

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. 10,888,601

Inter Partes Review No. IPR2023-00739

DECLARATION OF MICHAEL W. STEWART, M.D.

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I, Michael W. Stewart, M.D., declare as follows:

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 Regeneron’s Responses in connection with the *Inter Partes* Review of United States Patent No. 10,888,601 (“the ’601 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 ’601 Patent are patentable and nonobvious. The following is a summary of my opinions:

- The plain and ordinary meaning of the challenged claims requires a predetermined dosing regimen.
- The plain and ordinary meaning of the challenged claims requires both (1) an intent to treat a specific angiogenic disorder and (2) treating the angiogenic eye disorder with a level of efficacy comparable to monthly Lucentis or Avastin.

- The dosing regimen recited in the challenged claims of the '601 Patent is not obvious over the 2009 Press Release either alone or in combination with Shams.
- The recited dosing regimen is not obvious over the 2009 Press Release in view of Elman 2010.
- The prior art does not disclose the level of efficacy required by the challenged claims.
- The prior art does not disclose intent to treat diabetic retinopathy.
- Eylea embodies the claims of the '601 Patent such that there is a nexus between the '601 Patent and the commercial success of Eylea.

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 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 diabetic macular edema. 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 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 with this declaration as Ex.2028.

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 '601 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 9; 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 '601 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 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 the 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 path set out in a reference or would be led in a direction divergent from the path taken by the Patent Owner.

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 less 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. Diabetic retinopathy and diabetic macular edema

18. Diabetic retinopathy (DR) and diabetic macular edema (DME) are angiogenic eye disorders. Angiogenesis is the process of forming new blood vessels from preexisting vasculature. It is a complex process comprising multiple steps, illustrated in **Figure 1**:

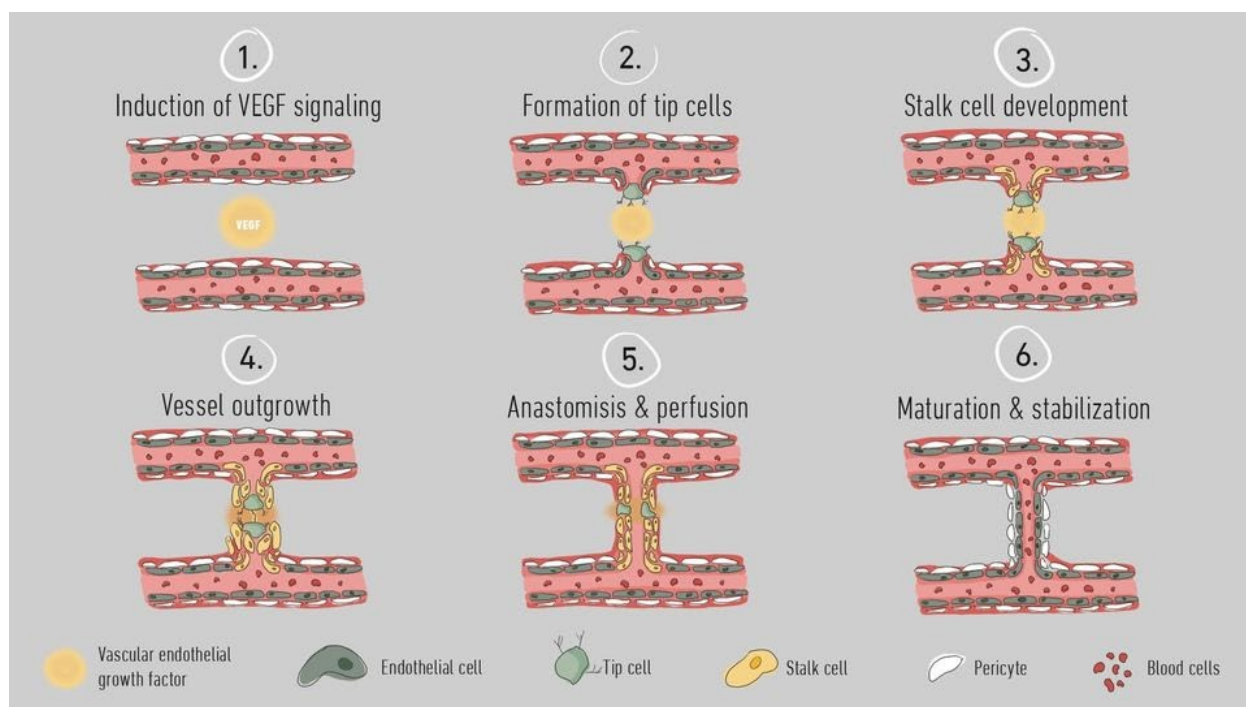


Figure 1: Steps of angiogenesis. Ex.2044, 3.

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.2045, 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 pathogenetic

findings in many diseases such as cancer metastasis, wet age-related macular degeneration (AMD), and DR. Ex.2045, 3, Figs.2–3.

20. DR and DME are related in that both occur 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. Retinopathy is the most common microvascular complication of diabetes. 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 (microaneurysms). 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.

21. Several pathologic findings characterize DR. In the earliest stage, microaneurysms can form as a result of weakened and/or blocked blood vessels. Moderate nonproliferative DR (NPDR), more than just microaneurysms, also has venous beading (a sausage-like dilatation), and intraretinal hemorrhages. Severe NPDR is characterized by many intraretinal hemorrhages in each of the 4 quadrants of the eye, definite venous beading in 2+ quadrants, and prominent intraretinal microvascular abnormalities in 1+ quadrant. The most advanced stage of DR is

proliferative diabetic retinopathy (PDR), wherein new blood vessels grow on the surface of the retina (neoangiogenesis), which causes scar tissue to also form. This scar tissue can contact and cause the retina to pull away from the back of the eye (detach), resulting in blurriness, reduced field of vision, or even permanent and complete blindness. Ex.2089, 6 Table 2; Ex.2091, 8.

22. Physicians commonly use ophthalmoscopy or multiple-field photography on the retina to observe these characteristics of DR. Ex.2089, 4. In clinical trials, it is desirable to reliably quantify progression or regression of disease. Therefore, a common measure of DR in clinical trials is the Diabetic Retinopathy Severity Score (DRSS). Ex.2091, 8. DRSS is a composite score graded on a 10-point scale by a central reading center by comparing patient fundus photographs with a set of standard images. A lower score indicates less severe diabetic retinopathy. Ex.2032. For example, the proportion of eyes with a 2-step or greater improvement in DRSS was used as the primary endpoint in the PANORAMA study evaluating intravitreal aflibercept for treatment of severe NPDR. Ex.2092, 2.

23. Leakage from the microvasculature can occur at any stage of DR and can cause swelling of the macula, a characteristic finding of DME. Ex.2090, 1. The macula is the part of the retina at the back of the eye responsible for central vision and fine detail. DME is the most common cause of vision loss among diabetic

patients. Ex.2097, 1; Ex.1001, 1:44–45. According to the guidelines of the Early Treatment of Diabetic Retinopathy Study (ETDRS), criteria for Clinically Significant Macular Edema (CSME) include:

- Retinal thickening at the center of the macula,
- Retinal thickening and/or adjacent hard exudates at or within 500 microns of the center of the macula,
- An area of retinal thickening greater than or equal to one disc area, any part of which is within 1 disc diameter of the center of the macula.

Id.; Ex.2098.

24. As a result, quantitative assessment of macular edema can be performed with optical coherence tomography, which allows a physician to measure the thickness of the retina. Ex.2093, 2.

B. Prior art therapies for angiogenic eye disorders

25. 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 is placed within the macula. Another type of laser treatment is scatter laser, or panretinal photocoagulation, which comprises more extensive laser treatment that treats multiple spots throughout the retina, the majority of which is placed outside the macula.

26. From the 1970s through the 1990s, the Diabetic Retinopathy Study (DRS) and ETDRS evaluated laser photocoagulation treatment for DR, PDR, and DME. Ex.2095; Ex.2098; Ex.2094. 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 PDR, however, 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.2095, 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.2094, 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 (*i.e.*, patients with severe DR, PDR, and DME), there was “small benefit of early photocoagulation in reducing risk of severe visual loss” for patients who had not yet reached such a stage. Ex.2094, 19. Focal laser became the gold standard for treating DME, while scatter laser was used when treating DR or PDR with laser. Ex.2099, 1–2; Ex.2100, 1–2.

27. Around the same time, researchers were characterizing a family of potent growth factors called VEGFs. As described above in VI.A and Figure 1, VEGF is a secreted endothelial cell mitogen and angiogenesis factor regulated by hypoxia (or low oxygen) conditions, which are known to stimulate neovascularization. Ex.1045, 1; Ex.2046, 3; Ex.2089, 3. VEGF levels are significantly increased in eyes with DR and other angiogenic eye disorders, and blocking VEGF leads to a pronounced reduction in retinal neovascularization. Ex.2046, 7, 11; Ex.2089, 3. VEGF soon became known as the principal mediator of angiogenic eye disorders.

28. Beginning in 2004, the U.S. FDA approved a series of anti-VEGF agents. Macugen (pegaptanib) was the first such agent for use in neovascular (wet) age-related macular degeneration (wAMD), an angiogenic eye disorder. Ex.2047. In the same year, the anti-VEGF monoclonal antibody Avastin (bevacizumab) was approved for use in advanced solid cancers and was soon adopted for off-label treatment of angiogenic eye disorders. Ex.2030, 2, 7; Ex.2031. Shortly after, in 2006, the antibody fragment Lucentis (ranibizumab) was approved for treatment of neovascular wAMD. Ex.1015, 2, 5.

29. 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 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.2055, 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 groups, while the sham treated subjects were losing a mean of -10.3 letters. Ex.1038, 1.

30. 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.1035, 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.2055, 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.1035, 1.

31. 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.2055, 3–4.

32. 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 DR and DME. The safety and efficacy of Lucentis was subsequently studied in more than 9,000 patients, across eight pivotal and 23 clinical trials. [Genentech-PR-Oct2016], 3. In 2007, the RISE and RIDE trials began enrollment to evaluate monthly Lucentis for the treatment of DME. Ex.2032, 4. The protocol comprised 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 patients who gained ≥ 15 letters in their Best Corrected Visual Acuity (BCVA) Score from baseline at month 24. Ex.2032, 8. A secondary endpoint was percentage of patients with a ≥ 3 -step worsening from baseline in the ETDRS Diabetic Retinopathy Severity Scale Score (DRSS) for eyes at months 24 and 36. Ex.2032, 8. Based on

the results from the pivotal RIDE and RISE Phase III clinical trials, Lucentis was approved for the treatment of DME in 2012 and DR in patients with DME in 2015. Ex.2033, 1–2.

33. In 2017, Lucentis was further approved for treatment of DR either with or without DME. This indication was approved based on based on the Diabetic Retinopathy Clinical Research Network's (DRCR.net) Protocol S study, a randomized, active-controlled study comparing Lucentis to panretinal or scatter photocoagulation (PRP) in 305 patients with PDR, including those with and without DME. Ex.2033, 1–2; Ex.2034; Ex.2101.

34. The Lucentis label instructs monthly injections for the treatment of AMD and DME. Ex.2034. 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 been able to get a less-frequent fixed dosing schedule approved on its Lucentis label. 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.2088, 6–7. However, each of these studies failed to demonstrate efficacy on par with that of monthly dosing with Lucentis.

35. For example, in the PIER study (2004–2007), AMD patients in the treatment groups received ranibizumab every month for three doses, followed by quarterly doses. Ex.1004, 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.1004, 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.1004, 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, it is clear why the PIER trial was regarded as “highly disappointing” and a “failure” by the investigators (Ex.2035 ¶ 22) 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.2006, 2; Ex.2007, 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.2006, 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.2004, 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 adopted into general practice before the priority date.

C. Eylea

36. 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.1050, 12.

37. In November 2011, Eylea first was approved by the FDA for the treatment of AMD. Ex.1001, 2:51-57. 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.1047, 11–13; Ex.1007; Ex.1001, 13:21–45.

38. In 2008, Regeneron began its Phase II DA VINCI trial testing aflibercept (originally referred to as VEGF-Trap-Eye) for use in DME. Ex.1045, 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.1045, 2. DA VINCI's primary endpoint was change in best corrected visual acuity (BCVA) from baseline to 24 weeks; a secondary endpoint was change from baseline to 52 weeks. Ex.2008, 4. Despite different dosing frequencies, at 24 weeks “all VEGF Trap-Eye-treated groups manifested comparable gains in visual acuity versus baseline.” Ex.1045, 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.2049, 6.

39. The Phase III VIVID and VISTA trials followed. Like DA VINCI, VIVID and VISTA included a monthly (2q4) arm. Ex.2003, 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.2003, 2.

40. 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 ten-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.2003; Ex.2010.

41. A secondary endpoint in VIVID/VISTA was proportion of eyes with a ≥ 2 step improvement in DRSS, which is a measure specific to DR. Ex.2003, 2. As explained previously in this Declaration, DR and DME are related disorders; however, improvement of DME, which affects the macula, does not necessarily result in treatment of the underlying DR, which affects the retina generally. Improvement in DRSS implies regression of the underlying diabetic retinopathy beyond the macular area. Ex.2003, 4. In the VISTA/VIVID study, significantly more

subjects in the aflibercept 2q8 arm (five initial doses followed by every 8 weeks) achieved a ≥ 2 step improvement in DRSS compared to the laser arm. Ex.2003, 6. Following the significant improvement in DRSS in DME patients shown in this study, the FDA granted additional approval on the Eylea label for “treatment of Diabetic Retinopathy (DR) in patients with Diabetic Macular Edema (DME).” Ex.2037; Ex.1050, 2, 24.

42. It is also possible for patients to have DR *without* DME. In fact, most patients with DR do not have DME. The efficacy of extended dosing with Eylea on patients with severe non-proliferative DR but without centrally involved DME was studied in a trial called PANORAMA.

43. PANORAMA’s primary endpoint was “the proportion of eyes with a 2-step or greater improvement in DRSS level from baseline to week 24... and week 52.” Ex.2092, 3. For patients receiving aflibercept at 2 mg every 8 weeks (2q8), the 52-week data showed that 79.9% of eyes achieved a 2-step or greater improvement in DRSS level. Ex.2092, 4–5, Fig. 2. This was significantly higher compared to the outcomes of the control group (“107 of 134 eyes [79.9%] in the 2q8/PRN group... vs 20 of 133 eyes [15.0%] in the control group; $P < .001$ ”). *Id.* at 3.

44. In May 2019, the FDA approved Eylea for DR (in patients with or without DME) with the results of the VIVID, VISTA, and PANORAMA studies. Ex.2038; Ex.1016.

VII. THE '601 PATENT

45. I understand that this proceeding concerns claims 10–12, 17–19, 21, 25–28, and 33 of the '601 Patent, owned by Regeneron.

46. Claim 10 of the '601 Patent covers a method of treating DME with aflibercept using a regimen of five monthly loading doses followed by doses every eight weeks. Specifically, claim 10 recites:

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

47. Claims 18 and 26 are the same as claim 10, except that claim 18 covers a method for treating “diabetic retinopathy in a patient in need thereof,” and claim 26 covers a method for treating “diabetic retinopathy in a patient with diabetic macular edema, who is in need of such treatment.”

48. I understand that Petitioner has also challenged claims 11–12, 17, 19, 21, 25, 27–28, and 33. I have reviewed these claims, but I have not been asked to

opine on whether the additional limitations stated in these claims help to make the claims non-obvious.

VIII. PETITIONER'S PRIOR ART REFERENCES

49. Petitioner's challenges to claims 10–12, 17–19, 21, 25–28, and 33 of the '601 Patent are based on three prior art references: the 2009 Press Release, Shams, and Elman 2010.

A. 2009 Press Release (Ex.1009)

50. 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.1009, 1. The 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 (PRN) 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. Shams (Ex.1010)

51. Shams is the publication of a Genentech patent application filed in 2004. Ex.1010, 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.1010, 26:6–8, 6:27–7:16, and “[t]he doses may be administered according to any time schedule which is appropriate,” Ex.1010, 22:30–31, 23:7–9. Shams claims 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” by monitoring patients. Ex.1010, 22:30–23:7.

52. 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.1010, 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.1010, 31:8–19; Ex.1004.

C. Elman 2010 (Ex.1006)

53. Elman 2010 is an article by the Diabetic Retinopathy Clinical Research Network (DRCR) disclosing a study that compared various treatments for DME. Ex.1006. The treatments included focal laser photocoagulation, the anti-VEGF agent ranibizumab, and a corticosteroid called triamcinolone. Ex.1006, 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.1006, 3. First, ranibizumab was administered every four weeks through the 12-week visit (*i.e.*, four monthly doses). Ex.1006, 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.1006, 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.1006, 3, 15–16. At the 24-week and later visits, drug was administered at investigator discretion if the study eye was deemed “no improvement,” and laser photocoagulation could be applied as well. Ex.1006, 3, 15–16.

54. 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.1006, 6 Fig. 3. Similarly, the average OCT thickness improved quickly over the first three months, and then only gradually through week 52. Ex.1006, 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 μm , and 22% of eyes in the group did not receive a fifth monthly injection. Ex.1006, 4, 10 Fig. 6. At week 20, the fraction of subjects in the deferred laser group with a central retinal thickness <250 μm had decreased slightly. Ex.1006, 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.1006, 6 Fig. 3, 35 Fig. 8.

IX. PERSON OF ORDINARY SKILL IN THE ART

55. I understand that Petitioner has proposed the following definition of a POSA:

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.14–15.

56. I have used the above definition of a POSA throughout this declaration.

57. I hold all of the above-listed qualifications and have held these qualifications since before 2011. I thus consider myself qualified to opine on the perspective of a POSA in this case.

X. CLAIM CONSTRUCTION

A. “[E]very 4 weeks for the first 5 injections followed by... every 8 weeks” refers to a predetermined dosing regimen.

58. I understand that Petitioner and Patent Owner disagree about whether the challenged claims require a predetermined dosing regimen or if they also include individualized dosing regimens that are not predetermined and happen to coincide with the claimed dosing schedule. It is my opinion based on the claims and

specification of the '601 Patent that a POSA would understand the challenged claims to be limited to predetermined fixed dosing schedules.

59. 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 their anatomical 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.

60. The descriptions of clinical trials in examples 2, 4, and 5 of the patent show the distinction between individualized 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, 8:30–60. 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 were fixed and determined prior to treatment, and any variance would be a deviation from the trial protocol.

61. The plain and ordinary meaning of the challenged claims show that the administered dosing regimen follows a predetermined, fixed schedule. “[E]very 4 weeks for the first 5 injections followed by... every 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 and number of doses in the loading phase. If a POSA were describing an individualized regimen, by contrast, they would not describe the regimen solely in terms of dosing intervals and omit information about patient assessment that defines the type of regimen. The specification of the ’601 Patent illustrates this by using different language to describe individualized regimens.

62. Consistent with this understanding, the “every x weeks” language found in the claims refers to predetermined dosing schedules when used throughout the specification of the ’601 Patent. In the specification, such language is contrasted with the language used to describe individualized dosing schedules including PRN, which are not non-predetermined. Thus, it is my opinion that a POSA would interpret the claims, with “every x weeks” language, to refer to predetermined dosing schedules.

63. The examples that describe clinical trials show this distinction. Example 2 initially dosed patients “on a fixed interval” every 4 or 12 weeks before switching to as-needed doses based on specified criteria. Ex.1001, 8:40. It is my opinion that a POSA would recognize the significance and distinction between “every x weeks” dosing and dosing based on specified retreatment criteria.

64. 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).” *Id.*, 14:18–24 (emphasis 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.

65. Example 4 also describes a predetermined, fixed dosing regimen using similar language. Patients started at “every 4 weeks” and then, for some groups, switched to “every 8 weeks.” Ex.1001, 9:58–66. In addition, Example 4 discusses a period during the trial where doses were administered “as frequently as every 4 weeks, but no less frequently than every 12 weeks.” *Id.*, 10:13–14. It is my opinion that this shows as-needed dosing bounded by predetermined fixed intervals (4 and 12 weeks respectively). Thus, it is my opinion that a POSA reading this example would understand the described dosing regimens that follow an “every x weeks” schedule to be fixed and predetermined.

66. Example 7 directly contrasts between 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).

Id., 16:7–22 (emphases added).

67. 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 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—five loading doses followed by doses every eight weeks—with an individualized regimen in which the doses at weeks 12 and 16 are administered based on assessment of the patient. *Id.*, 15:46-57 (emphases added). 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 “every x weeks” language and individualized dosing schedules using assessment or PRN language.

68. 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.” *Id.* 4:30–46. It is my opinion that a POSA would understand this contrast to be significant and recognize a distinction between individualized treatment and predetermined treatment.

69. It is my opinion that other patents that share the specification of the ’601 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 ’601 Patent. It claims dosing regimens “wherein each tertiary dose is administered on an as needed or pro re nata (PRN) basis.” *See* Ex.2040, 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 regimens. It is my opinion that a POSA would see this as further evidence that the ’601 Patent claims are drawn to predetermined, fixed dosing regimens.

70. It is my opinion that Petitioner’s proposed interpretation does not make sense in light of the specification. As I discuss above, the specification consistently

contrasts predetermined, fixed dosing regimens and dosing regimens that are based on individual patient assessment on an as-needed basis. My interpretation of the claims of the '601 Patent mirrors that first major category, that of predetermined, fixed-interval dosing regimens.

B. “[M]ethod for treating” / “effective amount”

1. The claims require efficacy comparable to monthly ranibizumab or bevacizumab

71. The independent claims of the '601 Patent recite a “method for treating” certain angiogenic eye disorders in a patient in need thereof, comprising “administering, to said patient, an effective amount” of the drug on a specific dosing regimen. I have been asked by counsel to consider the meaning of “method for treating... comprising intravitreally administering... an effective amount of aflibercept.” It is my opinion that this language, when read in the context of the '601 Patent as whole, in view of the state of the art in at the time, requires administering a treatment that was as effective as monthly Lucentis (or off-label Avastin).

72. The specification of the '601 Patent confirms my opinion. After citing to prior art dosing regimens—including a U.S. patent application (US2007/0190058) that I understand corresponds to Petitioner’s asserted Shams reference—the

'601 Patent specifically notes the remaining “need in the art for new administration regimens for angiogenic eye disorders, especially those which allow for less frequent dosing *while maintaining a high level of efficacy*.” Ex.1001, 1:61–67 (emphasis added). The specification emphasizes the “surprising[]... beneficial therapeutic effects” (*id.*, 2:11–17) achieved by extended Q8 dosing. It then explains that “one advantage of such a dosing regimen is that... it allows for less frequent dosing (*e.g.*, once every 8 weeks) compared to prior administration regimens for angiogenic eye disorders which require monthly administrations throughout the entire course of treatment,” citing to the approved monthly dosing regimen for Lucentis. *Id.*, 2:24–32; *see also, id.* at 7:30–35 (“Generally, the methods of *the present invention demonstrate efficacy* within 104 weeks of the initiation of the treatment regimen (with the initial dose administered at ‘week 0’), *e.g.*, by the end of week 16, by the end of week 24, by the end of week 32, by the end of week 40, by the end of week 48, by the end of week 56, etc.”). In addition, Example 5, a Phase II Clinical Trial treating DME patients with anti-VEGF is detailed in Example 5 of the '601 Patent discloses that patients who were administered 2 mg VEGFT monthly or every 8 weeks showed significant visual acuity gains compared to baseline. Ex.1001, 14:9–54.

73. It is my opinion that in view of at least these disclosures, a POSA reading the '601 specification would understand that the recited treatment must actually *treat* the angiogenic eye disorder, and that the goal of the invention is to maintain standard-of-care efficacy—which, by 2011, was understood to mean efficacy as good as that of monthly Lucentis (or off-label Avastin)—while extending the dosing interval.

74. In 2006, Lucentis was approved based on the positive results of the ANCHOR and MARINA trials. ANCHOR and MARINA, described in more detail in VI.B above, showed that monthly ranibizumab injections not only slowed or arrested vision loss in wAMD patients, but that treatment of wAMD with an anti-VEGF can *improve* visual acuity and sustain those improvements over time. Ex.1035, Ex.1038. The approval of Lucentis and strong visual acuity gains achieved in ANCHOR and MARINA were the main drivers of an improved standard of care for AMD in the years leading up to the priority date of the '601 Patent.

75. Researchers likewise recognized around the same time that Lucentis and Avastin would set the standard for angiogenic eye disorders in general, including DME and DR. *See* Ex.2057; Ex.2102; Ex.2104. The clinical trial endpoints for multiple studies conducted after the approval of Lucentis also reflect the expectation in the art that visual acuity gains could be achieved with anti-VEGF agents. The

RISE (Ex.2032) and RIDE (Ex.2050) studies, which were Phase III trials of the anti-VEGF agent ranibizumab (brand name Lucentis) in DME patients, measured visual acuity gains as primary outcome measures. Specifically, RISE and RIDE measured the proportion of subjects who gain at least 15 letters in BCVA at month 24 compared to baseline. This clinical endpoint reflects what a POSA around the time of the priority date regarded as a significant measure of efficacy, as the protocol was first published in 2007 with primary completion in 2009. The field's expectation for efficacy of anti-VEGF as measured by *gains* in visual acuity is also reflected in the other anti-VEGF studies around that time, *e.g.*,

- BRAVO (Ex.2051)/CRUISE (Ex.2052): measuring mean change from baseline in BCVA score at 6 months; protocol first published in 2007, with primary completion in 2009 and
- Copernicus (Ex.2053)/Galileo (Ex.2054): measuring percentage of participants who gained at least 15 letters in BCVA as measured by ETDRS Letter Score at week 24; protocol first published in 2009, with primary completion in 2012.

76. By 2011, the retinal community had moved past treatments that could simply slow progression of disease, as a treatment which could *improve* vision and maintain those gains over course of treatment now existed. Based on my

understanding of the literature and my experience as a practicing ophthalmologist at this time, monthly Lucentis and off-label Avastin set the standard for effective treatment of angiogenic eye disorders including DR and DME by January of 2011.

77. In light of the above evidence of the efficacy of Lucentis and Avastin for angiogenic eye disorders 2011, a POSA would not consider a method of treatment which did not at least achieve efficacy comparable to frequent dosing with monthly Lucentis or Avastin to be an “effective” treatment.

2. The claims require intent to treat a specific angiogenic eye disorder

78. The independent claims of the '601 Patent recite methods of treating specific angiogenic eye disorders, namely DME (claim 10) and DR (claims 18 and 26). It is my understanding that the Petitioner and Board have acknowledged that the “treating” portion of the preamble is limiting, in other words that the preamble of the Challenged Claims requires an intent to treat the angiogenic eye disorders specified in the respective claims. Paper 9, page 8.

79. I agree that the claims require an intent to treat the specific conditions recited in the challenged claims. The specification of the '601 Patent names a number of specific angiogenic eye disorders: “The methods of the present invention are useful for the treatment of angiogenic eye disorders such as *age related macular*

degeneration, diabetic retinopathy, diabetic macular edema, central retinal vein occlusion, branch retinal vein occlusion, and corneal neovascularization.”

Ex.1001, Abstract; *see*, claim 42. The independent claims then recite methods for treating specific disorders: “diabetic macular edema” (claim 10), “diabetic retinopathy” (claim 18), or “diabetic retinopathy in a patient with diabetic macular edema” (claim 26). From this claim language, a POSA would understand that the claims require, at a minimum,¹ an intent to treat not just any angiogenic eye disorder, but the specific disorder recited in each independent claim. In other words, the POSA would understand the claim term “treating diabetic macular edema” to require an intent to treat DME. Likewise, a POSA would understand “treating diabetic retinopathy” and “treating diabetic retinopathy in a patient with diabetic macular edema” to require an intent to treat diabetic retinopathy.

XI. THE FIVE LOADING-DOSE REGIMEN RECITED IN THE CHALLENGED CLAIMS IS NOT OBVIOUS

80. It is my opinion that the recited dosing regimen in the '601 Patent would not have been obvious to a POSA based on the 2009 Press Release either alone or

¹ As explained in X.B.1 above, it is my opinion that the Challenged Claims require not only an intent to treat, but also that the recited methods actually treat the recited disorders.

together with Shams (“Ground 2” in the Petition) or based on the 2009 Press Release with Elman 2010 (“Ground 3” in the Petition).

81. Petitioner and Dr. Chaum contend that a POSA would arrive at the recited dosing regimen 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 predetermined regimen of three monthly loading doses followed by maintenance doses every eight weeks. The claims require a predetermined 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 on a predetermined basis and not based on individual patient assessments during the course of treatment.

82. I disagree with the suggestion by Petitioner and Dr. Chaum, Ex.1002 ¶ 152, that a POSA would arrive at the claimed dosing regimen by adding just one dose to the DA VINCI 2q8 regimen. 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).

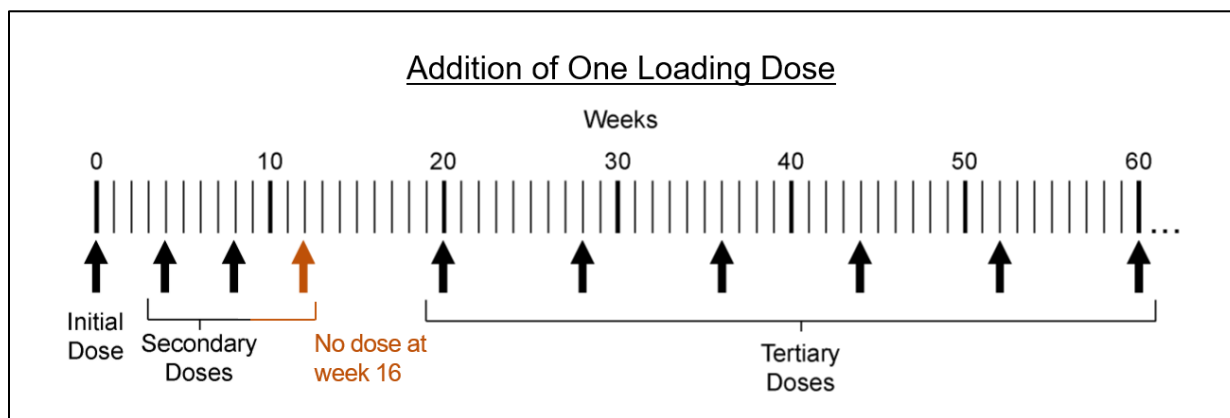


Figure 2: Illustration of adding one loading dose to the DA VINCI 2q8 arm.

A. The dosing regimen recited in the '601 claims is not obvious over the 2009 Press Release alone or in view of Shams

83. Dr. Chaum explains a POSA would be motivated to optimize the aflibercept dosing regimen “for efficaciously treating DME with aflibercept, while minimizing the number of injections so as to minimize potential complications from repeated intravitreal injections.” Ex.1002 ¶¶ 148–149, 155 (citing Ex.1010, 2). Petitioner and Dr. Chaum argue that the POSA having such motivation would modify the 2q8 dosing regimen disclosed in the 2009 Press Release to include five monthly loading doses for at least some patients. I disagree. First, nothing in the 2009 Press Release or Shams would teach or suggest increasing the number of loading doses in the 2q8 regimen from three to five. Both teach no more than three

loading doses, and in any event, a POSA would consider Shams to be a flawed and unreliable source. Second, a POSA would not arrive at the claimed regimen through routine optimization or routine adjustments.

1. The 2009 Press Release and Shams do not teach toward five loading doses.

84. It is my opinion that neither the 2009 Press Release nor Shams would lead a POSA toward a dosing regimen with five monthly loading doses, as claimed in the '601 Patent. Neither reference explicitly discloses five loading doses. The 2009 Press release does not include any data or explanation for how a POSA would choose the number of loading doses. And Shams includes broad, contradictory assertions that would not assist a POSA in choosing the appropriate number of loading doses. If a POSA would look to these references at all for guidance on the appropriate number of loading doses, it is my opinion that the 2009 Press Release guides a POSA towards three loading doses and Shams guides a POSA towards three or fewer loading doses.

a) The 2009 Press Release does not teach or suggest more loading doses

85. 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 to teach a POSA how the regimens might need to be modified.

86. 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.1009. 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.

87. 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.1009. The monthly dosing arm does not involve a maintenance phase teach a loading 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 the 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.

88. Dr. Chaum asserts that a POSA would consider adding loading doses to ensure sufficient drying of the retina. Ex.1002 ¶¶ 150–151, 153. The 2009 Press Release includes no data indicating whether three doses was enough to dry the subjects' retinas, so it cannot show that patients would benefit from more than three loading doses.

b) Shams does not teach or suggest more loading doses

89. 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 ¶ 154. 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.

90. 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.1010, 26:6–8. Shams also discloses that “[t]he doses may be administered according to any time schedule which is appropriate...” Ex.1010, 22:30–31. Disclosures such as these provide no guidance on how to select and implement a dosing regimen.

91. 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.1010, 22:31–34. A POSA would understand such administration to be completely unnecessary, risky, and burdensome.

92. 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.1010, 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 monthly loading doses followed by quarterly dosing. Ex.1010, 31:8–11, Fig. 2.

93. Shams focuses on the PIER trial, although I understand that Shams was written before the first readouts from the PIER trial in 2006. Ex.1010, 1; Ex.2035 ¶ 22. 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 quickly, but very little information was available about what would happen if Lucentis were dosed less frequently after AMD symptoms had been alleviated. Ex.1010, 1; *see* Ex.2035, ¶¶ 13–15, 21. 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.2035, ¶ 21; *e.g.*, Ex.1010, 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.2035, ¶¶ 30, 22–28. 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.1010, 22:34–23:2.

94. 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.1010, 23:13–16. 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.

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

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

96. Shams teaches the use of “any time schedule,” which could conceivably include including any number of loading doses and expressly includes any interval from daily to quarterly for loading and maintenance dosing. Ex.1010, 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 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.

97. The DA VINCI trial PRN arm encompasses hundreds of possible dosing schedules. At any monthly visit after the first three, 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.

98. 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.

99. The 2009 Press Release and Shams could offer no more than general guidance as to which of many possible dosing regimens to try, so they do not render the claimed regimen obvious.

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

100. Petitioner and Dr. Chaum assert that the POSA would be motivated to optimize the dosing regimen “for efficaciously treating DME with aflibercept, while minimizing the number of injections so as to minimize potential complications from repeated intravitreal injections.” Ex.1002 ¶¶ 148–149, 155. They assert that such optimization could be accomplished through the POSA’s “routine adjustments” to the dosing schedule. Pet. 36–39.

a) The prior art does not disclose a range over which to optimize

101. 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 ¶¶ 148–153. 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.

102. As discussed in XI.A.1.a) above, the 2009 Press Release teaches only three loading doses. I understand that Petitioner has suggested in passing that the 2009 Press Release discloses a regimen with six monthly loading doses. Pet. 26. This

is incorrect. The 2009 Press Release discloses the COPERNICUS and GALILEO trials in Central Retinal Vein Occlusion (CRVO), in which subjects received six monthly doses. A POSA would understand that these trials tested a monthly dosing regimen because the primary endpoint was improvement in visual acuity at six months. Ex.1009, 1. The Eylea label accordingly recommends monthly dosing for CRVO, based on the six-month results of the COPERNICUS and GALILEO trials *see* Ex.1050, 2, 17–19. Subjects were dosed on a PRN basis after six months, that does not mean Regeneron was investigating whether six would be an appropriate number of loading doses before switching to PRN. Rather, a POSA would believe that, consistent with common practice in anti-VEGF clinical trials, Regeneron switched to PRN dosing after assessing the primary endpoints as a cost-saving measure. Further, the appropriate number of loading doses varies by condition, and a POSA would not assume that the number of monthly doses investigated for CRVO would be the right number for DR or DME.

103. As discussed in XI.A.1.b) above, Shams discloses a narrow range for the number of loading doses: “one, two or three.” Ex.1010, 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.

104. Any broader statements in Shams are also not disclosures of 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.1010, 22:30–31. Setting aside the fact that a POSA would not credit Shams’s generalizations for the reasons discussed in XI.A.1.b) 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. *See* XII.A.1.c). 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 ¶¶ 148–149. 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.

b) Petitioner does not show that five loading doses is optimal as a *predetermined* regimen

105. 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 ¶¶ 150–151, 157. The claims, as discussed in X.A, refer to predetermined, fixed dosing regimens, and thus no individualized approach would lead to a predetermined fixed five-loading dose regimen.

106. Even if the evidence did show that five loading doses would be an optimal number for some fraction of patients, that information would not be enough to show 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.

107. 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 that could be identified in advance of treatment. There was no consensus among physicians in 2011 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.

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

108. The 2009 Press Release discusses a clinical trial that would compare monthly dosing, PRN dosing, and 2q8 dosing. Ex.1009. 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 ¶¶ 148–149, then they would not expect to achieve this objective using fixed extended dosing.

109. Until Regeneron announced the successful results of its VIEW trial, no fixed extended dosing regimen of a VEGF agent had been shown to be effective to maintain a 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.” A POSA would have considered fixed extended dosing to provide far less certainty of success achieving these objectives in light of prior art failures, especially the PIER trial.

110. 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.1038, 8 Fig. 2A.

111. 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.

112. Some less-frequent dosing regimens for Lucentis had been tested in clinical trials by 2011. These trials include SUSTAIN, EXCITE, SAILOR, and PIER, none of which demonstrated efficacy on par with monthly Lucentis. *See* Ex.2088, 6–7; Ex.1004.

113. Moreover, if an anti-VEGF drug were to be administered less often than monthly, then a POSA would expect an individualized regimen, rather than a fixed regimen to meet the objective stated by Dr. Chaum to “minimiz[e] the number of injections.” 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.

114. The SUSTAIN trial was designed to evaluate the safety and efficacy of individualized ranibizumab treatment for patients with AMD. Ex.2042. Subjects received three monthly doses followed by PRN dosing. Ex.2042, 1. Patients would receive a maintenance dose if they had either lost visual acuity or had experienced

an increase in retinal thickness. Ex.2042, 1–2. From months 3 to 11, patients received on average of 2.7 doses. Ex.2042, 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.2042, 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.1004, 5 Fig. 1; Ex.2041; Ex.2042.

115. 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 '601 Patent for the purposes Dr. Chaum identifies.

B. The recited dosing regimen is not obvious over the 2009 Press Release in view of Elman 2010.

116. It is my opinion that the recited dosing regimen in the '601 Patent would not have been obvious to a POSA based on the 2009 Press Release either alone or in further view of Elman 2010. Elman 2010 does not teach toward five loading doses, and a POSA would not be motivated to combine monthly doses in Elman 2010 with the 2q8 dosing regimen disclosed in the 2009 Press Release.

1. Elman 2010 does not teach toward five loading doses

117. 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 the challenged claims of the '601 Patent, which recite five fixed monthly loading doses, followed by fixed eight-week maintenance dosing. Contrary to the Petitioner's assertion that Elman 2010 discloses "the use of five initial loading doses," 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

118. The Petitioner argues that Elman 2010 "strongly suggests the use of five initial monthly loading doses, at least for some patients." Pet. 42. I see no reasonable basis for this assertion.

119. 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.1006, 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....” 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 loading dose according to the Elman 2010 protocol was **not** predetermined and was instead 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 loading 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 loading doses after the fourth based on patient assessments. This is in direct contrast to the fixed regimen

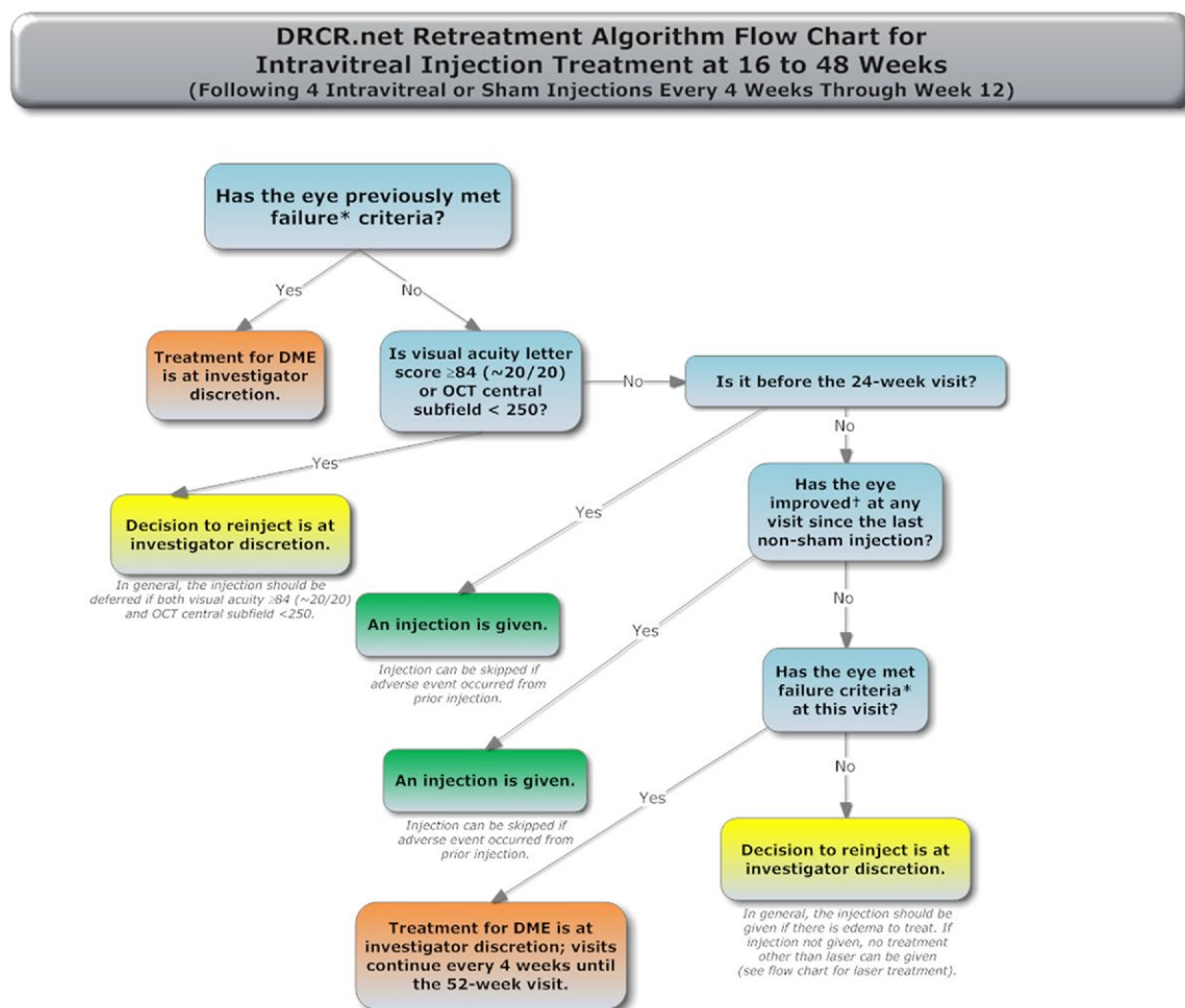
of the challenged claims, in which all patients receive five monthly loading doses followed by another fixed maintenance dosing regimen.

120. 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 dosing regimen, never mind a fixed dosing regimen with five loading doses.

b) Elman's protocol does not teach five loading doses

121. The 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,” in order to argue that this means “at least 78% of patients receiv[ed] a fifth initial monthly dose[] (*i.e.* an injection at the fifth visit).” Ex.1006, 4; Pet. 26. 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 in fact the Elman 2010 protocol makes this possibility unlikely for reasons explained below. To the contrary, the retreatment protocol made it far more likely that patients would have received at least six initial doses.

122. In order to receive exactly five loading doses, a patient must receive a dose at weeks 0, 4, 8, 12, 16, but **not** week 20 and onward. As explained previously in ¶99, 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, wherein “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.1006, 3, 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.1006, 4. In my own practice, I use $325\text{--}350$ 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.1006, 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.1006, 16.

123. 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 ranibizimab + deferred laser arm, between weeks 16 and 20. Ex.1006, 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.1006, 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 was unlikely that subjects would have received a dose at week 16 but not 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. *See*, Figure 4Fig.2; Ex.1006, 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.

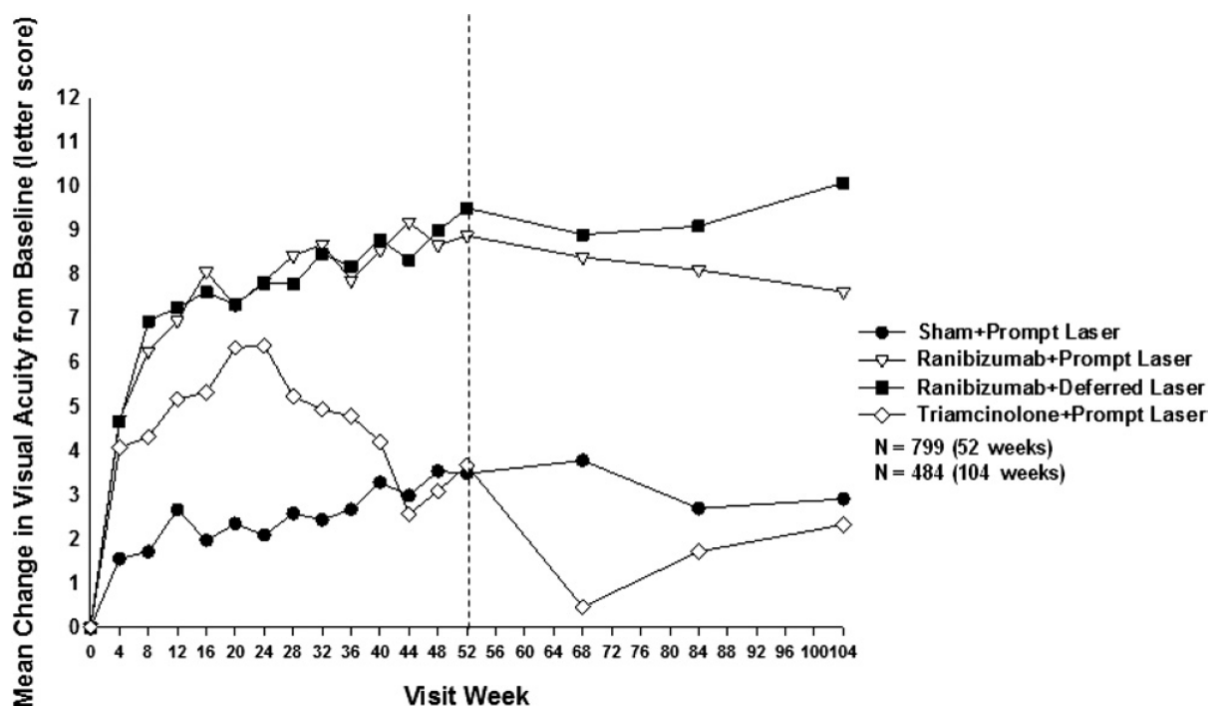


Figure 4: Mean change in visual acuity at follow-up visits. Ex.1006, 6, Fig. 3.

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

124. The Petitioner argues that Elman 2010 would have taught a POSA toward five loading doses, 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 ¶¶ 151–152. However, not only does Elman 2010 not disclose or suggest using exactly five loading doses, the results reported in Elman 2010 also does not suggest any benefit to administering using exactly five loading

doses for drying the retina. Figure 6 of this report (Ex.1006, 6, Fig.3) 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.

125. 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.

126. The Petitioners assert that Elman 2010 “strongly suggests the use of five initial loading doses, *at least for some patients.*” Pet. 42. 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.1006, 6 Fig. 3, 35 Fig. 8.

127. 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.1006, 10, Fig. 6. However, only 22% of this arm did not receive an injection. *Id.*, 4.

128. 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 ¶¶ 151–152.

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

129. 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 doses every eight weeks.

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

130. While Dr. Chaum's point that a POSA would have been motivated to "look to dosing regimens of ranibizumab to treat DME—where that dosing regimen has already proved efficacious in treating DME" is reasonable, dosing regimens of ranibizumab 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 other anti-VEGF treatments.

131. 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. Firstly, 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 aflibercept 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.1016, 20. Ranibizumab has a molecular weight of approximately 48 kDa. Ex.1015, 5. Given that 1 kDa = 1.66×10^{-18} mg, 1 molecule of aflibercept is equivalent to 1.61×10^{-16} mg while 1 molecule of Lucentis is equivalent to 7.97×10^{-17} . Therefore, in 2 mg of aflibercept, there are $\frac{1 \text{ molecule}}{1.61 \times 10^{-16} \text{ mg}} \times 2 \text{ mg} = 1.24 \times 10^{16}$ 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 much as 0.5 mg of ranibizumab.

132. Secondly, a POSA would know from Dixon *et al.* (Ex.1008) 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.1008, 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.

b) Elman 2010 itself would not motivate a POSA to combine five loading doses with a fixed extended regimen

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

134. For one, a patient in the Elman study who has received five fixed 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 previously in IX.B.2.b, 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.1006, 20. 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.1006, 11.

135. The Petitioner argues that “[w]hile Elman 2010 does not specifically report how many patients received an injection at the sixth visit, it does report 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).’” Pet. 26. The Petitioner seems to suggest that the nine median doses make it 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 nine median 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.

136. For one, the Petitioner points to the median of nine total doses over one year in the ranibizumab + deferred laser arm but, contradictorily, contends that it is the subgroup of 78% of subjects who received a dose at week 16 that is relevant: “This means that Elman 2010 teaches both that at least 78% of patients received a fifth dose and, if the median is applied to those 78% of patients they received only four additional doses out of the eight possible doses remaining after their fifth injection.” Pet. 26; Ex.1006, 4. But the median reported in Elman 2010 of nine for the whole arm cannot be applied to the subgroup. Elman 2010 gives no indication that the median of the whole ranibizumab + deferred laser arm is the same as the subgroup of 78% of subjects who received a dose at week 16, and 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.

137. Secondly, regardless of the actual median of the subgroup of interest, it cannot be assumed that a patient who received nine doses received 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. This nine-dose regimen is consistent with the Elman protocol and yet does not meet the requirements of 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 does not suggest that her treatment regimen met the requirement of the '601 claims, *i.e.*, five, and exactly five, initial monthly loading doses. And a POSA experienced with individualized dosing regimens would expect that subjects who had responded well to anti-VEGF treatment in the loading phase could then go longer than average without such a recurrence, meaning they would receive fewer than the average number of total doses.

138. Furthermore, putting aside the fact that Elman 2010 does not disclose a single patient who 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 necessitate that the patient would receive any doses on an eight-week interval. 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 subsequently to the loading doses, as the challenged claims require.

139. 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.

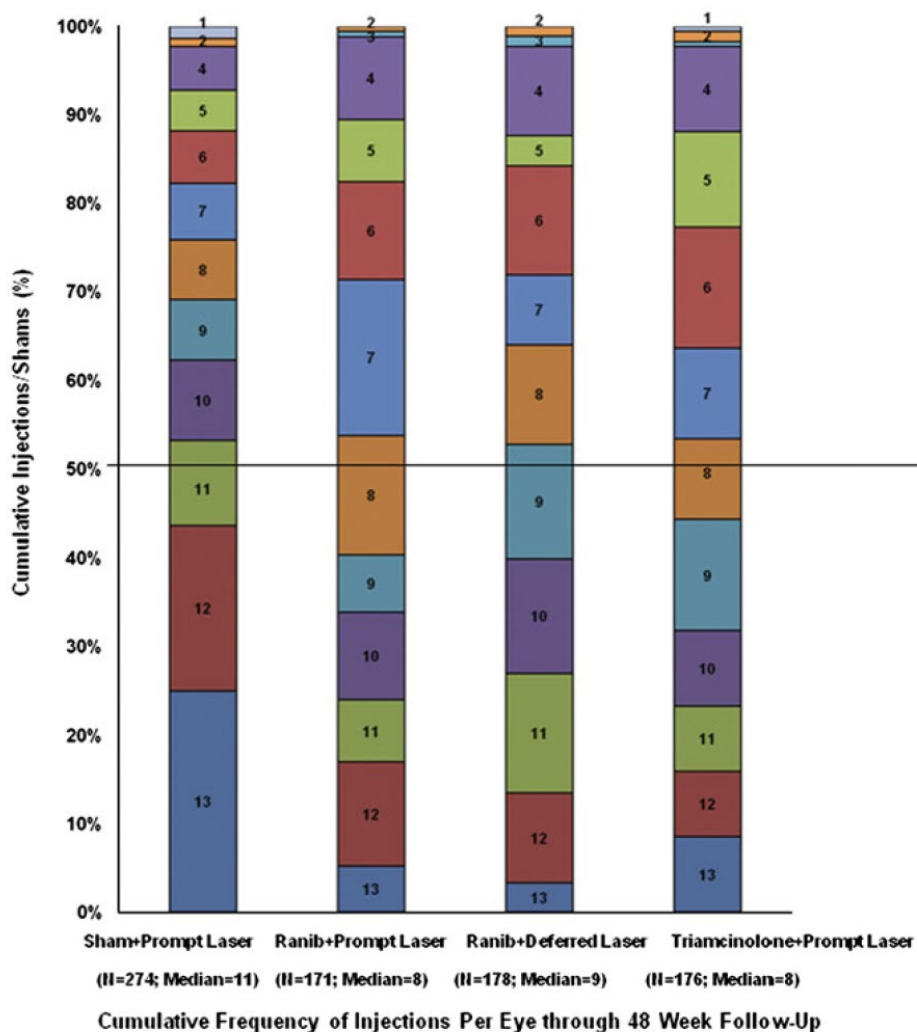


Figure 5: Cumulative distribution of injections/sham with randomized assigned treatment before the 52-week study visit. Ex.1006, 28, Fig. 2.

140. 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.

141. 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.

c) The prior art does not provide motivation to add loading doses to the 2q8 regimen

142. Nothing in the 2009 Press Release or Elman 2010 would motivate a POSA to add additional loading doses beyond the three in the 2009 Press Release. The 2009 Press Release does not include any data at all for any of the arms it discloses. In Elman 2010, the data does not show that initial monthly doses beyond three were helpful, as discussed above in XI.B.1.c). 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.1006, 7.

143. The Petitioner cites to post-priority date articles Heier 2011 (Ex.1005) and Heier 2012 (Ex.1007), 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...’” Pet. 43-44. Heier 2011 describes the results of CLEAR-IT2, 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.” *Id.*, 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.

144. 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). Petitioner and Dr. Chaum do 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.

145. 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 the '601 claims. 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.

146. 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.

147. 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.

148. 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, would not reach the dosing regimen recited in the '601 Patent.

XII. THE PRIOR ART DOES NOT DISCLOSE THE REQUIRED EFFICACY.

149. As discussed in X.B.1, the claims require a level of efficacy comparable to the standard of care in 2011. It is my opinion that none of the prior art references discloses or renders obvious achieving this level of efficacy with the aflibercept dosing regimen recited in the claims. For example, several of the references do not disclose any data or results and so a POSA would not be able to determine the level of efficacy from their disclosures. For those references that do disclose results data, the references involve different drugs, targeted diseases, and dosing regimens and

thus do not provide any insight on the efficacy of the specific regimen claimed in the '601 Patent.

A. 2009 Press Release

150. It is my opinion that the 2009 Press Release does not disclose anything that would lead a POSA to believe that the dosing regimen as claimed in the '601 Patent would achieve a level of efficacy comparable to the standard of care for angiogenic eye disorders in 2011. Nothing in the 2009 Press Release discloses data, results, or any other indication that any arms of the trial would be efficacious.

151. Further, the 2009 Press Release could not have disclosed such information, as there were not yet any results associated with the DA VINCI trial. As Dr. Chaum states, the “2009 Press Release teaches that Regeneron was beginning clinical trials studying the efficacy of aflibercept to treat DME via three different dosing regimens for 2 mg VEGF Trap-Eye.” Ex.1002, ¶ 147. That Regeneron was “beginning clinical trials” with multiple does not show that any one regimen would be effective.

152. Further, the 2009 Press Release notes that “[t]he primary efficacy endpoint evaluation is mean improvement in visual acuity at six months.” Ex.1009, 1. The 2009 Press Release itself could not report whether the dosing arms would reach that efficacy endpoint, as the initial data would not be available until at least

the first half of 2010. Ex.1009, 1. It is my opinion that a POSA would not have relied on the 2009 Press Release for the effectiveness of the DA VINCI trial.

153. And as discussed in XI.A.1.a) above, the 2009 Press Release does not even disclose the same regimen ultimately claimed in the '601 Patent, and so has even less bearing on whether the claimed regimen would be effective. It is my opinion that nothing in the 2009 Press Release guarantees that any of the arms would be efficacious, let alone the claimed dosing regimen.

154. Dr. Chaum further opines that since the 2009 Press Release includes other dosing regimens, a POSA would have a reasonable expectation of success for dosing regimens with more loading doses. Ex.1002, ¶ 148. But in the short section discussing the DA VINCI trial, there is no disclosure that would give a POSA an expectation that other dosing regimens would achieve a high level of efficacy. The 2009 Press Release discloses no data, no indication of efficacy, and no encouragement to try other numbers of loading doses. Thus, it is my opinion that a POSA would not glean any expectation of the effectiveness of the dosing regimen in the '601 Patent from the 2009 Press Release.

B. Shams

155. Shams also does not give a POSA any indication that the claimed dosing regimens would show a high level of efficacy. Shams focuses on the use of

Ranibizumab to treat AMD and so does not disclose any information regarding the efficacy of aflibercept to treat DME.

156. Shams discusses efficacy in broad terms but does not describe any results to show that the regimens it discloses achieve that efficacy. Shams refers to an “effective amount” as the amount that “can reduce or prevent vision loss.” Ex.1010, 20:19-21. Shams also describes how efficacy can be assessed for a trial testing ranibizumab, but nowhere does Shams disclose results or show actual efficacy from that trial. Thus, it is my opinion that a POSA would not find the efficacy limitation of the ’601 Patent obvious based on any disclosure in Shams.

C. Elman 2010

157. Elman 2010 does not disclose to a POSA that the claimed dosing regimens would show a high level of efficacy. Elman 2010 focuses on the use of Ranibizumab and so does not disclose any information regarding the efficacy of aflibercept to treat DME.

158. Further, Elman 2010 discloses a treatment algorithm that can, and did, lead to subjects receiving ranibizumab injections on widely varying schedules. *See* Ex.1006, 28, Fig. 2. The efficacy data in Elman 2010 lumps all these dosing schedules together and thus does not inform a POSA of the efficacy of any particular dosing schedule, let alone the schedule recited in the claims.

D. PIER

159. I understand that Petitioner has asserted that some claims of the '601 Patent are obvious over a combination of references including the PIER trial publication (Ex.1004). The PIER publication does not disclose the required efficacy and instead discloses a *lack* of efficacy using a fixed extended dosing regimen. Patients in the treatment arm gained visual acuity during the first three monthly injections but then lost all visual acuity gains after moving to fixed quarterly maintenance dosing. Ex.1004, 5 Fig. 1.

E. CATT

160. I understand that Petitioner has asserted that some claims of the '601 Patent are obvious over a combination of references including the CATT trial exclusion criteria (Ex.1018). The CATT publication does not disclose the required efficacy because it does not disclose any efficacy information for any dosing regimen.

XIII. THE PRIOR ART DOES NOT DISCLOSE INTENT TO TREAT DIABETIC RETINOPATHY.

161. As discussed in X.B.2, claims 18 and 26 require an intent to treat DR. It is my opinion that that nothing in the 2009 Press Release shows intent to treat DR. Instead, the 2009 Press Release was focused on treatment of DME in the DA VINCI

trial. Petitioner and Dr. Chaum assert that an intent to treat DME counts as intent to treat DR, but this assertion is out of line with the approved Eylea labels and other evidence.

A. DR and DME are defined and measured differently.

162. The '601 Patent, Eylea label, and Lucentis label all distinguish between DR and DME. The '601 Patent lists DR and DME as separate angiogenic eye disorders and includes separate sets of claims drawn to each condition. Ex.1001. The Eylea and Lucentis labels list the conditions as separate indications and provide separate clinical trial data supporting the different indications. Ex.2034; Ex.1050; Ex.1016.

163. The distinction reflects differences in the definition and assessment of DR and DME. As explained in section VI.A, DR is characterized by abnormalities in the retinal microvasculature causing hemorrhages and abnormal blood vessel configurations, whereas DME is characterized leaking blood vessels causing a fluid buildup in the macula. Ex.2089, 6, Table 2; Ex.1001, 1:41–45.

164. Composite scores such as the DRSS are measures specific to DR. The DRSS considers the size and number of retinal abnormalities such as microaneurysms, hemorrhages, and venous beading in the microvasculature. Unlike previous assessment methods used, the DRSS provides an overall severity scale and

corresponds to risk of progression to visual loss. Ex.2091, 1. To this day, the DRSS continues to be used as an important endpoint for measuring DR in studies such as PANORAMA (Ex.2092, 2) and VIVID/VISTA (Ex.2003, 6). Though simplified classifications are used in clinical practice, measures for DR take into account these retinal abnormalities.

165. On the other hand, retinal thickness and area of thickening can be used to assess DME severity. Ex.2093, 1-2. DME is not included in the DRSS classification. Ex.2091, 8.

166. Tables 2 and 3 of Ex.2089 are reproduced as **Figure 6** below to directly compare the different scales used to measure DR and DME. Whereas microaneurysms, hemorrhages, and venous beading are used to measure the severity of DR, they are not taken into account at all for DME. The reverse is true. The severity of DME is based on retinal thickening and hard exudes in the macula, which are not included in the DR scale. DME is not part of this assessment or scale for DR.

Table 2—*International Clinical Diabetic Retinopathy Disease Severity Scale (ref. 63)*

Proposed disease severity level	Findings observable upon dilated ophthalmoscopy
No apparent retinopathy	No abnormalities
Mild NPDR	Microaneurysms only
Moderate NPDR	More than just microaneurysms but less than severe NPDR
Severe NPDR	Any of the following: >20 intraretinal hemorrhages in each of 4 quadrants Definite venous beading in 2+ quadrants Prominent intraretinal microvascular abnormalities in 1+ quadrant
PDR	And no signs of proliferative retinopathy One or more of the following: Neovascularization Vitreous/preretinal hemorrhage

Table 3—*International Clinical Diabetic Macular Edema Disease Severity Scale (ref. 63)*

Proposed disease severity level	Findings observable upon dilated ophthalmoscopy*
DME apparently absent	No apparent retinal thickening or hard exudates in posterior pole
DME apparently present	Some apparent retinal thickening or hard exudates in posterior pole
DME present	Mild DME (some retinal thickening or hard exudates in posterior pole but distant from the center of the macula) Moderate DME (retinal thickening or hard exudates approaching the center of the macula but not involving the center) Severe DME (retinal thickening or hard exudates involving the center of the macula)

*Hard exudates are a sign of current or previous macular edema. DME is defined as retinal thickening requiring a three-dimensional assessment that is best performed by a dilated examination using slit-lamp biomicroscopy and/or stereo fundus photography.

Figure 6: DR and DME severity classifications. Ex.2089, 6, Tables 2 and 3.

167. Though DME and DR are related disorders, DME can occur at any stage of DR, and DME is not a part of the definition of DR in clinical trials or clinical practice.

168. Recognizing the distinction between the two conditions, physicians can and do administer anti-VEGF agents for the purpose of treating DME rather than DR in patients who have both conditions. DME is an immediately vision-threatening condition, whereas DR in its early stages has less of an impact on vision. So, in a patient with DME and DR, the highest priority is treating the DME, and a physician may not be concerned with whether the patient's DR is treated as well.

B. The 2009 Press Release does not disclose any indication of intent to treat DR.

169. The 2009 Press Release does not mention DR at all, let alone suggest an intent to treat DR. The 2009 Press Release also does not mention any endpoint that is specific to DR, such as DRSS. Instead, the Press Release discloses that “VEGF Trap-Eye is also in Phase 2 development for the treatment of Diabetic Macular Edema (DME).” Ex.1009, 1. As explained previously in section VI.A, DME and DR are related but distinct angiogenic disorders. This statement in the 2009 Press Release would tell a POSA that the investigators were studying VEGF Trap-Eye for DME, *i.e.* fluid buildup in the macula, but it does not say anything

about the investigators' interest in treating treat the various retinal microvascular abnormalities that define DR.

170. The 2009 Press Release also discloses that the Phase 2 DME trial included a focal laser treatment comparator arm. Ex.1009, 1. Focal laser treatment, which involves intensive laser on or near the macula, is not typically used to treat DR, so it would not be meaningful as a comparator arm in a trial with any intent to treat DR. Meanwhile, focal laser treatment had long been a standard treatment for DME. Elman 2010 teaches that “focal/grid laser has been the mainstay of treatment for DME during the past 25 years.” Ex.1006, 13. Ex.2094 describes a foundational study “to assess the effect of timing of photocoagulation.” Ex.2094, 2. The laser treatment strategies tested immediate focal photocoagulation in patients with DME and deferral of photocoagulation once DME presented in patients who did not have DME. *Id.*, 3-4. The study concluded that “focal photocoagulation should be considered for all eyes with clinically significant macular edema.” *Id.*, 19. On other hand, “[f]or eyes without macular edema,” *i.e.*, patients with DR but no DME, “neither of the strategies for early photocoagulation... was better than deferral of photocoagulation for preventing either moderate or severe visual loss....” *Id.*, 17.

171. Another layer of the study was that it tested for the difference in treatment with scatter laser treatment and focal laser treatment. *Id.*, 3–4. Ex.2094

details the difference in size and placement of the burns in focal vs. scatter photocoagulation: scatter laser treatment uses larger laser spots (up to 500 μm in diameter) with placement >2 disc diameters (or about 3 mm) from the fovea (depression in the very center of the macula), whereas focal laser uses smaller spots (<200 μm in diameter) placed 500–3000 μm from the center of the fovea. *Id.*, 4. This reflects an important distinction between DME, which primarily affects the macula, and DR, which affects the peripheral retina. The DRS graded macular edema based on having retinal thickening within 1 disc diameter (approximately 1.5 mm) of the center of the macula or hard exudates within a 30-degree photographic field centered on the macula, which is called “field 2.” Ex.2091, 2. In the photographic field numbering system, which is used by clinicians to describe areas of the eye, the higher field number indicates farther distance from the macula. The DRS graded DR based on the on the presence of abnormalities in fields 3–7 or 4–7. Fields 4–7 are peripheral fields that do not encompass the fovea. Ex.2091, 2–5. As such, scatter laser treatment, which is positioned further out from the center of the macula, spares the macula from direct treatment-related damage, would be more suitable for DR, and is used for PDR and severe non-proliferative DR. The study described in Ex.2094 found that while scatter photocoagulation provided more harm than benefit when administered in early non-nonproliferative DR, “[a]s retinopathy approaches

the high-risk stage (very severe nonproliferative retinopathy...), the benefits and risks of early photocoagulation may be roughly balanced.” Ex.2094, 19.

172. As such, a POSA would recognize that while focal laser treatment would be a meaningful comparator arm to use in a clinical trial studying the efficacy of aflibercept treatment on DME, it would not be very relevant as a comparison against established therapies for DR, as focal laser treatment is not a standard of care therapy used alone to treat DR.

C. Treating DME is not tantamount to treating DR.

173. I disagree with the Petitioner and Dr. Chaum’s assertions that intent to treat DME satisfies the claim requirement of intent to treat DR. Though it is true that DME is a complication of DR, it would be inaccurate to assume that “treating DME was a way to address the underlying DR” and “the effectiveness of a treatment for DME is directly linked to its effectiveness for DR.” (Ex.1002 ¶¶ 138, 143–144). These statements are wrong because they imply that a therapy is a treatment for DR merely because it is a treatment for DME, regardless of whether the treatment addresses or is intended to address the underlying DR.

174. Treatment of a single complication, “symptom” or “manifestation” of a disease is not always considered treatment of the disease. This notion is supported by the FDA’s regulation published in 2010 governing indications and usage section

of a label, which distinguishes between “the treatment... of a recognized disease or condition,” and the treatment “of a manifestation of a recognized disease or condition, or for the relief of symptoms associated with a recognized disease or condition.” 21 CFR § 201.57(c)(2) (2010). Furthermore, the FDA has expanded on this position in its draft guidance for industry for “Indications and Usage Section of Labeling for Human Prescription Drug and Biological Products,” where the guidance discusses that “[i]n some cases [] a broad disease indication may not be appropriate because, for example, the drug may affect only certain signs, symptoms, or manifestations of the disease.” Ex.2096, 17. It is clear from the distinction that the FDA makes between treating a disease and certain “symptoms” or “manifestations” of the disease that the two are not one and the same.

175. In fact, the Eylea label includes separate indications for DR and DME. In particular, the Eylea label approved in 2015 has a separate indication for treatment of patients with “Diabetic Macular Edema” and “Diabetic Retinopathy (DR) in Patients with DME.” Ex.1050, 2. The indication for treating DR in patients with DME references DR-specific data from the VIVID/VISTA studies showing number of patients (%) with a ≥ 2 -step improvement on the ETDRS-DRSS from baseline. If simply treating DME were tantamount to treating DR, then there would be no cause to distinguish these as two separate indications on the label and even less cause to

point to DR-specific data to support efficacy and approval. In the current label, the DR indication is supported not just by DR-specific DRSS data but also by a DR-specific trial, PANORAMA, in which subjects did not have center-involved DME. Ex.1016, 34-36. This further supports my understanding that “treatment of Diabetic Retinopathy” in the label refers to treatment of the underlying DR and not to treating just DME.

176. It is true that some therapies, including anti-VEGF drugs, have turned out to be effective for both DME and DR. But other DME therapies, such as focal laser photocoagulation, are not considered effective for DR and would typically not be administered with the intent to treat DR.

177. A POSA would have understood DME and DR as two related but distinct angiogenic eye disorders and would not consider intent to treat DME to be tantamount to intent to treat the underlying DR. Accordingly, the 2009 Press Release, which focuses on DME, does not suggest or indicate an intent to treat DR with the disclosed VEGF Trap-Eye dosing regimens.

XIV. COMMERCIAL SUCCESS

178. I understand that when considering obviousness, the commercial success of a patented product can be an indicator that the claims are less 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 the claims of the '601 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. Doctors regularly use Eylea to treat angiogenic eye disorders including DME, DR, and DR in patients with DME. One difficulty that doctors frequently face with these diseases is the hardship of maintaining a regular injection schedule. The '601 Patent, as embodied by Eylea, directly relates to such treatment, and 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 '601 Patent. By the time Eylea was first approved in 2011, Regeneron's VIEW and DA VINCI trials had demonstrated that Eylea administered on a q8 dosing interval could treat angiogenic eye disorders with efficacy comparable to monthly ranibizumab. The later VIVID, VISTA, and PANORAMA trials tested the specific regimen of five loading doses followed by doses every eight weeks that is claimed in the '601 Patent, and these trials and showed effective treatment of DR, DME, and DR in patients with DME using that regimen. Ex.2003; Ex.2092.

182. The FDA-approved label for Eylea includes indications for DR and DME and recommends using the dosing regimens claimed in the '601 Patent for these conditions. The current labeling instructs:

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

The recommended dose for EYLEA is 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months).

Ex.1016, 1. From 2012 to 2017, the DR indication of the Eylea label was limited to DR in patients with DME. The label instructed as follows:

2.5 Diabetic Retinopathy (DR) in Patients with DME

The recommended dose for EYLEA is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (monthly) for the first 5 injections, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months). ...

Ex.1050, 3.

183. The Eylea label shows the connection between the success of the VIVID, VISTA, and PANORAMA trials and the recommended dosing regimens for DR and DME. Sections 14.4 and 14.5 of the label report data from the VIVID, VISTA, and PANORAMA trials demonstrating the efficacy of the recommended regimen for DME and DR. Ex.1016, 30–36. Before 2017, section 14.5 supported the “Diabetic Retinopathy (DR) in Patients with DME” indication with data from the VIVID and VISTA trials. Ex.1050, 24.

184. The wide adoption of Eylea for DR, DME, and DR in patients with DME is based on the success of the dosing regimen claimed in the '601 Patent. DR and DME patients need efficacious treatment for their conditions and prefer longer intervals between treatment. Physicians choose Eylea to satisfy this patient preference because of the efficacy achieved in the VIVID, VISTA, and PANORAMA trials using the dosing regimen claimed in the '601 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.2084, 84; Ex.2085, 73.

185. Therefore, it is my opinion that Eylea embodies the claim limitations in the '601 Patent. The claimed features, including the dosing amount, dosing regimen, and disease indications, have all contributed to Eylea's medical success and adoption by physicians.

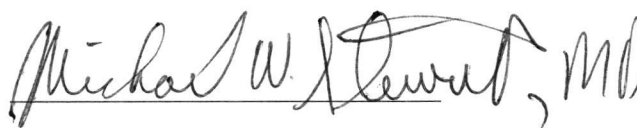
B. Commercial success of Eylea

186. 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.

IPR2023-00739

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: 1/25/2024

A handwritten signature in black ink that reads "Michael W. Stewart, MD". The signature is written in a cursive style with a horizontal line underneath the name.

Michael W. Stewart, M.D.