

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

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

v.

REGENERON PHARMACEUTICAL, INC.,
Patent Owner

Inter Partes Review No. 2021-00881¹
U.S. Patent No. 9,254,338 B2

DECLARATION OF DIANA V. DO, M.D.

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

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I, Dr. Diana Do, declare:

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 (“IPR”) of U.S. Patent No. 9,254,338 (the “’338 patent”) (Ex. 1001) and, in particular, how the person of skill in the art as of the filing date of the ’338 patent would have understood certain terms of the ’338 patent claims. I have also been asked to provide my opinions and views about whether the dosage and administration criteria set forth in the FDA label for Eylea practice one or more of the claims of the ’338 patent and whether physicians in clinical practice treat patients with Eylea using the methods recited in one or more claims of the ’338 patent. I have been further asked to respond to the opinions and views of Petitioner’s declarant, Dr. Thomas A. Albini. I submit this declaration in support of Regeneron’s Patent Owner Response (“POR”). I reserve the right to provide further and additional opinions in the event that IPR is instituted.

2. I am being paid at an hourly rate for my work on this matter. I have no personal or financial stake in the outcome of the present proceeding.

II. QUALIFICATIONS AND EXPERIENCE

3. I am a Professor of Ophthalmology and the Vice Chair for Clinical Affairs at the Byers Eye Institute at Stanford University School of Medicine and have been since 2017. I also serve as a Physician Improvement Leader at Byers Eye Institute, a position I have held since 2018. I have an active clinical and surgical practice and I work as a clinical investigator to study novel treatments for retinal diseases. In addition, I teach students, residents, and retina fellows at Stanford and am a member of the Stanford Ophthalmology Education Committee.

4. I graduated from the University of California Berkeley (summa cum laude) with a B.A. degree in Molecular and Cellular Biology in 1995 and earned my M.D. (Alpha Omega Alpha) from the University of California San Francisco School of Medicine in 1999. Following medical school, I completed an internship in internal medicine at Massachusetts General Hospital at Harvard Medical School. From 2000-2003, I completed my residency in Ophthalmology at the Wilmer Eye Institute at Johns Hopkins University School of Medicine, and then remained at the Wilmer Eye Institute for a Retina Fellowship in surgical and medical retina from 2003-2005.

5. From 2005 through 2010, I served as Assistant Professor of Ophthalmology and Assistant Head of the Retina Fellowship Training Program at the Wilmer Eye Institute. In 2011, I was promoted to Associate Professor and Head of the Retina Fellowship Training Program, positions I held through 2013.

6. In 2013, I joined the faculty at the Truhlsen Eye Institute at the University of Nebraska College of Medicine, where I became a full Professor of Ophthalmology in 2015. At the Truhlsen Eye Institute, I was Head of the Retina Fellowship Training Program and Program Director for the Ophthalmology Residency. In my leadership roles at the Truhlsen Eye Institute, I also served as Vice Chair of Education. I was recruited by Stanford University's Ophthalmology Department (the Byers Eye Institute) at Stanford in the beginning of 2017.

7. As a physician-scientist, I am an international leader in the treatment of diabetic retinopathy and wet AMD ("wAMD"). My research has led to more than 140 peer-reviewed publications. My research interest focuses on evaluating the efficacy and safety of novel pharmacologic therapies for diabetic macular edema, diabetic retinopathy, wAMD, retinal vein occlusion, and ocular inflammation. I have led national and global clinical trials investigating intravitreal VEGF inhibitors (aflibercept and ranibizumab) for diabetic eye disease and wet AMD. Our research developed a greater understanding of how intraocular inhibition of VEGF reduces vascular permeability and angiogenesis in diabetic eye disease, thereby reducing diabetic macular edema and improving visual acuity. Before the onset of pharmacologic therapies, thermal laser photocoagulation was the only treatment option for diabetic macular edema and laser was not effective in improving vision. Our research led to new treatment paradigms and better vision outcomes for patients

with diabetic macular edema, diabetic retinopathy, and wAMD. The results from the collaborative research that I led has revolutionized how ophthalmologists throughout the world think about and treat patients with VEGF-mediated retinal diseases.

8. Since 2009, I have been the lead investigator and a Steering Committee member for the evaluation of aflibercept, a fusion protein that inhibits VEGF, in diabetic macular edema. I initiated the first-in-human clinical trial of aflibercept. In addition, I also was the principal investigator for the Phase II and III clinical trials of aflibercept for diabetic macular edema to further evaluate efficacy, dosing regimens, and safety. My leadership in these global clinical trials, which enrolled over 1,000 subjects, contributed to FDA approval of aflibercept for diabetic macular edema. Aflibercept has also been approved by FDA for other angiogenic ocular diseases such as wAMD, central retinal vein occlusion, branch retinal vein occlusion, and diabetic retinopathy.

9. My research efforts have also led to a greater understanding of the role of ranibizumab, an intravitreal VEGF antibody fragment biologic, in diabetic macular edema. I was a lead investigator in the Ranibizumab for Edema of the Macula in Diabetes (READ) Study Group and was the lead author on multiple manuscripts evaluating the efficacy and safety of ranibizumab. The collaborative studies that I led contributed to understanding dosing regimens for intravitreal

VEGF inhibitors, and led to the design of pivotal clinical trials involving ranibizumab for diabetic macular edema. Ranibizumab was the first FDA approved intravitreal VEGF inhibitor for diabetic macular edema, and helped to transform the management of diabetic retinopathy. I continue to lead clinical trials investigating new treatments for retinal diseases.

10. As a result of my research, I am recognized as an international thought leader on the subject of the retina and am regularly invited to lecture and teach at international and national meetings including the American Academy of Ophthalmology Retina Sub-Specialty Meeting, American Society of Retina Specialists, Asian Pacific Vitreo-Retinal Society Meeting, Canadian Ophthalmology Society Meeting, and congresses throughout Europe. I have organized and participated as a faculty member in national continuing medical education courses to teach my retina colleagues how to manage and treat diabetic macular edema, wet AMD, retinal vein occlusion, diabetic retinopathy, and other retinal disorders. Furthermore, I have held leadership positions at the American Society of Retina Specialists (Communications Committee Member to curate and develop online educational material), Women in Retina (Board Member and Secretary), Maryland Eye Society (President).

11. I am a practicing ophthalmologist with over 15 years of clinical and surgical practice in retina. I am a leader in the management of diabetic retinopathy,

the leading cause of blindness in working age adults, and wAMD, the leading cause of vision loss in elderly individuals in developed countries. I have a high-volume clinical and surgical practice and spend approximately 1.5 days per week in clinic at the Byers Eye Institute and half-day per week at the Santa Clara Valley County Medical Center seeing patients in my clinical practice. In addition, I operate approximately one day per week at the Byers Eye Institute.

12. Given my extensive experience and research on diabetic retinopathy and wAMD, I have become the expert retinal specialist and surgeon in our department for evaluating these chronic eye diseases. Since joining Stanford's Ophthalmology Department, I have also become one of the highest volume retina surgeons among our faculty. Because proliferative diabetic retinopathy can lead to tractional retinal detachment and bleeding within the eye, I am referred complex cases that often require clinic-based treatments (such as intravitreal injections of medicines or pan retinal laser photocoagulation) or surgical management. Since I have clinical and research expertise using intravitreal vascular endothelial growth factor (VEGF) inhibitors in wAMD, ophthalmologists refer patients to me for consultation or co-management, particularly of chronic cases that have not responded to therapy. The majority of my patients are from the Bay Area or central California, and approximately 10% travel from more than 5 hours away to seek my expert opinion. I have been recognized as a "Top Doctor" in the Bay Area for the

past three years.

13. I understand that a copy of my curriculum vitae was previously submitted as Ex. 2002. That copy is still current.

III. SUMMARY OF OPINIONS

14. 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.

15. In forming my opinions, I have reviewed the following materials: (a) the Petition for *Inter Partes* Review of the '338 patent, IPR2021-00881, including all cited exhibits, (b) all priority applications leading to the issuance of the '338 patent, (c) all other documents and references herein, and (d) Patent Owner's Response to which my declaration relates.

16. It is my opinion, for at least the reasons set forth below, that the "method for treating" preamble language of Claims 1 and 14 requires treatment of an angiogenic eye disorder.

17. It is also my opinion, for at least the reasons set forth below, that the claimed "method for treating" must achieve a high level of efficacy, one that is non-inferior to the existing standard of care at the time the '338 patent was filed.

18. Further, it is my opinion, for the reasons set forth below, that “tertiary dose(s)” means “dose(s), administered after the initial and secondary doses, that maintain(s) the efficacy gain achieved after the initial and secondary doses.”

IX. LEGAL FRAMEWORK

19. For purposes of this declaration, I have been informed by counsel for Patent Owner about certain aspects of the law that are relevant to my analysis and opinions.

20. I have been informed that patent claim terms are construed from the vantage point of a skilled artisan to which the invention relates at the time of the invention (or as of the effective filing date of the patent application). The skilled artisan, I understand, is presumed to be familiar with what was known in the art at the time.

21. I have been informed that to determine the level of skill of the skilled artisan, courts may consider several factors including, but not limited to: (1) the educational level of the inventor; (2) type of problems encountered in the art; (3) prior art solutions to those problems; (4) rapidity with which innovations are made; (5) sophistication of the technology; and (6) educational level of active workers in the field. I have also been informed that the skilled artisan is someone who must be concerned with the problems the patent seeks to address.

22. I have been informed that claim terms should be considered in the

context of the entire patent claim where they appear, as well as in the context of the other claims, the specification, and the prosecution history of the patent at issue (collectively, “intrinsic evidence”), taken as a whole (as opposed to in isolation and/or out of context).

23. I have been informed that absent an explicit statement to the contrary by the patent applicant, a patent claim term should have its ordinary and customary meaning and not be limited to a specific example that may appear in the patent specification as referring to a preferred embodiment.

24. I have been informed that where a term has no ordinary and customary meaning to those of ordinary skill in the prior art, one looks to the specification in the patent.

25. I have also been informed that it is only necessary to construe terms that are in controversy, and only to the extent necessary to resolve the controversy.

26. I have also been informed that a nexus between a claimed invention and a commercially successful product or process can be shown to exist by demonstrating that the commercially successful product or process embodies or practices the claimed invention, here, the Challenged Claims.

IV. THE PERSON OF ORDINARY SKILL IN THE ART

27. I understand that Dr. Albini has offered a definition of a person of ordinary skill in the art (who I also refer to as the “skilled artisan”):

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

Ex. 1002², ¶ 28.

28. In my view, the skilled artisan is an ophthalmologist with experience in treating angiogenic eye disorders, including through the use of VEGF antagonists. In the event that Mylan argues that the skilled artisan need not be a licensed physician (ophthalmologist), whatever other qualification they must possess, I disagree because only an ophthalmologist would have the firsthand experience of diagnosing and treating angiogenic eye disorders to which the patent is plainly directed.

29. My opinions set forth in this declaration remain the same under either Patent Owner's or Petitioner's definition of the skilled artisan. Also, under either definition, I would have been at least a skilled artisan when the '338 patent was filed.

² Expert Declaration of Dr. Thomas A. Albini.

30. Likewise, for the purpose of preparing this declaration, I have been informed and understand that the earliest filing date of the '338 patent is January 13, 2011, based on the filing of a Provisional Application on that date.

V. THE '338 PATENT

31. I understand that Petitioner has challenged claims 1, 3-11, 13-14, 16-24 and 26 of the '338 Patent (the "Challenged Claims").

A. Claim 1

32. The '338 Patent has two independent claims, claim 1 and 14.

33. Claim 1 recites:

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.

34. The dosing regimen of Claim 1 is directed to the treatment of any type

of angiogenic eye disorder with a VEGF antagonist that has a particular amino acid sequence.

35. 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.

36. Challenged Claims 3-11 and 13 depend from Claim 1, and further limit the timing between dosage administration, the specific angiogenic eye disorder, administration route, and dosage amount.

B. Claim 14

37. Claim 14 recites:

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

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

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

wherein the VEGF antagonist is a VEGF receptor-based chimeric molecule comprising VEGFR1R2-FcΔC1(a) encoded by the nucleic acid sequence of SEQ ID NO:1.

Ex. 1001 at 24:3-15.

38. The dosing regimen of Claim 14 is directed to the treatment of any type of angiogenic eye disorder with a particular VEGF antagonist that is encoded by the recited nucleic acid sequence.

39. Like Claim 1, the dosing regimen of Claim 14 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.

40. Thus, 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 corresponding amino acid sequence of the nucleic acid sequence SEQ ID NO:1.

41. Challenged Claims 16-24 and 26 depend from Claim 14, and further limit the timing between dose administration, the specific angiogenic eye disorder, administration route, and dose amount.

VI. CLAIM CONSTRUCTION

42. I have been asked to consider the meaning of “[a] method for treating an angiogenic eye disorder in a patient” and “tertiary dose(s)” from the perspective of a skilled artisan as of January 13, 2011, and respond to Dr. Albini’s opinions

regarding the meaning of these terms.

A. “A Method for Treating an Angiogenic Eye Disorder in a Patient”

43. The preamble of Claims 1 and 14 recites “[a] method for treating an angiogenic eye disorder in a patient.” Ex. 1001 at 23:2-3, 24:3-4.

1. Limiting preamble

44. Dr. Albini states that the preamble language “method for treating” simply means “administering a therapeutic agent to a patient.” Ex. 1002 (Albini Declaration), ¶ 43. This, however, ignores the remaining language in the preamble which specifies what is being treated: “an angiogenic eye disorder in a patient.” No ordinarily skilled artisan would think that this language encompasses administering the specified treatment to a person suffering, for example, solely from arthritis. Nor would the ordinarily skilled artisan think that the administration of an infinitesimal amount of the specified compound is encompassed by the claim. Neither would constitute a “method for treating an angiogenic eye disorder in a patient.” Instead, a skilled artisan would understand the language “[a] method for treating an angiogenic eye disorder in a patient” in the context of the ’338 patent to require actually treating a patient’s angiogenic eye condition.

45. It is my understanding that in its Institution Decision, the Board preliminarily construed the preamble “[a] method for treating an angiogenic eye disorder in a patient” to be a limitation of the claim. Paper 21 at 18. That is, the

Board found that the preamble requires an intent to treat a patient with an angiogenic eye disorder. I agree with this determination.

2. Treatment requires efficacy

46. It is also my understanding that the Board preliminarily determined that the preamble does not “requir[e] any ‘specific degree of efficacy.’” Paper 21 at 20. For the reasons below, I disagree with this determination. It is my opinion that the claims of the recited “method for treating” require not only an intent to treat, but also that the treatment be effective. If administration of the drug is not effective, it would not be a treatment. Furthermore, it would not be ethical for a clinician at the time of filing to administer a drug according to an ineffective dosing regimen because there were effective treatments available that had already established a relatively high standard of care.

47. The ’338 Patent explains that the invention is a new method of treatment which is effective, and not inferior to, the existing standard of care, because it “allow[s] for less frequent dosing while *maintaining a high level of efficacy*.” Ex. 1001 at 1:57-58; *see also id.* at 2:3-10 (“The present inventors have surprisingly discovered that *beneficial therapeutic effects* can be achieved...”) (emphasis added).

48. The ’338 patent states, “[t]he amount of VEGF antagonist administered in each dose is, in most cases, a therapeutically effective amount.” Ex. 1001 at

6:48-50. The '338 Patent's specification defines "therapeutically effective amount" as "a dose of VEGF antagonist that results in a detectable improvement in or more symptoms or indicia of an angiogenic eye disorder, or a dose of VEGF antagonist that inhibits, prevents, lessens or delays the progression of an angiogenic eye disorder." *Id.* at 6:50-55.

49. I understand that the Patent Trial and Appeal Board ("PTAB") concluded that the "claims do not require the recited method steps to provide an effective treatment" because the patent states: "[t]he amount of VEGF antagonist administered to the patient in each dose is, *in most cases*, a therapeutically effective amount." Ex. 1001 at 6:48-50 (emphasis added)." Paper 21 at 20.

50. I do not agree with this interpretation of the specification or the Board's conclusion. A skilled artisan would not read this passage in the context of the overall disclosure or what was known at the time about standard of care treatments as describing as part of the patentee's invention, methods of treatment that did not in fact treat anyone because they were not effective. Instead, the passages quoted by the PTAB from column 6 merely observe that an amount which is therapeutically effective is effective "in most cases" even if some patients do not respond. That is consistent with the data reported in the specification that show that while around 96% of the treated subjects achieved the "primary endpoint (prevention of moderate

or severe vision loss as defined above),” the remaining ~ 4% did not achieve this endpoint. Ex. 1001 at 12:66-13:23.

51. The skilled artisan would not understand the passages in column 6 to redefine the invention to include methods that are *not* therapeutically effective. Such methods would not be considered “treatment” as that term is understood by the skilled artisan. The ’338 patent’s specification elsewhere makes clear, repeatedly, that the “present invention” relates to “therapeutic treatment.” *See* Ex. 1001 at Abstract (“The methods of the *present invention* are useful for the treatment of angiogenic eye disorders...”); 1:17-20 (“The *present invention* relates to the field of *therapeutic treatments*...”); 2:3-10 (“The *present inventors* have surprisingly discovered that beneficial *therapeutic* effects can be achieved in patients suffering from angiogenic eye disorders by administering a VEGF antagonist to a patient at a frequency of once every 8 or more weeks, especially when such doses are preceded by about three doses administered to the patient at a frequency of about 2 to 4 weeks.”); 7:19-24 (“Generally, the methods of *the present invention demonstrate efficacy* within 104 weeks of the initiation of the treatment regimen (with the initial dose administered at ‘week 0’), e.g., by the end of week 16, by the end of week 24, by the end of week 32, by the end of week 40, by the end of week 48, by the end of week 56, etc.’”).

52. Furthermore, the '338 patent specification also describes administration in some cases of non-therapeutically effective amounts—not as methods of treatment—but as a means to test the safety of a method in a Phase I clinical trial. In this trial, some doses were as low as 0.05 mg, which is 10-fold lower than the lowest dose in the Phase III clinical trial designed to test efficacy. Ex. 1001 at 7:60-67, 13:5-23. A skilled artisan would understand the need for including testing of non-therapeutic doses in a safety trial and would not view that as a “method for treating” as required by the claims.

53. It is therefore my opinion that the recited “method for treatment” not only requires an intent to treat, but must actually treat.

3. A treatment's efficacy must be non-inferior to the existing standard of care

54. The standard of care for treating wet AMD and many other angiogenic eye disorders improved drastically in the years leading up to the '338 patent filing date, driven in large part by the testing and approval of Lucentis® (ranibizumab).

55. Wet AMD is an angiogenic eye disorder characterized by abnormal growth of new blood vessels in the macula, the central portion of the retina responsible for high-resolution vision. Ex. 2025³ at 2. Historically, wAMD was a

³ A Phase 3 Safety and Efficacy Study of Fovista® (E10030) Intravitreal Administration in Combination With Lucentis® Compared to Lucentis® Monotherapy, ClinicalTrials.gov (August 2, 2021),

devastating diagnosis that frequently led to irreversible vision loss. Early treatments with laser and photodynamic therapy would often, at best, slow inevitable vision loss. At worst, these treatments could cause further vision damage through retinal scarring. Wet AMD was the first angiogenic eye disorder where anti-VEGF agents were widely tested as a potential therapy.

56. 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®).

57. Macugen® was the first anti-VEGF agent approved for treatment of neovascular (wet) age-related macular degeneration. Ex. 2117⁴. Macugen was approved in 2004 based on two pivotal Phase 3 studies and its label instructs that it should be administered once every six weeks by intravitreal injection.” Ex. 2038⁵ at 7. The primary efficacy endpoint for Macugen trials was the proportion of patients losing less than 15 letters of visual acuity as measured by ETDRS. *Id.* at 3-4. “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

<https://clinicaltrials.gov/ct2/show/NCT01940900?term=fovista&phase=2&draw=2&rank=2>.

⁴ Macugen Approval Letter (December 17, 2004).

⁵ Macugen label submitted with NDA 21-756.

group was slower than the rate in the patients who received sham treatment.” *Id.* at 4 (emphasis added).

58. It was Phase III clinical testing of Genentech’s drug, ranibizumab (Lucentis®), a VEGF antibody fragment, that established for the retinal community the potential effectiveness of anti-VEGF therapy.

59. In 2003, Genentech began two large-scale, Phase III studies to test monthly ranibizumab injections in patients with wAMD—MARINA and ANCHOR. Ex. 2118⁶; Ex. 2119⁷.

a. MARINA

60. 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 who were randomly assigned to receive 24 monthly intravitreal injections of ranibizumab (either 0.3 mg or 0.5 mg) or sham injections. Ex. 2119 (Rosenfeld) at 1419. The primary endpoint of the study was the proportion of patients losing fewer than 15 letters from baseline visual acuity at 12 months. *Id.*

61. The one-year results of MARINA were presented in July of 2005 and showed that nearly ninety-five percent of patients treated with ranibizumab satisfied

⁶ Brown DM, et al., *Ranibizumab versus verteporfin for neovascular age-related macular degeneration*, N Engl J Med. 2006;355(14):1432-44.

⁷ Rosenfeld PJ, Brown DM, et al., *Ranibizumab for neovascular age-related macular degeneration*, N Engl J Med. 2006;355(14):1419-31.

the primary endpoint. Ex. 2120⁸ at 4. The two-year results of the MARINA trial were then published in October of 2006 and showed that the mean improvement in vision demonstrated in the first 12 months of the study were sustained through the second years of study. Ex. 2119 (Rosenfeld) at 1419. The mean increases in visual acuity far exceeded the primary endpoint, resulting in gains of +6.5 letters in the 0.3 mg group and +7.2 letters in the 0.5 mg groups (compared with a decrease of -10.3 letters in the sham group). *Id.*

62. The unmasking of the one-year results of the MARINA study prompted a protocol amendment in the second year that allowed subjects still in the sham arm to be offered ranibizumab injections. 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 the hope for sustained improvements in visual acuity.

b. ANCHOR

63. The ANCHOR trial ran from May of 2003 to September of 2006 and enrolled 423 patients with predominantly classic choroidal neovascularization in wAMD. Ex. 2118 (Brown 2006) at 1432. Patients were randomized to receive

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

monthly intravitreal ranibizumab (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.*

64. One year results of the ANCHOR trial were presented by Genentech in November of 2005 and showed that approximately 94 percent of patients treated with 0.3 mg of ranibizumab and 96 percent of those treated with 0.5 mg of ranibizumab maintained or improved vision compared to approximately 64 percent of those treated with PDT alone. Ex. 2120 (Dec. 30, 2005 Genentech Press Release) at 2-3. 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. Ex. 2118 (Brown 2006) at 1432. As in MARINA, the positive results demonstrated in the ranibizumab treatment arms resulted in a protocol amendment that allowed patients in the PDT-alone arm of the study to cross over to ranibizumab injections during the latter part of the study. Ex. 2120 (Dec. 30, 2005 Genentech Press Release) at 3.

c. Lucentis Approval and the New Standard of Care

65. Based on this data from MARINA and ANCHOR, Lucentis (ranibizumab) received FDA approval for the treatment of wAMD in June 2006. Ex.

2121⁹ at 2. 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 (laser or PDT) for wAMD to frequent intravitreal injections of ranibizumab (or off-label bevacizumab (Avastin®)), which could improve patients' vision and maintain those gains over the course of treatment.

66. Indeed, Macugen use plummeted once Lucentis was approved, even though Macugen was indicated for injection every 6 weeks (as compared to Lucentis's recommended dosing regimen of every 4 weeks). This is because retina doctors no longer believed that simply slowing vision decline was enough for effective treatment when therapy was now available that could actually produce visual acuity gains.

67. The successes seen in the treatment of wAMD with ranibizumab and off-label bevacizumab were a game-changer for the treatment of angiogenic eye disorders. As Ciulla and Rosenfeld noted in 2009, "[t]he success of anti-vascular endothelial growth factor (VEGF) therapies in neovascular age-related macular degeneration (AMD) has spurred investigation of similar treatment strategies for

⁹ Genentech News Release, *FDA Approves Lucentis for the Treatment of Wet Age-Related Macular Degeneration*, (June 30, 2006).

other exudative ocular diseases.” Ex. 1074¹⁰ at 158.

68. After Lucentis’ approval, the skilled artisan would have thought that an effective treatment for an angiogenic eye disorder would achieve a similar level of efficacy to Lucentis, *i.e.*, in the case of wet AMD, mean increase in visual acuity and satisfaction of the primary endpoint as described above. In other words, the standard of care was to use Lucentis (or off-label Avastin) to treat wAMD, and, therefore, an anti-VEGF agent had to be administered according to a dosing regimen that was not inferior to this standard of care at the time.

d. Clinical Trial Efficacy Endpoints

69. The skilled artisan reviewing the ’338 patent specification would understand that the “Treatment Population and Efficacy” provides a general reference to the clinical studies that are set forth in the ’338 Patent. Ex. 1001 at 7:15. The passage refers to methods for treating angiogenic eye disorders “such as AMD, CRVO, and DME.” *Id.* at 7:24-26. The ’338 patent includes several clinical trial examples setting forth results from the administration of VEGF Trap in AMD (Example 4), DME (example 5), and CRVO (Example 6).

70. The skilled artisan reviewing Column 7 would understand that loss of

¹⁰ Ciulla, TA & Rosenfeld, PJ, *Antivascular Endothelial Growth Factor Therapy For Neovascular Age-Related Macular Degeneration*, Current Opinion in Ophthalmology 2009, 20:158-165.

15 or fewer letters on ETDRS (Ex. 1001 at 7:24-29), as well as a gain of letters on ETDRS (Ex. 1001 at 7:29-32), correspond to clinical trial endpoints that were used to measure or assess the clinical results of anti-VEGF agents in the art.

71. After Lucentis was approved, anti-VEGF studies, including some of the examples reported in the '338 patent, began using clinical trial endpoints that measured visual acuity *gains* as primary outcome measures:

- **RISE/RIDE** (Genentech, Inc.): percentage of patients who gained ≥ 15 letters in BCVA at month 24 (Ex. 2122¹¹, Ex. 2123¹²);
- **BRAVO/CRUISE** (Genentech, Inc.): mean change from baseline in BCVA score at 6 months (Ex. 2124¹³, Ex. 2125¹⁴);

¹¹ A Study of Ranibizumab Injection in Subjects With Clinically Significant Macular Edema (ME) With Center Involvement Secondary to Diabetes Mellitus (RISE), NCT00473330, ClinicalTrials.gov (December 22, 2021), <https://www.clinicaltrials.gov/ct2/show/NCT00473330>.

¹² A Study of Ranibizumab Injection in Subjects With Clinically Significant Macular Edema (ME) With Center Involvement Secondary to Diabetes Mellitus (RIDE), NCT00473382 ClinicalTrials.gov (December 22, 2021), <https://clinicaltrials.gov/ct2/show/NCT00473382>.

¹³ A Study of the Efficacy and Safety of Ranibizumab Injection in Patients With Macular Edema Secondary to Branch Retinal Vein Occlusion (BRAVO), NCT00486018 (December 22, 2021), <https://clinicaltrials.gov/ct2/show/NCT00486018>.

¹⁴ A Study of the Efficacy and Safety of Ranibizumab Injection in Patients With Macular Edema Secondary to Central Retinal Vein Occlusion (CRUISE), NCT00485836 (December 22, 2021), <https://clinicaltrials.gov/ct2/show/NCT00485836>.

- **COPERNICUS/GALILEO** (Bayer/Regeneron): percentage of participants who gained at least 15 letters in BCVA as measured by ETDRS Letter Score at week 24 (Ex. 2126¹⁵, Ex. 2127¹⁶).

72. In addition to the clinical trial endpoints mentioned in Column 7, the '338 Patent's specification discloses the use of a number of different clinical trial endpoints to measure the results of VEGF Trap in different angiogenic eye disorders. *See, e.g.*, Ex. 1001 at 8:34-41 (Example 2 primary endpoint of reduction in retinal thickness after 12 weeks; secondary endpoint of mean change in visual acuity); 9:37-44 (Example 4 primary endpoint prevention of vision loss of greater than or equal to 15 letters on the ETDRS chart at 52 weeks; secondary endpoints were (a) change in letter score on the ETDRS chart at 52 weeks; (b) gain of 15 letters or more on the ETDRS chart at 52 weeks; (c) change in total NEI VFQ-25 score at 52 weeks; and (d) change in CNV area at 52 weeks); 14:52-54 (Example 6 primary endpoint proportion of patients who gained greater than or equal to 15 ETDRS letters from baseline at Week 24). For clinical trials of VEGF Trap-Eye that were not designed as non-inferiority studies, Regeneron used mean change in visual acuity from

¹⁵ Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO), NCT00943072 (December 22, 2021), <https://clinicaltrials.gov/ct2/show/NCT00943072>.

¹⁶ Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO) (GALILEO), NCT01012973 (December 22, 2021), <https://clinicaltrials.gov/ct2/show/NCT01012973>.

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. *See* Ex. 1001 at 14: 5-26, 52-56.

73. The skilled artisan would have been able to evaluate these clinical trial results to assess the therapeutic effectiveness of an anti-VEGF treatment method. However, as discussed above, because the standard-of-care for treating angiogenic eye disorders had evolved from observation and monitoring or destructive therapies (laser or PDT) to ranibizumab or off-label bevacizumab, the skilled artisan would not have assumed that simply meeting a clinical trial endpoint, standing alone, would mean that an anti-VEGF agent would be an effective treatment for angiogenic eye disorders as of 2011. Instead, the skilled artisan would compare the clinical trial results with results for the prevailing standard of care at the time of filing. For instance, Macugen received FDA approval in 2004 based on outperforming sham using the clinical efficacy endpoint of loss of 15 or fewer letters on ETDRS. Yet, by 2011, the POSA would not have considered Macugen to be an effective method for treating an angiogenic eye disorder.

e. VIEW 1 and VIEW 2

74. Regeneron conducted two Phase 3 studies in wet AMD, also called VIEW 1 and VIEW 2, which are described in Example 4 of the '338 patent. Ex. 1001 at 9:12-13:48. "The primary objective of these studies was to assess the efficacy of

IVT [intravitreally] administered VEGFT compared to ranibizumab (Lucentis®, Genentech, Inc.) in a non-inferiority paradigm.” Ex. 1001 at 9:21-25.

75. For each study, subjects were randomly assigned in a 1:1:1:1 ratio to one of the four following regimens: (1) 2 mg VEGFT every 4 weeks (2Q4); (2) 0.5 mg VEGFT every 4 weeks (0.5Q4); (3) 2 mg VEGFT every 4 weeks to week 8 and then every 8 weeks (2Q8) (to maintain masking, sham injections were given at the interim 4-week visits after week 8); and (4) 0.5 mg ranibizumab every 4 weeks (RQ4). Ex. 1001 at 9:46-57.

76. “The primary hypothesis of these studies was that the proportion of subjects treated with VEGFT with stable or improved BCVA (< 15 letters lost) is similar to the proportion treated with ranibizumab who have stable or improved BCVA, thereby demonstrating non-inferiority.” Ex. 1001 at 9:32-36.

77. The “reason” for using a “non-inferiority” study is “an ethical one.” Ex. 2097¹⁷ at 7. “Specifically, this design is chosen when it would not be ethical to use a placebo ... because there is an effective treatment that provides an important benefit ... available to patients for the condition to be studied in the trial.” *Id.* As discussed above, because Lucentis was an available, effective treatment for

¹⁷ Non-Inferiority Clinical Trials to Establish Effectiveness, Guidance for Industry, November 2016.

angiogenic eye disorders, Regeneron ran its VIEW 1 and VIEW 2 Phase III trials as noninferiority studies against Lucentis as an active comparator.

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 (Non-Inferiority Clinical Trials to Establish Effectiveness, Guidance for Industry) at 8, 12.

79. The '338 patent summarizes the 52 week results for VIEW 1 and VIEW 2. Ex. 1001 at 12:65-13:48. The primary endpoint analysis showed that all three VEGF Trap dosing arms, including the group receiving 2Q8 treatment, achieved noninferiority compared with monthly ranibizumab. *Id.* 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 dosing arm also met this primary endpoint. *Id.* at 13:5-20 (Table 1). Both trials reported that 95.1% and 95.6% of patients dosed 2Q8 met this same endpoint. *Id.*

80. In addition, the study results also showed that subjects in each of the VEGF Trap dosing arms had similar visual acuity gains as compared to the ranibizumab. Ex. 1001 at Table 1. These data are presented together in the '338 specification and the POSA would have interpreted these data collectively to mean that each VEGF Trap-Eye dosing arm, including 2Q8, was non-inferior to ranibizumab.

81. Based on these findings, Regeneron sought and received approval of VEGF Trap-Eye (later known as Eylea[®] or aflibercept)¹⁸ 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. 2019¹⁹ at § 2.2.

82. I understand that Mylan argues that if the Challenged Claims require efficacy, the '338 Patent specification only requires that “efficacy” be a “loss of fifteen or fewer letters in the Early Treatment Diabetic Retinopathy Study

¹⁸ “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 et al., *Intravitreal Aflibercept (VEGF Trap-Eye) in Wet Age-Related Macular Degeneration*, *Ophthalmology*, 119(12):2537-2548 (2012)) at 2539.

¹⁹ Eylea (aflibercept) Injection label, revised May 2016.

(‘ETDRS’) visual acuity chart within 104 weeks of treatment initiation.” Petition at 21. Mylan bases this argument on a misreading of the patent’s explanation that “efficacy,” defined “in the context of methods for treating angiogenic eye disorders such as AMD” means “that, from the initiation of treatment, the patient exhibits a loss of 15 or fewer letters on the Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity chart.” Ex. 1001 at 7:25-30. As explained above, this level of efficacy was the primary endpoint in the pivotal Phase 3 ranibizumab trials and was therefore also the primary endpoint for the Eylea’s non-inferiority Phase 3 wAMD trials described above. Non-inferiority was established by matching or exceeding ranibizumab’s success at achieving this endpoint for about 95% of the patients treated according to the protocol. Ex. 1001 at 13:18-21 (“Statistically non-inferior based on a non-inferiority margin of 10%, using confidence interval approach (95.1% and 95% for Study 1 and Study 2, respectively).”). Efficacy, based on this particular measure, is not achieved merely by a single patient satisfying the “loss of 15 or fewer letters” endpoint but instead by having about 95% or more of all patients meeting this endpoint. Moreover, although this was the primary endpoint, as explained above, the treatment also resulted in an average gain of 7 or more letters. The skilled artisan would have concluded from the totality of data presented in Example 4 that VEGF Trap, administered on a Q8 dosing schedule, achieved and maintained a high level of efficacy that was non-inferior to

ranibizumab.

83. A skilled artisan would not have read the sentence in column 7 of the patent upon which Mylan relies in isolation from the remainder of the specification and knowledge of the state of the art at the time. Nor would a skilled artisan accept any treatment that merely prevented a patient from losing “fifteen or fewer letters” as even approaching the standard of care at the time of filing. I did not see anything in Mylan’s submission that argued otherwise. Instead, the skilled artisan would understand that the level of efficacy achieved by the claimed invention is non-inferior to the existing standard of care which, for the average patient, is far more than the mere loss of 15 or fewer letters.

f. Conclusion

84. It is therefore my opinion that, as of January 13, 2011, the POSA would consider the claimed method of treatment as one that achieves a high level of efficacy that is non-inferior to the standard of care at the time of patent filing. This may vary somewhat depending on the particular angiogenic eye disorder. When treating wet AMD, for example, the patent makes clear that the treatment is one that results in an average gain of approximately 7 or more letters and the loss of 15 letters or fewer for at least 95% of all patients constitutes an effective treatment. Ex. 1001 at 13:28-30 (“patients receiving VEGFT 2 mg monthly on average gained 10.9 letters ... every month”); 13:5-23 (showing mean gains of between 6.9 and 10.9

letters); 9:32-36 (“The primary hypothesis of these studies was that the proportion of subjects treated with VEGFT with stable or improved BCVA (<15 letters lost) is similar to the proportion treated with ranibizumab who have stable or improved BCVA, thereby demonstrating non-inferiority.”); 12:66-13:1 (“The primary endpoint (prevention of moderate or severe vision loss as defined above) was met for all three VEGFT groups.”).

B. “Tertiary Dose(s)”

85. Claims 1 and 14 requires that “tertiary dose(s)” are “administered at least 8 weeks after the immediately preceding dose.” Ex. 1001 at 23:10-11.

86. It is my understanding that the Board found that specification does not “require the ‘tertiary dose[s]’ to maintain any efficacy gain achieved after the initial and secondary doses, or that the term ‘connotes a specific level of efficacy’” and preliminarily construed “tertiary dose(s) as doses “which are administered after the secondary doses.” Paper 21 at 23. For the following reasons, I disagree with the Board’s preliminary construction.

87. It is my opinion that “tertiary dose(s)” means “dose(s), administered after the initial and secondary doses, that maintain(s) the efficacy gain achieved after the initial and secondary doses.”

88. As of the filing date, and even today, the term “tertiary dose(s)” does not have a well-understood meaning to a skilled artisan in the fields of

ophthalmology or retina medicine outside the context of the '338 Patent. In my experience, with which Dr. Albini agrees, the term “tertiary dose(s)” is not typically used by clinicians or the skilled artisan. Ex. 1002 (Albini Declaration), ¶ 41.

89. Dr. Albini states that a skilled artisan would understand the term “tertiary dose(s)” as used in the claims of the '338 Patent based solely on the following passage from the '338 patent specification:

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

Ex. 1001 at 3:31-45.

90. But in my view, the '338 patent specification provides more context for the meaning of the term “tertiary dose” than the isolated passage above. Indeed, the '338 Patent specification explains that, at the time of patent filing in January 2011, therapies for the treatment of angiogenic eye disorders using VEGF antagonists existed in the art. Ex. 1001 at 1:49-52. Nonetheless, the '338 Patent recognized that

there remained a need for less frequent dosing regimens that could maintain a high degree of efficacy. *Id.* at 1: 55-59. The '338 patent successfully addressed this long-felt need:

“The present inventors have ***surprisingly*** discovered that ***beneficial therapeutic effects*** can be achieved in patients suffering from angiogenic eye disorders by administering a VEGF antagonist to a patient at a frequency of once every 8 or more weeks, especially when such doses are preceded by about three doses administered to the patient at a frequency of about 2 to 4 weeks.”

Id. at 2:3-10 (emphases added).

91. The '338 Patent specification makes clear that a key benefit of the claimed dosing regimens is that for “most of the course of treatment (i.e., the tertiary doses)” patients may be treated less frequently as compared to therapies that existed in the art (i.e., monthly dosing). *Id.* at 2:15-22 (emphasis added). In my opinion, the disclosed dosing regimens were a significant advance over existing therapies because they enabled physicians, like myself, to treat patients using less frequent dosing, but to maintain a high degree of therapeutic efficacy.

92. I agree with Dr. Albini that the passage at column 3, lines 31-45 quoted above informs the temporal sequence of “initial dose,” “secondary dose” and “tertiary dose(s).” I also agree that the “tertiary dose(s)” are third in the sequence of these doses but, in my opinion, this passage does not provide any guidance as to how to determine the appropriate magnitude of the “tertiary dose(s).” However, Patent

Owner's construction captures the full meaning of the term "tertiary dose(s)" in the context of the specification.

93. I also understand that Petitioner argues, and Dr. Albini agrees, that in the context of the '338 patent, "efficacy" "only requires that the patient exhibit a loss of fifteen or fewer letters on the Early Treatment Diabetic Retinopathy Study ("ETDRS") visual acuity chart within 104 weeks of treatment initiation." Petition at 21; Ex. 1002 (Albini Declaration), ¶ 43. As I read the claims of the '338 Patent, in view of the specification, this level of efficacy would not be sufficient for the dosing regimens claimed in the '338 Patent. For example, if a patient achieved a letter gain after the initial and secondary doses and then declined after the tertiary dose(s) began, but nonetheless exhibited a loss of fewer than 15 letters during the tertiary dosing, I would not consider this level of efficacy to be sufficient for the dosing regimen claimed in the '338 Patent. Rather, I understand "tertiary dose(s)" to require that the efficacy gain achieved from the initial and secondary doses are maintained after the initial and secondary doses. *See, e.g., supra* at ¶ 45 (discussing passage in the specification that "[t]he present inventors have surprisingly discovered that beneficial therapeutic effects can be achieved in patients suffering from angiogenic eye disorders by administering a VEGF antagonist to a patient at a frequency of once every 8 or more weeks, especially when such doses are preceded by about three doses administered to the patient at a frequency of about 2 to 4 weeks.").

94. Consequently, in my opinion, the term “tertiary dose(s),” when viewed from the perspective of a skilled artisan in the context of the specification, means “dose(s), administered after the initial and secondary doses, that maintain(s) the efficacy gain achieved after the initial and secondary doses.”

VII. BOTH THE EYLEA LABEL AND PHYSICIAN’S ADMINISTRATION OF EYLEA PRACTICE THE CHALLENGED CLAIMS

A. The United States Prescribing Information for Eylea Demonstrates Practice of the Challenged Claims

95. Eylea was approved for intravitreal injection in November 2011. Ex. 2019 (Eylea USPI) at 1. The United States Prescribing Information for Eylea (hereinafter “Eylea USPI” or “Eylea Label”) states that it is indicated for the treatment of patients with (1) Neovascular (Wet) Age-Related Macular Degeneration (AMD); (2) Macular Edema Following Retinal Vein Occlusion (RVO); (3) Diabetic Macular Edema (DME); and (4) Diabetic Retinopathy (DR). *Id.*

96. For wAMD, the Eylea Label provides that the recommended dose is “2 mg (0.05 mL) administered by intravitreal injection 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).” Ex. 2019 (Eylea USPI) at § 2.2.

97. For DME and DR, the Eylea Label provides that the recommended dose is “The recommended dose for EYLEA is 2 mg (0.05 mL) administered by

intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months).” Ex. 2019 (Eylea USPI) at §§ 2.4, 2.5.

1. Claim 1

a. [1.pre.]: A method for treating an angiogenic eye disorder in a patient, said method comprising

98. The Full Prescribing Information for the treatment of wAMD, DME and DR using Eylea (hereinafter the “Eylea PI”) set forth in the Eylea Label satisfies the preamble of claim 1. Ex. 2019 (Eylea USPI) at §§ 2.2, 2.4, 2.5. Each of wAMD, DME and DR is an angiogenic eye disorder in a patient, and the dosing and administration information in the Eylea PI constitutes a method for treating those angiogenic eye disorders.

b. [1.a]: 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;

99. Eylea is a VEGF antagonist. Ex. 2019 (Eylea USPI) at § 12.1. Furthermore, the dosing and administration for each of wAMD, DME and DR involves the sequential administration to the patient a single initial dose of Eylea, followed by two secondary doses (wAMD) or four secondary doses (DME and DR) of Eylea, followed by one or more tertiary doses of the Eylea. *Id.* at §§ 2.2, 2.4, 2.5.

- c. **[1.b]: wherein each secondary dose is administered 2 to 4 weeks after the immediately preceding dose; and**

100. The Eylea PI for wAMD, DME and DR set forth in the Eylea USPI satisfies this requirement. The dosing and administration for each of wAMD, DME and DR includes two secondary doses (wAMD) or four secondary doses (DME and DR) of Eylea administered “every 4 weeks.” Ex. 2019 (Eylea USPI) at §§ 2.2, 2.4, 2.5.

- d. **[1.c]: wherein each tertiary dose is administered at least 8 weeks after the immediately preceding dose;**

101. The Eylea PI for wAMD, DME and DR set forth in the Eylea USPI satisfies this requirement. The dosing and administration for each of wAMD, DME and DR includes tertiary dosing where each tertiary dose is administered “once every 8 weeks (2 months)” after the immediately preceding dose. Ex. 2019 (Eylea USPI) at §§ 2.2, 2.4, 2.5.

- e. **[1.d]: 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.**

102. I have reviewed Exhibit 1024²⁰ in this proceeding. I am informed that Exhibit 1024 is an Application for Extension of Patent Term under 35 U.S.C. § 156,

²⁰ File History of U.S. Patent No. 7,374,758 B2, 12/22/2011 Patent Term Extension Application (“758 FH, 12/22/2011 PTE”).

and that the application references Eylea. Based on my review of Exhibit 1024, I understand that Eylea is a recombinant fusion protein consisting of a VEGF receptor component having Ig domains consisting of an Ig domain 2 of human Flt1 and an Ig domain 3 of human Flk1, fused to an Fc domain of human IgG1. Ex. 1024 at 6. Accordingly, a person of ordinary skill in the art would understand that Eylea is a chimeric molecule that combines two components having different origins—Ig domain 2 from VEGFR1 and Ig domain 3 from VEGFR2—that are linked together—fused to an Fc portion of human IgG1—to form a biological agent. VEGFR1 is also known as Flt-1, and VEGFR2 is also known as Flk-1. *Id.* I further understand that Exhibit 1024 explains that the amino acid sequence of VEGFR1 spans amino acid residues 27 through 129 of the sequence disclosed in Figures 24A to 24C. *Id.* Exhibit 1024 also explains that the amino acid sequence of VEGFR2 spans amino acid residues 130 through 231 of the sequence disclosed in Figures 24A to 24C of the '758 patent. *Id.* Finally, Exhibit 1024 explains that Eylea includes a multimerization component, also discussed in Example 20 of the '758 patent, with an amino acid sequence disclosed in Figures 24A to 24C that spans amino acid residue 232 through 458. *Id.* I note that claim 1 recites that the multimerization component comprises amino acids 232-457 of SEQ ID NO:2. The inclusion of amino acid residue 458 from Figures 24A to 24C of the '758 patent does not alter the fact that Eylea's multimerization component includes amino acids 232 through

457 of SEQ ID NO:2 in the '338 patent.

2. Claim 3

- a. [3.a]: The method of claim 1, wherein only two secondary doses are administered to the patient, and**

103. The Eylea PI for wAMD recommends a 2 mg dose of Eylea “administered by intravitreal injection every 4 weeks for the first 12 weeks (3 months).” Ex. 2019 (Eylea USPI) at § 2.2. Thus, the Eylea PI provide for three monthly loading doses, an initial dose followed by two secondary doses.

- b. [3.b]: wherein each secondary dose is administered 4 weeks after the immediately preceding dose.**

104. The Eylea PI recommend that each secondary dose is administered 4 weeks after the immediately preceding dose. Ex. 2019 (Eylea USPI) at §§ 2.2, 2.4, 2.5.

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

105. The Eylea PI recommend, following the initial and secondary doses, the administration of 2 mg of Eylea “via intravitreal injection once every 8 weeks (2 months).” Ex. 2019 (Eylea USPI) at §§ 2.2, 2.4, 2.5. This means that each tertiary dose is administered every 8 weeks after the immediately preceding dose.

4. Claim 5:

- a. [5.a]: The method of claim 1, wherein at least 5 tertiary doses of the VEGF antagonist are administered to the patient, and**

106. The Eylea PI include the results of 52-week clinical studies in which patients were administered three loading doses of 2 mg of Eylea followed by the administration of 2 mg of Eylea every eight weeks. Ex. 2019 (Eylea USPI) at §§ 14.1, 14.4. During 52 weeks of treatment, as reflected by the Eylea PI, patients were administered 5 tertiary doses. *Id.*

- b. [5.b]: wherein the first four tertiary doses are administered 8 weeks after the immediately preceding dose, and**

107. Each of the tertiary doses of Eylea administered in the clinical studies reported in the Eylea PI was administered 8 weeks after the immediately preceding dose. Ex. 2019 (Eylea USPI) at §§ 14.1, 14.4. For that reason, the first four tertiary doses in the clinical studies reported in the Eylea PI were administered 8 weeks after the immediately preceding dose.

- c. [5.c]: wherein each subsequent tertiary dose is administered 8 or 12 weeks after the immediately preceding dose.**

108. Each of the tertiary doses of Eylea administered in the clinical studies reported in the Eylea PI was administered 8 weeks after the immediately preceding dose. Ex. 2019 (Eylea USPI) at §§ 14.1, 14.4. For that reason, the fifth tertiary dose in the clinical studies reported in the Eylea PI was administered 8 or 12 weeks after

the immediately preceding dose.

- 5. Claim 6: The method of claim 1, wherein the angiogenic eye disorder is selected from the group consisting of: age related macular degeneration, diabetic retinopathy, diabetic macular edema, central retinal vein occlusion, branch retinal vein occlusion, and corneal neovascularization.**

109. The Eylea PI for wAMD, DME and DR set forth in the Eylea USPI satisfies this requirement. The Eylea USPI applies to wAMD, which is a form of age related macular degeneration, DR, which is diabetic retinopathy, and DME, which is diabetic macular edema. Ex. 2019 (Eylea USPI) at §§ 2.2, 2.4, 2.5.

- 6. Claim 7: The method of claim 6, wherein the angiogenic eye disorder is age related macular degeneration.**

110. The Eylea PI for wAMD set forth in the Eylea USPI satisfies this requirement. The Eylea USPI applies to wAMD, which is a form of age related macular degeneration, DR, which is diabetic retinopathy, and DME, which is diabetic macular edema. Ex. 2019 (Eylea USPI) at §§ 2.2, 2.4, 2.5.

- 7. Claim 8: The method of claim 1, wherein all doses of the VEGF antagonist are administered to the patient by topical administration or by intraocular administration.**

111. The Eylea PI for wAMD, DME and DR set forth in the Eylea USPI satisfies this requirement. For each of wAMD, DME and DR, Eylea is administered to the patient by intravitreal injection, which constitutes intraocular administration. Ex. 2019 (Eylea USPI) at §§ 2.1, 2.2, 2.4, 2.5.

8. Claim 9: The method of claim 8, wherein all doses of the VEGF antagonist are administered to the patient by intraocular administration.

112. The Eylea PI for wAMD, DME and DR set forth in the Eylea USPI satisfies this requirement. For each of wAMD, DME and DR, Eylea is administered to the patient by intravitreal injection, which constitutes intraocular administration. Ex. 2019 (Eylea USPI) at §§ 2.1, 2.2, 2.4, 2.5.

9. Claim 10: The method of claim 9, wherein the intraocular administration is intravitreal administration.

113. The Eylea PI for wAMD, DME and DR set forth in the Eylea USPI satisfies this requirement. For each of wAMD, DME and DR, Eylea is administered to the patient by intravitreal injection, which constitutes intraocular administration. Ex. 2019 (Eylea USPI) at §§ 2.1, 2.2, 2.4, 2.5.

10. Claim 11: The method of claim 10, wherein all doses of the VEGF antagonist comprise from about 0.5 mg to about 2 mg of the VEGF antagonist.

114. The Eylea PI for wAMD, DME and DR set forth in the Eylea USPI satisfies this requirement. For each of wAMD, DME and DR, Eylea is administered to the patient at a dosage of 2 mg. Ex. 2019 (Eylea USPI) at §§ 2.2, 2.4, 2.5.

11. Claim 13: The method of claim 11, wherein all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist.

115. The Eylea PI for wAMD, DME and DR set forth in the Eylea USPI satisfies this requirement. For each of wAMD, DME and DR, Eylea is administered to the patient at a dosage of 2 mg. Ex. 2019 (Eylea USPI) at §§ 2.2, 2.4, 2.5

12. Claim 14

a. [14.pre.]: A method for treating an angiogenic eye disorder in a patient, said method comprising

116. The Eylea PI for wAMD, DME and DR set forth in the Eylea USPI satisfies this requirement. The Full Prescribing Information for the treatment of wAMD, DME and DR using Eylea (hereinafter the “Eylea PI”) set forth in the Eylea Label satisfies the preamble of claim 1. Ex. 2019 (Eylea USPI) at §§ 2.2, 2.4, 2.5. Each of wAMD, DME and DR is an angiogenic eye disorder in a patient, and the dosing and administration information in the Eylea PI constitutes a method for treating those angiogenic eye disorders.

b. [14.a]: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;

117. The Eylea PI for wAMD, DME and DR set forth in the Eylea USPI satisfies this requirement. Eylea is a VEGF antagonist. Ex. 2019 (Eylea USPI) at § 12.1. The dosing and administration for each of wAMD, DME and DR involves the sequential administration to the patient a single initial dose of Eylea, followed by two secondary doses (wAMD) or four secondary doses (DME and DR) of Eylea, followed by one or more tertiary doses of the Eylea. *Id.* at §§ 2.2, 2.4, 2.5.

c. [14.b]: wherein each secondary dose is administered 2 to 4 weeks after the immediately preceding dose; and

118. The Eylea PI for wAMD, DME and DR set forth in the Eylea USPI

satisfies this requirement. The dosing and administration for each of wAMD, DME and DR includes two secondary doses (wAMD) or four secondary doses (DME and DR) of Eylea administered “every 4 weeks.” Ex. 2019 (Eylea USPI) at §§ 2.2, 2.4, 2.5.

d. [14.c]: wherein each tertiary dose is administered at least 8 weeks after the immediately preceding dose;

119. The Eylea PI for wAMD, DME and DR set forth in the Eylea USPI satisfies this requirement. The dosing and administration for each of wAMD, DME and DR includes tertiary dosing where each tertiary dose is administered “once every 8 weeks (2 months)” after the immediately preceding dose. Ex. 2019 (Eylea USPI) at §§ 2.2, 2.4, 2.5.

e. [14.d]: wherein the VEGF antagonist is a VEGF receptor-based chimeric molecule comprising VEGFR1R2-FcΔC1(a) encoded by the nucleic acid sequence of SEQ ID NO:1.

120. I have reviewed Exhibit 1024 (’758 FH, 12/22/2011 PTE) in this proceeding. I am informed that Exhibit 1024 is an Application for Extension of Patent Term under 35 U.S.C. § 156, and that the application references Eylea. Based on my review of Exhibit 1024, I understand that Eylea is a recombinant fusion protein consisting of a VEGF receptor component having Ig domains consisting of an Ig domain 2 of human Flt1 and an Ig domain 3 of human Flk1, fused to the Fc domain of human IgG1. Ex. 1024 at 6. Accordingly, a person of ordinary skill in the

art would understand that Eylea is a chimeric molecule that combines two components having different origins—Ig domain 2 from VEGFR1 and Ig domain 3 from VEGFR2—that are linked together—fused to the Fc portion of human IgG1—to form a biological agent. VEGFR1 is also known as Flt-1, and VEGFR2 is also known as Flk-1. *Id.* Furthermore, the specification of the '338 Patent provides that the nucleic acid sequence of SEQ ID NO:1 comprises amino acid sequence of SEQ ID NO:2. Ex. 1001 at 4:58-5:3.

13. Claim 16

a. [16.a]: The method of claim 14, wherein only two secondary doses are administered to the patient, and

121. The Eylea PI for wAMD set forth in the Eylea USPI satisfies this requirement. The Eylea PI for wAMD recommends a 2 mg dose of Eylea “administered by intravitreal injection every 4 weeks for the first 12 weeks (3 months) ” Ex. 2019 (Eylea USPI) at § 2.2. Thus, the Eylea PI provide for three monthly loading doses, an initial dose followed by two secondary doses.

b. [16.b]: wherein each secondary dose is administered 4 weeks after the immediately preceding dose.

122. The Eylea PI for wAMD set forth in the Eylea USPI satisfies this requirement. The Eylea PI recommend that each secondary dose is administered 4 weeks after the immediately preceding dose. Ex. 2019 (Eylea USPI) at §§ 2.2, 2.4, 2.5.

14. Claim 17: The method of claim 16, wherein each tertiary dose is administered 8 weeks after the immediately preceding dose.

123. The Eylea PI for wAMD set forth in the Eylea USPI satisfies this requirement. The Eylea PI recommend, following the initial and secondary doses, the administration of 2 mg of Eylea “via intravitreal injection once every 8 weeks (2 months).” Ex. 2019 (Eylea USPI) at §§ 2.2, 2.4, 2.5. This means that each tertiary dose is administered every 8 weeks after the immediately preceding dose.

15. Claim 18: The method of claim 17, wherein the angiogenic eye disorder is age related macular degeneration.

124. The Eylea PI for wAMD set forth in the Eylea USPI satisfies this requirement. The Eylea USPI applies to wAMD, which is a form of age related macular degeneration, DR, which is diabetic retinopathy, and DME, which is diabetic macular edema. Ex. 2019 (Eylea USPI) at §§ 2.2, 2.4, 2.5.

16. Claim 19:

a. [19.a]: The method of claim 14, wherein at least 5 tertiary doses of the VEGF antagonist are administered to the patient, and

125. The Eylea PI for wAMD set forth in the Eylea USPI satisfies this requirement. The Eylea PI include the results of 52-week clinical studies in which patients were administered three loading doses of 2 mg of Eylea followed by the administration of 2 mg of Eylea every eight weeks. Ex. 2019 (Eylea USPI) at §§ 14.1, 14.4. During 52 weeks of treatment, as reflected by the Eylea PI, patients were

administered 5 tertiary doses. *Id.*

- b. [19.b]: wherein the first four tertiary doses are administered 8 weeks after the immediately preceding dose,**

126. The Eylea PI for wAMD set forth in the Eylea USPI satisfies this requirement. Each of the tertiary doses of Eylea administered in the clinical studies reported in the Eylea PI was administered 8 weeks after the immediately preceding dose. Ex. 2019 (Eylea USPI) at §§ 14.1, 14.4. For that reason, the first four tertiary doses in the clinical studies reported in the Eylea PI were administered 8 weeks after the immediately preceding dose.

- c. [19.c]: and wherein each subsequent tertiary dose is administered 8 or 12 weeks after the immediately preceding dose.**

127. The Eylea PI for wAMD set forth in the Eylea USPI satisfies this requirement. Each of the tertiary doses of Eylea administered in the clinical studies reported in the Eylea PI was administered 8 weeks after the immediately preceding dose. Ex. 2019 (Eylea USPI) at §§ 14.1, 14.4. For that reason, the fifth tertiary dose in the clinical studies reported in the Eylea PI was administered 8 or 12 weeks after the immediately preceding dose.

- 17. Claim 20: The method of claim 14, wherein the angiogenic eye disorder is selected from the group consisting of: age related macular degeneration, diabetic retinopathy, diabetic macular edema, central retinal vein occlusion, branch retinal vein occlusion, and corneal neovascularization.**

128. The Eylea PI for wAMD, DME and DR set forth in the Eylea USPI

satisfies this requirement. The Eylea USPI applies to wAMD, which is a form of age related macular degeneration, DR, which is diabetic retinopathy, and DME, which is diabetic macular edema. Ex. 2019 (Eylea USPI) at §§ 2.2, 2.4, 2.5.

18. Claim 21: The method of claim 14, wherein all doses of the VEGF antagonist are administered to the patient by topical administration or by intraocular administration.

129. The Eylea PI for wAMD, DME and DR set forth in the Eylea USPI satisfies this requirement. For each of wAMD, DME and DR, Eylea is administered to the patient by intravitreal injection, which constitutes intraocular administration. Ex. 2019 (Eylea USPI) at §§ 2.1, 2.2, 2.4, 2.5.

19. Claim 22: The method of claim 21, wherein all doses of the VEGF antagonist are administered to the patient by intraocular administration.

130. The Eylea PI for wAMD, DME and DR set forth in the Eylea USPI satisfies this requirement. For each of wAMD, DME and DR, Eylea is administered to the patient by intravitreal injection, which constitutes intraocular administration. Ex. 2019 (Eylea USPI) at §§ 2.1, 2.2, 2.4, 2.5.

20. Claim 23: The method of claim 22, wherein the intraocular administration is intravitreal administration.

131. The Eylea PI for wAMD, DME and DR set forth in the Eylea USPI satisfies this requirement. For each of wAMD, DME and DR, Eylea is administered to the patient by intravitreal injection, which constitutes intraocular administration. Ex. 2019 (Eylea USPI) at §§ 2.1, 2.2, 2.4, 2.5

21. Claim 24: The method of claim 23, wherein all doses of the VEGF antagonist comprise from about 0.5 mg to about 2 mg of the VEGF antagonist.

132. The Eylea PI for wAMD, DME and DR set forth in the Eylea USPI satisfies this requirement. For each of wAMD, DME and DR, Eylea is administered to the patient at a dosage of 2 mg. Ex. 2019 (Eylea USPI) at §§ 2.2, 2.4, 2.5.

22. Claim 26: The method of claim 24, wherein all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist

133. The Eylea PI for wAMD, DME and DR set forth in the Eylea USPI satisfies this requirement. For each of wAMD, DME and DR, Eylea is administered to the patient at a dosage of 2 mg. Ex. 2019 (Eylea USPI) at §§ 2.2, 2.4, 2.5.

B. Physicians' Administration of Eylea to Patients Practices the Challenged Claims

134. I have personal experience administering Eylea to patients and am also aware, through my interactions with other physicians, of how other physicians' administer Eylea to patients.

1. Claim 1

a. [1.pre.]: A method for treating an angiogenic eye disorder in a patient, said method comprising

135. In my experience and to my knowledge, physicians, including myself, treat various angiogenic eye disorders, including wAMD, DME, DR and RVO, by administering Eylea to a patient having such a disorder.

- b. **[1.a]: 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;**

136. Such administration typically and frequently involves administration of two or more monthly loading doses, *i.e.*, a single initial dose and at least one secondary dose, followed by several, *i.e.*, one or more, tertiary doses of Eylea. As described above, Eylea is a VEGF antagonist. Ex. 2019 (Eylea USPI) at § 12.1.

- c. **[1.b]: wherein each secondary dose is administered 2 to 4 weeks after the immediately preceding dose; and**

137. Physicians, including myself, typically and frequently treat wAMD, DME, DR and RVO by administering one or more monthly doses subsequent to the initial dose, *i.e.*, the secondary doses, approximately four weeks after the immediately preceding dose.

- d. **[1.c]: wherein each tertiary dose is administered at least 8 weeks after the immediately preceding dose;**

138. If patients experiencing wAMD, DME, DR and RVO react well to the loading doses, meaning that the diseased eye shows improvement as measured by letters gained and, in the case of wAMD, reductions in intraretinal or subretinal fluid on retinal imaging, physicians, including myself, typically and frequently follow the monthly loading doses by transitioning the patient from monthly or four-week visits and injections to bimonthly or eight-week visits and injections. While the Eylea® label's recommended dosing regimen for macular edema following retinal vein

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occlusion (RVO) is one intravitreal injection once every four weeks, in clinical practice for appropriate RVO patients, physicians will use eight-week or longer dosing intervals. This is based, at least in part, on the 52-week results of Regeneron's pivotal RVO studies. Ex. 2131²¹ at 434 ("The mean numbers of injections were 3.9 (SE = 0.3) and 2.7 (SE = 0.2) in the sham + IAI PRN and IAI 2Q4 + PRN groups, respectively (Figure 5, Bottom panel)."); Ex. 1060²² at 205 ("Most IVT-AFL 2Q4 + PRN patients (64 of 91 patients completing week 52 [70.3%]) received 3 or fewer IVT-AFL injections during weeks 24 to 52, with a mean $\pm$ SD of 2.5 ± 1.7 injections during the PRN phase of study (Table 3).").

- e. **[1.d]: 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.**

139. Eylea, as administered by physicians, satisfies this claim element. As described above, I understand that Eylea is a recombinant fusion protein consisting of a VEGF receptor component having Ig domains consisting of an Ig domain 2 of

²¹ Brown DM, et al., *Intravitreal Aflibercept Injection for Macular Edema Secondary to Central Retinal Vein Occlusion: 1-Year Results from the Phase 3 COPERNICUS Study*, Am J Ophthalmol 2013;155:329-437.

²² Korobelnik, JF, et al., *Intravitreal Aflibercept Injection for Macular Edema Resulting from Central Retinal Vein Occlusion: One-Year Results of the Phase 3 GALILEO Study*, Ophthalmology 2014;121(1):200-208.

human Flt1 and an Ig domain 3 of human Flk1, fused to the Fc domain of human IgG1. Ex. 1024 ('758 FH, 12/22/2011 PTE) at 6. Accordingly, a person of ordinary skill in the art would understand that Eylea is a chimeric molecule that combines two components having different origins—Ig domain 2 from VEGFR1 and Ig domain 3 from VEGFR2—that are linked together—fused to the Fc portion of human IgG1—to form a biological agent. VEGFR1 is also known as Flt-1, and VEGFR2 is also known as Flk-1. *Id.* I further understand that Exhibit 1024 explains that the amino acid sequence of VEGFR1 spans amino acid residues 27 through 129 of the sequence disclosed in Figures 24A to 24C. *Id.* Exhibit 1024 also explains that the amino acid sequence of VEGFR2 spans amino acid residues 130 through 231 of the sequence disclosed in Figures 24A the '758 patent. *Id.* Finally, Exhibit 1024 explains that Eylea includes a multimerization component, also discussed in Example 20 of the '758 patent, with an amino acid sequence disclosed in Figures 24A to 24C that spans amino acid residue 232 through 458. *Id.* I note that claim 1 recites that the multimerization component comprises amino acids 232-457 of SEQ ID NO:2. The inclusion of amino acid residue 458 from Figures 24A to 24C of the '758 patent does not alter that Eylea's multimerization component includes amino acids 232 through 457 of SEQ ID NO:2 in the '338 patent. As such, Eylea, as administered by physicians, satisfies this claim element.

2. Claim 3

- a. [3.a]: The method of claim 1, wherein only two secondary doses are administered to the patient, and**

140. In my experience and to my knowledge, patients are at times administered only three loading doses, *i.e.*, an initial dose of Eylea followed by two secondary doses.

- b. [3.b]: wherein each secondary dose is administered 4 weeks after the immediately preceding dose.**

141. When three loading doses are used, each of the secondary loading doses is typically and frequently administered approximately monthly or four weeks after the immediately preceding dose.

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

142. When three loading doses are used and the physician determines that the patient is a good candidate for bimonthly or eight-week dosing, then doses have been administered approximately bimonthly or 8 weeks after the immediately preceding dose.

4. Claim 5:

- a. [5.a]: The method of claim 1, wherein at least 5 tertiary doses of the VEGF antagonist are administered to the patient, and**

143. Physicians, including myself, have treated wAMD, DME, DR and RVO by administering at least 5 bimonthly or approximately 8 week doses following

the loading doses. Particularly for wAMD and DME, which are chronic conditions, patients are typically treated for more than a year. When 3 loading doses are used in advance of 8-week maintenance dosing, this results in the administration of at least 5 tertiary doses. I note that this is also true for some patients experiencing DR and RVO.

- b. [5.b]: wherein the first four tertiary doses are administered 8 weeks after the immediately preceding dose, and**

144. The first four of these tertiary doses are typically and frequently administered bimonthly or approximately 8 weeks after the immediately preceding dose.

- c. [5.c]: wherein each subsequent tertiary dose is administered 8 or 12 weeks after the immediately preceding dose.**

145. Each subsequent tertiary dose is typically and frequently administered bimonthly or approximately 8 weeks or greater after the immediately preceding dose.

- 5. Claim 6: The method of claim 1, wherein the angiogenic eye disorder is selected from the group consisting of: age related macular degeneration, diabetic retinopathy, diabetic macular edema, central retinal vein occlusion, branch retinal vein occlusion, and corneal neovascularization.**

146. Physicians, including myself, treat patients experiencing wAMD, DME, DR and RVO using the treatment method described by claim 1.

6. Claim 7: The method of claim 6, wherein the angiogenic eye disorder is age related macular degeneration.

147. Physicians, including myself, treat patients experiencing w/AMD using the treatment method described by claim 1.

7. Claim 8: The method of claim 1, wherein all doses of the VEGF antagonist are administered to the patient by topical administration or by intraocular administration.

148. Physicians, including myself, administer Eylea to the patient through an intravitreal injection, which constitutes interocular administration.

8. Claim 9: The method of claim 8, wherein all doses of the VEGF antagonist are administered to the patient by intraocular administration.

149. Physicians, including myself, administer Eylea to the patient through an intravitreal injection, which constitutes interocular administration.

9. Claim 10: The method of claim 9, wherein the intraocular administration is intravitreal administration.

150. Physicians, including myself, administer Eylea to the patient through an intravitreal injection.

10. Claim 11: The method of claim 10, wherein all doses of the VEGF antagonist comprise from about 0.5 mg to about 2 mg of the VEGF antagonist.

151. Physicians, including myself, administer Eylea to the patient through an intravitreal injection of about 2 mg.

11. Claim 13: The method of claim 11, wherein all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist.

152. Physicians, including myself, administer Eylea to the patient through an intravitreal injection of about 2 mg.

12. Claim 14

a. [14.pre.]: A method for treating an angiogenic eye disorder in a patient, said method comprising

153. In my experience and to my knowledge, physicians, including myself, treat various angiogenic eye disorders, including wAMD, DME, DR and RVO, by administering Eylea to a patient having such a disorder.

b. [14.a]: 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;

154. Such administration typically and frequently involves administration of two or more monthly loading doses, *i.e.*, a single initial dose and at least one secondary dose, followed by several, *i.e.*, one or more, tertiary doses of Eylea. Eylea is a VEGF antagonist. Ex. 2019 (Eylea USPI) at § 12.1.

c. [14.b]: wherein each secondary dose is administered 2 to 4 weeks after the immediately preceding dose; and

155. Physicians, including myself, typically and frequently treat wAMD, DME, DR and RVO by administering one or more monthly doses subsequent to the initial dose, *i.e.*, the secondary doses, approximately four weeks after the

immediately preceding dose.

d. [14.c]: wherein each tertiary dose is administered at least 8 weeks after the immediately preceding dose;

156. Physicians administer the tertiary doses as described by this claim language. If patients experiencing wAMD, DME, DR and RVO react well to the loading doses, meaning that the diseased eye shows improvement as measured by letters gained and, in the case of wAMD, reductions in intraretinal or subretinal fluid on retinal imaging, physicians, including myself, typically and frequently follow the monthly loading doses by transitioning the patient from monthly or four-week visits and injections to bimonthly or eight-week visits and injections. While the Eylea® label's recommended dosing regimen for macular edema following retinal vein occlusion (RVO) is one intravitreal injection once every four weeks, in clinical practice for appropriate RVO patients, physicians will use eight-week or longer dosing intervals. This is based, at least in part, on the 52-week results of Regeneron's pivotal RVO studies. Ex. 2129 (Brown 2013) at 434 ("The mean numbers of injections were 3.9 (SE = 0.3) and 2.7 (SE = 0.2) in the sham + IAI PRN and IAI 2Q4 + PRN groups, respectively (Figure 5, Bottom panel)."); Ex. 1060 (Korobelnik) at 205 ("Most IVT-AFL 2Q4 + PRN patients (64 of 91 patients completing week 52 [70.3%]) received 3 or fewer IVT-AFL injections during weeks 24 to 52, with a mean $\pm$ SD of 2.5 ± 1.7 injections during the PRN phase of study (Table 3).").

- e. **[14.d]: wherein the VEGF antagonist is a VEGF receptor-based chimeric molecule comprising VEGFR1R2-FcΔC1(a) encoded by the nucleic acid sequence of SEQ ID NO:1.**

157. Eylea, as administered by physicians, satisfies this claim language. I have reviewed Exhibit 1024 ('758 FH, 12/22/2011 PTE) in this proceeding. I am informed that Exhibit 1024 is an Application for Extension of Patent Term under 35 U.S.C. § 156, and that the application references Eylea. Based on my review of Exhibit 1024, I understand that Eylea is a recombinant fusion protein consisting of a VEGF receptor component having Ig domains consisting of an Ig domain 2 of human Flt1 and an Ig domain 3 of human Flk1, fused to the Fc domain of human IgG1. Ex. 1024 at 6. Accordingly, a person of ordinary skill in the art would understand that Eylea is a chimeric molecule that combines two components having different origins—Ig domain 2 from VEGFR1 and Ig domain 3 from VEGFR2—that are linked together—fused to the Fc portion of human IgG1—to form a biological agent. VEGFR1 is also known as Flt-1, and VEGFR2 is also known as Flk-1. Ex. 1024 at 6. Furthermore, the specification of the '338 Patent provides that the nucleic acid sequence of SEQ ID NO:1 comprises amino acid sequence of SEQ ID NO:2. Ex. 1001 at 4:58-5:3.

13. Claim 16

- a. **[16.a]: The method of claim 14, wherein only two secondary doses are administered to the patient, and**

158. In my experience and to my knowledge, patients are at times

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administered only three loading doses, *i.e.*, an initial dose of Eylea followed by two secondary doses.

- b. [16.b]: wherein each secondary dose is administered 4 weeks after the immediately preceding dose.**

159. When three loading doses are used, each of the secondary loading doses is typically and frequently administered approximately monthly or four weeks after the immediately preceding dose.

- 14. Claim 17: The method of claim 16, wherein each tertiary dose is administered 8 weeks after the immediately preceding dose.**

160. When three loading doses are used and the physician determines that the patient is a good candidate for bimonthly or eight-week dosing, then doses have been administered approximately bimonthly or 8 weeks after the immediately preceding dose.

- 15. Claim 18: The method of claim 17, wherein the angiogenic eye disorder is age related macular degeneration.**

161. Physicians, including myself, treat patients experiencing w/AMD using the treatment method described by claim 18.

- 16. Claim 19:**

- a. [19.a]: The method of claim 14, wherein at least 5 tertiary doses of the VEGF antagonist are administered to the patient, and**

162. Physicians, including myself, have treated wAMD, DME, DR and RVO by administering at least 5 bimonthly or approximately 8 week doses following

the loading doses. Particularly for wAMD and DME, which are chronic conditions, patients are typically treated for more than a year. When 3 loading doses are used in advance of 8-week maintenance dosing, this results in the administration of at least 5 tertiary doses. I note that this is also true for some patients experiencing DR and RVO.

- b. [19.b]: wherein the first four tertiary doses are administered 8 weeks after the immediately preceding dose,**

163. The first four of these tertiary doses are typically and frequently administered bimonthly or approximately 8 weeks after the immediately preceding dose.

- c. [19.c]: and wherein each subsequent tertiary dose is administered 8 or 12 weeks after the immediately preceding dose.**

164. Each subsequent tertiary dose is typically and frequently administered bimonthly or approximately 8 weeks or greater after the immediately preceding dose.

- 17. Claim 20: The method of claim 14, wherein the angiogenic eye disorder is selected from the group consisting of: age related macular degeneration, diabetic retinopathy, diabetic macular edema, central retinal vein occlusion, branch retinal vein occlusion, and corneal neovascularization.**

165. Physicians, including myself, treat patients experiencing wAMD, DME, DR and RVO using the treatment method described by claim 14.

- 18. Claim 21: The method of claim 14, wherein all doses of the VEGF antagonist are administered to the patient by topical administration or by intraocular administration.**

166. Physicians, including myself, administer Eylea to the patient through an intravitreal injection, which constitutes interocular administration.

- 19. Claim 22: The method of claim 21, wherein all doses of the VEGF antagonist are administered to the patient by intraocular administration.**

167. Physicians, including myself, administer Eylea to the patient through an intravitreal injection, which constitutes interocular administration.

- 20. Claim 23: The method of claim 22, wherein the intraocular administration is intravitreal administration.**

168. Physicians, including myself, administer Eylea to the patient through an intravitreal injection.

- 21. Claim 24: The method of claim 23, wherein all doses of the VEGF antagonist comprise from about 0.5 mg to about 2 mg of the VEGF antagonist.**

169. Physicians, including myself, administer Eylea to the patient through an intravitreal injection of about 2 mg.

- 22. Claim 26: The method of claim 24, wherein all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist.**

170. Physicians, including myself, administer Eylea to the patient through an intravitreal injection of about 2 mg.

VIII. CLINICAL TRIALS ARE CONFIDENTIAL

171. As noted above, I have served as a clinical investigator on pivotal trials

for VEGF Trap-Eye (now called aflibercept) as well as ranibizumab (Lucentis®). I was the lead investigator and Steering Committee member for the evaluation of aflibercept in clinical testing. I was the principal investigator on the Phase II and III clinical trials of aflibercept for diabetic macular edema to further evaluate efficacy, dosing regimens, and safety. In addition, my colleagues at the Wilmer Eye Institute at Johns Hopkins University School of Medicine were involved in the Phase I, II, and III testing of aflibercept in wet AMD.

172. In each of its clinical trials, Regeneron required its clinical investigators to sign confidentiality agreements and clinical trial agreements that limited the disclosure of confidential information regarding the investigational drug, VEGF Trap-Eye, and also limited the use of the investigational drug to participants registered in the clinical trial. This is consistent with my experience in conducting other therapeutic clinical trials. In my experience, VEGF Trap-Eye was not publicly available (or even available to Regeneron clinical investigators outside of clinical testing) until after it was approved by FDA on November 18, 2011.

173. I 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 that these statements were made with knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code.

Dated: February 10, 2022

Diana Do, MD

Diana V. Do, M.D.

Palo Alto, California

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