

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SAMSUNG BIOEPIS CO., LTD.
Petitioner,

v.

REGENERON PHARMACEUTICALS, INC.
Patent Owner.

Patent No. 11,253,572

Inter Partes Review No. IPR2023-00884

DECLARATION OF MICHAEL W. STEWART, M.D.

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I, Michael W. Stewart, M.D., make this declaration in connection with the proceeding identified above.

I. INTRODUCTION

1. I have been retained by counsel for Patent Owner, Regeneron Pharmaceuticals, Inc., (“Regeneron”) as a technical expert in connection with the proceeding identified above. I submit this declaration in support of Patent Owner’s Response in connection with the *Inter Partes* Review of United States Patent No. 11,253,572 (“the ’572 Patent”).

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

II. SUMMARY OF OPINIONS

3. It is my opinion that the challenged claims of the ’572 Patent are nonobvious and patentable. The following is a summary of my opinions:

- The results of the recited dosing regimens for angiogenic eye disorders, in general, and for age related macular degeneration, specifically, were not obvious over Dixon, either alone or in view of the 2006 Press Release.

- The results of the recited dosing regimen for diabetic macular edema were not obvious over the 2009 Press Release, either alone or in combination with the 2007 ARVO Abstract and/or Dixon.
- Formulating aflibercept in an isotonic solution or with a non-ionic surfactant was not obvious over Dixon, either alone or in combination with Hecht.
- Using exactly four secondary doses was not obvious over the 2009 Press Release, either alone or in combination with Shams and Elman 2010.
- Eylea embodies the claims of the '572 Patent such that there is a nexus between the '572 Patent and the commercial success of Eylea.
- I further am aware that Regeneron contends that the November 2010 Press Release (Ex.1007), the December 2010 Press Release (Ex.1006), and ARVO 2010 (Ex.1010) are not prior art to the challenged claims and thus I understand that Regeneron contends that challenges based on those references also do not establish obviousness. I offer no opinions regarding those references.

III. QUALIFICATIONS

4. I am the Chair of the Department of Ophthalmology at Mayo Clinic in Jacksonville, Florida, where I have been Chair since 2005 and Consultant since 2002. I have been a Professor of Ophthalmology at the Mayo Clinic College of Medicine and Science since 2014 and am currently the Knights Templar Eye Foundation, Inc. Professor of Ophthalmology Research.

5. I graduated from Harvard University with a degree in Chemistry cum laude in 1979. I received my M.D. at McGill University School of Medicine in 1983. I completed fellowships at the Retina Research Foundation and University of California, Davis, in Vitreoretinal Diseases from 1987 to 1989.

6. I have been a Councilor of the American Academy of Ophthalmology; Chief of Ophthalmology at St. Luke's Hospital at Mayo Clinic during 2002-2008; Executive or Associate Editor at the *American Journal of Ophthalmology* since 2013; President or Vice President of the Florida Society of Ophthalmology during 2004-2005; and President of Duval County Ophthalmology Society during 1992-1994. I am the current President of the International Joint Commission of Allied Health Personnel in Ophthalmology, and I have served in numerous additional leadership roles in professional organizations and societies in the ophthalmology field over the past three decades. I have also been a peer reviewer for more than 130

journals in the field, including *Retina*, *Ophthalmology*, and the *British Journal of Ophthalmology*.

7. I maintain an active medical and surgical practice and have been continuously elected as one of “America’s Best Physicians” since 2016. My honors include the American Academy of Ophthalmology Honor Award (2010); Hiram Hunn Award from Harvard University (2012); American Society of Retina Specialists Honor Award (2016); Marquis Who’s Who in America (2018); and President’s Award from the Florida Society of Ophthalmology (2020–2021).

8. I have written and published over 600 national and international meeting presentation, abstracts, book chapters, and scientific papers including many of the primary papers on treatment of diabetic retinopathy and diabetic macular edema, using anti-vascular endothelial growth factor (“anti-VEGF”) therapies, especially intravitreal aflibercept.

9. I have extensive experience as a Principal Investigator on a number of clinical trials, including clinical trials of anti-VEGF agents, such as aflibercept (Regeneron’s Eylea), in age-related macular degeneration and macular edema following central retinal vein occlusions. For example, I was a lead investigator on Regeneron’s Phase III studies of the efficacy, safety, and tolerability of repeated doses of intravitreal VEGF Trap in subjects with neovascular age-related macular

degeneration (VIEW1 and VIEW 2), as well as Regeneron's Investigation of Efficacy and Safety in Central Retinal Vein Occlusion ("CRVO") (GALILEO).

10. A current copy of my curriculum vitae is filed herewith as Ex.2096.

IV. MATERIALS CONSIDERED

11. In preparing this declaration, I have reviewed, among other things, the following materials:

- a. the Petition for *Inter Partes* Review of the '572 Patent, Paper 1 ("Petition");
- b. the Declaration of Dr. Edward Chaum, Ex.1002 ("Chaum Declaration");
- c. the Board's Decision Granting Institution of *Inter Partes* Review, Paper 13; and
- d. all exhibits cited in this declaration.

V. LEGAL STANDARDS

12. I have been informed that claim terms are given their plain and ordinary meaning as understood by a so-called "Person of Ordinary Skill in the Art," or "POSA" at the time of the invention. I understand that the most relevant information for construing claims is the intrinsic record of the patent. The intrinsic record includes the specification, prosecution history, claims, and related patents. If this record is inconclusive, I understand that extrinsic evidence, such as dictionary definitions and trade usage, may be used to inform the meaning of a term.

13. I have been informed that the obviousness of an invention is considered from the perspective of a POSA as of the priority date of the patent. The POSA is a hypothetical person who is presumed to have understood the state of the art in the field of the claimed invention and who can apply that understanding with ordinary creativity. I have been asked to assume that the priority date of the '572 Patent is January 13, 2011. I have therefore considered the art from the perspective of a POSA as of January 13, 2011. I understand that Petitioner has applied a priority date of July 12, 2013. My conclusions would be the same if I were to consider the art from the perspective of a POSA as of July 12, 2013.

14. I have also been informed and understand that the subject matter of a patent claim is obvious if the differences between the subject matter of the claim and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a POSA to which the subject matter pertains. I have also been informed that the framework for determining obviousness involves considering the following factors: (i) the scope and content of the prior art; (ii) the differences between the prior art and the claimed subject matter; (iii) the level of ordinary skill in the art; and (iv) any objective evidence of non-obviousness. I also understand that for a POSA to rely on the disclosures of multiple references, there must be some motivation to combine their respective disclosures. I understand that the claimed subject matter would have been obvious to a POSA if, for example, it

results from the combination of known elements according to known methods to yield predictable results, the simple substitution of one known element for another to obtain predictable results, or use of a known technique to improve similar devices in the same way or applying a known technique to a known device ready for improvement to yield predictable results. I have also been informed that the analysis of obviousness may include recourse to logic, judgment, and common sense available to the POSA, and is not limited to statements made in the prior art references.

15. I have been informed and understand that a result or solution may be “obvious to try” when a POSA is choosing from a finite number of identified, predictable solutions with a reasonable expectation of success. I have also been informed that, where the prior art only gives general guidance and gives no direction as to which of many possible choices is likely to be successful, relying on an obvious-to-try theory is not appropriate. Similarly, I have been informed that a POSA may arrive at a claimed invention using “routine optimization” within a limited range disclosed in the prior art.

16. I have also been informed and understand that whether a prior art document “teaches away” from a particular path or combination of elements may inform whether or not the claimed element is obvious. I understand “teaching away”

to mean that a POSA would be discouraged from following a particular path or would be led in a direction divergent from that path.

17. I have also been informed and understand that when considering obviousness, the commercial success of a patented product may indicate that the claims are not obvious. I understand that in order for commercial success to be considered, there must be a nexus between the claims and the product, meaning the value of the product is derived from the patented features. I understand that a nexus can be shown by demonstrating that the commercially successful product or method embodies or practices the claimed invention.

VI. TECHNICAL BACKGROUND

A. Angiogenic eye disorders

18. Angiogenesis is the process of forming new blood vessels from preexisting vasculature. It is a complex process comprising multiple steps, illustrated in **Figure 1**:

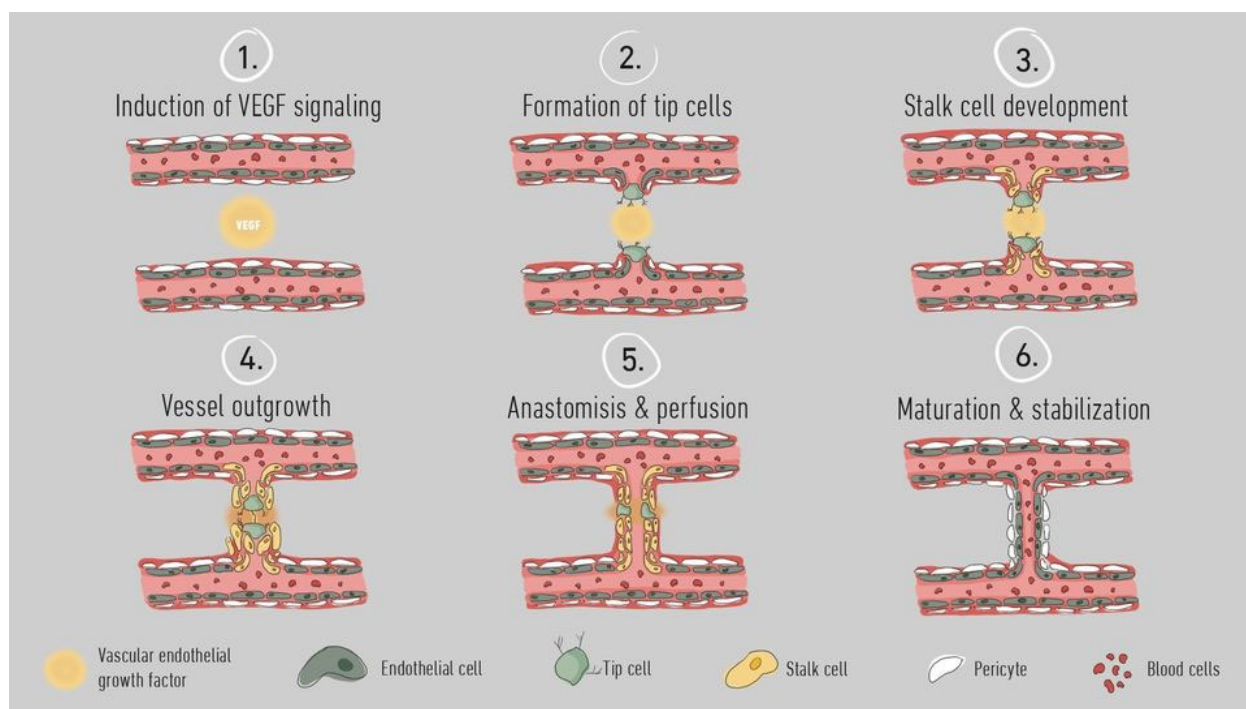


Figure 1: Steps of angiogenesis. Ex.2112, 3.

19. In the first step, an angiogenic “switch” is turned on by a proangiogenic growth factor, such as vascular endothelial growth factor (“VEGF”). From there, endothelial cells are stimulated to proliferate. While angiogenesis is a normal part of development and healing, as with most processes in the body, a balance must be achieved between production, degradation, and reformation. When there is imbalance between proangiogenic factors (e.g., VEGF) and antiangiogenic factors, pathology ensues. Ex.2113, 1. Since newly formed vessels do not yet have fully formed and functional endothelial and pericyte layers, blood vessel leakage is often associated with angiogenesis. Vascular leakage and angiogenesis are pathogenic

findings in many diseases such as diabetic macular edema (“DME”) and wet age-related macular degeneration (“AMD”). Ex.2113, 3, Figs.2–3; Ex.2123, 2.

20. DME is a chronic disease in individuals with diabetes as a result of damage to small blood vessels in the retina. The retina is the multi-layered structure of light-sensitive and processing cells in the back of the eye that converts light into electrical signals. In people with diabetes, high blood sugar levels over extended periods of time can damage the tiny blood vessels within the retina or cause them to block completely. As a result, tiny bulges called microaneurysms form in the blood vessels. Fluid may also leak from incompetent blood vessels. This leakage can cause swelling in the center part of the retina, which is called the macula, resulting in DME. DME causes diminished central vision and loss of fine detail and is the most common cause of vision loss among diabetic patients. Ex.2123, 1; Ex.1001, 1:47–60.

21. Like DME, AMD is a chronic disease mediated by VEGF that causes diminished central vision and loss of fine detail. Unlike DME, however, AMD is characterized by deposits of lipid (drusen) beneath the retinal pigment epithelium, pigmentary alterations in the macula, and thinning of the choroidal circulation beneath the macula. AMD begins as “dry AMD” and can progress to “wet AMD,” or “wAMD,” which involves the gradual, abnormal growth of blood vessels from the choroidal vasculature into the retina. Those vessels leak, spilling fluid into the

macula and thereby causing vision loss. Without treatment, most people with wAMD go blind.

B. Prior art therapies for angiogenic eye disorders

22. Retinal laser therapy has been used to treat angiogenic eye disorders for over 50 years. One type of laser treatment is focal laser treatment, wherein the laser treatment is placed within the macula. Another type of laser treatment is scatter laser, or panretinal photocoagulation, which comprises more extensive laser applied to the peripheral retina to reduce ischemia.

23. From the 1970s through the 1990s, the Diabetic Retinopathy Study (DRS) and ETDRS evaluated laser photocoagulation treatment for angiogenic eye disorders, including DME. Ex.2121; Ex.2122; Ex.2124. It had been recognized early on that “[h]armful effects of treatment” existed, namely, that laser photocoagulation caused injury to photoreceptor cells, and this could also lead to vision loss. For some disorders, it was recommended that “[t]he risk of severe visual loss without treatment substantially outweighs the risks of photocoagulation ... and prompt treatment is usually advisable.” Ex.2122, 7. On the other hand, “[f]or eyes without macular edema, neither of the strategies for early photocoagulation ... was better than deferral of photocoagulation for preventing either moderate or severe visual loss Eyes assigned to *early full scatter were more likely to have moderate visual loss during the first 2 years of follow-up than eyes assigned to deferral*” Ex.2121,

17 (emphasis added). In other words, while the risk of visual loss due to laser may have been balanced for patients at high risk of vision loss due to the underlying disease, there was “small benefit of early photocoagulation in reducing risk of severe visual loss” for patients who had not yet reached such an advanced stage. Ex.2121, 19. Focal laser became the gold standard for treating DME. Ex.2125, 1–2; Ex.2126, 1–2.

24. Laser therapies also have been used to treat wAMD. In 1999, the Treatment of Age-related Macular Degeneration with Photodynamic Therapy (TAP) Study Group published the results from two clinical trials that treated wAMD with photodynamic therapy with verteporfin. Ex.2127. The studies’ authors reported that photodynamic therapy slowed the rate of vision loss in some patients, and from 2000 and 2005, photodynamic therapy was the preferred therapy for patients with predominantly classic wAMD. Ex.2127, 1. Photocoagulation therapy also had been used to treat wAMD but can produce harmful side effects, frequently fails, and its benefits for wAMD were “limited.” Ex.2127, 4.

25. Around the same time as the DRS and TAP groups’ investigations, researchers were characterizing a family of potent growth factors called VEGFs. VEGF is a secreted endothelial cell mitogen and angiogenesis factor regulated by hypoxic (or low oxygen) conditions, which are known to stimulate neovascularization. Ex.2095, 1; Ex.2114, 3; Ex.2120, 3. VEGF levels are

significantly increased in eyes with DME and wAMD, and blocking VEGF leads to a pronounced reduction in retinal neovascularization. Ex.2132, 1–2. VEGF soon became known as the principal mediator of angiogenic eye disorders.

26. Beginning in 2004, the U.S. FDA approved a series of anti-VEGF agents. Macugen (pegaptanib) was the first such agent for use in wAMD. Ex.2115. In the same year, the anti-VEGF monoclonal antibody Avastin (bevacizumab) was approved for use in advanced solid cancers, and it was soon adopted for off-label treatment of angiogenic eye disorders. Ex.2107, 2, 7; Ex.2108. Shortly after, in 2006, the antibody fragment Lucentis (ranibizumab) was approved for treatment of wAMD. Ex.1034, 2, 5.

27. ANCHOR and MARINA were Genentech's pivotal trials evaluating Lucentis. Running from March 2003 to December 2005, the MARINA trial recruited 716 wAMD patients with either minimally classic or occult choroidal neovascularization. MARINA subjects were randomly assigned to receive 1) 24 monthly intravitreal injections of ranibizumab at a dose of 0.3 mg or 0.5 mg, or 2) sham injections. The one-year interim results, presented in July 2005, showed that nearly 95% of study subjects reached the primary endpoint of losing fewer than 15 letters from baseline visual acuity at 12 months. Ex.2118, 4. Furthermore, the two-year results, which were published in October 2006, showed that subjects were not merely *losing* less visual acuity, but in fact they were *gaining* a mean of +6.5 letters

in the 0.3 mg group and +7.2 letters in the 0.5 mg treatment group, while the sham treated subjects were losing a mean of -10.3 letters. Ex.1052, 1.

28. The ANCHOR trial, which ran from May 2003 to September 2006, had the same primary endpoint of measuring the proportion of patients losing fewer than 15 letters from baseline visual acuity at 12 months. In this study, 423 patients with predominantly classic choroidal neovascularization in wAMD were enrolled. Ex.1049, 1. ANCHOR subjects were randomly assigned to receive 1) monthly 0.3 mg or 0.5 mg ranibizumab or 2) photodynamic therapy every 3 months. Similar to the MARINA trial, interim one-year results showed that between 94% and 96% of the patients receiving ranibizumab maintained or improved vision. Ex.2118, 2–3. By two years, the ANCHOR study concluded that subjects treated with ranibizumab had gained a mean of +8.1 to +10.7 letters, while the comparator arm saw a mean loss of -9.8 letters. Ex.1049, 1.

29. In both ANCHOR and MARINA, the exceedingly positive outcomes for patients treated with ranibizumab resulted in a protocol amendment that allowed patients in the comparator arm to be offered monthly ranibizumab injections. Ex.2118, 3, 5.

30. Anti-VEGF drugs were believed to hold potential for the treatment of other angiogenic disorders, so several clinical trials were conducted to evaluate the efficacy of Lucentis for treatment of other disorders like DME. The safety and

efficacy of Lucentis was subsequently studied by the developer in more than 9,000 patients, across eight pivotal and 23 clinical trials. Ex.2116, 3. In 2007, the RISE and RIDE trials began enrollment to evaluate monthly Lucentis for the treatment of DME. Ex.2109, 4. The protocol entailed 0.3 mg or 0.5 mg monthly intravitreal injections of the study drug, with sham injections and deferred laser given to the control group. The primary endpoint was the percentage of subjects who gained ≥ 15 letters in their Best Corrected Visual Acuity (“BCVA”) Score from baseline at month 24. Ex.2109, 7–8. A secondary endpoint was percentage of subjects with a ≥ 3 -step worsening from baseline in the ETDRS Diabetic Retinopathy Severity Scale Score (“DRSS”) for eyes at months 24 and 36. Ex.2109, 8. Based on the results from the pivotal RIDE and RISE Phase III clinical trials, Lucentis was approved for the treatment of DME in 2015. Ex.2110, 1.

31. The Lucentis label instructs monthly injections for the treatment of AMD and DME. Ex.2111, 2. There are many reasons that monthly intravitreal injections are a less-than-ideal dosing regimen, including patient discomfort, inconvenience, cost, compliance, and risks associated with injections. It was not for lack of effort that Genentech has not found success with a less-frequent fixed dosing schedule. In fact, Genentech conducted several large-scale, expensive clinical trials in an attempt to demonstrate the efficacy of less-frequent dosing. These studies include SUSTAIN, EXCITE, SAILOR, and PIER. Ex.2119, 8–9. However, each of

these studies failed to demonstrate efficacy on par with that of monthly dosing with Lucentis.

32. For example, in the PIER study (2004–2007), wAMD patients in the treatment groups received ranibizumab every month for three doses, followed by quarterly doses. Ex.1021, 1. BCVA was measured per ETDRS standards. While patients experienced gains in visual acuity during the monthly dosing phase, “the treatment effect declined in the ranibizumab groups during quarterly dosing.” Ex.1021, 1. In fact, the gains in visual acuity were entirely lost once quarterly dosing began. Figure 1 from the 1-year report of the PIER study shows that one year after treatment with ranibizumab, patients were on average left with no better, or in some cases worse, vision than at the start of the study (loss of -0.2 to -1.6 letters in the ranibizumab-treated groups). Ex.1021, 5, Fig. 1. Compare this to Figure 2 of the MARINA study, showing mean change in visual acuity of patients receiving monthly dosing of ranibizumab throughout the 1-year period, wherein patients gained *and maintained* +6.5 to +7.2 letters, and it is clear why the PIER trial was regarded as “highly disappointing” and a “failure” by the investigators (Ex.2066 ¶¶25-26) and members of the retinal field, including myself, as well as why Genentech would amend the protocol to allow all patients to receive monthly dosing for the remainder of the two-year study. Ex.2103, 1–2; Ex.2104, 2. The two-year report notes that “switching to monthly ranibizumab treatment late in year 2

appeared to provide increased VA benefit to patients who had previously been treated quarterly.” Ex.2103, 2. The inferiority of quarterly dosing is further acknowledged on the Lucentis label, which notes that quarterly dosing is “less effective” and “[c]ompared to continued monthly dosing, dosing every 3 months will lead to an approximate 5-letter (1-line) loss of visual acuity benefit, on average, over the following 9 months.” Ex.2102, 1. Because the standard of care (monthly treatment with Lucentis) provided strong gains in visual acuity, and because abundant evidence showing that extended dosing regimens did not provide the same efficacy, extended dosing regimens such as the one tested in PIER were not generally adopted into clinical practice before the priority date.

C. Eylea

33. Unlike bevacizumab or ranibizumab, Regeneron’s aflibercept (Eylea) is not an antibody or antibody fragment but rather a fusion protein. A fusion protein is a chimeric molecule engineered from a receptor targeting a ligand of interest fused to another protein. Specifically, aflibercept is a soluble fusion protein which combines ligand-binding elements taken from the extracellular binding domains of VEGF receptor (VEGFR)-1 and VEGFR-2 fused to the tail region (Fc portion) of a type of antibody called IgG. Ex.2100, 12–13.

34. In November 2011, Eylea was first approved by the FDA for the treatment of wAMD. Ex.1001, 2:61–67. The initial approval was based on the results

of Regeneron's VIEW trials demonstrating that a regimen with an eight-week (q8) dosing interval was non-inferior to monthly Lucentis. *See* Ex.1059, 11–13; Ex.1038; Ex.1001, 13:4–27. Eylea is formulated as an isotonic solution and with a non-ionic surfactant, polysorbate 20.

35. In 2008, Regeneron began its Phase II DA VINCI trial testing aflibercept (originally referred to as VEGF-Trap-Eye) for use in DME. Ex.1031, 2. Subjects were assigned to five treatment arms: “0.5 mg VEGF Trap-Eye every 4 weeks (0.5q4); 2 mg VEGF Trap-Eye every 4 weeks (2q4); 2 mg VEGF Trap-Eye for 3 initial monthly doses and then every 8 weeks, (2q8); 2 mg VEGF Trap-Eye for 3 initial monthly doses and then on an as-needed (PRN) basis (2 PRN); or macular laser treatment.” Ex.1031, 2. DA VINCI's primary endpoint was change in BCVA from baseline to 24 weeks; a secondary endpoint was change from baseline to 52 weeks. Ex.2105, 4. Despite different dosing frequencies, at 24 weeks “all VEGF Trap-Eye-treated groups manifested comparable gains in visual acuity versus baseline.” Ex.1031, 6. And at 52 weeks, “all VEGF Trap-Eye doses and dosing regimens were found to be superior to macular laser photocoagulation for the treatment of DME over the course of 52 weeks and produced similar results in terms of preserving and improving visual acuity.” Ex.2014, 6.

36. The Phase III VIVID and VISTA trials followed. Like DA VINCI, VIVID and VISTA included a monthly (2q4) arm. Ex.2101, 2. VIVID and VISTA

also included an arm testing injections every eight weeks (2q8), but the VIVID/VISTA 2q8 arm used five monthly loading doses—two more than in DA VINCI. Ex.2101, 2.

37. The primary endpoint in VIVID/VISTA was change from baseline in BCVA in ETDRS letters at week 52. Subjects in the 2q4 and 2q8 arms achieved strong gains in visual acuity, with each arm averaging a 10-letter improvement or more. A secondary endpoint was change in central retinal thickness. Subjects in the 2q4 and 2q8 arms also achieved similar strong improvements in retinal thickness. The US FDA approved an additional EYLEA indication for DME in December 2013 based on the results of the phase 3 trials VISTA and VIVID. Ex.2106.

VII. THE '572 PATENT

38. I understand that this proceeding concerns claims 1-30 of the '572 Patent, owned by Regeneron.

39. Claim 1 of the '572 Patent covers a method of treating angiogenic eye disorders with aflibercept using a regimen of two or more monthly doses followed by doses every eight weeks. Specifically, claim 1 recites:

1. A method of treating an angiogenic eye disorder in a patient in need thereof comprising sequentially administering to the patient by intravitreal injection a single initial dose of 2 mg of aflibercept, followed by one or more secondary doses of 2 mg of aflibercept, followed by one or more tertiary doses of 2 mg of aflibercept;

wherein each secondary dose is administered approximately 4 weeks following the immediately preceding dose; and

wherein each tertiary dose is administered approximately 8 weeks following the immediately preceding dose;

wherein the patient achieves a gain in visual acuity within 52 weeks following the initial dose.

Ex.1001 (claim 1).

40. Claim 15 is the same as claim 1, except it is directed to treating DME and does not require a gain in visual acuity. Claims 26 and 29 are directed to treating AMD and, rather than a gain of visual acuity *within* 52 weeks, they require gains or maintenance of visual acuity equivalent to 0.5 mg monthly ranibizumab *at* 52 weeks. The '572 Patent also includes dependent claims, which variously recite gains within 24 weeks, using two or four secondary doses, gains in terms of ETDRS letter scores, gains of certain ETDRS letter scores, using exclusion criteria, and using isotonic solutions and cationic surfactants.

41. Although I have reviewed all of claims 1-30 of the '572 Patent, I have not been asked to opine on whether the limitations stated in claims 14, 15, and 24 help to make the claims non-obvious. I therefore offer no opinion on that subject.

VIII. PETITIONER'S PRIOR ART REFERENCES

42. I have been asked to consider whether the following references render obvious certain claims of the '572 Patent: the 2009 Press Release (Ex.1005); Dixon (Ex.1009); Hecht (Ex.1016); Shams (Ex.1017); Elman 2010 (Ex.1018); the 2006

Press Release (Ex.1027); the 2007 ARVO Abstract (Ex.1030); Randolph (Ex.1032); and Fraser (Ex.1033). I provide a short summary of each exhibit below.

A. 2009 Press Release (Ex.1005)

43. The 2009 Press Release is a Regeneron press release that describes aspects of Regeneron's Phase II DA VINCI clinical trial protocol. The press release states that the angiogenic eye disorder being investigated is "Diabetic Macular Edema (DME)." Ex.1005, 1. The 2009 Press Release lists the trial's five arms, which include four different VEGF Trap-Eye dosing regimens:

- 0.5 mg monthly
- 2 mg monthly
- 2 mg every eight weeks after three monthly loading doses
- 2 mg on an as-needed ("p.r.n.") basis after three monthly loading doses

A fifth group of subjects received focal laser treatment. *Id.* Finally, the 2009 Press Release states the primary efficacy endpoint of the trial: "mean improvement in visual acuity at six months." *Id.*

B. Dixon (Ex.1009)

44. Dixon is a scientific article titled *VEGF Trap-Eye for the treatment of neovascular age-related macular degeneration*. Ex.1009. Dixon highlights the unmet need for VEGF inhibitors and goes on to describe partial results from some of Regeneron's clinical trials. Ex.1009, 2. It describes partial results from

Regeneron's CLEAR-IT-1 and CLEAR-IT-2 Phase I and II clinical trials, which dosed subjects suffering from wAMD with VEGF Trap-Eye (now known as aflibercept), and "a small open-label safety study for the treatment of diabetic macular edema." Ex.1009, 3–4. Dixon also describes, in broad strokes, clinical trial protocols for Regeneron's Phase III VIEW 1 and VIEW 2 studies for the same drug and indication.

45. According to Dixon, Regeneron's Phase I CLEAR-IT-1 trial involved dosing 30 patients with "a single intravitreal injection of either 0.5 or 4 mg" and evaluating patients for eight weeks after that injection. Ex.1009, 3. Dixon states that the "small open-label safety study" for DME administered a 4 mg injection of VEGF Trap-Eye to five people, resulting in an increase in "BCVA ... by 9 letters at 4 weeks [that] regressed to a 3 letter improvement at 6 weeks." Ex.1009, 3. Dixon does not state, however, whether those nine and three letter gains were the mean, median, maximum, minimum, or universal outcome among study subjects.

46. For the Phase II CLEAR-IT-2 trial, Dixon states that the trial included 157 patients randomized to five dose groups. Ex.1009, 4. According to Dixon: one of those five groups was dosed with monthly doses of 2.0 mg of VEGF Trap-Eye for 12 weeks following which subjects were dosed on a p.r.n. (as needed) basis; the average ETDRS letter score increase in the 2.0 mg dose group was nine ETDRS letters, with 29% of the group gaining greater than or equal to 15 letters at 52 weeks;

and the 2.0 mg dose group received, on average, 1.6 injections following the four initial doses, where criteria for redosing included “a loss of ≥ 5 ETDRS letters in conjunction with recurrent fluid by OCT.” Ex.1009, 4. Dixon does not disclose, however, how many subjects were in each dose group, or how many subjects were in the 2.0 mg dose group, specifically. Dixon also does not disclose the timing of doses given in the PRN phase. As a result, it is unclear what number of people gained or maintained visual acuity after being dosed with monthly 2.0 mg VEGF Trap-Eye. Ex.1009, 4.

47. For the Phase III VIEW 1 clinical trial, Dixon discloses the following information: the trial would test efficacy and safety of VEGF Trap-Eye in patients with wAMD across ~1,200 patients; the trial would include a group of patients dosed at 2.0 mg at 8-week intervals following three monthly doses and a group dosed monthly with 0.5 mg ranibizumab; and the primary endpoint of the trial was to “be the proportion of patients who maintain vision at week 52 (defined as a loss of < 15 ETDRS letters).” Ex.1009, 4. It does not report results from that trial. Ex.1009, 4.

48. Dixon also notes that VEGF Trap-Eye is formulated with “different buffers and at different concentrations (for buffers in common) suitable for the comfortable, non-irritating, direct injection into the eye.” Ex.1009, 3. It does not specify whether those buffers are isotonic or include non-ionic surfactants.

C. Hecht (Ex.1016)

49. Hecht is a chapter from a textbook titled “Ophthalmic Preparations.” It broadly describes the anatomy of the eye, types of ophthalmic solutions, and preparation of those solutions. Ex.1016. It calls topical solutions “the most common means of administering a drug to the eye,” Ex.1016, 8, and also mentions injectable solutions under the header, “Other Modes of Administration,” Ex.1016, 10.

50. Hecht discusses formulating ophthalmic solutions under the header “Preparation.” Ex.1016, 10. It states that, in general, “[o]phthalmic solutions are formulated to be sterile, isotonic, and buffered to stability and comfort.” Ex.1016, 11. It acknowledges, however, that “finished solutions” including active ingredients may be “hypertonic somewhat but well within the comfort tolerance of the eye.” Ex.1016, 11. It also cautions that isotonicity should not be an “overriding concern” compared to other considerations, like stability. Ex.1016, 13.

51. Hecht discusses surfactants under the header, “Additives.” Ex.1016, 13. It states that non-ionic surfactants are used “particularly in steroid suspensions.” Ex.1016, 13. But it warns that non-ionic surfactants can deactivate antimicrobial preservative compounds. Ex.1016, 13. It also states that “[c]ationic surfactants are used frequently” and that one such surfactant is “the preservative used in the large majority of commercial ophthalmic solutions and suspensions.” Ex.1016, 13.

D. Shams (Ex.1017)

52. Shams is the publication of a Genentech patent application filed in 2004. Ex.1017, 1. Shams discusses the general concept of more-frequent followed by less-frequent dosing. It broadly discloses that the invention encompasses “[a]ny compound which binds to VEGF or a VEGF receptor and reduces the severity of symptoms... may be used in this embodiment of the invention,” Ex.1017, 26:6–8; *see also id.*, 6:27–7:16, and “[t]he doses may be administered according to any time schedule which is appropriate,” Ex.1017, 22:30–31; *see also id.*, 23:7–9. Shams claims that “[t]he specific time schedule can be readily determined by a physician having ordinary skill in administering the therapeutic compound by routine adjustments of the dosing schedule” by monitoring patients. Ex.1017, 22:30–23:7.

53. Through the rest of the specification and claims, though, Shams focuses not on patient-specific adjustments but on fixed dosing regimens; in particular, regimens of three or fewer monthly loading doses followed by quarterly dosing. Ex.1017, 5:20–6:2; 23:13–16, 36:30–37:25. In the examples section, Shams’ sole example is the fixed dosing regimen that is the same dosing regimen tested in Genentech’s PIER trial for ranibizumab: three loading doses followed by quarterly dosing, administered to subjects with choroidal neovascularization secondary to AMD. Ex.1017, 31:8–19; Ex.1004.

E. Elman 2010 (Ex. 1018)

54. Elman 2010 is an article by the Diabetic Retinopathy Clinical Research Network (DRCR) disclosing a study that compared various treatments for DME. Ex.1018. The treatments included focal laser photocoagulation, the anti-VEGF agent ranibizumab, and a corticosteroid called triamcinolone. Ex.1018, 2. In one arm of the trial, which Elman et al. called the “ranibizumab + deferred laser group,” subjects were treated following a three-part dosing protocol. Ex.1018, 3. First, ranibizumab was administered every four weeks through the 12-week visit (i.e., four monthly doses). Ex.1018, 3. Then at the 16- and 20-week visits (i.e., fifth and sixth monthly visits), subjects were evaluated to determine if they met the “success criteria” of a visual acuity letter score of 84 (corresponding to 20/20 vision) or central retinal thickness <250 μm . Ex.1018, 3, 15–16. Subjects who did not meet the success criteria received a dose of ranibizumab, and those who met the success criteria could receive a dose at the investigator’s discretion. Ex.1018, 3, 15–16. At the 24-week and later visits, the drug was administered at investigator discretion if the study eye was deemed “no improvement,” and laser photocoagulation could be applied as well. Ex.1018, 3, 15–16.

55. Elman does not disclose individual patient outcomes but does report averages for each arm. In the deferred laser group, the average visual acuity improved quickly over the first two months, and then climbed slowly through week

52. Ex.1018, 6 Fig. 3. Similarly, the average OCT thickness improved quickly over the first three months, and then only gradually through week 52. Ex.1018, 35 Fig. 8. Elman 2010 reports that at the 16-week study visit, at least about 37% of eyes in the ranibizumab + deferred laser group had achieved a central retinal thickness $<250\text{ }\mu\text{m}$, and 22% of eyes in the group did not receive a fifth monthly injection. Ex.1018, 4, 10 Fig. 6. At week 20, the fraction of subjects in the deferred laser group with a central retinal thickness $<250\text{ }\mu\text{m}$ had decreased slightly. Ex.1018, 10 Fig. 6. At week 20, the average visual acuity among subjects in the deferred laser arm had decreased, and the average central retinal thickness had increased. Ex.1018, 6 Fig. 3, 35 Fig. 8.

F. 2006 Press Release (Ex.1027)

56. The 2006 Press Release is a Regeneron press release titled “REGENERON REPORTS POSITIVE PHASE 1 DATA FOR THE VEGF TRAP IN AGE-RELATED MACULAR DEGENERATION.” Ex.1027. It announces preliminary results from a Phase I trial and states that Regeneron dosed 21 subjects suffering from wAMD with “a single intravitreal injection of 0.05, 0.15, 0.5, 1, 2, and 4 milligrams (mg) of VEGF Trap.” Ex.1027, 1. It discloses that, after six weeks, 95 percent of 20 patients “had stabilization or improvement in visual acuity, defined as ≤ 15 letter loss.” Ex.1027, 2. And it also states that the average improvement in patients dosed with 2 mg and 4 mg achieved a “mean improvement” of 13.5 letters,

with “three of six patients gaining 15 or more letters” at six weeks. Ex.1027, 2. The 2006 Press Release does not say how many subjects received the 2 mg dose or whether any patient that received the 2 mg dose gained or maintained their visual acuity compared to baseline.

G. 2007 ARVO Abstract (Ex.1030)

57. The 2007 ARVO abstract is a document titled, “Results of a Phase I Study of Intravitreal VEGF Trap in Subjects with Diabetic Macular Edema: The CLEAR-IT DME Study.” Ex.1030, 1. It states that five patients with DME each received a 4 mg dose of “VEGF Trap” and, after four weeks, gained between six and ten ETDRS letters. Ex.1030, 1.

H. Randolph (Ex. 1032)

58. Randolph is a document titled “Rational Design of Stable Protein Formulations.” It recommends “minimiz[ing] the addition of any excipient to a formulation” because “there is ample evidence that high concentrations of surfactants can be destabilizing.” Ex.1032, 14. It also states that “small amounts of surfactant often provide benefits” that “greatly outweigh any conformationally destabilizing effect.” Ex.1032, 14. About non-ionic surfactants, it observes that they can sometimes “destabilize[] the conformation of a protein” leading to “the formation of large, insoluble non-native aggregates.” Ex.1032, 13.

I. Fraser (Ex. 1033)

59. Fraser is a document titled “Single Injections of Vascular Endothelial Growth Factor Trap Block Ovulation in the Macaque and Produce a Prolonged, Dose-Related Suppression of Ovarian Function.” Ex.1033. It describes a study in which scientists injected monkeys with a VEGF inhibitor to suppress ovulation. Ex.1033. It does not relate to angiogenic eye disorders.

IX. PERSON OF ORDINARY SKILL IN THE ART

60. I understand that Petitioner has proposed the following definition of a person of ordinary skill in the art:

A person of ordinary skill in the art at the time of the invention would have had (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.

Pet. 16-17.

61. I have used the above definition of a Person of Ordinary Skill in the Art throughout this declaration.

62. I hold all of the above-listed qualifications, and I have held these qualifications since before 2011. I thus consider myself qualified to opine on the perspective of a person of ordinary skill in the art in this case.

X. CLAIM CONSTRUCTION

A. *results limitations*

63. I was asked to assume that the limitations reciting benefits to visual acuity (“*results limitations*”) are requirements that must be achieved to practice the claims. For example, I was asked to assume that practicing claim 1 requires that a patient achieves a gain in visual acuity within 52 weeks following an initial dose with aflibercept. I have applied this assumption in my analysis.

B. “approximately 4 weeks following the immediately preceding dose . . . approximately 8 weeks following the immediately preceding dose”

64. It is my opinion, based on the claims and specification of the ’572 Patent, that a POSA would understand the challenged claims, specifically claim 15 and thereby claim 25, to be limited to predetermined fixed dosing schedules.

65. Ophthalmologists who regularly prescribe anti-VEGF drugs recognized two basic categories of dosing regimens: fixed and individualized. Fixed regimens are those where doses are administered on a predetermined schedule regardless of observed outcomes at any given visit. Fixed regimens include monthly doses as well

as regimens involving a set number of loading doses followed by dosing on a longer fixed interval, as described in the Eylea label. Sometimes adherence to the predetermined schedule is imperfect, but the regimens are still considered fixed when the intended dosing interval is based on a schedule rather than on patient outcomes. Individualized regimens are those where the physician decides when to administer doses based on a patient's visual or anatomical outcomes. Individualized regimens include predominantly PRN regimens and treat-and-extend ("T&E") regimens. On a PRN regimen, the physician observes patients regularly but only administers a dose if the patient's anatomic or visual outcomes have worsened. On a T&E regimen, physicians gradually lengthen the dosing interval (*e.g.*, from four weeks to six weeks to eight weeks) to determine the maximum interval on which doses can be administered without recurrence of the disease.

66. The descriptions of clinical trials in examples 2, 4, and 5 of the patent show the distinction between individualized, as-needed regimens and fixed, predetermined regimens. Unless explicitly described as PRN (as-needed), these examples show dosing regimens that follow a schedule set in advance of treatment (fixed regimen). *See, e.g.*, Ex.1001, 8:12–36. Even for trials that do not explicitly state that the regimen was predetermined, it is my opinion that a POSA would understand that the dosing regimens described as "every x weeks" were fixed and

determined prior to treatment, and any variance would be a deviation from the trial protocol.

67. The plain and ordinary meaning of the challenged claims show that the administered dosing regimen follows a predetermined, fixed schedule. “[A]pproximately 4 weeks... approximately 8 weeks” is the sort of language a POSA would use to describe a predetermined, fixed regimen because fixed, predetermined dosing regimens are defined by the dosing intervals. If a POSA were describing an individualized regimen, by contrast, they would not describe the regimen solely in terms of dosing intervals. Rather, they would include information about patient assessment to define the type of regimen. The specification of the ’572 Patent illustrates this by using different language to describe individualized regimens.

68. Consistent with this understanding, the “[x] weeks” language found in the claims refers to predetermined dosing schedules when used throughout the specification of the ’572 Patent. In the specification, such language is contrasted with the language used to describe dosing schedules such as PRN, which are not non-predetermined. Thus, it is my opinion that a POSA would interpret the claims, with “[x] weeks” language, to refer to predetermined dosing schedules.

69. The examples that describe clinical trials show this distinction. Example 2 initially dosed patients “at a fixed interval” every 4 or 12 weeks before

switching to as-needed doses based on specified criteria. Ex.1001, 8:49–50. It is my opinion that a POSA would recognize the significance and distinction between “[x] weeks” dosing and dosing based on specified retreatment criteria.

70. Example 5 also describes a trial that draws a distinction between fixed interval dosing and as-needed dosing for VEGFT (a term the specification uses for aflibercept or VEGF-Trap Eye). “Two groups received three initial doses of 2 mg VEGFT once every *four weeks* (i.e., at baseline, and weeks 4 and 8), followed through week 52 *by either* once every *8 weeks* dosing (2Q8) *or as needed dosing* with very strict repeat dosing criteria (PRN).” Ex.1001, 14:44–49 (emphases added). It is my opinion that this distinction shows the difference between predetermined, fixed dosing regimens and regimens that switch to dosing on an as-needed schedule.

71. Example 7 directly contrasts predetermined, fixed dosing regimens and individualized dosing regimens using “every x weeks” language:

VEGFT 2 mg (0.5 mL) administered by intravitreal injection once every *4 weeks* for the first 16 weeks, followed by 2 mg (0.05 mL) via intravitreal injection once every *8 weeks*.

VEGFT 2 mg (0.5 mL) administered by intravitreal injection once every *4 weeks* for the first 16 weeks, followed by 2 mg (0.05 mL) via intravitreal injection on a *less frequent basis* based on visual and/or anatomical outcomes (*as assessed by a physician* or other qualified medical professional).

VEGFT 2 mg (0.5 mL) administered by intravitreal injection once every *4 weeks* for the first 16 weeks, followed by 2 mg (0.05 mL) via intravitreal injection administered *pro re nata (PRN)* based on visual

and/or anatomical outcomes (as assessed by a physician or other qualified medical professional).

Ex.1001, 16:1–16 (emphases added).

72. The first regimen described above is a predetermined, fixed dosing regimen. The two regimens that follow begin on a predetermined, fixed interval and then switch to dosing as-needed based on assessment. Example 7 repeats this type of language for other dosing amounts and schedules. For example, this part of the specification contrasts the above predetermined regimen—monthly loading doses followed by doses every eight weeks—with a regimen in which the doses at weeks 12 and 16 are administered based on assessment of the patient. Ex.1001, 16:5–16. Example 7 draws a clear contrast for a POSA reading the specification. It is my opinion that this contrast shows the difference between predetermined, fixed dosing schedules using “[x] weeks” language and individualized dosing schedules using assessment or PRN language.

73. Other parts of the specification make the same distinction. “For example, each tertiary dose may be administered to the patient 8 weeks after the immediately preceding dose. *Alternatively*, the frequency at which the secondary and/or tertiary doses are administered to a patient can vary over the course of the treatment regimen. ... The frequency of administration may also be adjusted during the course of treatment by a physician depending on the needs of the individual

patient following clinical examination.” Ex.1001, 4:39–55. It is my opinion that a POSA would understand this contrast to be significant and recognize a distinction between individualized, as-needed treatment and predetermined, fixed dosing treatment.

74. It is my opinion that other patents that share the specification of the ’572 Patent further demonstrate this contrast as they claim PRN dosing schedules as opposed to predetermined, fixed regimens. For example, I understand that U.S. Patent No. 11,730,794 has the same specification and thus is in the same family as the ’572 Patent. It claims dosing regimens “wherein each tertiary dose is administered on an as needed or pro re nata (PRN) basis.” *See* Ex.2146 (claims 1, 18, and 35). This contrast between claims from the different patents mirrors the contrast throughout the specification between predetermined, fixed regimens and individualized, as-needed regimens. It is my opinion that a POSA would see this as further evidence that the ’572 Patent claims are drawn to predetermined, fixed-interval dosing regimens.

XI. ANALYSIS OF PRIOR ART

A. The prior art does not disclose or suggest the required benefits to visual acuity for angiogenic eye disorders, in general, or for AMD, specifically

75. It is my opinion that neither Dixon nor the 2006 Press Release, alone or in combination, discloses or renders obvious claims 1-5, 8-11, and 26-30.

76. I understand Dr. Chaum has testified that “Dixon does not expressly disclose the ‘results limitations’ in independent claims 1, 26, or 29 or their dependents” but that “it renders them obvious alone or in view of the knowledge of a POSA regarding aflibercept efficacy” as illustrated by the 2006 Press Release. Ex.1002, ¶165; *see also* Ex.1002, ¶¶165–172. While I agree with Dr. Chaum that Dixon does not expressly disclose the *results limitations*, I disagree that Dixon, alone or in combination with the 2006 Press Release, renders them obvious.

77. It is my opinion that a POSA would not have found Dixon or the 2006 Press Release to render obvious claims 1-5, 8-11, and 26-30 for two overarching reasons: (1) in general, no POSA would have relied on partial results from Phase I and Phase II trials to draw conclusions about the outcome of a Phase III trial with a different dosing protocol; and (2) even if considered, no POSA would have reasonably believed that the VIEW trial protocol would succeed based on Dixon and the 2006 Press Release’s disclosures of partial results from such trials.

1. In general, partial results from Phase I and II clinical trials do not predict a Phase III clinical trial's outcome

78. It is my opinion that Dr. Chaum's opinion that claims 1-5, 8-11, and 26-30 are obvious rests on a flawed, underlying premise: because Dixon does not disclose any results for the VIEW trials, Dr. Chaum assumes that a POSA would reasonably believe that the VIEW trials' 2q8 protocol would yield the claimed benefits to visual acuity in view of partial results from Phase I and II trials. Ex.1002, ¶¶162–183. I disagree with this premise: results from Phase I and II trials, whether full or partial (as here), do not predict the outcome of a Phase III trial.

79. It is my opinion that a POSA would have known that Phase I trials are designed to test safety and dosage levels of drugs, not efficacy. A POSA also would have known that drugs that succeed at the Phase I clinical trial stage often go on to fail. As shown in Ex.2128, which is a printout of a page from the FDA's website summarizing success rates for drugs in clinical trials as of 2018, only 35% and 25-30% of drugs pass Phase II and III clinical trials, respectively. Ex.2128, 3–4. Those figures are roughly consistent with what a POSA would have understood in 2011: that most drug candidates, even those passing Phase I, would not receive FDA approval.

80. A POSA also would not have reasonably expected a drug to succeed based on results from a Phase II trial. The primary purpose of a Phase II trial is to

confirm whether and how to proceed with a Phase III trial. And a POSA would have known that, even for a drug that passed Phase II, FDA approval would be uncertain.

81. A POSA also would have been aware that other drugs directed at treating angiogenic eye disorders, specifically, had failed at Phase III following promising Phase I and II clinical trials. For example, bevasiranib, a gene-silencing agent for treating AMD, passed Phase I and II trials to much acclaim. Exs.2129–2131. Ahead of Phase III, the industry hailed bevasiranib as a “top five most promising drug” of 2007, and its manufacturer touted it as a “first in class” compound. Exs.2129–2131. Yet, bevasiranib failed at Phase III and never reached the market. Ex.2129. Thus, even for a “promising” drug, a POSA would not have reasonably expected success at Phase III.

2. No POSA would have reasonably expected the 2q8 regimen to succeed based on Dixon and the 2006 Press Release

82. It is my opinion that the disclosures that Dr. Chaum identifies from Dixon and the 2006 Press Release in paragraphs 162 to 183 of his report neither disclose nor render obvious the *results limitations* in claims 1-5, 8-11, and 26-30. Neither the 2006 Press Release nor Dixon discloses any results from the 2q8 protocol recited in Dixon. The 2006 Press Release and Dixon report only that some patients who received VEGF Trap-Eye achieved visual acuity gains, and those reported results relate to different dosing regimens than claimed. Ex.1009, 3; Ex.1027, 1. But

the fact that some dosing regimens of VEGF Trap-Eye can produce benefits to visual acuity for some patients does not predict whether other dosing regimens will produce the same benefits for others. Thus, as I explain in further detail in the following paragraphs, no POSA would have reasonably expected that the 2q8 regimen would yield the claimed results from the limited disclosures in the 2006 Press Release and Dixon.

a. Claim 1

83. Claim 1 requires 2q8 dosing and a gain in visual acuity within 52 weeks. I understand that Dr. Chaum opines the 2006 Press Release and Dixon render obvious that result for three reasons: (1) the 2006 Press Release reported a mean improvement in BCVA in some patients at 6 weeks following dosage with either 2 mg or 4 mg aflibercept; (2) a POSA would have expected the 2q8 regimen to achieve the VIEW 1 trial's clinical endpoint of gaining at least 15 letters at 52 weeks; and (3) Dixon reported that p.r.n. dosing yielded benefits to visual acuity for some subjects receiving 2 mg of aflibercept at 52 weeks. Ex.1002, ¶¶166–169, 171–174. I disagree with Dr. Chaum's opinions as set forth below.

84. **First**, it is my opinion that no POSA would have reasonably believed the 2q8 dosing regimen would achieve the claimed results based on the 2006 Press Release. The 2006 Press Release discloses results from a Phase I trial that, by definition, was designed to test safety and dosage, not efficacy. That goal is evident

from the design of the study: it included only 21 subjects and each subject received only a single dose of “VEGF Trap.” Ex.1027, 2. For the 20 subjects for which the 2006 Press Release reports information changes in visual acuity, the average gain in letters was 4.8, but at least one subject lost more than 15 letters following treatment. Ex.1027, 2. Moreover, the 2006 Press Release never actually identifies how many of those subjects received the 2 mg dose or whether those subjects achieved any benefit; it only states that, in total, six subjects received either the 2 mg or 4 mg dose and that, on average, those six subjects achieved a 13.5 letter gain. Ex.1027, 2. Dr. Chaum’s statement to the contrary, that “a single 2 mg dose in AMD patients produced a ‘mean improvement in BCVA [of] 13.5 letters’” is incorrect. Ex.1002, ¶168. In short, the 2006 Press Release does not provide sufficient detail to conclude that any subject receiving a 2 mg dose achieved any benefit to visual acuity.

85. Additionally, a POSA would have known that some patients recover from wAMD without intervention. For example, the Phase III results from the MARINA trial showed a portion of the patient population at least stabilized, if not improved, after receiving a sham injection. Ex.2118, 5 (28.6% of patients in wAMD control group “experienced a letter improvement of zero or more”). Thus, even if the 2006 Press Release had, for example, reported that an individual subject receiving a 2 mg dose achieved a 13.5 letter gain (or even if it reported five such

patients achieving that gain), a POSA would have hesitated to draw conclusions regarding efficacy from such a small sample size.

86. ***Second***, it is my opinion that a POSA would not have reasonably expected the 2q8 regimen to produce the claimed results based on the VIEW 1 trial's clinical endpoint. Clinical endpoints are goals that pharmaceutical companies hope to achieve, not results. No POSA would have reasonably believed a clinical endpoint predicted the result of a Phase III trial.

87. ***Third***, it is my opinion that a POSA would not have reasonably believed the 2q8 regimen would succeed based on the limited information about the CLEAR-IT-2 Phase II clinical trial recited in Dixon. According to Dixon, the CLEAR-IT-2 Phase II trial did not use the 2q8 dosing regimen. Ex.1009, 4. Instead, that trial included "157 patients ... randomized to five dose groups," of which one group received four monthly, 2 mg loading doses followed by p.r.n. dosing for the remainder of the year. Ex.1009, 4. And although Dixon states that subjects in the p.r.n. dosing group, on average, received 1.6 additional doses and, on average, achieved mean improvements of 9 letters with 29% gaining 15 or more letters, it never states how many subjects received 2.0 mg monthly dosing nor how many p.r.n. doses were required to achieve those gains in any particular subject. Ex.1009, 3. Nor does it identify at what specific intervals within the 52-week period each of those p.r.n. doses was administered. Ex.1009, 3. In short, the data reported in Dixon is too

limited for a POSA to develop a reasonable expectation of success regarding the efficacy of the 2q8 dosing regimen. Confirming this point, Dixon's authors declined to predict whether the Phase III trial would succeed: "***If*** [VEGF Trap-Eye is] effective at 8 week intervals, VEGF Trap-Eye offers the opportunity to significantly reduce treatment burden on patients and physicians, and would probably find wide acceptance." Ex.1009, 5 (emphasis added).

b. Claims 2, 3, 8, and 10

88. These claims depend from claim 1 and include the additional requirements that the gains in visual acuity are in ETDRS letter scores and/or that the patient achieves a gain of seven, eight, or nine letters. Ex.1001 (claims 2, 3, 8, 10). For the reasons I stated in paragraphs 84-87 of this declaration, I disagree with Dr. Chaum that any of these claims were obvious. Ex.1002, ¶¶171–174.

c. Claims 4 and 9

89. Claims 4 and 9 depend from claims 3 and 8, respectively, and include the additional requirement that the patient achieves the gain in visual acuity within 24 weeks. Ex.1001 (claims 3, 8). For the reasons I stated in paragraphs 84-87 of this declaration, I disagree with Dr. Chaum that any of these claims were obvious. Ex.1002, ¶¶170–174. Additionally, I note that Dixon's description of the CLEAR-IT-2 trial does not recite any results within 24 weeks. Ex.1009, 4. It is my opinion

that a POSA would not have believed results at 52 weeks predicted efficacy within 24 weeks because a patient's visual acuity at one point in time during treatment is not necessarily the same as their visual acuity at another. Thus, a POSA would not have reasonably expected to achieve results within 24 weeks based on Dixon's disclosures for this additional reason.

d. Claims 5 and 11

90. Claims 5 and 11 depend from claims 3 and 10 and include the additional requirement that "only two secondary doses are administered to the patient." Ex.1001 (claims 5, 11). For the reasons I stated in paragraphs 84-87, I disagree with Dr. Chaum that any of these claims were obvious. Ex.1002, ¶¶170–174. Additionally, I note that Dixon's description of the CLEAR-IT-2 trial described using three secondary doses, not two. A POSA would not have believed results from a protocol including three secondary doses predicted anything about the result of a protocol with only two secondary doses, and thus a POSA would not have reasonably expected to achieve the claimed results with only two secondary doses for this additional reason.

e. Claims 26-28

91. Claim 26 claims the same 2q8 dosing regimen as claim 1 but, rather than requiring a gain to visual acuity within 52 weeks, it requires that the claimed

method is “as effective in achieving a gain in visual acuity” as monthly 0.5 mg ranibizumab in patients suffering from AMD at 52 weeks. Claim 27 requires “only two secondary doses,” and claim 28 requires measuring “the gain in visual acuity ... using the ... ETDRS[] letter score.” Ex.1001 (claims 26-28). I understand that Dr. Chaum opines that these claims are obvious for three reasons: (1) because Dixon purportedly renders obvious gains of 9 letters at 52 weeks; (2) because VEGF Trap-Eye was “promising”; and (3) alternatively, because it purportedly would have been obvious to modify the VIEW trial protocol reported in Dixon “to include additional initial doses.” Ex.1002, ¶¶176–182. I disagree with Dr. Chaum for the following reasons.

92. **First**, for the same reasons I stated in paragraphs 84-87 of this declaration, no POSA would have reasonably believed that the 2q8 dosing regimen would have produced a gain in visual acuity at 52 weeks in view of Dixon’s limited disclosures, much less a specific letter gain of 8.1-9.4 letters, as Dr. Chaum proposes. Ex.1002, ¶¶177–181. Confirming my opinion, I note that Dixon’s authors wrote: “the results from the non-inferiority Phase III trials **will establish** [VEGF Trap-Eye’s] efficacy versus ranibizumab.” Ex.1009, 5 (emphasis added).

93. **Second**, for the same reasons I stated in paragraphs 78-81 of this declaration, no POSA would have reasonably believed that the 2q8 dosing regimen would have produced a gain in visual acuity at 52 weeks from Dixon’s statement

that VEGF Trap-Eye was the “most promising” anti-VEGF drug currently in Phase III trials. Ex.1009, 5; Ex.1002, ¶180.

94. **Third**, it would not have been obvious to modify Dixon’s Phase III, 2q8 regimen to include additional initial doses, as Dr. Chaum proposes. Ex.1002, ¶182. Dixon provides no motivation for a POSA to add injections to its dosing schedules; to the contrary, its authors wrote that longer dosing intervals were desirable because they could “significantly reduce treatment burden on patients and physicians” and would therefore “probably find wide acceptance.” Ex.1009, 5. Indeed, physicians were, if anything, motivated to decrease the number of injections to treat angiogenic eye disorders, not increase them; although as I have explained, any physician thinking of doing that would have concerns about efficacy. Nor, for the same reasons I discussed in paragraphs 83-87 of this declaration, would a POSA have reasonably expected that the addition of one more loading dose—given at the front-end of a year-long treatment—would yield the claimed results at 52 weeks based on Dixon’s disclosures. Regardless of whether a regimen included four loading doses or five, a POSA would not have known whether any benefits from those loading doses would persist after transitioning to doses every eight weeks. Finally, I see that Dr. Chaum has incorporated by reference his discussion of the obviousness of claim 25 and, in response, I do the same. *Infra* § XI.C.

95. **Fourth**, although Dr. Chaum does not separately address claim 27's additional requirement of only two loading doses, that claim also would not have been obvious for the reasons I stated for claims 5 and 11 in paragraph 90 of this declaration.

f. Claims 29 and 30

96. Claim 29 is the same as claim 28 except that it requires the claimed method is "as effective in maintaining visual acuity" as 0.5 mg monthly ranibizumab in patients suffering from AMD at 52 weeks. Ex.1001 (claim 29). Claim 30 additionally requires measuring "the gain in visual acuity ... using the ... ETDRS[] letter score." Ex.1001 (claim 30). It is my opinion that these claims are not obvious for the same reasons I stated for claims 26-28 in paragraphs 92-95 of this declaration.

97. Additionally, I see that Dr. Chaum has opined that a POSA would have reasonably expected the 2q8 dosing regimen to maintain vision above a loss of 15 letters at 52 weeks because VEGF Trap-Eye had a "higher binding affinity" and likely 'longer duration of effect in the eye' than ranibizumab." Ex.1002, ¶183 (quoting Ex.1009, 5). I disagree with Dr. Chaum's opinion. Dixon's authors cautioned that "VEGF Trap-Eye *may* have longer duration of effect in the eye." Ex.1009, 5 (emphasis added). The duration of a drug's effect depends on many factors, including the drug's binding affinity, half-life, and dosage, as just a few examples. Moreover, no POSA would have reasonably expected the 2q8 regimen

to yield the specific, claimed results based on Dixon's vague statement about binding affinity.

B. The prior art does not disclose or suggest the required benefits to visual acuity in the context of DME

98. It is my opinion that the 2009 Press Release, either alone or in combination with the 2007 ARVO Abstract and/or Dixon, does not render claims 16, 17, 20, and 21 of the '572 Patent obvious. Claim 16 requires "a gain in visual acuity within 52 weeks," claim 17 requires a gain of "9 letters" within that span, claim 20 requires "a gain in visual acuity within 24 weeks," and claim 21 requires a gain of at least "8 letters" within 52 weeks. Ex.1001 (claims 16, 17, 20, 21).

99. Broadly speaking, the 2009 Press Release, the 2007 ARVO Abstract, and Dixon describe partial results from Phase I and Phase II trials and the prospective VIEW 2q8 dosing regimen. Exs. 1005, 1009, 1030. As I explained in paragraphs 79-81 of this declaration, a POSA would not have reasonably expected a Phase III trial to succeed based on partial results from Phase I and II trials. Furthermore, and as set forth below, a POSA also would not have reasonably expected the results from any of these references' disclosures.

100. The 2009 Press Release states that, in 2009, a Phase II clinical trial testing a 2q8 dosing regimen of VEGF Trap-Eye for treatment of DME was in progress. Ex.1005, 1. It discloses that the "primary efficacy endpoint evaluation is

mean improvement in visual acuity at six months.” Ex.1005, 1. It also mentions a target endpoint for the VIEW clinical trials, which involved AMD, not DME. It does not, however, disclose any results. Ex.1005. It is my opinion that no POSA would have reasonably believed 2q8 dosing would produce the claimed results in patients with DME based on the 2009 Press Release. Once again, clinical endpoints are goals that pharmaceutical companies hope to achieve, not results.

101. It is my opinion that a POSA also would not have found these claims obvious over the combination of the 2009 Press Release, Dixon and the 2007 ARVO Abstract. Dixon only discusses treating DME in the context of a Phase I clinical trial involving five patients, all of whom received a single 4 mg dose of VEGF Trap-Eye. Ex.1009, 3. The 2007 ARVO abstract is the same. Ex.1030, 1. No POSA would have drawn conclusions about the efficacy of a 2 mg dose from the result of a trial involving a 4 mg dose.

102. Finally, I understand that Dr. Chaum also has testified that these claims were obvious in part because AMD and DME share the same underlying mechanism of action (fluid leaking into the macula). Ex.1002, ¶188. Dr. Chaum’s opinion appears to depend on a flawed, underlying premise: that the 2009 Press Release, Dixon, or the 2007 ARVO Abstract discloses that the 2q8 regimen was effective in patients with AMD. Neither the 2009 Press Release nor the 2007 ARVO Abstract discusses efficacy for AMD and, as I explained above, Dixon’s disclosures do not

provide a reasonable expectation that the claimed 2q8 regimen would yield the claimed visual acuity gains. I therefore disagree with Dr. Chaum's reasoning on this point, as well.

C. It was not obvious to formulate aflibercept as an isotonic solution or with a non-ionic surfactant

1. Neither Dixon nor Hecht renders obvious an isotonic solution

103. It is my opinion that formulating aflibercept as an isotonic solution as required by claims 6, 12, 18, and 22 was not obvious in view of Dixon and Hecht.

104. First, Dixon does not render an isotonic solution obvious. Dr. Chaum relies on Dixon's statement that VEGF Trap-Eye is "formulated with different buffers and at different concentrations (for buffers in common) suitable for comfortable, non-irritating, direct injection into the eye," to show obviousness. Ex.1002, ¶192 (quoting Ex.1009, 3). Dixon does not, however, mention tonicity.

105. Second, Hecht in combination with Dixon also does not render an isotonic formulation obvious. Contrary to Dr. Chaum's testimony, Hecht does not teach that ophthalmic solutions *must* be isotonic. Ex.1002, ¶193 (citing Ex.1016, 11). Hecht states that "finished" ophthalmic solutions may be hypertonic because, during preparation, an active ingredient is added to an isotonic solution. Ex.1016, 10-11. And although Dr. Chaum is correct that Hecht calls isotonicity "always ... desirable," Hecht also states that isotonicity "need not ... be an overriding concern

when total product stability is to be considered.” Ex.1016, 13. That is because, as Hecht explains, “[t]he eye usually can tolerate solutions equivalent to a range of 0.5% to 1.8% sodium chloride,” or roughly from half to double the standard, 0.9% sodium chloride concentration considered to be isotonic with the interior of the human eye. Ex.1016, 13. Thus, a POSA reading Hecht would have recognized that mildly hyper- and hypo-tonic solutions were acceptable and would have prioritized other considerations, like stability, over-achieving isotonicity.

2. *Neither Dixon nor Hecht renders obvious a non-ionic surfactant*

106. It is my opinion that formulating aflibercept with a non-ionic surfactant as required by claims 7, 13, 19, and 23 of the ’572 Patent was not obvious in view of Dixon and Hecht.

107. First, Dixon does not render formulating aflibercept with a non-ionic surfactant obvious. To begin with, I do not see any discussion by Dr. Chaum as to why Dixon would render obvious a non-ionic surfactant. Ex.1002, ¶¶191–195. And while Dixon describes formulating VEGF Trap-Eye for a “comfortable, non-irritating, direct injection into the eye,” it does not describe using a non-ionic surfactant. Ex.1009, 3. Thus, it is my opinion that Dixon’s disclosure would not motivate a POSA to use a non-ionic surfactant when formulating aflibercept.

108. Second, Hecht in combination with Dixon does not render formulating aflibercept with a non-ionic surfactant obvious. Hecht briefly discusses non-ionic

and ionic surfactants under the header “Additives.” Ex.1016, 13. Dr. Chaum opines that Hecht’s disclosures that non-ionic surfactants are “least toxic to ophthalmic tissues” and are “aids in achieving solution clarity” would have motivated a POSA to use them when formulating aflibercept. Ex. 1016, 13. But, at least solution clarity would not have motivated a POSA to use a non-ionic surfactant: by 2010, doctors routinely administered intraocular injections of methotrexate, a yellow fluid for treating intraocular cancers. Methotrexate’s yellow color did not deter its use.

109. Dr. Chaum also fails to mention other, contrary disclosures. Hecht states non-ionic surfactants are used “particularly in steroid suspensions,” which are administered topically, not intravitreally. Ex.1016, 13. It cautions that non-ionic surfactants can “inactivate much of the preservative system” by “binding with antimicrobial preservative compounds.” Ex.1016, 13. And it states that cationic surfactants are “used frequently in ophthalmic solutions” with benzalkonium chloride “used in the large majority of commercial ophthalmic solutions and suspensions.” Ex.1016, 13. Thus, it is my opinion that Hecht’s disclosures would not have motivated a POSA to formulate aflibercept with a non-ionic surfactant.

110. Finally, it is my opinion that neither of the two references that Dr. Chaum cites in passing, Randolph (Ex.1032) and Fraser (Ex.1033), support obviousness. Ex.1002, ¶194. The first page of Randolph’s introduction, and the only page that Dr. Chaum cites, does not mention non-ionic surfactants. Ex.1032, 3. Nor

does Randolph anywhere say what surfactant to pair with aflibercept. Ex.1032. It cautions against using non-ionic surfactants for some proteins because such surfactants can denature proteins, leading to “the formation of large, insoluble non-native aggregates.” Ex.1032, 13. And it concludes, in essence, by observing that whether to add a surfactant to a protein formulation depends on the particular protein. Ex.1032, 15 (“The choice of surfactant may be dictated by the degree of stabilization ... provided to a protein by a particular surfactant”). Thus, it is my opinion that Randolph’s disclosures would not have motivated a POSA to formulate aflibercept, specifically, with a non-ionic surfactant.

111. The second reference that Dr. Chaum cites in passing, Fraser, also does not support obviousness. Fraser discloses using intravenous injections of aflibercept formulated with a non-ionic surfactant to suppress ovarian function in macaques (a kind of monkey). Ex.1033. A POSA would not have reasonably expected that a formulation suitable for suppressing ovulation in monkeys also was suitable for treating angiogenic eye disorders. Nor would a POSA have reasonably expected that a formulation suitable for intravenous injection in monkeys would be suitable for intravitreal injection in humans; as a POSA would have known, the endothelial lining of blood vessels is different than the sensitive neurological tissue inside the human eye and a formulation compatible with blood vessels might not also be compatible with neurological tissue. Thus, it is my opinion that Fraser’s disclosures

would not have motivated a POSA to formulate aflibercept with a non-ionic surfactant.

D. Using exactly four secondary doses was not obvious from the 2009 Press Release, Shams, and Elman 2010

112. It is my opinion that the dosing regimen recited in claim 25 would not have been obvious to a POSA based on the 2009 Press Release either alone or in combination with Shams or Elman 2010.

113. Petitioner and Dr. Chaum contend that a POSA would arrive at the dosing regimen of Claim 25 by modifying the DA VINCI 2q8 dosing regimen disclosed in the 2009 Press Release. I begin by noting the specific modification that would be required in order to arrive at the claimed dosing regimen. The 2009 Press Release discloses a regimen of three monthly loading doses followed by maintenance doses every eight weeks. Claim 25 requires a regimen of five loading doses followed by maintenance doses every eight weeks. Thus, to arrive at the claimed regimen, a POSA would have to decide to add exactly two loading doses before moving to maintenance dosing.

114. Dr. Chaum opines that a POSA would arrive at the claimed dosing regimen by adding just one dose to the 2q8 arm of the DA VINCI regimen. Ex.1002, ¶210. This opinion does not comport with a POSA's approach to loading doses. The DA VINCI 2q8 regimen is made up of two distinct phases: a loading phase

immediately followed by a maintenance phase. A dose added at the fourth month would be an addition to the loading phase and would push back the start of the maintenance phase by one month. The resulting regimen would have a dose at week 12 (the fourth month) and none at week 16 (the fifth month), as illustrated in **Figure 2** below. This is not the claimed dosing regimen, which requires a dose at the fifth month (week 16).

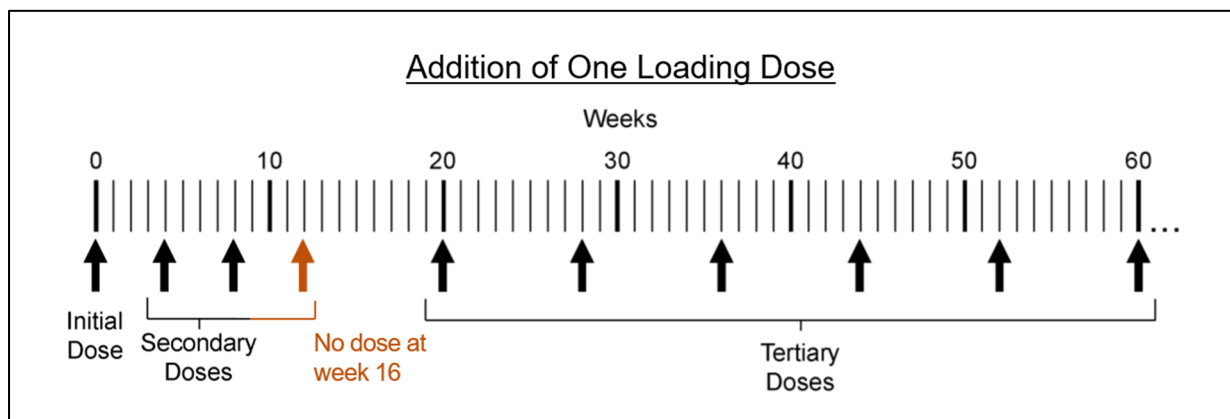


Figure 2: Illustration of adding one loading dose to the DA VINCI 2q8 arm.

1. The 2009 Press Release does not teach or suggest the dosing regimen of claim 25

115. The 2009 Press Release does not provide any explanation for the choice of dosing regimens or any outcomes. Nothing in the press release would inform a POSA which dosing regimen would be a promising starting point or teach a POSA how the regimens might need to be modified.

116. If a POSA nevertheless looked to the 2009 Press Release as a starting point for choosing a dosing regimen, it would teach a POSA to use three monthly

loading doses. The 2009 Press release discloses three separate dosing regimen arms of the DA VINCI trial: monthly dosing, PRN dosing after *three* loading doses, and 2q8 dosing after *three* loading doses. Ex.1005. Thus, the 2009 Press Release discloses regimens using three monthly loading doses and no other number of loading doses. A POSA would view this disclosure as teaching toward the use of three monthly loading doses.

117. It is also my opinion that the monthly dosing arm disclosed in the 2009 Press Release would not teach a POSA toward varying the number of loading doses for other dosing regimens. Ex.1005. The monthly dosing arm does not involve a loading dose phase at all, so would not teach how many loading doses are necessary before extending the dosing interval. If a POSA were to speculate on why the monthly dosing arm were included, they would likely understand it to serve as a comparison for the other treatment arms. Given a POSA's knowledge of the standard monthly dosing of anti-VEGF agents, it is my opinion that a POSA would have assumed that the monthly dosing arm was included in the DA VINCI trial for comparison. A POSA would have understood that Regeneron hoped to show that 2q8 dosing could be as effective as monthly dosing and so included both arms to show whether efficacy was similar. Thus, it is my opinion that the 2009 Press Release's disclosure regarding the monthly dosing arm would not have taught a

POSA toward experimenting with different numbers of loading doses for other dosing regimens, let alone toward choosing a five loading dose regimen.

118. Dr. Chaum asserts that a POSA would consider adding loading doses to ensure sufficient drying of the retina. Ex.1002 ¶¶ 208–209, 215. The 2009 Press Release includes no data indicating whether three doses were enough to dry the subjects’ retinas, so it cannot show that patients would benefit from more than three loading doses.

2. The 2009 Press Release in combination with Shams does not teach or suggest the dosing regimen of claim 25

a. Shams does not teach or suggest more loading doses

119. Dr. Chaum also opines that Shams would lead a POSA towards experimenting with the number of loading doses, and ultimately lead to five loading doses. Ex.1002, ¶213. I disagree. It is my opinion that a POSA would not have considered Shams to include any reliable teachings on how to select a dosing regimen. And, if anything, Shams teaches toward three or fewer loading doses.

120. Shams includes some very broad disclosures. For example, Shams discloses that “[a]ny compound which binds to VEGF or a VEGF receptor and reduces the severity of symptoms ... may be used in this embodiment of the invention.” Ex.1017, 26:6–8. Shams also discloses that “[t]he doses may be administered according to any time schedule which is appropriate” Ex.1017,

22:30–31. Disclosures such as these provide no guidance on how to select and implement a dosing regimen.

121. Shams also includes some guidance that a POSA would know to be erroneous. Shams discloses dosing as often as daily or weekly, and dosing before the development of a disease. Ex.1017, 22:31–34. A POSA would understand such administration to be completely unnecessary, risky, and burdensome.

122. To the extent that Shams does teach ways of selecting a dosing regimen, it describes contradictory approaches. It focuses on fixed regimens but discusses various individualized approaches to reach such a schedule. For example, Shams discloses that “[t]he occurrence of adverse effects can be monitored by routine patient interviews and adjusted to minimize the occurrence of side effects by adjusting the time of the dosing.” Ex.1017, 23:5–7. A POSA would understand this as individualized, as-needed dosing. But the dosing regimen disclosed in the only example in Shams shows fixed monthly loading doses followed by fixed quarterly maintenance dosing. Ex.1017, 31:8–11, Fig. 2.

123. Shams focuses on the PIER trial, although I understand that Shams was written before the first readouts from the PIER trial in 2006. Ex.1017, 1; Ex.2066 ¶ 25. It is my opinion that the failure of the PIER trial after Shams was written would color a POSA’s reading of Shams in 2011. When Shams was filed in October 2005, the ANCHOR and MARINA investigators had seen that monthly dosing could treat

AMD relatively effectively, but very little information was available about what would happen if Lucentis were dosed less frequently after AMD symptoms had been alleviated. Ex.1017, 1; *see* Ex.2066 ¶¶24–25, 33. Shams’ statements about quarterly dosing and about the ease with which a physician could choose an appropriate dosing regimen reflect optimism at the time that frequent dosing would not be required after the first few doses. Ex.2066 ¶24; *e.g.*, Ex.1017, 22:30–23:11. But the PIER trial failed and showed that researchers had underestimated the difficulty of finding an extended dosing regimen that could effectively treat AMD and other angiogenic eye disorders. Ex.2066 ¶¶22–34. Thus, it is my opinion that a POSA reading Shams in view of the PIER trial results would not credit Shams, especially the assertion that “the specific time schedule can be readily determined by a physician having ordinary skill in administering the therapeutic compound by routine adjustments of the dosing schedule.” Ex.1017, 22:34–23:2.

124. Further, even if a POSA did rely on Shams to choose a number of loading doses, Shams teaches three or fewer doses: “The first dose may be administered, for example, one, two or three times, typically three times.” Ex.1017, 23:14–15. It is my opinion that a POSA reading Shams would not be motivated to test a regimen using five loading doses since Shams explicitly points to three or fewer loading doses.

b. Shams and the 2009 Press Release do not narrow down the numerous ways to modify the DA VINCI 2q8 dosing regimen

125. Even if Shams or the other DA VINCI trial arms in the 2009 Press Release suggested that a POSA should try modifying the 2q8 arm, they do not narrow down the many possible ways in which to do so.

126. Shams teaches the use of “any time schedule,” which could conceivably include any number of loading doses and expressly includes any interval from daily to quarterly for loading and maintenance dosing. Ex.1017, 22:30–31, 23:7–9. The number of possible modifications Shams could suggest would be numerous. For example, using 2, 4, 5, 6, 7, or more loading doses; decreasing the interval for initial doses to every 1, 2, or 3 weeks, or increasing it to every 5, 6, 7, or more weeks; decreasing the interval for maintenance doses to every 5, 6, or 7 weeks, or increasing it to every 9, 10, 11, or more weeks. Shams gives no reason why these modifications could not also be combined to generate hundreds or more possibilities. The possible modified schedules also include regimens with both more and fewer doses than the DA VINCI 2q8 regimen, so Shams does not even teach in the general direction that Petitioner proposes.

127. The DA VINCI trial PRN arm encompasses hundreds of possible dosing schedules. At any monthly visit after the first three monthly loading doses, a dose may either be administered or withheld. Over just the first 12 months, there

would be nine such visits for a total of $2^9 = 512$ possible dosing schedules. Again, these schedules could involve more or fewer doses than the DA VINCI 2q8 regimen, so the PRN arm does not teach in the general direction of more doses.

128. Finally, the DA VINCI monthly dosing arm does not teach a loading phase at all, so would not teach five monthly loading doses any more than it teaches four, six, or more.

129. The 2009 Press Release and Shams could offer no more than general guidance as to which of many possible dosing regimens to try. Determining the optimal dosing regimen from all these options would require long and costly clinical trials, rendering it impractical to test all the various options. Shams and the 2009 Press Release do not render the claimed regimen obvious.

c. A POSA would not arrive at the claimed regimen with “routine optimization” or “routine adjustments”

130. Dr. Chaum opines that a POSA who started with the 2q8 regimen described in the 2009 Press Release would arrive at the claimed five-loading dose regimen through routine optimization. Ex.1002, ¶213. I disagree, and my opinion on this point is the same whether or not the claims require a predetermined dosing regimen. The prior art does not disclose a range of dosing options that encompasses the claimed five loading doses. And it would not be simple for a physician making

adjustments in individual patients to find an optimum, nor is five doses necessarily the optimum for every patient.

131. As discussed above, the 2009 Press Release teaches only three loading doses. Shams discloses a narrow range for the number of loading doses: “one, two or three.” Ex.1017, 23:13–16. This disclosed range may encourage a POSA to experiment within that range, but provides no reason to experiment with more doses, or with five doses specifically.

132. Any broader statements in Shams also do not disclose a range over which to optimize. For example, Shams states that, “[t]he doses may be administered according to any time schedule which is appropriate.” Ex.1017, 22:30–31. Setting aside the fact that a POSA would not credit Shams’ generalizations for the reasons discussed above, the statement encompasses a large set of possibilities. The possible modifications include varying the number and frequency of loading doses, but also the number and frequency of maintenance dosing. A POSA could not feasibly test all of them to determine the combination that was optimal for “efficaciously treating DME with aflibercept, while minimizing the number of injections.” Ex.1002, ¶¶206–207. What’s more, it would be difficult to know whether a particular schedule was optimal to minimize the number of injections for either an individual patient or a population without comparing different regimens over many months or years.

Thus, a POSA would not reasonably expect to succeed in optimizing the number of loading doses based on the broad disclosures of Shams.

133. Further, Petitioner does not show that five loading doses is optimal as a *predetermined, fixed-interval* regimen. Dr. Chaum opines that a POSA would arrive at five doses through adjustments based on individual patient assessments, and in particular that a POSA would continue monthly dosing until observing that the retina was dry. Ex.1002, ¶¶213–215. The claims, as discussed above, refer to predetermined, fixed dosing regimens, and thus no individualized approach would lead to a predetermined fixed five-loading dose regimen.

134. Even if the evidence did show that five loading doses would be an optimal number for some fraction of patients, which Petitioner has not shown, that information would not be enough to show that five loading doses was optimal as a *predetermined* fixed regimen for those patients. Instead, a POSA would need some way to know in advance which patients should receive five loading doses. Petitioner and Dr. Chaum propose none.

135. It is my opinion that nothing in the prior art would lead a POSA to five loading doses as an optimum, efficacious aflibercept treatment for DME, either for the entire patient population or for a subset of patients that could be identified in advance of treatment. There was no consensus among physicians in 2011 regarding how to best balance the minimization of injections while maximizing efficacy. It

was only after Regeneron's Phase III VISTA and VIVID trials that a five-loading dose regimen was shown to be a highly effective predetermined fixed dosing regimen. The optimization process that Dr. Chaum propounds would not necessarily lead a POSA to a predetermined five-loading dose regimen.

d. A POSA would not have a reasonable expectation of success in using a fixed extended dosing regimen in order to treat effectively while minimizing the number of loading doses

136. The 2009 Press Release discusses a clinical trial that would compare monthly dosing, PRN dosing, and 2q8 dosing. Ex.1005. In 2011, if a POSA sought to optimize for, as Dr. Chaum puts it, “efficaciously treating[] DME... while minimizing the number of injections,” Ex.1002, ¶¶206–207, then they would not expect to achieve this objective using fixed extended dosing.

137. Until Regeneron announced the successful results of its VIEW trial, no fixed extended dosing regimen of an anti-VEGF agent had been shown to be effective to maintain visual acuity gain over time. Based on the prior art clinical trials in wAMD, a POSA would have understood that monthly dosing would be most likely to “efficaciously treat[] DME,” and that individualized regimens offered a better possibility of “minimizing the number of injections.” *See* Ex.1002, ¶¶206–207. A POSA would have considered fixed extended dosing to provide far less

certainty of success achieving these objectives in light of prior art failures, including the PIER trial.

138. Genentech's phase III MARINA and ANCHOR trials showed monthly dosing of Lucentis to be highly effective. At the two-year mark, subjects gained and maintained a mean of +6.5 letters with a 0.3 mg monthly treatment and +7.2 letters with 0.5 mg monthly dosing. Ex.1052, 8 Fig. 2A.

139. A POSA in 2011 would understand these monthly trials to set the standard for efficacy of anti-VEGF agents and would inform what a POSA would understand as the level of efficacy to target with a less-frequent dosing regimen.

140. Some less-frequent dosing regimens for Lucentis had been tested in clinical trials by 2011. These trials included SUSTAIN, EXCITE, SAILOR, and PIER, none of which demonstrated efficacy on par with monthly Lucentis. *See* Ex.2119, 6–7; Ex.2066, ¶22.

141. Moreover, if an anti-VEGF drug were to be administered less often than monthly, then a POSA would more likely expect an individualized regimen, rather than a fixed regimen to meet the objective stated by Dr. Chaum to “minimiz[e] the number of injections.” Ex.1002, ¶206. Individualized treatment regimens attempted to ensure that patients who need it get continued frequent dosing, while sparing patients who respond well to therapy from frequent additional doses. A POSA would

have expected that by tailoring a dosing regimen, the POSA could use fewer doses, on average, than with fixed extended regimens.

142. The SUSTAIN trial was designed to evaluate the safety and efficacy of individualized ranibizumab treatment for patients with wAMD. Ex.2098. Subjects received three monthly doses followed by PRN dosing. Ex.2098, 1. Patients would receive a maintenance dose if they had either lost visual acuity or had experienced an increase in retinal thickness. Ex.2098, 1–2. From months 3 to 11, patients received on average of 2.7 doses. Ex.2098, 2. The visual acuity outcomes were not as good as in ANCHOR and MARINA: subjects achieved average visual acuity gains of only +3.6 to +5.8 letters. Ex.2098, 2. The outcomes were better than in PIER, even though subjects in SUSTAIN received approximately the same number of doses in the PRN phase that subjects in the PIER trial received during its quarterly dosing phase. Subjects in SUSTAIN received 2.7 doses over 9 months, and in PIER received 3 doses over 9 months. Ex.2094, 5 Fig. 1; Ex.2097; Ex.2098.

143. Thus, it is my opinion that a POSA, considering this evidence, would not have had a reasonable expectation of success in pursuing extended, fixed-interval dosing such as that claimed in the '572 Patent for the purposes Dr. Chaum identifies.

3. The 2009 Press Release in combination with Elman 2010 does not teach or suggest the dosing regimen of claim 25

144. It is my opinion that the claimed dosing regimen would not have been obvious to a POSA based on the 2009 Press Release in further view of Elman 2010. Elman 2010 does not teach toward five loading doses and a POSA would not be motivated to combine the regimen in Elman with the 2q8 regimen in the 2009 Press Release.

145. The Elman 2010 study discloses fixed dosing followed by individualized patient assessments, with the transition to a first individualized dosing protocol after the fourth dose, and a further transition to a second, different individualized dosing protocol after the sixth dose. This is in contrast to claim 25, which recites five fixed monthly loading doses, followed by eight-week maintenance dosing. The study design of Elman did not include any arm with five fixed monthly loading doses, and Elman does not disclose any single patient who received five loading doses or teach or suggest any potential benefit of using exactly five loading doses.

a. Elman teaches monthly doses based on individual patient assessments

146. Dr. Chaum opines that in view of Elman 2010, “a POSA would have found it obvious to treat at least some patients with DME by administering five initial monthly loading doses.” Ex.1002, ¶221. I disagree.

147. According to the treatment protocol of Elman 2010, patients received “a baseline treatment followed by intravitreal study drug or sham injection retreatments every 4 weeks through the 12-week study visit.” Ex.1018, 3. That means that all patients received an injection at weeks 0, 4, 8, and 12, or four predetermined monthly loading doses. *Id.* According to the protocol, “[f]rom the 16-week study visit and thereafter, a retreatment algorithm for study drug injections and sham injections... was designed to require retreatment unless a study was deemed a ‘success’... at which point retreatment was at investigator discretion....” *Id.* The retreatment algorithm was based “mainly on visual acuity and OCT measurements over time,” and “[a]t each follow-up visit, the system provided real-time feedback to the treating physician regarding whether treatment was required or at investigator discretion.” *Id.* In other words, whether a patient would receive a fifth dose according to the Elman 2010 protocol was based on patient assessments during each follow-up visit. Whether a patient would receive a fifth loading dose was not even determined based purely on the retreatment algorithm but may also be determined by the opinion of the treating physician. Elman 2010 does not disclose any rules or even general guidance on how to predetermine if a patient should receive a fifth dose ***without*** assessing the patient. Elman 2010 does not at all teach or suggest the use of five predetermined loading doses, and instead determines all doses after the fourth based on patient assessments. This is in direct contrast to

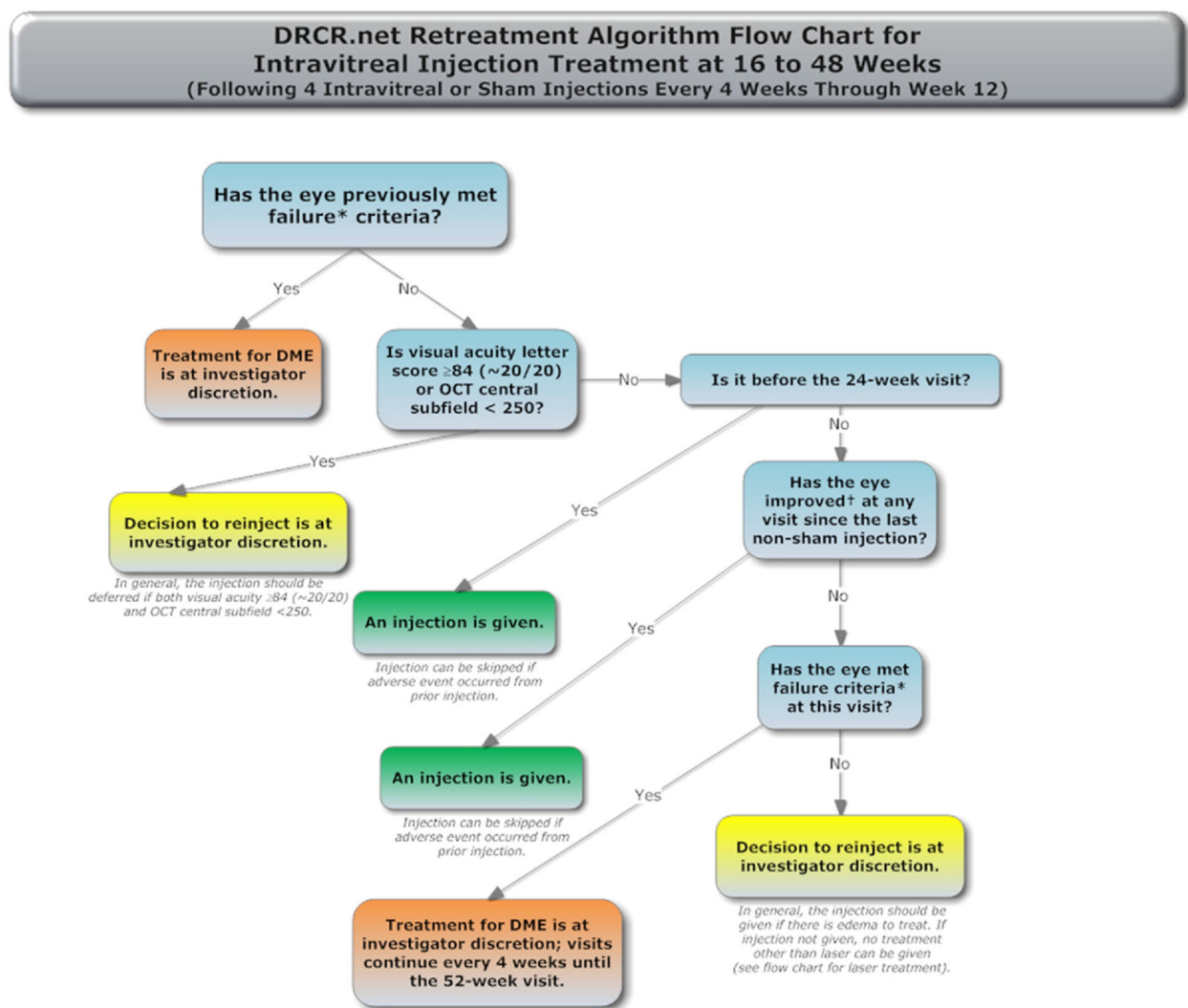
the regimen of claim 25, which requires patients to receive exactly five monthly loading doses, regardless of assessment.

148. It is therefore my opinion that a POSA would not be motivated to modify the fixed regimen of 2009 Press Release so that some patients receive five predetermined monthly loading doses in view of Elman 2010, which does not teach a fixed extended dosing regimen, never mind a fixed extended dosing regimen with five loading doses.

b. Elman does not teach using exactly five loading doses

149. Petitioner points to the disclosure in Elman 2010 that “[a]t the 16-week study visit... 41 (22%) of the 188 eyes in the ranibizumab + deferred laser group... did not receive an injection,” to argue that “at least 78% of patients receiv[ed] a fifth initial monthly dose.” Ex.1018, 4; Pet. 55. However, this does not mean that these patients received five and only five initial monthly doses. Elman 2010 does not disclose patient-level data regarding the number of loading doses each patient received. In fact, none of the 78% of patients in this group may have received exactly five initial monthly doses. It is a mere *possibility* that some patients might have received exactly five monthly doses, and the Elman 2010 protocol makes this possibility unlikely for reasons explained below. The retreatment protocol made it far more likely that patients would have received at least six initial doses.

150. In order to receive exactly five loading doses, a patient must receive a dose at weeks 0, 4, 8, 12, and 16, but **not** week 20 and onward. As explained previously, the treatment protocol of Elman 2010 required four predetermined loading doses for all patients at weeks 0, 4, 8, and 12. Subsequently, from the week 16 visit and onward, whether or not a patient received further doses was based on whether treatment was deemed “success” or “failure” by the criteria of a retreatment algorithm. “Success” is defined as a patient having “[e]ither visual acuity letter score ≥ 84 (20/20) or OCT central subfield thickness < 250 microns since the last non-sham injection or since baseline for the sham+prompt laser group.” Ex.1018, 25. These criteria were very stringent given that the mean baseline visual acuity letter score was 63 ± 12 and the mean OCT central subfield retinal thickness was 405 ± 134 μm , and made it likely for a patient not to meet the “success” criteria. Ex.1018, 4. In my own practice, I use 325–350 μm or the presence of intraretinal or subretinal fluid as a threshold for switching to less-frequent dosing, whereas Elman uses 250 μm . According to the flowchart from Elman 2010 reproduced below as **Figure 3**, a patient who has not yet met failure criteria but did not meet the success criteria would receive an additional dose at 16 and 20 weeks. Ex.1018, 16. In fact, about 78% of the patients in the ranibizumab + deferred laser arm received a dose at 16 weeks.



Definition of abbreviations used: DRCR.net = Diabetic Retinopathy Clinical Research Network; OCT = Optical Coherence Tomography; DME = Diabetic Macular Edema

* **Failure is defined as:** Visual acuity 10 or more letters worse than baseline, OCT central subfield ≥ 250 microns, DME present on clinical exam that is the cause of the visual loss, complete laser given AND ≥ 13 weeks since last laser treatment with no improvement since the last laser treatment.

† **Improvement defined as:** OCT central subfield thickness decreased by $\geq 10\%$ or visual acuity letter score improved by ≥ 5 .

Figure 3: DRCR.net Retreatment Algorithm Flow Chart. Ex.1018, 16.

151. Furthermore, the criteria for receiving a dose at the week 20 visit is exactly the same as that of the week 16 visit. Figure 3 of Elman 2010 (reproduced as **Figure 4** below) shows that most of the change in visual acuity occurred between

weeks 0 and 8, and mean change in visual acuity from baseline stayed the same, or even *decreased* slightly for the ranibizumab + deferred laser arm, between weeks 16 and 20. Ex.1018, 6 Fig. 3. Likewise, Figure 6 showed a decrease from week 16 to week 20 in the number of patients who had achieved a retinal thickness less than 250 μm . Ex.1018, 10 Fig. 6. These results of Elman suggest that “success” was, on average, no more likely at week 20 than it had been at week 16, making it unlikely that subjects would have received a dose at week 16 but not at week 20. Additional doses after the 20-week visit were discretionary, which made it possible for patients to receive even further monthly doses beyond the sixth dose. Ex.1018, 6. Elman 2010 does not expressly teach any particular number of monthly loading doses, but if a POSA were to deduce such a number, it would be at least six loading doses, not five.

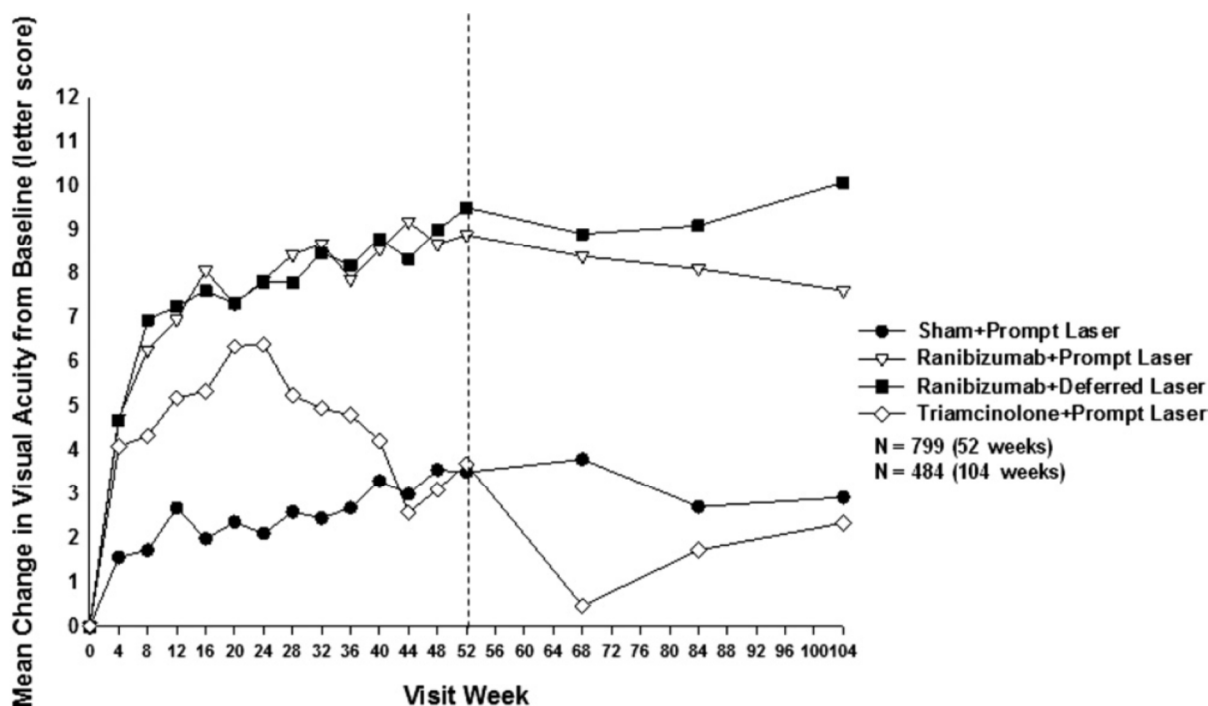


Figure 4: Mean change in visual acuity at follow-up visits. Ex.1018, 6, Fig. 3.

c. Elman’s results do not show any benefit of five loading doses

152. Petitioner argues that Elman 2010 would have taught a POSA toward five loading doses, Pet. 55, and Dr. Chaum argues that Elman 2010 effectively “sought, through routine variation in the number of initial doses, to determine the optimal number of initial injections” before moving to less-frequent dosing “[b]ecause there was a need to ‘dry’ the retina before proceeding to reduce the frequency of injections,” Ex.1002, ¶209. However, not only does Elman 2010 not disclose or suggest using exactly five loading doses, the results reported in Elman

2010 also do not suggest any benefit to administering using exactly five loading doses for drying the retina.

153. Figure 3 of Elman 2010 (Ex.1018, 6) shows no improvement in visual acuity of patients, 78% of whom received a fifth loading dose, between weeks 16 (after receiving the fifth loading dose) and week 20. Actually, the visual acuity got slightly worse. Figure 8 of Elman shows that nearly all of the improvement in retinal thickness and visual acuity achieved by week 52 had been achieved by week 12, and similar to visual acuity, retinal thickness also got slightly worse between weeks 16 and 20. Only modest changes were observed in visual acuity and retinal thickness from week 12 (after patients received four monthly doses) to week 52. Elman, therefore, does not teach that using exactly five monthly doses is any more helpful to dry the retina than three monthly doses or four, six, or more.

154. In view of the above, it is my opinion that a POSA would not read Elman as teaching that a dosing regimen requiring exactly five loading doses is more beneficial to treating angiogenic eye disorders, *e.g.*, by drying the retina, than four monthly doses, or six or more monthly doses.

155. Petitioner asserts a POSA “would have been motivated to use the five loading doses that were shown by Elman to be efficacious in the vast majority of patients.” Pet. 55. However, nothing in Elman supports the idea that any individual patient received exactly five loading doses, and even if they did, that the five loading

doses provided that subject any benefit. Elman 2010 shows only aggregate data for improvement in retinal thickness or visual acuity on average. Ex.1018, 6 Fig. 3, 35 Fig. 8.

156. Further, Elman 2010 does not provide precise information about the circumstances under which a patient should receive a fifth monthly dose. According to the protocol, a patient who did not achieve the stringent “success” criteria at week 16 would receive a fifth dose, but even if the patient did achieve these criteria, the patient could still receive a fifth dose at the investigator’s discretion. Figure 6 shows the proportion of patients who met the “success” criterion of $< 250 \mu\text{m}$ retinal thickness. At week 16, about 37% of subjects in the ranibizumab + deferred laser arm had retinal thickness $< 250 \mu\text{m}$, thereby achieving the success criteria. Ex.1018, 10, Fig. 6. However, only 22% of this arm did not receive an injection. *Id.*, 4.

157. Retinal thickness is used as a proxy for abnormal fluid accumulation in the retina, so the fact that some subjects received a fifth monthly dose despite having achieved retinal thickness $< 250 \mu\text{m}$ is contrary to Dr. Chaum’s arguments that a POSA would have switched to less-frequent dosing based on whether a patient’s retina was dry. Ex.1002, ¶¶208–209.

d. There is no motivation to combine Elman 2010 with the 2009 Press Release

158. Elman 2010 fails to teach toward five loading doses of ranibizumab. But even if it did, a POSA would not be motivated to combine this teaching with the regimen disclosed in 2009 Press Release of three loading doses of VEGF Trap-Eye followed by maintenance doses every eight weeks.

i. A POSA would not expect the optimal ranibizumab and aflibercept dosing regimens to be exactly the same

159. Dosing regimens of ranibizumab, such as that in Elman 2010, would have only offered some general guidance for finding an efficacious dosing regimen for other anti-VEGF treatments. It is a major goal of early-phase clinical trials to test the pharmacokinetic and pharmacodynamic properties of a drug and to adjust the dose and dosing regimen based on the clinical data. Absent clinical data, a POSA would not assume that the same dosing regimen optimized for ranibizumab is also the optimal dosing regimen for aflibercept or other anti-VEGF treatments.

160. Not only would a POSA understand ranibizumab and aflibercept to have different pharmacokinetic and pharmacodynamic properties simply because they are different drugs but known differences between the molecules would suggest to the POSA that aflibercept might dry the retina differently than ranibizumab. First, both the 2009 Press Release and Elman 2010 disclosed ranibizumab to be

administered at a dose of 0.5 mg, while the 2009 Press Release disclosed VEGF Trap-Eye to be administered at a dose of 2 mg. According to the Eylea label, aflibercept has “a protein molecular weight of 97 kilodaltons (kDa).” Ex.1059, 9. Ranibizumab has a molecular weight of approximately 48 kDa. Ex.1034, 5. Given that $1 \text{ kDa} = 1.66 \times 10^{-18} \text{ mg}$, 1 molecule of aflibercept is equivalent to $1.61 \times 10^{-16} \text{ mg}$ while 1 molecule of Lucentis is equivalent to 7.97×10^{-17} . Therefore, 2 mg of aflibercept contains $\frac{1 \text{ molecule}}{1.61 \times 10^{-16} \text{ mg}} \times 2 \text{ mg} = 1.24 \times 10^{16}$ molecules of protein. On the other hand, in 0.5 mg of ranibizumab, there are $\frac{1 \text{ molecule}}{7.97 \times 10^{-17} \text{ mg}} \times 0.5 \text{ mg} = 6.27 \times 10^{15}$ molecules of protein. In other words, even accounting for the larger size of aflibercept, administering 2 mg of aflibercept effectively means administering almost two times as many molecules as 0.5 mg of ranibizumab.

161. Second, a POSA would know from Dixon *et al.* (Ex.1009) that “VEGF Trap-Eye differs from established anti-VEGF therapies in its higher binding affinity for VEGF-A and its blockage of placental growth factors-1 and -2.” Ex.1009, 5. Because VEGF Trap-Eye interacted differently with the factors that lead to unstable, leaky blood vessel growth in the eye, a POSA would have reason to think that VEGF Trap-Eye could dry the retina using a different number of monthly doses than ranibizumab.

ii. Elman 2010 itself would not motivate a POSA to combine five loading doses with a fixed-interval extended dosing regimen

162. Elman does not provide any reason to follow five monthly doses with a fixed eight-week dosing interval.

163. For one, a patient in the Elman study who has received five monthly doses would be unlikely to begin fixed eight-week doses thereafter. As explained previously, the treatment protocol of Elman included a baseline fixed dosing every four weeks through the 12-week study visit, with the transition to individualized dosing after the fourth dose, and a further transition to a different individualized dosing methodology after the sixth dose. As explained above, for a patient who has received five initial doses, the only way to not receive a sixth loading dose would be to reach the study's stringent criteria for "success": "either visual acuity letter score ≥ 84 (20/20) or OCT central subfield thickness ≥ 250 μm since the last non-sham injection or since baseline for the sham+prompt laser group," which would be unlikely for most patients who qualified for this study. Ex.1018, 25. On the other hand, for the small minority of patients deemed a "success," these patients would likely not have received any further injections at all, since "[a]ccording to the DRCR.net retreatment algorithm used in this study, eyes assigned to ranibizumab that met 'success' criteria at the 16-week study visit [*i.e.*, after five doses] were not

required to have continued injections unless visual acuity worsened or macular edema returned.” Ex.1018, 11.

164. Dr. Chaum opines that “Elman 2010 does not specifically report how many patients received an injection at the sixth visit. It does report, however, that for the deferred laser group, the ‘median number of study drug injections before the 1-year primary outcome visit was... 9 (6, 11) ranibizumab injections (of 13 maximally possible injections).’” Ex.1002, ¶123. Dr. Chaum may suggest that the median nine doses make a fixed eight-week schedule possible after the initial doses, envisioning a scenario in which a patient receives five loading doses up to week 16, followed by four more eight-week doses up to and including week 48. However, it is my opinion for the reasons below that the median nine doses and a fixed eight-week schedule after initial dosing has no connection and does not offer a POSA any motivation to combine the two elements.

165. First, the median dose number of nine reported in Elman 2010 for the whole arm cannot be applied to the subgroup who received at least five monthly doses. Elman 2010 gives no indication that the median number of doses for of the whole ranibizumab + deferred laser arm is the same as the median number of doses for the subgroup of 78% of subjects who received a dose at week 16. Excluding the patients who did not receive a dose at week 16 would skew the median number of total doses, likely resulting in a higher median than nine doses.

166. Moreover, regardless of the actual median number of doses for the subgroup of interest, it cannot be assumed that a patient who received nine doses over a year received exactly five initial loading doses. There are a number of ways in which a patient could receive nine doses and yet not receive exactly five monthly loading doses. For example, a patient may receive injections at 0, 4, 8, 12, 16, 20, 28, 32, and 36 weeks. This nine-dose regimen is consistent with the Elman protocol and yet does not meet the requirements of the dosing regimen recited in the challenged claims, as the patient would have received six monthly loading doses. Thus, just because a patient received nine doses by the Elman protocol does not suggest that her treatment regimen met the requirement of claim 25, *i.e.*, five, and exactly five, initial monthly loading doses followed by q8 maintenance dosing. And a POSA experienced with individualized dosing regimens would expect that subjects who had responded well to treatment and received fewer than five initial doses could then go longer than average without such a recurrence, meaning they would skew the median dose number downward.

167. Furthermore, putting aside the fact that Elman 2010 does not disclose that any single patient received exactly five initial monthly doses, even if a patient received exactly five initial monthly doses and nine doses over the course of a year, those facts do not necessarily mean that the patient would receive any doses on an eight-week interval. Take, for example, a patient who received injections at weeks

0, 4, 8, 12, 16, 28, 32, 36, and 48. In this example, the patient received five monthly loading doses and a total of nine doses over the course of one year but would not have received a single dose that was eight weeks after the previous dose. Therefore, the fact that the median total dose over 1 year for the ranibizumab + deferred laser arm is nine and the possibility that some number of those patients *could* have received five loading doses does not indicate or suggest that any patients received exactly five loading doses and received eight-week dosing subsequent to the loading doses, as the challenged claims require.

168. Finally, the median nine doses in ranibizumab + deferred laser arm is merely that—a median. Figure 2 of Elman 2010 (reproduced below as **Figure 5**) reveals that only a small proportion of patients received nine doses over the first year.

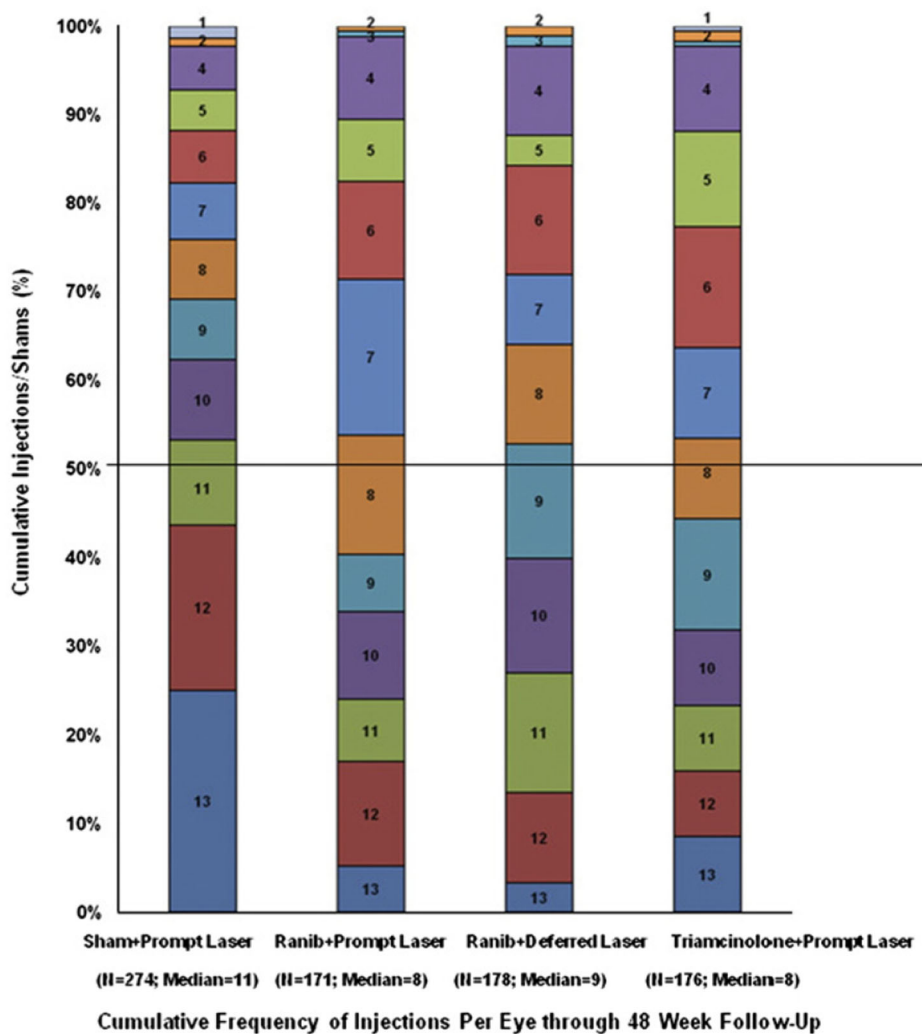


Figure 5: Cumulative distribution of injections/sham with randomized assigned treatment before the 52-week study visit. Ex.1018, 28, Fig. 2.

169. In fact, only about 10% of patients in the ranibizumab + deferred laser arm that the Petitioner relies on actually received nine doses. As calculated previously, nine is the number of doses a patient must have received within one year in order to have had five monthly loading doses followed by eight-week dosing. In other words, around 90% of ranibizumab + deferred laser arm that the Petitioner

relies on had no chance of receiving five monthly loading doses followed by eight-week dosing. The proportion of patients who received nine doses is around the same in the ranibizumab + prompt laser arm. Even among the 10% of these patients who received nine doses, there is no indication that any of these patients actually received any doses on an eight-week schedule.

170. For at least the reasons above, a POSA reading Elman would not rely on Elman 2010 to arrive at the dosing regimen of the challenge claims.

iii. The prior art does not provide motivation to add loading doses to the 2q8 regimen

171. Nothing in the 2009 Press Release or Elman 2010 would motivate a POSA to add loading doses beyond the three in the 2009 Press Release. The 2009 Press Release does not include any data for any of the arms it discloses. In Elman 2010, the data do not show that initial monthly doses beyond three were helpful, as discussed above. Instead, “[m]ost of the overall improvement in mean visual acuity... and proportion with ≥ 10 letter improvement from baseline... within the ranibizumab-treated groups occurred by the 8-week study visit.” Ex.1018, 7.

172. Dr. Chaum points to post-priority-date articles Heier 2011 (Ex.1039) and Heier 2012 (Ex.1038), alleging that these articles suggest that “based on clinical experience and trial results that showed that without sufficient initial monthly dosing, it was more difficult to use the ‘less frequent’ maintenance dosing to sustain

‘control of neovascular leakage and... gains in visual acuity...’” Ex.1002, ¶222. Heier 2011 describes the results of CLEAR-IT-2, a Phase 2 study of VEGF Trap-Eye for neovascular AMD. In one study arm, subjects received four monthly doses at weeks 0, 4, 8, and 12. In another, subjects received a dose at week 0 and a dose at week 12. The study concludes that “[b]y the end of the fixed-dosing phase at week 12, VEGF Trap-Eye showed a significant improvement in visual acuity from baseline, and this efficacy was maintained to week 52” and it is within this context that Heier 2011 remarks, “initial sequential monthly loading doses seem to provide better control of neovascular leakage and lead to superior gains in visual acuity that can be subsequently maintained with less frequent dosing.” Ex.1039, 7. This statement refers to the additional benefits offered by doses at weeks 4 and 8, and thus does not suggest that five monthly doses would be helpful.

173. The Heier 2012 paper reports on the results of two similarly designed Phase 3 studies (VIEW 1/2) for treating wAMD. The study protocol had four arms: intravitreal aflibercept 0.5 mg monthly (0.5q4), 2 mg monthly (2q4), 2 mg every two months after three initial monthly doses (2q8), or ranibizumab 0.5 mg monthly (Rq4). Dr. Chaum does not identify any relevant data or language in Heier 2012, but none of the results suggest that the three loading doses used in that trial were insufficient. To the contrary, Heier reported that the 2q8 arm was noninferior and

clinically equivalent to monthly ranibizumab, which would have suggested to a POSA that three loading doses was enough. Ex.1038.

174. Even if a POSA were motivated to add doses to the regimens disclosed in the 2009 Press Release, that is not to say that the POSA would have necessarily arrived at the exact dosing regimen recited in claim 25. There are numerous ways to add doses. For example, rather than adding two loading doses to the three loading doses disclosed by the 2009 Press Release, a POSA could have added one, three, or four loading doses. A POSA could have added monthly doses sometime after a period of every eight-week dosing. Alternatively, rather than adding loading doses, the POSA could have shortened the dosing interval. Combining these possible modifications results in a very large number of possible ways to add additional doses. Further, in view of the teachings of Elman 2010 and the 2009 Press Release, both of which taught individualized dosing regimens, a POSA could add subsequent doses on an individualized basis.

175. Although administering any one of the many possible dosing schedules would not be difficult, the possibilities are not easily traversed because the variability in patient responses to a dosing regimen make it impossible to know, without testing on a population of patients over many months or even years, whether a particular regimen or schedule is better than another.

176. The 2009 Press Release and Elman 2010 offer no more than general guidance as to which of many possible ways to add doses, so they do not render the claimed regimen obvious.

177. For the above reasons, a POSA would not have been motivated to combine the teachings of the 2009 Press Release and Elman 2010, and even if the POSA would have done so, they would not reach the dosing regimen recited in claim 25.

XII. COMMERCIAL SUCCESS

178. I understand that when considering obviousness, the commercial success of a patented product can be an indicator that the claims are non-obvious. I understand that in order for commercial success to be considered, there must be a nexus between the claims and the product such that the value of the product is derived from the patented features. It is my opinion that Eylea embodies claims of the '572 Patent and that the claimed features have contributed to the commercial success of Eylea.

A. Nexus to Eylea

179. Eylea is the brand name under which Regeneron markets its anti-VEGF agent aflibercept for the treatment of angiogenic eye disorders, including DME and AMD. Doctors frequently face the difficult task of maintaining a regular injection schedule for patients suffering from these diseases. The '572 patent, embodied by

Eylea, directly relates to such treatment, and it provides a regimen that patients find less burdensome than monthly injections.

180. Intravitreal injections can cause patients significant pain and discomfort. Each intravitreal injection carries a risk of infection, and such infections can lead to blindness, so administering fewer injections reduces the chance of a negative outcome. The cost and inconvenience of monthly visits and injections can be a major drawback for patients, many of whom are elderly and may be unable to drive due to deteriorating vision. The retinal community recognized these risks and drawbacks in the mid- and late-2000s, when the use of anti-VEGF drugs for angiogenic eye disorders became widespread. At that time, we were in search of a treatment regimen that reduced the frequency of injections required to effectively treat patients.

181. Clinical trials of Eylea showed comparable or better efficacy compared to other treatment options using an extended dosing regimen as claimed in the '572 Patent. By the time Eylea was first approved in 2011, Regeneron's DA VINCI and VIEW trials had demonstrated that Eylea administered via 2q8 dosing could treat angiogenic eye disorders with efficacy comparable to monthly ranibizumab. Those trials encompassed sequentially administering by intravitreal injection a single initial dose of 2mg of aflibercept, followed by one or more secondary doses of 2mg of aflibercept, followed by one or more tertiary doses of 2mg of aflibercept, with the

secondary dose administered about 4 weeks following the preceding dose and the tertiary dose administered approximately 8 weeks after the preceding dose as claimed by the independent claims of the '572 Patent.

182. Specifically, the DA VINCI trial demonstrated gains in visual acuity for patients suffering from DME. Satisfying claims 1-24 of the '572 Patent, those gains included, on average, 8.5 and 9.7 ETDRS letters by 24 weeks and 52 weeks, respectively, after three monthly loading doses followed by q8 dosing of 2mg Eylea. Ex.1001, 14:51-65. Satisfying claim 14 of the '572 Patent, the DA VINCI trial protocol excluded patients with active ocular inflammation and active ocular or periocular inflammation. Ex. 2048, 37–38. Satisfying claims 10 and 17 of the '572 patent, the DA VINCI trial demonstrated that patients achieved gains of 9 letters by 24 weeks because, even though the DA VINCI trial only reported average 24-week gains of 8.5 ETDRS letters, ETDRS letters are measured in whole-letter intervals and thus an average 8.5 letter gain meant that some patients achieved 9 or more letters by 24 weeks. Satisfying claims 6-7, 12-13, 18-19, and 22-23 of the '572 Patent, the Eylea used in the DA VINCI trial was formulated as an isotonic solution and with a non-ionic surfactant (as it is today). Ex. 2048, 88.

183. The VIEW trials similarly demonstrated that 2mg Eylea administered as three monthly loading doses followed by q8 dosing provides benefits to patients suffering from wAMD. Ex.1001, 13:7–27. Satisfying claims 26-28 of the '572

Patent, those benefits included gains of between 7.9 and 8.9 ETDRS letters, or roughly the same amount achieved by 0.5 monthly ranibizumab. Ex.1001, 13:7–27. And as noted above, an average gain of between 8 and 9 ETDRS letters meant some patients achieved gains of at least 9 letters. Satisfying claims 29-30 of the '572 patent, those benefits also included maintenance of vision that was as effective as 0.5 mg monthly ranibizumab at 52 weeks, as measured as the total number of letters read correctly on an ETDRS eye chart. Ex.1001, 13:7–27.

184. Regeneron's later VIVID, VISTA, and PANORAMA trials also included dosing arms in which subjects received sequentially administered intravitreal injections of a single initial dose of 2 mg of aflibercept, followed by one or more secondary doses of 2mg of aflibercept, followed by one or more tertiary doses of 2mg of aflibercept, with the secondary dose administered about 4 weeks following the preceding dose and the tertiary dose administered approximately 8 weeks after the preceding dose as claimed by the independent claims of the '572 Patent. In VIVID and VISTA, satisfying claim 25 of the '572 patent, a group of patients with DME received four 2mg secondary doses of Eylea (a total of five loading doses) and then q8 dosing with 2mg Eylea. Ex.2139, 1. Those patients achieved gains of 10.5 and 11.7 letters in the VIVID and VISTA trials, respectively. Ex.2139, 1. PANORAMA tested the same, five loading dose protocol in patients with DR (another angiogenic eye disorder) through 52 weeks and demonstrated

improvements in DRSS score (a metric by which doctors assess the progression of DR) at 52 weeks. Ex.2138, 1. (At 56 weeks, the PANORAMA q8 arm transitioned to p.r.n. dosing).

185. The FDA-approved label for Eylea recommends using the dosing regimens claimed in the '572 Patent. The current labeling instructs:

Neovascular (Wet) Age-Related Macular Degeneration (AMD)

The recommended dose for EYLEA is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 12 weeks (3 months), followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months). Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (approximately every 25 days, monthly), additional efficacy was not demonstrated in most patients when EYLEA was dosed every 4 weeks compared to every 8 weeks. Some patients may need every 4 week (monthly) dosing after the first 12 weeks (3 months). Although not as effective as the recommended every 8 week dosing regimen, patients may also be treated with one dose every 12 weeks after one year of effective therapy. Patients should be assessed regularly.

Diabetic Macular Edema (DME) and Diabetic Retinopathy (DR)

The recommended dose for EYLEA is 2 mg (0.05 mL or 50 microliters) 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). Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (approximately every 25 days, monthly), additional efficacy was not demonstrated in most patients when EYLEA was dosed every 4 weeks compared to every 8 weeks. Some patients may need every 4 week (monthly) dosing after the first 20 weeks (5 months).

Ex. 2140, 10 (internal bracketed citations omitted)

186. The Eylea label shows the connection between the success of the VIEW, VIVID, and VISTA, and PANORAMA trials and the recommended dosing regimens. The label recommends treating patients with wAMD using the three loading dose, 2q8 regimen tested in the VIEW trials, and patients with DME and DR using the five-loading dose, 2q8 regimen tested in the VIVID, VISTA, and PANORAMA trials. Sections 14.1, 14.4, and 14.5 of the label also report data from the VIEW, VIVID, VISTA, and PANORAMA trials demonstrating the efficacy of the recommended regimen for AMD, DME, and DR. Ex.2140, 24–36.

187. Industry practice shows the connection between the DA VINCI trial and Eylea dosing regimens. Although the label recommends treating patients with DME using the five-loading dose, 2q8 regimen tested in the VIVID, VISTA, and PANORAMA trials, physicians know of the DA VINCI trial, and it is common practice to administer Eylea to patients suffering from DME using only three loading doses according to the regimen tested in DA VINCI.

188. The wide adoption of Eylea is based on the success of the dosing regimens claimed in the '572 Patent, the demonstrated gains in efficacy from the claimed dosing regimens, its formulation, and its use in patients without active ocular inflammation or ocular or periocular infection. Patients with angiogenic eye disorders need efficacious treatment for their conditions and prefer longer intervals

between treatment. Physicians choose Eylea to satisfy this patient preference because of the efficacy and durability demonstrated in the DA VINCI, VIEW, VIVID, VISTA, and PANORAMA trials using the dosing regimen claimed in the '572 Patent and recommended in the Eylea label. Surveys by the American Society of Retina Specialists accordingly show that physicians believe Eylea is the anti-VEGF agent most likely to extend treatment duration without a loss of efficacy. Ex.2141, 84; Ex.2142, 73.

189. Therefore, it is my opinion that Eylea embodies the claim limitations in the '572 Patent. The claimed features, including the dosing amount, dosing regimen, disease indications, gains in visual acuity, formulation, and exclusion criteria have all contributed to Eylea's widespread adoption by physicians.

B. Commercial success of Eylea

190. Eylea has achieved widespread commercial success due to its impressive medical efficacy and ability to treat patients on less frequent, easier to follow dosing regimens.

XIII. EXHIBITS 2109 & 2112-2114

191. I understand from counsel that, in a related IPR Proceeding (IPR2023-00739), Samsung objected to Exhibits 2109 and 2112–2114 (labelled Exhibits 2032, and 2044-2046, respectively, in that proceeding). Exhibit 2109 is a printout from ClinicalTrials.gov of the RISE clinical trial, NCT00473330. Exhibits 2112–2114

are articles that provide background information on angiogenesis and angiogenic eye disorders. I understand that one of Samsung's objections to these exhibits was that the exhibits allegedly postdate the priority date of U.S. Patent No. 10,888,601 (the "'601 Patent"). In the remainder of this declaration, I explain that Exhibits 2109 and 2112-2114 show information that would have been known to a POSA as of the January 13, 2011 priority date of the '572 Patent. I also note that I would have reached the same conclusions I recite in the foregoing paragraphs of this declaration without the benefit of these four exhibits.

192. Exhibit 2109 is a printout of the "Record History Tab" for NCT00473330. Ex.2109, 1. In the Record History Tab on ClinicalTrials.gov, a user can "view a version of a study record" by selecting a link corresponding to "the date the study record was updated." Ex.2109, 1. The version displayed in Exhibit 2109 is "Version 9: 2010-11-11." Ex.2109, 3. Version 9 is the version that would have been available on ClinicalTrials.gov from when the study was updated in November 2010 until it was updated again in December 2012. Ex.2109, 2–3.

193. Exhibit 2133 confirms my understanding of the Record History Tab. Exhibit 2133 is a printout of a subpage of ClinicalTrials.gov entitled "How to Read a Study Record." It explains how to read the Record History Tab. Ex.2133, 10. The webpage explains, "You can use this tab to see different versions of the study record and compare the changes made to the study record over time." Ex.2133, 10.

194. Exhibit 2134 confirms that the information for which I have relied on Exhibit 2109 was available before the priority date. Exhibit 2134 is a printout from the Wayback Machine of the ClinicalTrials.gov site for NCT00473330 as it existed on June 9, 2010. Researchers can use the Wayback Machine website to understand how a particular website appeared on a certain date. I used the Wayback Machine to navigate to the June 9, 2010 version of the ClinicalTrials.gov site for NCT00473330. Exhibit 2134 includes the ClinicalTrials.gov header, as well as the government insignia for the National Institutes of Health, the National Library of Medicine, and the Department of Health and Human Services. Ex.2134, 1, 4. From this, I know that Exhibit 2134 is the version of the ClinicalTrials.gov site for NCT00473330 that was available online as of June 9, 2010.

195. The version of the Study Record shown in Exhibit 2134 is nearly identical to the version shown in Exhibit 2109, and the relevant portions are identical. As Exhibit 2109 shows, the study record was updated in November 2010. Ex.2109, 2–3. Exhibit 2109 includes the updates made in November 2010, but Exhibit 2134 does not because it is from June 2010. I rely on Exhibit 2109 for the RISE clinical trial endpoints and study start date in paragraph 30 of this declaration. Exhibit 2134 shows that the same endpoints and start date were available in June 2010. Ex.2134 1–2. This information is also consistent with my experience. I knew in 2010 that the RISE trial was underway and that aspects of the protocol had been

disclosed. In conclusion, Exhibit 2109 presents information that would have been known to a POSA before January 13, 2011.

196. Exhibit 2112 is an article authored by Sarah Whelan entitled “What is Angiogenesis?” The article is available online at <https://www.technology networks.com/cancer-research/articles/what-is-angiogenesis-363436>. Exhibit 2112 is a printout of the website, and Exhibit 2135 is a PDF version of the article also available for download from the same site. I rely on Exhibit 2112 for a figure depicting sprouting angiogenesis in paragraph 18 of this declaration. In support of its description of sprouting angiogenesis, Exhibit 2112 cites a 2010 book chapter by Adair & Montani entitled “Overview of Angiogenesis.” Ex.2112, 5–6, 9. Exhibit 2136 is a copy of the Adair book in which this chapter is found. Adair 2010 describes sprouting angiogenesis and includes a figure very similar to the one found in Exhibit 2112. Ex.2136, 15–16. In conclusion, the portion of Exhibit 2112 that I cite presents information that would have been known to a POSA before January 13, 2011.

197. Exhibit 2113 is an article by Dr. Matthew Dombrow and Dr. Ron Adelman. Exhibit 2113 bears a date of January 1, 2011, which is before the January 13, 2011 priority date of the ’572 Patent. Ex.2113, 1. The article does not present original research but instead reviews prior existing literature on ocular angiogenesis.

The article presents information that would have been known to a POSA before January 13, 2011.

198. Exhibit 2114 is a publication of a lecture by Joan Miller entitled “VEGF: From Discovery to Therapy.” I cite the Miller article for its discussion of the role of VEGF in general and the discovery of its role in angiogenic eye disorders in paragraph 25 of this declaration. Miller summarizes discoveries made in the 1980s and 1990s about role of VEGF. Ex.2114, 3. Miller also summarizes discoveries made before 1996 about the role of VEGF in angiogenic eye disorders. Ex.2114, 7, 11. Miller cites several articles from this time frame, including a 1996 article by Tolentino et al. that reports research on the role of VEGF in diabetic retinopathy. Exhibit 2137 is a copy of the Tolentino article. In conclusion, the portion of Exhibit 2114 that I have cited in my declaration presents information that would have been known to a POSA before January 13, 2011.

199. As a physician researcher in the retinal community, I regularly rely on peer-reviewed articles and published conference materials as reliable summaries of what was known in the retinal community at various times. Exhibits 2113 and 2114 are peer-reviewed articles and published conference materials that I have relied on for their summaries of what would have been known to a POSA before January 13, 2011.

* * *

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 21, 2024

/Michael W. Stewart, MD/

Michael W. Stewart, M.D.