nata*, the physician examines the patient and makes a clinical determination at each visit as to whether administration of an injection is appropriate. For that reason, I disagree with Dr. Albini that Dixon's disclosure of an 8-week dosing interval discloses treatment on an as-needed basis following the administration of the monthly loading doses. Ex. 1002 ¶¶ 367-68; IPR2021-00880 Ex. 1002 ¶ 157.

B. The POSA Would Not Have Been Motivated to Replace VIEW's 8-Week Fixed Dosing Regimen with PRN Dosing.

132. The POSA would not have been motivated to replace the 8-week fixed dosing regimen arm of the VIEW studies with an as-needed or PRN regimen dosing based on Dixon and other information available to the POSA in and around 2011.

The POSA would have considered a fixed 8-week maintenance dosing regimen to be much less burdensome for patients, caregivers, and physicians than a PRN dosing regimen that requires monthly monitoring visits.

133. Fixed, 8-week dosing reduces the number of visits that the patient must make to the physician during the maintenance dosing period as compared to PRN dosing. With a PRN dosing schedule, even if the patient does not require an injection at every visit, they must still undergo dilated testing, which typically takes three hours. Rather than having to visit the physician every month, using a Q8 dosing regimen, patients can visit their physician every other month. This is a significant benefit to patients, many of whom are elderly. Not only does a visit to the physician require the patient to take time out of his or her schedule, it frequently requires coordination and time from family members, friends, or caregivers to assist the patient. *See* Ex. 1006 (Dixon 2009) at 4 (“However, the monthly dosing schedules used in these trials present a financial and time burden to patients and healthcare practitioners.”).

134. In contrast to 8-week fixed dosing, PRN dosing requires monthly office visits so that the physician can evaluate the patient to determine whether an injection is required:

Nonetheless, this [PRN dosing] strategy does require monthly visits, clinical examinations, and OCTs, and patients are uncertain if or when they will need treatment. In addition, there have been more recent concerns that

patients who are no longer receiving regular maintenance intravitreal anti-VEGF injections can occasionally experience sudden sight-threatening macular hemorrhages within days or weeks after a stable clinical examination and an OCT showing no apparent sub- or intraretinal fluid.

Ex. 1025 at 2.⁴⁵ Thus, if PRN maintenance dosing is used, patients must make the same number of office visits as with monthly dosing, which means that PRN dosing, even if it reduces the frequency of injection, does not reduce patient, caregiver, or physician burden. For this reason, I disagree with Dr. Albini that the POSA would have been motivated to switch from a fixed 8-week dosing regimen to a PRN dosing regimen.

135. In addition to viewing PRN dosing as burdensome, by 2011, the POSA would have understood that PRN dosing presented risks to the patient that outweighed the benefit of reducing the number of injections but not the number of office visits. This is particularly true because physicians generally prefer treatment regimens that maximize therapeutic benefit, and several studies showed that the visual acuity of patients being treated with ranibizumab (Lucentis) decreased when switched from monthly dosing to PRN dosing, as discussed above. For example, the SUSTAIN study showed that visual acuity peaked after three monthly loading doses

⁴⁵ Michael Engelbert et al., *Long-term Follow-up for Type 1 (Subretinal Pigment Epithelium) Neovascularization Using a Modified “Treat and Extend” Dosing Regimen of Intravitreal Antivascular Endothelial Growth Factor Therapy*, 30 Retina 1368 (2010).

and then declined over the PRN maintenance dosing period. Ex. 1030 (Mitchell 2010) at 9 (“However, some VA loss occurred after month 3 [in PRN], whereas fixed monthly injections resulted in further VA improvement during the maintenance phase.”). Additional studies involving PRN dosing with ranibizumab demonstrated the same outcomes:

- **SAILOR:** “In the SAILOR study, VA increased with 3 loading doses of ranibizumab and then decreased from month 3 to 12 [with PRN dosing].” Ex. 2032 (Boyer 2009) at 8. “The visual outcomes achieved with the variable PRN regimen in the SAILOR trial compare unfavorably with those reported in the MARINA and ANCHOR trials, in which continuous monthly therapy was used.” Ex. 2029 (Bhisitkul 2010) at 5.
- **HORIZON:** “Patients in the [PRN] treated cohort showed a mean VA loss of 5.3 letters from study baseline, a reversal of the mean VA gains achieved (+9.4 letters) with their previous monthly treatments within the MARINA, ANCHOR and FOCUS trials.” Ex. 2029 at 5.

136. In addition to the SAILOR and HORIZON studies, which showed that PRN dosing regimens could not maintain the visual acuity gains achieved with monthly dosing of ranibizumab, by 2011 the POSA was also aware of reports that patients treated with a PRN ranibizumab dosing regimen had experienced sudden, vision-threatening macular hemorrhages.

137. The Engelbert paper, cited above (Ex. 1025 at 2), mentioned such concerns, which were based in part on a 2009 article published in Retina, the Journal of Retinal and Vitreous Diseases. Ex. 2042 (Levine 2009). The 2009 Retina

publication described PrONTO as “a small nonrandomized trial,” and presented “a case series of six eyes” in patients “with a history of neovascular AMD ... who were initially stabilized with intravitreal bevacizumab or ranibizumab therapy and who subsequently developed a new sight-threatening macular hemorrhage between February 2006 and July 2007.” *Id.* at 1-2. “Four of 6 patients had baseline vision of 20/200 or better, whereas 2 had vision worse than 20/400 (Table 1). Five eyes were treated with an OCT-guided regimen, whereas one was treated with a ‘treat and extend’ strategy.” *Id.* at 2. The authors explained the assumptions underlying the PrONTO strategy:

The PrONTO strategy is based on the assumption that fluid in the macula will occur before sight-threatening macular hemorrhages and that treating after fluid recurs, rather than before, will give visual results similar to monthly maintenance injections.

Id. at 4. The authors of the Retina publication questioned the assumptions on which the PrONTO PRN strategy was based and deemed a monthly maintenance regimen more appropriate for at least eyes identified as high risk:

For some patients, a monthly examination schedule similar to the PrONTO strategy may be sufficient to detect early recurrence and allow for timely treatment as needed with fewer treatments than a monthly dosing regimen. However, our findings related to the timing and severity of macular hemorrhages in three of our patients challenge the strategy of treating all patients in this manner. A maintenance regimen may be more appropriate for eyes identified as high risk, in particular eyes with preserved

foveal function and patients with poor vision in the fellow eye.

Id. at 5. Similarly:

For some patients, however, a sight-threatening macular hemorrhage can occur without the presence of preceding fluid on OCT performed as recently as 1 day before the event. Prophylactic maintenance therapy may be appropriate in some cases.

Id. at 6. The “[p]rophylactic maintenance therapy” mentioned by the authors referred to monthly dosing.

138. Based on the burden and potential risks of a PRN dosing regimen and the continued desire in the art to develop a reliable extended dosing regimen, the POSA **would not** have been motivated to eliminate VIEW’s fixed, 8-week dosing regimen and replace it with PRN dosing.

XII. ’069 PATENT, GROUND 5: THE CHALLENGED CLAIMS ARE NOT OBVIOUS BASED ON HEIER-2009 IN VIEW OF MITCHELL OR DIXON.

139. Dr. Albini opines that it would have been obvious to modify the CLEAR-IT 2 dosing regimen as disclosed in Heier 2009 to drop a monthly loading dose (*i.e.*, go from 4 to 3 monthly loading doses), based on ranibizumab dosing regimens in the art as disclosed in Mitchell. IPR2021-00880 Ex. 1002 ¶ 197. I disagree. In my opinion, the POSA would not have been motivated to lower the number of loading doses used in the CLEAR-IT 2 dosing regimen, as described in Heier 2009 or Dixon, from four to three based on Mitchell or the VIEW dosing

regimen because CLEAR-IT-2 data demonstrated the benefits of administering a fourth loading dose, as described above.

140. The POSAs would therefore have known that the PrONTO study used 3 monthly loading doses, and also would have known that Regeneron chose to use four monthly loading doses, rather than the three that had been reported for Lucentis PRN dosing regimens in the art. Regeneron's selection of four loading doses for CLEAR-IT 2, notwithstanding the existing knowledge of PRN studies of ranibizumab using 3 monthly loading doses in the prior art, further demonstrates that the POSA would not have been motivated to lower the number of loading doses from four to three based on the PrONTO study protocol.

141. Instead, by 2011, conventional wisdom in the clinical practice of anti-VEGF injections was (and is) to give monthly loading doses until retina drying and initial visual acuity gains have plateaued, after which most doctors move to maintenance dosing approach.

142. Based on the results of ANCHOR and MARINA, the POSA would have known that initial visual acuity gains and retina drying (as measured by central retinal thickness, or CRT), plateaued after the third monthly injection of ranibizumab. The clinical trial results of MARINA and ANCHOR showed no meaningful or detectable visual acuity improvement from the fourth monthly injection. Ex. 2119 (MARINA) at 7 fig.2; Ex. 2118 (ANCHOR 2006) at 8 fig.2. Mitchell confirms this

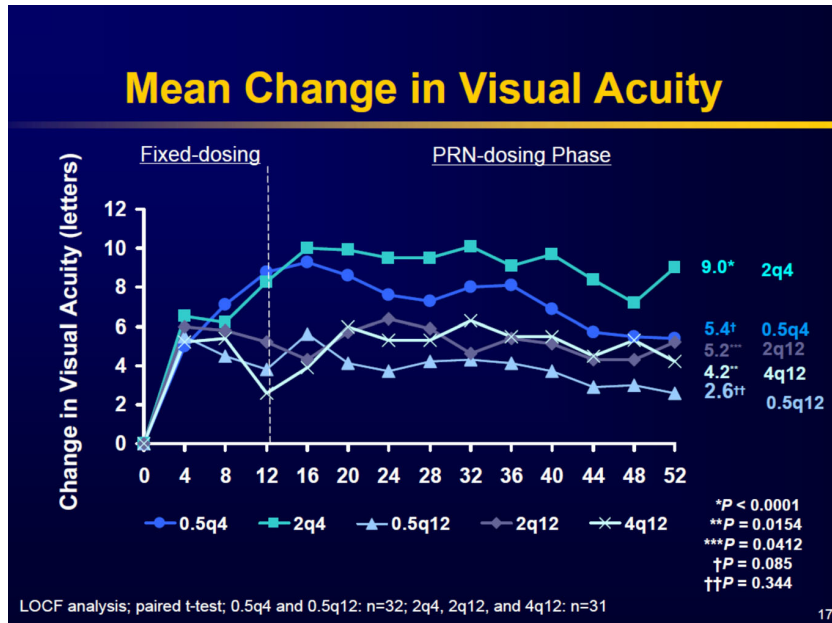
fact and reports that “[r]anibizumab initiation with three consecutive monthly injections appears optimal as this is when the majority of patients experienced most VA gain in all studies.” Ex. 1030 (Mitchell 2010) at 6. Mitchell also includes a Figure that depicts this plateau in visual acuity gains with three initial monthly doses based on the data from MARINA and ANCHOR. *See id.* at 9 fig.2. Thus, the Mitchell authors recommend that “0.5 mg of ranibizumab should be initiated with ***at least three*** consecutive monthly intravitreal injections, using an aseptic procedure.” *Id.* at 6 (emphasis added).

143. Even before the CLEAR-IT 2 results were obtained, the POSA would have understood that ranibizumab and VEGF Trap-Eye were different proteins with different binding domains, which could affect how the drugs worked in vivo. Consequently, the POSA would not have just indiscriminately copied ranibizumab prior art PRN dosing regimens and applied them to VEGF Trap-Eye. For example, when Genentech began clinical testing of ranibizumab, it did not just copy the Q6 dosing regimen from Macugen’s Phase 3 trials. In fact, the PrONTO investigators presented their methodology and results at an ASRS meeting in 2005 before the CLEAR-IT 2 study even began. Ex. 2100.⁴⁶ Notwithstanding the purportedly

⁴⁶ Jeffrey S. Heier & FOCUS Study Group, *Abstract: Intravitreal Ranibizumab (Lucentis™) with Verteporfin Photodynamic Therapy for Neovascular Age-Related Macular Degeneration: Year One Results*, Am. Soc’y Retina Specialists Ann. Meeting 94 (2005).

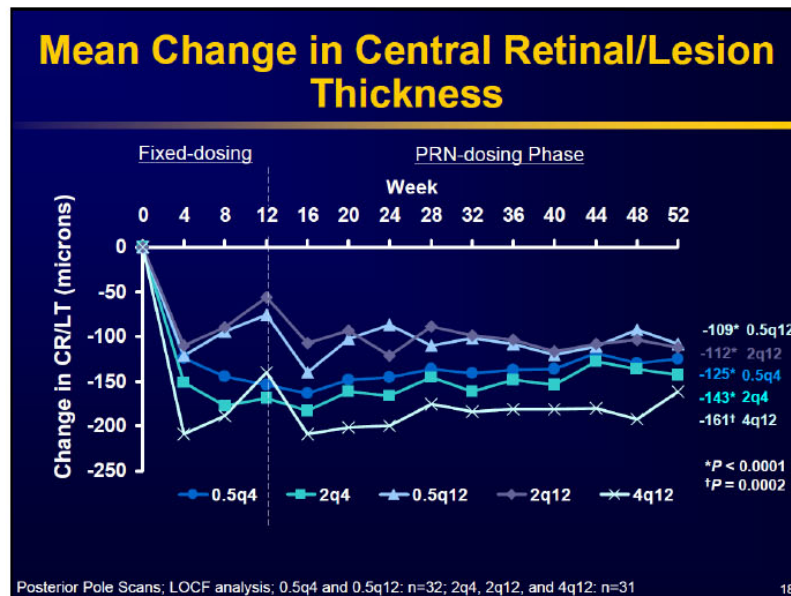
positive results from PrONTO, Regeneron designed and initiated the CLEAR-IT 2 study with four monthly loading doses in April 2006. Ex. 2101 at 2-4.⁴⁷

144. Moreover, once CLEAR-IT 2 results were revealed, the POSA would have been *discouraged* from adopting a three monthly loading dose design for a PRN dosing regimen with VEGF Trap-Eye. As discussed above in ¶¶ 124-127, the CLEAR-IT-2 results showed visual acuity improvement and further retinal drying (decrease in CRT) based on the administration of the fourth monthly loading dose:



Ex. 1055 (Sept. 28, 2008, Retina Society Meeting Presentation) at 17.

⁴⁷ *Safety and Efficacy of Repeated Intravitreal Administration of Vascular Endothelial Growth Factor (VEGF) Trap in Patients With Wet Age-Related Macular Degeneration (AMD)*, ClinicalTrials.gov, <https://clinicaltrials.gov/ct2/show/NCT00320788>.



Id. at 18. The data from CLEAR-IT show that CRT reaches its lowest point for the monthly loading dose arms after the fourth monthly loading dose. Thus, the CLEAR-IT 2 data would have actively discouraged the POSA from reducing the number of monthly loading doses with VEGF Trap-Eye from four to three, as Challenged Claim 8 requires, because visual acuity and retinal dryness had not yet plateaued after three monthly loading doses.

145. As discussed above, most physicians would be guided in clinical practice by giving monthly loading doses until the patient's fluid on retina had dried and visual acuity gains had plateaued. CLEAR-IT 2's interim results suggest that, for most patients, that plateau will not occur until after the fourth loading dose. As such, the POSA would not have been motivated to drop a monthly loading dose from the CLEAR-IT 2 dosing regimen (from four to three), and, if anything, the CLEAR-

IT 2 results would have discouraged the POSA from dropping the fourth monthly loading dose before proceeding to a maintenance dosing schedule, such as PRN, for VEGF Trap-Eye.

146. In addition, the POSA would have understood that PrONTO, EXCITE, and SUSTAIN studied a different molecule, ranibizumab, and that the differences between ranibizumab and VEGF Trap-Eye, including differences in the binding domains, would affect how they worked in the body. These differences would have led the POSA to regard the Lucentis PRN dosing regimen designs as less meaningful than the CLEAR-IT 2 dosing regimen when designing a PRN method of treatment for VEGF Trap-Eye. While three monthly loading doses appeared to optimize initial visual acuity gains for ranibizumab based on the results seen in ANCHOR and MARINA, the POSA would not have assumed the same would necessarily be true for VEGF Trap-Eye. Once the POSA saw the clinical trial results of CLEAR-IT 2, they would have understood that four, not three, monthly loading doses appeared optimal to maximize initial visual acuity gain and retinal drying. Therefore, the POSA would not have been motivated to modify the CLEAR-IT 2 dosing regimen based on PRN dosing regimens of Lucentis disclosed in Mitchell.

147. Dr. Albin opines that given “concerns over dosing frequency and the motivation to reduce the number of doses patients received, a person of ordinary skill in the art would have been motivated to reduce the four monthly loading doses

of the Phase 2 CLEAR-IT-2 trial to the three monthly loading doses planned for the Phase 3 VIEW regimens.” IPR2021-00880 Ex. 1002 ¶ 199; see also *id.* ¶¶ 76-77, 168. I disagree.

148. First, the recognized need in the art was focused on reducing the treatment burden of chronic diseases like wAMD and DME, not shortening the number of loading doses. For example, Dixon notes that “limitations of current therapy include the need for frequent intraocular injections, as often as monthly, without a defined stopping point,” and, further, that, “[a] significant time and financial burden falls on patients during their treatment course.” Ex. 1006 (Dixon 2009) at 5. Notably, after ANCHOR and MARINA showed optimal visual acuity gains after three monthly loading doses, all of Genentech’s studies that were designed to explore less frequent dosing (PIER, SAILOR, EXCITE, SUSTAIN, and PrONTO) retained the three “optimal” monthly loading doses. Ex. 1030 (Mitchell 2010) at 6, 9 fig.2, 11. Dropping a loading dose would do little, if anything, to reduce the patient’s long-term treatment burden, particularly as compared to the reduced burden achieved through fixed, extended maintenance dosing.

149. Even today, with the advent of Eylea’s fixed extended dosing regimen, physicians will typically give monthly loading until the retina appears dry on OCT before moving to a maintenance dosing regimen or attempting to extend the dosing interval. Indeed, for diabetic macular edema (DME), Eylea’s recommended label

dosing regimen calls for five monthly loading doses of Eylea before extending to Q8 dosing. Ex. 1091 at § 2.4. Even so, Eylea is recognized as both the most effective and most popular treatment for DME. Ex. 2102 at 2⁴⁸. Therefore, I disagree with Dr. Albini that the motivation to reduce injection frequency in the art would have influenced the number of monthly loading doses included in a dosing regimen.

XIII. OBJECTIVE INDICIA OF NON-OBVIOUSNESS

150. It is my opinion that objective indicia, such as a long-felt but unmet need and failure by others in the prior art; unexpected benefit of the claimed invention to patients; and industry praise and commercial success of the claimed invention, also support the conclusion that the method of treating patients with angiogenic eyes disorders as claimed in the '338 patent was *not* obvious before Regeneron completed its Phase 3 studies.

A. Long-Felt Need for an Extended Dosing Regimen

151. As described above in Section VI.B, the POSA understood, by at least 2006-2007 (following Lucentis' approval and clinical use), that a need existed for an extended dosing regimen that would reduce the cost and burden imposed by frequent office visits and treatments on patients, their caregivers, and physician practices. The existence of this need—and its recognition by the POSA—is

⁴⁸ John A. Wells, et al., *Aflibercept, Bevacizumab, or Ranibizumab for Diabetic Macular Edema*, 372 The New England Journal of Medicine 1193 (2015).

demonstrated by the unsuccessful efforts by others to achieve an extended dosing regimen as described above and below.

152. A persistent goal of the retinal community has been to find an effective treatment regimen that required less than monthly visits to an ophthalmologist to treat and/or monitor the progression of wAMD. Intravitreal injections, while generally safe, present the risk of rare but serious adverse events such as endophthalmitis, severe intraocular inflammation, and retinal detachment. Further, monthly visits for injections are costly and burdensome to patients. Even monthly monitoring (or even more frequently in a hypervigilant PRN approach such as PrONTO), while reducing risk from IVT injections themselves, is burdensome, as patients with wAMD are typically elderly and in-person visits present a challenge for the patient and their caretakers. *See* Ex. 1018 (Heier 2012) at 9 (“Because of the large treatment burden, extensive efforts have been devoted toward developing an optimized treatment paradigm that avoids the need for monthly injections or monitoring visits.”).

153. The need for an effective treatment regimen was widely recognized before Eylea because “practically speaking, monthly treatment is a tremendous

burden for our patients and practices.” Ex. 2103 at 1⁴⁹; *see also* Ex. 2104 at 4⁵⁰ (“[M]onthly dosing entails greater risks of complications from intravitreal injections, costs more money, is less convenient for patients, and may incur long-term safety concerns.... [M]onthly dosing is often logistically difficult with the population of patients with AMD.”).

154. Physicians also recognized that the need was unmet by treatment with ranibizumab. *See* Section VI.C *supra*; *see also* Ex. 2029 (Bhisitkul 2010) at 3-6; Ex. 2104 (Mathis 2009) at 5 (Dr. Bailey Freund “compared the patients in the ANCHOR, MARINA and PIER studies, concluding that macular hemorrhages occurred in patients more often when dosing was quarterly rather than monthly”).

155. Thus, despite the benefits seen with Lucentis monthly dosage, “significant challenges remain[ed], especially trying to balance maximizing visual acuity against treatment burden and safety” prior to VIEW 1/2. Ex. 2105 at 7⁵¹; Ex.

⁴⁹ *Ongoing Treatment for Patients with Neovascular AMD*, Retinal Physician (Oct. 1, 2007), <https://www.retinalphysician.com/issues/2007/october-2007/ongoing-treatment-for-patients-with-neovascular-am>.

⁵⁰ Andrew E. Mathis, *Fine-Tuning Your Anti-VEGF Injection Protocols: The Second Article in Our Series Recapping Research and Analysis Presented at Our Annual Meeting*, Retinal Physician (Oct. 1, 2009), <https://www.retinalphysician.com/issues/2009/october-2009/fine-tuning-your-anti-vegf-injection-protocols>.

⁵¹ Scott W. Cousins, *Controversies in the Long-term Management of Neovascular AMD: The Role of Imaging in Clinical Decision Making*, Retinal Physician (Jan. 1, 2010), <https://www.retinalphysician.com/issues/2010/jan-feb/controversies-in-the-long-term-management-of-neova>.

2106 at 2⁵² (“The need for multiple treatments at 4-week intervals with no definite endpoint is a significant drawback,’ says Sharon Fekrat, M.D.”).

B. Satisfaction of a Long-Felt Need

156. I am informed that evidence that an invention met a long-felt but unmet need is evidence of non-obviousness. In my opinion, the treatment of patients with angiogenic eye disorders through the intravitreal injection of Eylea[®] every 4 weeks for the first 3 month, followed by intravitreal injection of Eylea[®] once every 8 or more weeks satisfied the long-felt but unmet need for less frequent injections (and the risk associated with each injection procedure, such as retinal detachments and endophthalmitis), and also reduced the need for costly and time-consuming monthly office visits for patients and their caregivers. This long-felt need that Eylea[®] satisfied further confirms the non-obviousness of the asserted claims.

157. As described in Section VII.B *supra*, Regeneron conducted Phase 3 clinical trials, VIEW 1/2, that showed that wAMD patients receiving 2Q8 dosing of Eylea “achieved statistical noninferiority compared with monthly ranibizumab.” Ex. 1018 (Heier 2012) at 5; *see also id.* at 10 (“[T]he 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

⁵² Jerry Helzner, *Lucentis After 1 Year: Doctors Praise This Practice-transforming Therapy—But Find Drawbacks*, Retinal Physician (July 1, 2007), <https://www.retinalphysician.com/issues/2007/july-aug/lucentis-after-1-year>.

visits provides an important advance for both patients and their treating physicians.”). Based on the results in VIEW 1/2, Regeneron sought and received approval of Eylea for the treatment of wAMD—administered in 2 mg (0.05 mL) dose of Eylea® via intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 3 months, followed by 2 mg (0.05 mL) dose via intravitreal injection once every 8 weeks (2 months) or longer. Ex. 1091 (Eylea label) at § 2.2.

158. This represented a major breakthrough for patients with wAMD and met the need for less frequent injections and office visits, thereby reducing the risks, expense, and burden for patients, their caregivers, and busy physician practices. Indeed, Jeffrey Heier, M.D., a clinical ophthalmologist and retinal specialist at Ophthalmic Consultants of Boston, Assistant Professor of Ophthalmology at Tufts School of Medicine, and Chair of the Steering Committee for the VIEW 1 trial stated that “[t]he approval of EYLEA offers a much needed new treatment option for patients with wet AMD.” Ex. 2116 (Nov. 18, 2011, Regeneron Press Release) at 1.

159. I understand that FDA granted priority review for the use of Eylea to treat wAMD using the claimed Q8 dosing regimen, which reflects that Eylea satisfied a need for an improved treatment for wAMD. According to FDA “[a]n application for a drug will receive priority review designation if it is for a drug that treats a serious condition and, if approved, would provide a significant improvement

in safety or effectiveness.” Ex. 2108 at 28⁵³; *see also* Ex. 2116 (Nov. 18, 2011, Regeneron Press Release) at 1 (“The approval of EYLEA was granted under a Priority Review, a designation that is given to drugs that offer major advances in treatment, or provide a treatment where there were no adequate therapy exists.”). The FDA’s designation of Eylea® for priority review further supports the conclusion that there was a long-felt but unmet need for a treatment that improves visual acuity while reducing the burden of frequent injections or monitoring visits.

C. Failure of Others to Achieve an Extended Dosing Regimen

160. I am informed that evidence of the failure by others to achieve an invention is evidence of non-obviousness. Before the approval of Eylea®, others tried and failed to develop treatments that would permit a fixed, extended dosing regimen for the treatment of wAMD—*i.e.*, the claimed dosing regimen. Even after the approval of Eylea®, others have tried and failed to achieve a fixed, extended dosing regimen for the treatment of wAMD.

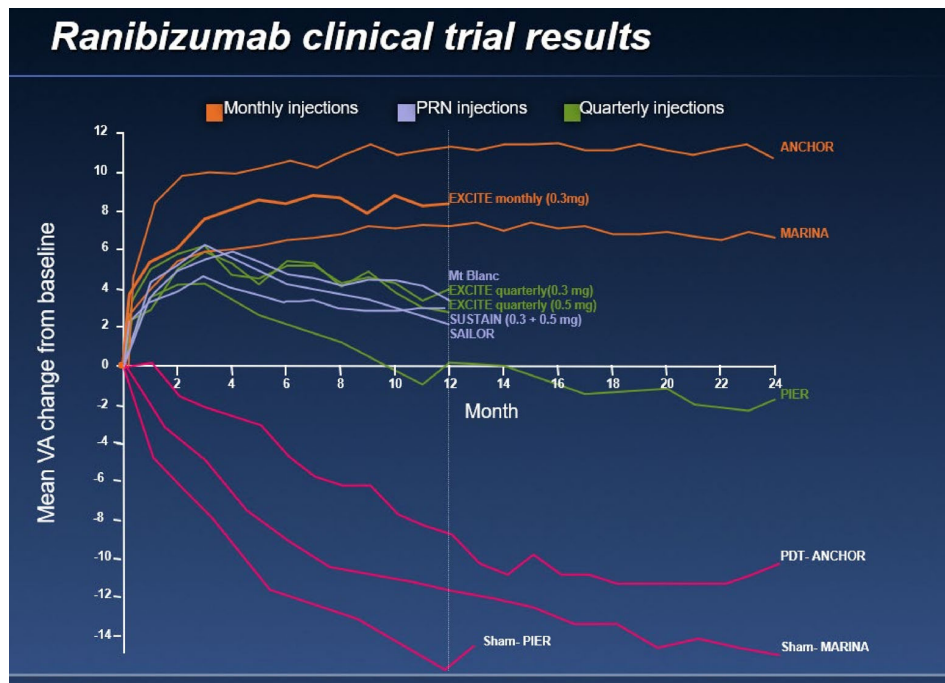
1. Lucentis (ranibizumab)

161. Genentech repeatedly tried and failed to demonstrate that Lucentis could be used to effectively treat wAMD on an extended dosing regimen.

⁵³ FDA, Guidance for Industry: Expedited Programs for Serious Conditions—Drugs and Biologics (May 2014), <https://www.fda.gov/media/86377/download>.

162. As discussed above, the PIER, PrONTO, SAILOR, EXCITE, and SUSTAIN trials confirmed either inferior results with quarterly dosing (as compared to monthly dosing of ranibizumab) or resulted in loss of visual acuity gains and, in some cases, vision-threatening complications with PRN dosing as compared to monthly dosing with ranibizumab. *See* Section VI.C *supra*.

163. I have prepared a summary of the ranibizumab clinical trial results, which show the need for monthly injections as shown by mean VA change from baseline and the failure of extended dosing regimens:



164. These studies, taken together, provide evidence of failure of others, namely Genentech, to achieve an extended dosing regimen with ranibizumab.

2. Macugen

165. Macugen (pegaptanib sodium injection) represents another treatment for wAMD that failed to provide effective treatment of wAMD, including an extended dosing regimen of 8 weeks or more as recited in the '338 Patent.

166. Macugen was approved by the FDA in 2004 for the treatment of neovascular (wet) age-related macular degeneration. Ex. 2117 (Macugen Approval Letter) at 4. Macugen's label instructs that it should be administered "once every six weeks by intravitreal injection." Ex. 2038 (Macugen 2004 label) at 7.

167. Based on the initial approval of Macugen, Pfizer sponsored a clinical trial (M-PDRS ED) to determine if it was feasible to extend dosing of Macugen in the treatment of proliferative diabetic retinopathy, an angiogenic eye disorders. The proposed dosing regimen was 3 initial doses at 6-week intervals, followed by 3 additional injections at 12-week intervals. Ex. 2109 at 4.⁵⁴ While the study began on November 2007, no results from the study were ever reported, indicating that the trial failed.

⁵⁴ *Macugen for Proliferative Diabetic Retinopathy Study With Extended Dosing (M-PDRS ED)*, ClinicalTrials.gov, <https://clinicaltrials.gov/ct2/show/NCT01486771>.

168. In practice, Macugen, failed to provide adequate treatment for wAMD as it merely slowed the rate of vision loss: “On average, Macugen 0.3 mg treated patients and sham treated patients continued to experience vision loss. However, the rate of vision decline in the Macugen treated group was slower than the rate in the patients who received sham treatment.” Ex. 2038 (Macugen 2004 label) at 4.

169. Macugen’s inability to provide a viable treatment option for patients with wAMD was widely recognized in the retinal medical community. Specifically, “there were significant treatment failures with [Macugen], as well as ‘treatment disappointments’ in a substantial proportion of ‘responders’ who continued to lose vision over time.” Ex. 2110 at 3.⁵⁵ By 2009, Dixon reported, “Pegaptanib was the first anti-VEGF drug approved by the FDA for the treatment of AMD; however, it proved less efficacious than current treatments ... and is no longer widely used in most countries.” Ex. 1006 (Dixon 2009) 2.

170. Macugen was expected to rapidly become a key play in the wAMD market. Once Lucentis was approved, however, physicians all but discontinued treatment with Macugen.

⁵⁵ Ron P. Gallemore & David Nguyen, *When Anti-VEGF Treatment Fails: Retina Specialists Are Charting New Territory and Learning How to Spot and React to Failed Anti-VEGF Therapy*, Rev. Ophthalmology (Mar. 20, 2008).

3. Conbercept

171. Conbercept is another VEGF antagonist fusion protein developed by Chengdu Kanghong (“Kanghong”). Whereas Macugen and Lucentis were approved for the treatment of wAMD before Eylea, the efforts to bring Conbercept to market occurred after Eylea’s approval. Kanghong tested Conbercept in two global Phase 3 clinical trials, PANDA 1 & 2. Ex. 2023,⁵⁶ Ex. 2022.⁵⁷ The studies were designed to “evaluate the efficacy and safety of two different levels of conbercept intravitreal (IVT) injection as compared to the approved vascular endothelial growth factor (VEGF) antagonist active control, aflibercept intravitreal injection (2.0 mg/eye, Eylea®), in subjects with neovascular AMD.” Ex. 2023 at 2; Ex. 2022 at 2. 1157 subjects were randomized in a ratio of 1:1:1 to receive IVT injections of: (a) 3 loading doses of 0.5 mg Conbercept at 4-week intervals followed by 0.5 mg doses every 8 weeks thereafter; (b) 3 loading doses of 1.0 mg Conbercept at 4-week intervals followed by every 1.0 mg doses every 12 weeks thereafter; or (c) 3 loading doses of 2.0 mg aflibercept at 4-week intervals followed by 2.0 mg doses every 8 weeks thereafter. Ex. 2023 at 2-4; Ex. 2022 at 2-4.

⁵⁶ ClinicalTrials.gov, *Efficacy and Safety Trial of Conbercept Intravitreal Injection for Neovascular AMD (PANDA-1)*, <https://clinicaltrials.gov/ct2/show/NCT03577899>.

⁵⁷ ClinicalTrials.gov, *Efficacy and Safety Trial of Conbercept Intravitreal Injection for Neovascular AMD (PANDA-2)*, <https://clinicaltrials.gov/ct2/show/NCT03630952>.

172. On April 9, 2021, Kanghong announced that it was stopping the PANDA trials globally. The announcement noted that in “as many as 68 trial centers, more than half of the subjects’ vision changes from baseline after injection are equal to or even lower than zero” and the steering committee believed that “the PANDA trial has failed to achieve the expected goals.” Ex. 2112 at 2.⁵⁸

173. Conbercept’s failure to meet its primary endpoint in Phase 3 studies represents yet another failure to develop an extended dosing regimen for an anti-VEGF drug.

D. Unexpected Benefits

174. I am informed that evidence that an invention has unexpected benefit may support non-obviousness, because that which is surprising tends to not be obvious. As discussed in Section VI.C *supra*, the extensive industry failure to develop a less frequent dosing regimen for the treatment of wAMD provided the POSA no expectation that extended dosing could be achieved. In my opinion, the results of the VIEW 1/2 clinical trials—*i.e.*, the claimed dosing regimen—were unexpected and therefore further confirms the non-obviousness of the Challenged Claims of the ’338 Patent.

⁵⁸Press Release, Kanghong Pharmaceutical, *Announcement of Chengdu Kanghong Pharmaceutical Group Co., Ltd. on Stopping the Global Multi-center Clinical Trial of Conbercept Ophthalmic Injection*, http://epaper.zqrb.cn/html/2021-04/10/content_716426.htm?div=-1 (English translation of Ex. 2111).

175. The Eylea dosing regimen for the treatment of wAMD unexpectedly improved treatment for patients with wAMD. Before Regeneron's Phase 3 VIEW 1/2 trials, no anti-VEGF agent had demonstrated the ability to provide a safe and effective treatment for wAMD on a fixed extended dosing regimen. As discussed above, the VIEW trials compared intravitreal aflibercept 0.5 mg monthly, 2 mg monthly, 2 mg every 2 months after 3 initial monthly doses, and ranibizumab 0.5 mg monthly. *See* Section VII.B; Ex. 1018 (Heier 2012) at 4.

176. The one-year results from the VIEW trials demonstrated that intravitreal Eylea dosed every two months after the three initial loading doses produced similar efficacy outcomes on average to monthly ranibizumab. Ex. 1018 (Heier 2012) at 5. This finding of the VIEW trials was viewed with excitement across the retina community. As Heier 2012 noted: "[T]he 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." *Id.* at 10. Moreover, patients treated with Eylea® every two months after three initial monthly doses had similar systemic and ocular safety experiences as those receiving ranibizumab monthly. *Id.* at 8. Eylea dosed every two months after three initial monthly doses also had a similar tolerability profile as ranibizumab dosed monthly. *Id.* at 11.

E. Industry Praise and Recognition

177. I am informed that industry praise and recognition can also provide evidence that an invention was not obvious.

178. After the results of VIEW 1 and VIEW 2 were reported, many physicians praised the unique attributes of Eylea. For example, Dr. Michael Thomas noted that “Aflibercept is an intriguing choice for patients who have a difficult time with the intravitreal injections.” Ex. 2113 at 5.⁵⁹

179. Drs. Matthew Ohr and Peter Kaiser similarly noted that “the VIEW 1 and VIEW 2 studies have further demonstrated the ability of aflibercept to maintain the visual gains attained in the first year of the study with a significantly smaller number of injections compared with ranibizumab.” Ex. 2114 at 7.⁶⁰

180. Edward Cox, M.D., M.P.H, director of the Office of Antimicrobial Products in FDA’s Center for Drug Evaluation and Research said that “Eylea is an important new treatment option for adults with wet AMD.... It is a potentially

⁵⁹ Michael Thomas et al., *Comparative Effectiveness of Aflibercept for the Treatment of Patients with Neovascular Age-related Macular Degeneration*, 7 Clinical Ophthalmology 495 (2013).

⁶⁰ Matthew Ohr & Peter K. Kaiser, *Aflibercept in Wet Age-related Macular Degeneration: A Perspective Review*, 3 Therapeutic Advances Chronic Disease 153 (2012).

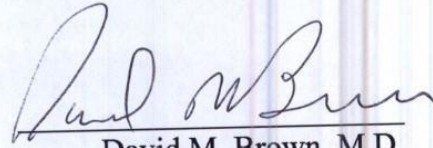
blinding disease and the availability of new treatment options is important.” Ex. 2115 at 1.⁶¹

181. The FDA’s grant of priority review to Eylea[®] for the treatment of wet AMD under the claimed dosing regimen, taken together with its ultimate approval of Eylea[®], also reflect praise for the claimed invention. The grant of priority review, as I discussed above indicates that FDA concluded that Eylea provided “a significant improvement in safety or effectiveness of the treatment, prevention or, or diagnosis of” wAMD. Ex. 2108 at 28; Ex. 2116 (Nov. 18, 2011, Regeneron Press Release) at 1.

⁶¹ *FDA Approves Eylea for Wet Age-Related Macular Degeneration*, Drugs.com, (Nov. 18, 2011), <https://www.drugs.com/newdrugs/fda-approves-cylea-wet-age-related-macular-degeneration-2955.html>.

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

Dated: Feb 10, 2022


David M. Brown, M.D.
Houston, Texas