

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SAMSUNG BIOEPIS CO., LTD. and BIOCON BIOLOGICS INC.,
Petitioners,

v.

REGENERON PHARMACEUTICALS, INC.,
Patent Owner.

U.S. Patent No. 10,888,601

Inter Parts Review No. IPR2023-00739¹

PATENT OWNER'S RESPONSE

¹ IPR2024-00201 has been joined with IPR2023-00739.

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I. INTRODUCTION

In 2006, the FDA approved Genentech's anti-VEGF agent Lucentis® for wet age-related macular degeneration (AMD). Lucentis® set the new standard for efficacious treatment of angiogenic eye disorders, and with that, an expectation about how frequently patients should be given anti-VEGF agents. The recommended dosing regimen for Lucentis® was (and still is) monthly injections into the eye—a burdensome regimen carrying risks with each injection that patients will endure for life. And yet, despite the best efforts of Genentech and other research groups, that was the standard for years, because that was the regimen that worked. No fixed-interval regimen with a more extended schedule was as good as monthly Lucentis®.

Against this backdrop, Regeneron developed a different anti-VEGF agent, Eylea® (known prior to approval as VEGF Trap-Eye). In its clinical trials, Regeneron discovered that a VEGF Trap-Eye dosing regimen of several monthly loading doses followed by doses every eight weeks—not monthly—was as effective as monthly Lucentis®. At the outset of the trials, prevailing wisdom and the prior art taught that Regeneron would fail, but Regeneron nevertheless began testing the regimen in its Phase III trial in AMD, and in 2009 it initiated a Phase II trial for diabetic macular edema (DME). Regeneron tested a number of regimens in its Phase II DME clinical trial, DA VINCI, including a regimen of three loading

doses followed by doses every eight weeks. Then, based on confidential results of its DA VINCI trials obtained in late 2010, Regeneron proceeded with the fixed eight-week interval in its Phase III VIVID and VISTA trials but increased the number of loading doses from three to five. VIVID and VISTA measured the effect of Eylea® on subjects' DME, *i.e.*, fluid buildup in the center of the retina, and on the diabetic retinopathy (DR), *i.e.*, hemorrhages and other microvascular abnormalities across the retina. The VIVID and VISTA trials confirmed that a regimen of five monthly loading doses followed by doses every eight weeks was highly effective. These results supported the addition of DME and DR indications to the Eylea® label, which recommends the five-loading-dose regimen.

Regeneron's innovative work led to the challenged claims of the '601 Patent, which cover the five loading-dose regimen for DME and DR. The '601 Patent claims priority to January 2011, when Regeneron had obtained the Phase II DA VINCI results and was finalizing the protocol for its VIVID/VISTA clinical trials, but notably *before* either the full DA VINCI results or the VIVID/VISTA dosing regimen had published. Petitioner does not contend that the claimed five-loading dose regimen of VEGF Trap-Eye was disclosed in the prior art. Instead, Petitioner challenges these claims as obvious over the Regeneron's own 2009 Press Release, which does *not* disclose five loading doses at all, let alone five loading doses administered every four weeks, followed by maintenance

doses administered every eight weeks. Moreover, Regeneron's 2009 Press Release does not disclose **any** results. Recognizing the deficiencies in the 2009 Press Release alone, Petitioner therefore proposes combining the three-loading dose arm from the 2009 Press Release with two references, Shams and Elman 2010, that describe clinical trials for an entirely different anti-VEGF agent, Genentech's Lucentis®.

Petitioner's hindsight-driven arguments fail and cannot establish obviousness by a preponderance of the evidence for the following reasons:

First, the proper construction of the claim language "every 4 weeks for the first 5 injections followed by ... every 8 weeks" requires a **predetermined** dosing schedule. But Petitioner's obviousness theories focus on **individualized** dosing regimens, which are not determined *ex ante*. Dosing is instead determined on an "as needed" basis, which is not covered by the claims.

Second, a POSA would not consider Shams or Elman 2010 in combination with the 2009 Press Release, because both Shams and Elman 2010 pertain to Lucentis®, and the POSA would not rely on Lucentis® dosing regimens to guide dosing of a different anti-VEGF agent. Moreover, Shams teaches using three or fewer monthly doses of Lucentis®. Elman 2010 does not disclose any subject receiving exactly five monthly doses of Lucentis® either, let alone a subject that received exactly five monthly doses, followed by doses every eight weeks.

Third, even if the POSA had some reason to consider modifying the dosing regimens set forth in the prior art as Petitioner contends, the POSA could do so in innumerable ways besides adding exactly two more loading doses to the three-loading dose, every eight weeks arm described in the 2009 Press Release.

“Routine optimization” case law does not apply here because the ways to add doses is not limited to a range encompassing exactly five loading doses; that is a relevant number only in hindsight. Further, the optimization would be challenging, and the POSA would have no reasonable expectation of success, because using an “as needed” dosing strategy on individual patients, would not demonstrate whether a given dosing regimen was actually optimal.

For at least these reasons, and those discussed in further detail below, the patentability of the challenged claims should be upheld.

II. BACKGROUND

A. Diabetic retinopathy and diabetic macular edema

DR and DME are angiogenic eye disorders that are common complications of diabetes. Ex.2027 ¶¶20-23; Ex.2003, 1. Chronic high blood sugar in individuals with diabetes causes damage to small blood vessels throughout the body. Ex.2027 ¶20; Ex.2089, 2-3; Ex.2090, 2; Ex.2003, 1. DR and DME result from damage to the small blood vessels in the retina, which is the light-sensitive layer of tissue at the back of the eye. Ex.2027 ¶¶20-23.

DR is characterized by a range of abnormalities in the retinal microvasculature, including microaneurysms, hemorrhages, and venous beading. Ex.2027 ¶21; Ex.2089, 6 Table 2; Ex.2091, 2. In clinical trials, DR can be assessed using the Diabetic Retinopathy Severity Scale (DRSS), a composite measure of microvascular abnormalities. Ex.2027 ¶22; Ex.2091, 8; *e.g.*, Ex.2092, 2.

Some DR patients also experience DME. DME is swelling of the macula, which is the part of the retina responsible for sharp, direct vision. Ex.2027 ¶23; Ex.2003, 1; Ex.1001, 1:42-44; Ex.2029, 30:24-31:15. DME occurs when the microvasculature becomes leaky, which can occur at any stage of DR. Ex.2027 ¶23; Ex.2090, 1; Ex.2029, 19:19-20:2. Macular edema can be assessed with optical coherence tomography, which allows a physician to measure the thickness of the retina. Ex.2027 ¶24; Ex.2093, 2; Ex.2029, 32:7-17.

B. Prior art therapies for angiogenic eye disorders

A protein called vascular endothelial growth factor (VEGF) is present at elevated levels in angiogenic eye disorders such as DR and DME and contributes to the pathophysiology of these disorders. Ex.2027 ¶27; Ex.1045, 1; *see* Ex.2089, 3; Ex.2029, 18:13-20:2. From 2004 to 2006, FDA approved the first anti-VEGF agents that were used to treat angiogenic eye disorders, including the antibody fragment Lucentis® (ranibizumab) and the full-length antibody Avastin®

(bevacizumab), which is approved for cancer but used off-label for angiogenic eye disorders. Ex.2027 ¶¶28; Ex.1015, 2, 5; Ex.2030, 2, 7; Ex.2031.

Lucentis® was initially approved for only one angiogenic eye disorder: wet age-related macular degeneration. Ex.2027 ¶¶28; Ex.1015, 2. But by 2010, a number of trials were completed or underway to confirm that anti-VEGF agents were effective to treat other angiogenic eye disorders, including DME and DR. Ex.2027 ¶¶32; *e.g.*, Ex.2032; Ex.1006. The FDA approved DME as an indication for Lucentis® in 2012 and approved DR as an indication in 2015. Ex.2027 ¶¶32; Ex.2004, 1; Ex.2033.

For AMD, DME, and DR, the Lucentis® label recommends monthly dosing. Ex.2027 ¶¶34; Ex.2034, 2. Despite the discomfort, inconvenience, and risks associated with injections into the eye, the label recommends monthly dosing because a less-frequent dosing interval was shown to be far less effective. Ex.2027 ¶¶34-35. In Genentech’s PIER study, AMD patients in the treatment arms received ranibizumab every month for three doses, followed by quarterly doses. Ex.2027 ¶¶35; Ex.2035 ¶¶20; Ex.1004, 2. Subjects gained visual acuity from the first three monthly injections but then lost all visual acuity gains after moving to fixed quarterly dosing. Ex.2027 ¶¶35; Ex.2035 ¶¶22; Ex.1004, 5 Fig.1. By 2011, the PIER trial was regarded as “highly disappointing,” and a “failure,” Ex.2035 ¶¶22-23; Ex.2027 ¶¶35, and Genentech allowed all patients in the quarterly arms to

switch from quarterly dosing to monthly dosing for the remainder of the study. Ex.2035 ¶25; Ex.2027 ¶35; Ex.2006, 2; Ex.2007, 2.² The Lucentis® label itself notes that quarterly dosing is “less effective.” Ex.2027 ¶35; Ex.2035 ¶31; Ex.2004, 1.

C. Eylea®

Regeneron developed a different anti-VEGF agent, sometimes referred to as VEGF Trap-Eye, and now known as Eylea® (aflibercept). Aflibercept is not an antibody or antibody fragment but rather a fusion protein made from domains of human VEGF receptors grafted onto an Fc portion of an antibody. Ex.1050, 12. FDA first approved Eylea® in November 2011 for AMD. Ex.1001, 2:51-57.

In 2008, Regeneron began enrolling DME patients in a Phase II trial, DA VINCI. Ex.1045, 2; Ex.2027 ¶38. 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;

² The sole example of Petitioner’s Shams reference is a prospective disclosure of the PIER trial protocol, without any of these results showing failure of the trial. Ex.1010.

Ex.2027 ¶38. 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; Ex.2009, 1615:15-20.³

Regeneron obtained the 24-week DA VINCI results by mid-2010, Ex.2009, 1615:15-24, and published the full 24-week results in May 2011, Ex.1045, 8. At 24 weeks, “[i]n the 2Q8 and 2 PRN arms, the treatment interval for VEGF Trap-Eye administration was prolonged after the loading phase without a trade-off in efficacy, because all VEGF Trap-Eye–treated groups manifested comparable gains in visual acuity versus baseline.” Ex.1045, 6; Ex.2027 ¶38. With these results in hand, Regeneron began planning its Phase III trials. As of October 2010, Regeneron planned to test the 2q8 regimen that it had used in the DA VINCI trial, Ex.2009, 162:7-9, 1616:19-25, but it awaited the DA VINCI 52-week data to “provide additional guidance on the number of loading doses,” *id.* 162:10-163:3.

Then, in late 2010, Dr. George Yancopoulos, Regeneron's co-founder, and sole inventor of the '601 Patent, reviewed the 52-week data, including unpublished patient-level data. Ex.2009, 163:5-165:13, 1620:6-1621:23. He made the decision

³ Citations in the page:line format use the original page numbering of the document.

to test five loading doses followed by additional doses every eight weeks in the Phase III trial. *Id.* 1622:15-1623:14, 1234:8-1235:4, 167:25-168:22; Ex.2003, 2.

Regeneron completed its Phase III VIVID and VISTA trials, and FDA approved an additional Eylea® indication for DME in December 2013. *See* Ex.2003; Ex.2010. For DME, the Eylea® label recommends the dosing regimen recited in the challenged claims of the '601 Patent: five monthly loading doses followed by additional doses every eight weeks. Ex.1050, 1.

In VIVID and VISTA, Regeneron measured the effect of Eylea® on the subjects' DR. All subjects in the trial had both DR and DME, and one endpoint was change in central retinal thickness, a measure of DME. Ex.2003, 2; Ex.2027 ¶40. But in addition, the trials included an endpoint specific to DR: "proportion of eyes with a ≥ 2 step improvement in the ETDRS Diabetic Retinopathy Severity Scale (DRSS) score." Ex.2003, 2; Ex.2027 ¶41. Significantly more subjects in the VEGF Trap-Eye 2q8 arm (five initial doses followed by doses every eight weeks) achieved a ≥ 2 step improvement in DRSS compared to the laser arm. Ex.2027 ¶41; Ex.2003, 6. With the DRSS data from VIVID and VISTA, Regeneron obtained FDA approval for the indication "treatment of Diabetic Retinopathy (DR) in patients with Diabetic Macular Edema (DME)." Ex.2037; Ex.1050, 2, 24; Ex.2027 ¶41.

After VIVID and VISTA, Regeneron undertook a trial called PANORAMA, which enrolled patients with severe non-proliferative diabetic retinopathy without center-involved DME. Ex.2027 ¶42; Ex.2092, 2. The 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.2027 ¶43; Ex.2092, 3. Significantly more subjects in the VEGF Trap-Eye 2q8 arm (five initial doses followed by doses every eight weeks) achieved a ≥ 2 step improvement in DRSS compared to sham treatment. Ex.2027 ¶43; Ex.2092, 5 Fig.2. With the DRSS results of VIVID, VISTA, and PANORAMA, Eylea® was approved for DR in May 2019. Ex.2027 ¶44; Ex.2038; Ex.1016.

D. The Challenged Claims of the '601 Patent

The challenged claims of the '601 Patent are directed to therapeutic treatments for DME and DR. Independent claim 10 is specifically directed to a “method for treating diabetic macular edema.” Independent claim 18 is specifically directed to a “method for treating diabetic retinopathy,” and independent claim 26 is specifically directed to a “method for treating diabetic retinopathy in a patient with diabetic macular edema.”⁴

⁴ On December 27, 2023, the U.S. District Court for the Northern District of West Virginia held claims 11 and 19 of the '601 Patent invalid. Ex.2039.

The specification explains the state of the art and notes a “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, 1:64-67. The inventor “surprisingly discovered that beneficial therapeutic effects can be achieved in patients suffering from angiogenic eye disorders by administering a VEGF antagonist to a patient at a frequency of once every 8 or more weeks.” Ex.1001, 2:11-18.

All of the challenged claims require five monthly loading doses followed by doses every eight weeks. As explained below, this is a predetermined dosing regimen with fixed dosing intervals, in contrast to other regimens disclosed in the specification, which may vary during the course of treatment based on patient outcomes. For example, at column 16, lines 23-26, the ’601 Patent describes the dosing regimen set forth in the challenged claims, which Petitioner’s expert acknowledges is a predetermined dosing schedule, (Ex.2029, 220:4-221:7), decided upon *before* treatment has begun. The ’601 separately describes a PRN dosing schedule at column 16, lines 33-38 (Ex.2029, 216:17-217:4), in which the dosing schedule after five loading does is *not* predetermined, but is instead determined at each office visit and on an “as needed” basis, based on physician assessment *after* treatment has begun. Ex.1001, 16:33-38.

III. PRIOR ART

A. 2009 Press Release (Ex.1009)

The 2009 Press Release is a Regeneron press release that discloses certain aspects of the design of Regeneron's Phase II DA VINCI clinical trial for DME. Ex.1009; Ex.2027 ¶50. The press release discloses that the trial included four different VEGF Trap-Eye dosing regimens, "0.5 mg or 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...." Ex.1009.

B. Shams (Ex.1010)

Shams is the publication of a Genentech patent application filed in 2004. Ex.1010, 1; Ex.2027 ¶¶51-52. Shams discusses the general concept of more-frequent followed by less-frequent dosing, but without any evidence that such regimens could work. 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 asserts 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.

Through the rest of the specification and claims, Shams focuses on a regimen of three or fewer monthly loading doses followed by quarterly dosing. Ex.1010, 5:20-6:2; 23:13-16, 36:30-37:25. Not only did Shams not show that quarterly dosing would work, but the opposite is true: Shams' sole example is a prospective disclosure of the dosing regimen used by Genentech in the PIER trial, which would ultimately fail. Ex.1010, 31:8-19; Ex.2027 ¶¶52 Ex.2035 ¶¶22-31; Ex.1004.

C. Elman 2010 (Ex.1006)

Elman 2010 is an article that describes a study comparing various ranibizumab (Lucentis®), laser, and steroid regimens for DME. Ex.1006; Ex.2027 ¶¶53-54. In one arm of the trial, referred to as the “ranibizumab + deferred laser group,” subjects followed 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. Second, 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 <250µm. 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 also received a dose at the investigator's discretion. Ex.1006, 3, 15-16. Third, at the 24-week and later visits, drug was administered at the

investigator's discretion if the study eye was deemed "no improvement," and laser photocoagulation could be applied as well. Ex.1006, 3, 15-16.

Elman 2010 does not disclose individual results data, but, but it does report average outcomes. Ex.2027 ¶54. In the deferred laser group, the average visual acuity improved quickly over the first two to three months, and then climbed slowly through week 52. Ex.1006, 6 Fig.3; Ex.1006, 35 Fig.8.

IV. PRIORITY DATE

The challenged claims of the '601 Patent have a priority date of January 13, 2011, at the latest. The disclosure of provisional application No. 61/432,245, filed on January 13, 2011, provides adequate written description support for the elements of the challenged claims.

Petitioner contends that the date should instead be no earlier than July 12, 2013. Petitioner points to the recited dosage, the recited interval between secondary (loading) doses and tertiary (maintenance) doses, the recited indications, and the "effective" combination of those variables as aspects that allegedly lack written description prior to July 12, 2013. Each of these elements, however, is supported by the original provisional application.

The Board addressed a virtually identical argument in Samsung's challenge to the related '572 Patent, IPR2023-00884. One claim of that patent covers a method for treating DME involving five monthly loading doses followed by

bimonthly dosing. The Board found this claim to be entitled to a priority date of January 2011.⁵ IPR2023-00884, Paper 13, 33-34. The Board noted the provisional application expressly identifies four secondary doses (*i.e.*, five loading doses total) as an embodiment of the invention, reasoning that “[a] specific example perfectly and verbatim embodying [the claim with 5 loading doses] is not required.” *Id.*, 33 (citing Ex.2011, [0018-19]). The same analysis applies here.

Example 5 of the ’245 application discloses all but one limitation of claim 10. It discloses a clinical trial testing DME treatment, where one of the tested groups received “three initial doses of 2 mg VEGFT once every four weeks ... followed through week 52 by [] once every 8 weeks dosing....” Ex.2011, [0061]. The trial includes efficacy results for the group. Ex.2011, Table 2. This Example discloses the dosage, interval between doses, the DME indication, and a level of efficacy. The only other limitation of claim 10, five loading doses (*i.e.*, one initial dose plus four secondary doses), is expressly disclosed in paragraph 18, which states that “In other embodiments, two or more (*e.g.*, 2, 3, **4**, 5, 6, 7, 8, or more) secondary doses are administered to the patient.” Ex.2011, [0018]. The

⁵ The Petitioner and Board in IPR2023-00884 relied on Regeneron’s January 21, 2011 provisional application, 61/434,836, but the January 13, 2011 provisional application includes the same relevant disclosures.

'245 application also discloses both DR and DME as potential targeted diseases. Ex.2011, [0024].

Dr. Chaum's opinion regarding priority date should be given no weight. In his deposition, Dr. Chaum demonstrated a lack of understanding of the written description requirement. Ex.2029,40:13-22. Dr. Chaum also did not review any provisional applications in reaching his opinion regarding priority date. Ex.2029, 154:4-22. When presented with disclosure present in the provisional application, he agreed that it disclosed five monthly doses. Ex.2029, 230:6-19.

V. CLAIM CONSTRUCTION⁶

A. “[E]very 4 weeks for the first 5 injections followed by ... every 8 weeks”

The plain and ordinary meaning of the challenged independent claims makes clear that the administered dosing regimen follows a predetermined, fixed dosing schedule, “every 4 weeks for the first 5 injections followed by ... every 8 weeks,”

⁶ Patent Owner disagrees with Petitioner's argument that the exclusion criteria limitations of claims 17, 25, and 33 are entitled to no patentable weight. Pet. 21-22. Petitioner does not advance any non-obviousness arguments involving these limitations, so the Board need not resolve the dispute in this proceeding. *Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co*, 868 F.3d 1013, 1017 (Fed. Cir. 2017).

that is determined before treatment begins. Ex.2027 ¶¶61. Petitioner argues that the claims should not be limited to predetermined, fixed dosing schedules, and should instead be broadly construed to encompass individualized, variable dosing schedules, which are decided during (not before) treatment. Paper 7, 6-9.

According to Petitioner, provided that the dosing intervals of such individualized schedules coincidentally line up with the intervals specified in the claims, the claimed dosing regimen is met. Paper 7, 7.

Not so. The specification explicitly distinguishes between the individualized dosing strategies contemplated by Petitioner and the predetermined, fixed dosing schedules actually claimed. Ex.2027 ¶¶62-67. Indeed, as discussed above, at column 16, lines 23-26, the '601 Patent describes the dosing regimen set forth in the challenged claims. Petitioner's expert acknowledged at his deposition that this refers to a predetermined dosing schedule, (Ex.2029, 220:4-221:7), decided upon **before** treatment has begun. The Eylea® label describes this same regimen, which Petitioner's expert agreed is a "fixed dosing regimen." Ex.1002, ¶¶61; Ex.1050, 1. Dr. Chaum further confirmed that a "fixed dosing regimen" means "that it's prespecified in some regimen as opposed to being given based upon the patient's response." Ex.2029, 141:4-9.

In contrast, the '601 Patent separately describes individualized, "as needed"/*pro ne rata* (PRN) dosing schedules. *E.g.*, Ex.1001, 15:46-57, 16:33-38;

Ex.2029, 216:17-217:4. For example, with the option described at 15:46-51, the dosing schedule after three loading doses (including at months four and five) is *not* predetermined, and is instead determined based on physician assessment *after* treatment has begun. ‘601 Patent at 15:46-51; Ex.2027 ¶67. As Petitioner’s expert acknowledged, a PRN dosing strategy allows for “multiple dosing regimens” (Ex.2029, 277:5-11), none of which are determined in advance.

Throughout the specification, the same language used in the claims—“every [x] weeks”—is used to refer to a fixed, predetermined dosing regimen, and individualized dosing strategies are described using different language, such as “administered pro re nata (PRN) based on visual and/or anatomical outcomes (as assessed by a physician or other medical professional).” *See, e.g.*, Ex.1001, 16:33-38; Ex.2027 ¶¶62-67.

Example 5 is illustrative. It describes a trial in which two groups both received three initial loading doses through week 8 but were administered anti-VEGF agents on different dosing schedules thereafter. Ex.2027 ¶64. One group received “every 8 weeks dosing (2Q8)” and the other group received “as needed dosing with very strict repeat dosing criteria (PRN)”. *Id.* 14:18-24; Ex.2027 ¶64.

Example 7 also refers to predetermined, fixed dosing schedules using “every [x] weeks” language and distinguishes these dosing schedules from

individualized/PRN strategies, which are described using phrases like “as assessed by a physician” or “pro re nata (PRN).” *Id.*, 16:7-22; Ex.2027 ¶¶66-67.

The specification also describes individualized/PRN dosing as an *alternative* to dosing every 8 weeks:

“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; Ex.2027 ¶68.

Petitioner relies on this description to argue that the specification focuses on variable dosing regimens. Paper 7, at 7. But Petitioner only cites to the second portion of this description and ignores the fact that this portion of the specification describes variable dosing regimens as an *alternative* to fixed, predetermined dosing “every [x] weeks.” *Compare* Paper 7, at 7 with Ex.1001, 4:30-46.

In its Decision on Institution, the Board states that the only explicit reference to “fixed” doses is in Example 2 describing a clinical study which involved fixed dosing for the first 12 weeks followed by dosing after evaluation for pre-specified

criteria. D.I. 41. But the record now confirms that the specification discloses the claimed predetermined dosing schedules and distinguishes them from individualized/PRN dosing strategies, which Patent Owner elected not to claim. Ex.2027 ¶¶62-68; Ex.2029, 216:17-217:4, 220:4-221:7. The claims of related patents further demonstrate that Patent Owner knew how to claim individualized/PRN dosing strategies and chose not to do so in the '601 Patent. Ex.2027 ¶69. For example, U.S. Patent No. 11,730,794, which issued from continuation of the '601 Patent, 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; Ex.2027 ¶69. As discussed above, PRN dosing is described as an *alternative* option to dosing “every [x] weeks,” not something encompassed by it. Patent Owner’s own claims further reinforce this distinction and confirm the error in Petitioner’s position.

The portions of the specification relied upon by the Petitioner (and the Board) are not to the contrary. While the specification does describe variable dosing schedules (D.I. 40 (citing Ex.1001, 4:13-15)), the claims are not directed to these embodiments. Ex.2027 ¶70; *see Pacing Techs., LLC v. Garmin Int’l, Inc.*, 778 F.3d 1021, 1026 (Fed. Cir. 2015) (“every claim does not need to cover every embodiment”). Here, the challenged claims refer to dosing “every [x] weeks,” which the POSA would recognize, based on the explicit claim language and the

specification, refers to a predetermined, fixed dosing strategy, not an individualized, variable strategy that by chance meets the schedule recited in the claims. Ex.2027 ¶¶58-62. Petitioner is improperly trying to expand the scope of the claims to include such “as needed” strategies, because of the lack of any disclosure in the prior art of five monthly doses followed by additional doses every eight weeks. But Petitioner’s proposed construction is contrary to the language of the claims and the specification, and it should therefore be rejected.

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

1. The challenged claims require effective treatment

Patent Owner maintains its position that “[a] method for treating [comprising] an effective amount” in Claims 10, 18, and 26 each recite “[a] method for *treating* [DR/DME]” and further specify that the amount of VEGF Trap-Eye administered must be “*effective*” for this purpose.

The Board need not address this claim construction issue to find the claims patentable over the instituted grounds. For that reason, and given the Board’s previous rejection of Patent Owner’s proposed construction, *see* IPR2022-01226, Paper 101, at 48-49, Patent Owner addresses the issue only briefly.

By 2011, the POSA would have understood effective treatment of angiogenic eye disorders to require efficacy that is on par with the standard of care at the time, *i.e.*, monthly Lucentis® or Avastin®. Ex.2027 ¶¶73-77. Patent

Owner's construction is confirmed by reading the specification as a whole, in the context of the state of the art at the time. Ex.1001, 1:25-27, 2:3-5, 2:11-17, 3:29-30, 7:27-30; Ex.2027 ¶¶72-73.

In contrast, Petitioner's position proposed construction both ignores the stated purpose of the '601 claims ("treating" DR/DME) and strikes the word "effective" from the claims altogether. The claims could read "administering, to said patient, an amount of aflibercept which is 2mg" and have the meaning Petitioner proposes. This violates the axiom that each word in a claim should be given meaning. *See Merck & Co., Inc. v. Teva Pharms. USA, Inc.*, 395 F.3d 1364, 1372 (Fed. Cir. 2005).

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

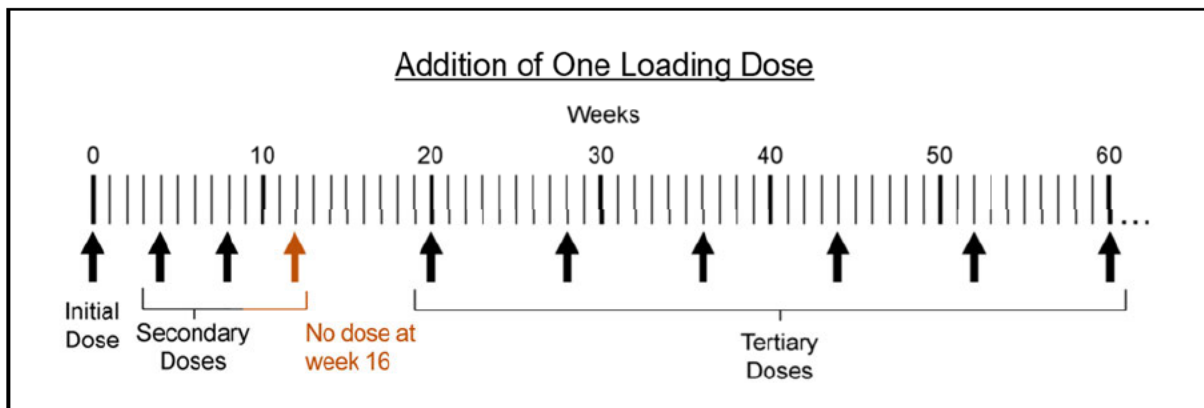
Petitioner, Patent Owner, and the Board appear to agree that the claims require at least an intent to treat specific angiogenic eye disorders, namely DME and DR.

The Petition and Decision on Institution note that "the Board found that administering a compound—the recited VEGF antagonist—to [a] patient for the purpose of improving or providing a beneficial effect on their angiogenic eye disorder' satisfies the 'treating' portion of the preamble." D.I. 8; *see also* Paper 1, at 16. To practice a method of treatment with the "intent" to treat a disease, the POSA must have some basis to believe that the method could bring about a desired

result. *See Eli Lilly & Co. v. Teva Pharms. Int'l GmbH*, IPR2018-01710, 2020 WL 1540364, *8 (P.T.A.B. Mar. 31, 2020), *aff'd* 8 F.4th 1331 at 1342. Here, the explicit language of the challenged claims requires an intent to treat the specific angiogenic eye disorders recited in each independent claim. Ex.2027 ¶¶78-79.

VI. THE CLAIMED FIVE LOADING-DOSE REGIMEN IS NON-OBVIOUS

There is no merit to Petitioner's suggestion that arriving at the claimed regimen requires the addition of only one dose to the loading phase. Pet. 4. That still is not the claimed regimen. As the Board acknowledged, the 2009 Press Release discloses a regimen where three monthly loading doses are followed immediately by doses administered on an eight-week interval. D.I. 33. Adding an additional monthly dose, as Petitioner contends, would result in a regimen of four monthly loading doses without a dose at the fifth month, as illustrated below:



Ex.2027 ¶¶81-82, Fig. 2. Thus, Petitioner's burden is to show that the POSA would modify the three loading-dose 2q8 dosing regimen disclosed in the 2009

Press Release by adding two predetermined monthly doses to the loading phase—not by adding one more loading dose, or taking away a loading dose, or adding three loading doses, or leaving the loading doses exactly as-is, or switching to PRN, or any other changes that the POSA could conceivably make—and would have a reasonable expectation of success. And Petitioner must show why a POSA would add these two doses in the face of their acknowledged motivation to “minimiz[e] the number of injections so as to minimize potential complications from repeated intravitreal injections.” Ex.1002 ¶¶148-49. Petitioner fails to meet this burden.

A. Petitioner has not demonstrated obviousness over the 2009 Press Release alone or in view of Shams (all claims; Grounds 2 and 6)

Petitioner argues that the POSA would arrive at the claimed dosing regimen by modifying the 2009 Press Release’s 2q8 regimen in view of Shams. But neither the 2009 Press Release nor Shams teaches toward five loading doses, and the POSA would not consider Shams a reliable source in any event. Further, Petitioner’s “routine optimization” or “routine adjustments” reasoning is inapplicable here.

1. The 2009 Press Release and Shams do not teach toward the claimed five loading-dose regimen

The 2009 Press Release and Shams provide the POSA with little guidance because of the 2009 Press Release’s lack of data or explanation, and Shams’ broad

and contradictory assertions. “To render a claim obvious, prior art cannot be ‘vague’ and must collectively, although not explicitly, guide an artisan of ordinary skill towards a particular solution.” *In re Fowler*, APPEAL 2018-003968, 2020 WL 289565, at *4 (P.T.A.B. Jan. 15, 2020) (quoting *Unigene Lab’ys, Inc. v. Aptoex, Inc.*, 655 F.3d 1352, 1361 (Fed. Cir. 2011)). If the 2009 Press Release and Shams guide the POSA anywhere other than the drawing board, they point toward three or fewer monthly doses, not to five. *Id.* (finding that a reference disclosing emulsions with 26 to 60% water did not render obvious a composition with 2% or less water).

a) The 2009 Press Release does not teach or suggest the claimed regimen

The 2009 Press Release does not provide any explanation for the choice of dosing regimens in the DA VINCI trial or any results from that or other clinical trials. The POSA could not rely on such a bare-bones disclosure to know which dosing regimen would be promising as a starting point or know how it should be modified. Ex.2027 ¶85. Petitioner’s expert, Dr. Chaum, concedes this.

Dr. Chaum testified that the 2009 Press Release is “not specific enough” to enable the POSA to practice the claims. Ex.2029, 296:13-20; *see also* Ex.2029, 76:22-77:25, 80:13-19, 81:1-5, 81:9-12, 99:25-100:2 (explaining the purpose of a phase II trial and the uncertainty involved at the outset). He accordingly explained that he

was “not relying on the press release alone, rather in combination with Shams.”

Ex.2029, 266:12-16, 265:13-20.

But if the POSA were nevertheless inclined to use the 2009 Press Release as a starting point, that starting point would be exactly three loading doses. None of the prospective extended dosing regimens disclosed in the 2009 Press Release uses more than three loading doses.⁷ Ex.2027 ¶¶86; Ex.1009. In other words, the POSA

⁷ To the extent Petitioner contends that Regeneron’s 2009 Press Release discloses six loading doses (an argument that is confined to Ground 3 in the Petition, Pet. 36, and thus should not be considered for Ground 2), this is incorrect. The 2009 Press Release discloses the COPENICUS and GALILEO trials in Central Retinal Vein Occlusion (CRVO), and Petitioner fails to explain why trials for these conditions would show the appropriate number of loading doses for DR or DME. And the trials tested a monthly dosing regimen, not an extended dosing regimen, with the primary endpoint of improvement in visual acuity at six months. Ex.2027 ¶¶102; Ex.1009; *see* Ex.1050, 2, 17-19 (recommending monthly dosing for CRVO, based on the six-month results of the COPENICUS and GALILEO trials). Subjects were dosed on a PRN basis after six months, but the 2009 Press Release would not teach the POSA that Regeneron was investigating whether a PRN dosing regimen would work or whether six would be an appropriate number of loading doses.

combining these two references would take from the combined teachings that exactly three loading doses was ideal. Assuming the POSA wanted to change the regimen at all, there is no reason the POSA would vary the number of loading doses rather than some other aspect of the regimen.

Attempting to overcome this issue, Petitioner points to the disclosure of DA VINCI's monthly and PRN arms as a teaching toward more loading doses. Pet. 35. The PRN arm used exactly three monthly loading doses before switching to extended dosing. The monthly dosing arm does not involve extended dosing intervals at all, so it provides the POSA with no guidance about how many loading doses are necessary before extending the dosing intervals. Ex.2027, ¶87. Further, the press release does not state why the monthly (or any other) arm was included in the DA VINCI trial, and so the POSA could at most speculate about what the inclusion of the monthly arm meant about Regeneron's hypotheses about the optimal dosing regimen. Ex.2027 ¶87; Ex.2029, 283:2-20. If the POSA were to undertake such speculation, the 2009 Press Release would still not teach toward more loading doses. The POSA would have understood the purpose of the

Ex.2027 ¶102. 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. *Id.*

monthly arm to be a comparison arm, not an arm included for the purpose of determining the optimal number of loading doses. Ex.2027 ¶87. As Petitioner agrees, monthly dosing was “a standard and proven safe for other anti-VEGF agents.” Pet. 35; *see* Ex.2027 ¶¶28-35, 87. Regeneron would have wanted to explore whether the eight-week and PRN dosing regimens could provide equivalent efficacy to monthly administration. Ex.2027 ¶87.

Further, Dr. Chaum asserts that the benefit of additional loading from the POSA’s perspective would be to ensure sufficient drying of the retina. Ex.1002 ¶¶150-151, 153. The 2009 Press Release includes no data indicating whether the subjects’ retinas were dry after the third monthly dose in any arm of the DA VINCI trial. Ex.1009. Contrary to Petitioner’s assertion, the press release does not show that “some patients might benefit from more than three loading doses.” Pet. 35; Ex.2027 ¶88.

b) Shams does not teach or suggest the proposed modification

Petitioner and Dr. Chaum rely on Shams to meet the five loading-dose limitation absent from the 2009 Press Release, but the POSA would not derive that teaching from Shams. As an initial matter, the POSA would not have considered Shams to be a dependable reference, and so would not have relied on it at all. Ex.2027 ¶¶89-93; *see* Ex.2029, 128:8-18. Shams provides little rhyme or reason for how to pick through its divergent approaches that are allegedly appropriate for

a huge range of compounds and a huge range of dose schedules; namely, “[a]ny compound which binds to VEGF or a VEGF receptor and reduces the severity of symptoms,” Ex.1010, 26:6-8, 6:27-7:16, “administered according to any time schedule which is appropriate,” Ex.1010, 22:30-31., Ex.2027 ¶90; *cf.* Ex.2029, 301:15-302:19. Shams discloses dosing as often as daily or weekly, and as well as prophylactic administration before development of a disorder, all of which the POSA would have known to be inappropriate. Ex.1010, 22:31-34; Ex.2027 ¶91; Ex.2029, 285:22-286:14, 287:1-13; *see also* Ex.2029, 279:10-23.

To the extent Shams teaches ways of selecting a dosing regimen, it explains individualized approaches, but the sole example diverges from that teaching, focusing on a fixed regimen that was known by 2011 to have failed. Ex.2027 ¶93; *compare* Ex.1010, 22:30-23:7 *with* Ex.1010, 23:13-23:28, 31:8-11, Fig.2.

Specifically, Shams’s example focuses on a dosing regimen that, by the priority date, had been tested in the PIER trial and shown not to work—a regimen that resulted in vision loss (a fact Dr. Chaum had not considered, Ex.2029, 112:17-25).

Ex.1010, 31:8-11; Ex.2035 ¶¶22-31; Ex.2027 ¶93; Ex.1004; Ex.2029, 294:4-23.

This was despite the fact that the PIER trial was designed with input from “physician[s] having [at least] ordinary skill in administering the therapeutic compound.” Ex.1010, 23:1; Ex.2035 ¶21. The POSA would therefore understand from reading Shams in view of the PIER trial results that Shams had

underestimated the difficulty of choosing a dosing regimen that maximizes efficacy while reducing the number of loading doses. Ex.2027 ¶93. In other words, Shams’s own failure disproves its assertion that arriving at an optimal regimen would be “routine” for a physician. *Id.*

Even if the POSA would have relied on Shams, the reference never mentions using more than three loading doses. Ex.1010, 23:14-16 (“The first dose may be administered, for example, one, two or three times, typically three times”). Thus, if the POSA chose to review the 2009 Press Release and Shams both and use those to create a regiment as Petitioner argues, the POSA would have every reason to pick three loading doses or fewer, and no reason to pick a higher number. Ex.2027 ¶94.

c) Even if Shams or the 2009 Press Release suggested modifying the 2q8 regimen, the possibilities would be numerous

Even if Shams or the 2009 Press Release suggested modifying the DA VINCI 2q8 arm to a different predetermined dosing regimen, they would suggest numerous ways to do so. Ex.2027 ¶95. That is fatal to Petitioner’s theories. “[W]here the prior art[] at best gives only general guidance as to the particular form of the claimed invention or how to achieve it, relying on an obvious-to-try theory to support an obviousness finding is impermissible.” *Roxane Lab’ys, Inc. v. Vanda Pharms. Inc.*, No. IPR2016-00690, 2016 WL 5226531 (P.T.A.B. Aug.

30, 2016) (quoting *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litigation*, 676 F.3d 1063, 1073 (Fed. Cir. 2012)). The teachings of Shams fall squarely within the category of those giving only general guidance, as Shams teaches the use of “any time schedule,” including any number of initial doses and any interval for initial and subsequent dosing. Ex.1010, 22:30-31, 23:7-9; Ex.2027 ¶96. The numerous possible modifications Shams could suggest would include many modified schedules with both more and fewer doses than the DA VINCI 2q8 arm—in other words, there is not even a teaching toward increasing the total number of doses. Ex.2027 ¶96. The DA VINCI trial PRN arm encompasses hundreds of possible dosing schedules, roughly half involving fewer doses than the 2q8 regimen. Ex.2029, 280:22-282:16; Ex.2027 ¶97. And the arm encompasses schedules that begin with any number of additional monthly doses. Ex.2027 ¶97. Finally, the DA VINCI monthly dosing arm would not teach five monthly loading doses any more than it teaches four, six, or more. Ex.2027 ¶98. The 2009 Press Release and Shams thus offer no more than “general guidance” that the number of doses could be varied. Ex.2027 ¶99.

2. Petitioner does not show that the POSA would arrive at the claimed regimen with “routine optimization” and “routine adjustments”

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 ¶¶148-49; *see also* Ex.1002 ¶155 (citing Ex.1010 22); D.I. 34-35 (citing Ex.1010, 22-23). They further contend that such optimization could be accomplished through the POSA’s “routine adjustments” of the dosing schedule. Pet. 36-39. Petitioner fails to prove that the POSA would undertake such optimization or that it would lead the POSA to the claimed regimen.

a) The prior art does not disclose a limited range encompassing the claimed regimen

The Decision on Institution preliminarily found that the POSA who started with the 2q8 regimen would arrive at the claimed five loading-dose regimen through “routine optimization.” D.I. 36-37; Pet. 4-5 (“A POSA would have found this sort of routine dose optimization obvious for patients still obtaining gains for monthly dosing”); Ex.1002 ¶¶148-153. But “routine optimization” reasoning is inapplicable here because the prior art does not disclose a limited range for the number of loading doses that encompasses the claimed five loading doses, and because optimizing the dosing regimen would be difficult for a physician providing individualized dosing to patients.

The 2009 Press Release and Shams do not disclose limited ranges that could support a routine optimization theory. “Prior art ‘ranges that are not especially broad invite routine experimentation to discover optimum values.’” *Genetics Inst.*,

LLC v. Novartis Vaccines & Diagnostics, Inc., 655 F.3d 1291, 1306 (Fed. Cir. 2011) (quoting *In re Peterson*, 315 F.3d 1325, 1330 n.1 (Fed. Cir. 2003)). But the same cannot be said where the art does not disclose a limited range or where the proposed modification falls outside the range disclosed in the prior art. *Id.*

Petitioner's prior art combinations present just such a situation, with the modification falling outside the range disclosed in the art. Shams discloses a narrow range for the number of loading doses: "one, two or three." Ex.1010, 23:13-16; Ex.2027 ¶103. Although Shams focuses on three loading doses, this limited range could invite experimentation to determine whether one, two, or three loading doses was optimal. This narrow range would not invite experimentation with more than three loading doses. *See Red Diamond, Inc. v. S. Visions, LLP*, No. PGR2019-00045, 2020 WL 2046054, at *8 (P.T.A.B. Apr. 28, 2020) (finding a limitation on the size of sugar particles would not have been achieved as a matter of routine experimentation in view of prior art teaching that smaller, common grocery store sugar would have been suitable); *In re Sebek*, 465 F.2d 904, 907 (CCPA 1972) (prior art's disclosure of a range may indicate that the "determination of optimum values outside that range may not [have been] obvious").

To the extent Petitioner argues that the generalized language in Shams could support a routine optimization theory, this theory also fails. Shams's very broad

disclosure that “the doses may be administered according to any time schedule which is appropriate,” Ex.1010, 22:30-31, is not an invitation to optimize within a range because it is no range at all. Ex.2027 ¶104. Instead, the disclosure has no bounds and is no more than an invitation to “vary all parameters” of the dosing regimen, as discussed in VI.A.1.c) above. *In re Stepan Co.*, 868 F.3d 1342, 1346–47 (Fed. Cir. 2017). Further, although administering any one of the many possible dosing schedules would not be difficult, the variability in patient responses to a dosing regimen make it impossible to know, without testing the regimen on a population of patients over many months or even years, whether a particular schedule is the optimal one. Ex.2027 ¶104. Petitioner does not show that five loading doses is optimal as a *predetermined* regimen.

As discussed in V.A above, the claims recite a dosing regimen that is fixed, rather than based on individualized patient assessments, throughout the course of treatment, with a transition to extended (but still fixed) dosing after the fifth dose. Petitioner and Dr. Chaum propose arriving at five doses through adjustments based on individual patient assessments. Pet. 31; Ex.1002 ¶¶150-51, 157; Ex.2029, 99:25-100:2; Ex.2027 ¶105. Petitioner fails to propose a combination that results in a predetermined dosing regimen, and thus fails to propose a regimen that satisfies the claims. Ex.2027 ¶106.

To the extent Petitioner contends that a predetermined five loading-dose regimen would be optimal for just “some patients,” *see* Pet. 35; Reply, Paper 7, at 9-10, this theory fails too. Petitioner does not explain how a physician would know *ex ante* which patients should receive the regimen. Further Petitioner fails to show that the POSA would arrive at that five as an optimum number for “for efficaciously treating DME with aflibercept, while minimizing the number of injections so as to minimize potential complications from repeated intravitreal injections,” Ex.1002 ¶¶148-49, either for the entire patient population or for a subset that could be identified *ex ante*. Ex.2027 ¶106. Opinions vary among physicians regarding how best to balance these two objectives. Ex.2027 ¶107. Regeneron determined only through a Phase III clinical trial that a regimen with five loading doses is a highly effective predetermined regimen. Ex.2027 ¶107; Ex.2003. Thus, Petitioner has not shown that its proposed optimization process would actually lead the POSA to a predetermined five loading-dose regimen. Ex.2027 ¶107.

b) The POSA would not expect to achieve Petitioner’s proposed optimization objective using fixed, extended dosing intervals

If the POSA sought to optimize for, as Dr. Chaum puts it, “efficaciously treating[] DME ... while minimizing the number of injections,” Ex.1002 ¶¶148-49, they would not reasonably expect to achieve this objective using fixed,

extended dosing intervals. In the prior art, no fixed extended dosing regimen of a VEGF agent had been shown to be effective to maintain a visual acuity gain over time. Ex.2027 ¶109. Instead, conventional thinking, informed by prior art clinical trials in AMD, was that monthly injections would be most likely to “efficaciously treat[] DME” and that individualized regimens offered a better possibility of “minimizing the number of injections.” Ex.2027 ¶¶109-111. After the PIER trial, there were serious concerns that fixed extending dosing regimens were untenable, given that companies as sophisticated as Genentech had tried such regimens, but failed to demonstrate efficacy. Ex.2027 ¶112.

At best, only limited information can be gleaned from the 2009 Press Release itself about the chance of success of its disclosed dosing regimens, as discussed above in VI.A.1.a). Based on the Phase II dosing regimens alone, the POSA could not conclude that the DA VINCI 2q8 regimen, rather than monthly or PRN, would be the starting point that could allow them to achieve efficacy while minimizing the number of loading doses. Ex.2027 ¶108; *see* Ex.2029, 76:22-77:25, 80:13-19, 81:1-5, 81:9-12, 99:25-100:2.

Petitioner’s other prior art is about Genentech’s Lucentis®, and the Lucentis® art shows that the POSA would expect failure, not success, in “efficaciously treating[] DME ... while minimizing the number of injections” with fixed extended dosing intervals. Petitioner repeatedly argues that the POSA would

look to publications about Lucentis® to guide development efforts regarding VEGF Trap-Eye. Even if so, the Lucentis® references point to monthly dosing for efficacious dosing regimens using predetermined, fixed intervals. Genentech's Phase III ANCHOR and MARINA trials showed that Lucentis®, dosed monthly, was highly effective. Ex.2027 ¶110. At two years, subjects had gained and sustained an average of 6.5 to 7.2 letters of visual acuity. Ex.2027 ¶110; Ex.1038, 8 Figure 2A. These trials set the standard for efficacy of anti-VEGF agents and would inform what the POSA would understand the level of efficacy to target with a less-frequent dosing regimen. Ex.2027 ¶111; *see* Ex.1002 ¶¶148-49; Ex.1002 ¶155 (citing Ex.1010, 22); D.I. 34-35 (citing Ex.1010, 22-23).

The Lucentis® art also taught that such efficacy was unlikely with fixed dosing intervals longer than a month. In the PIER trial, Genentech evaluated a fixed-interval regimen of three monthly loading doses followed by quarterly doses. Ex.2035 ¶20; Ex.2027 ¶35; Ex.1004, 2. The trial was a failure. Ex.2035 ¶22; *see* Ex.2029, 294:4-23. Patients gained visual acuity from the three monthly loading doses, but by one year, subjects in the quarterly dosing arms had lost visual acuity compared to baseline. Ex.2035 ¶22; [Stewart] ¶35; Ex.1004, 5 Fig.1, 7.

The POSA would also glean from the Lucentis® prior art that none of the extended dosing regimens tested was as efficacious as fixed, monthly dosing. Ex.2027 ¶112. Moreover, if the POSA departed from monthly dosing, they would

expect an individualized regimen, rather than a fixed regimen, to meet the objective put forth by Petitioner, *i.e.*, “minimiz[e] the number of injections.” Ex.1002 ¶¶148-49; Ex.2027 ¶¶113-14. Indeed, Dr. Chaum has employed PRN regimens in order to “maximize the benefit to a patient and yet reduce the number of interactions that might be problematic for the patient in terms of risk.” Ex.2029, 198:21-201:1, 203:23-204:1. And an individualized approach is described in Elman 2010. Thus, the POSA looking at Lucentis® art would come away with two viable options: fixed monthly and variable/PRN dosing. Ex.2027 ¶¶109, 113. The POSA would not come away from that art looking at fixed extended dosing intervals as claimed, because no prior art discloses using five loading doses as claimed, and the data from Genentech’s PIER trial would have further caused the POSA to expect that fixed, extended dosing schedules for VEGF Trap-Eye would not work to achieve the proposed objective. Ex.2027 ¶¶115.

c) “Common sense” cannot supply the disclosures missing from the prior art

Without a teaching of five loading doses or a range over which to optimize to arrive at five loading doses, Petitioner is left with no more than “common sense” to arrive at the claimed dosing regimen. The Federal Circuit has cautioned against relying on common sense to supply a missing claim limitation. *Arendi S.A.R.L. v. Apple Inc.*, 832 F.3d 1355, 1361–62 (Fed. Cir. 2016).

Dr. Chaum’s supposed reasoning from common sense lacks support in any event. *See id.* at 1362 (“‘common sense’ ... cannot be used as a wholesale substitute for reasoned analysis and evidentiary support, especially when dealing with a limitation missing from the prior art references specified.”). Dr. Chaum proposes that the POSA would arrive at five doses by administering monthly doses until the retina was dry, and then switch to less-frequent dosing. Ex.1002 ¶¶150-151, 153. That testimony is entitled to no weight. These paragraphs cite no supporting literature. *Id.* And Dr. Chaum testified that he determines the appropriate treatment based on more than just the amount of fluid or retinal thickness—disease history, blood sugar, and hypertension matter too. Ex.2029, 213:15-214:12. “[I]n a patient who has just a little bit of fluid,” he explains that the best course of action may be not a VEGF injection but “better blood sugar control” or “laser treatment.” Ex.2029, 67:22-68:8, 70:17-22, 73:22-74:21.

B. The recited dosing regimen is not obvious over the 2009 Press Release in view of Elman 2010 (all claims; Grounds 3 and 6)

For Ground 3, Petitioner relies on the DA VINCI 2q8 arm disclosed in the 2009 Press Release and on the “deferred laser” arm of the study described in Elman 2010. Pet., 24–25. But again, the 2q8 arm involved three loading doses, not five, and Elman 2010 does not disclose or teach toward five loading doses. The prior art does not supply a motivation to combine the fifth monthly dose in Elman 2010 with the 2q8 dosing regimen.

1. Elman 2010 does not teach toward five loading doses

Petitioner asserts that Elman 2010 teaches “the use of five initial loading doses.” Pet. 41. Not so. In fact, the dosing protocol used in Elman did not involve five fixed monthly loading doses for any arm, and Elman 2010 does not disclose that the study included even a single patient who received five (and only five) initial monthly doses of ranibizumab. Further, the results disclosed in Elman do not reveal any benefits of a fifth loading dose or provide enough information for a POSA to select an optimal number of loading doses to try in a fixed dosing regimen.

a) Elman teaches monthly doses based on individual patient assessments

As discussed in V.A above, the claims recite a dosing regimen that is fixed, rather than based on individualized patient assessments, throughout the course of treatment, with a transition to extended (but still fixed) dosing after the fifth dose.

By contrast, Elman 2010 discloses four monthly loading doses, followed by an individualized dosing methodology, and further followed by different individualized dosing methodology after the sixth monthly visit. Ex.2027 ¶119; Ex.1006, 16. Petitioner argues that Elman 2010 “suggests the use of five initial monthly loading doses, at least for some patients.” Pet. 42. Petitioner does not argue that Elman 2010 discloses any *ex ante* way to determine which patients would benefit from a fifth loading dose, but rather teaches only making the

determination based on ongoing patient assessments. Ex.2027 ¶119; *see id.*; Ex.2029, 99:25-100:2. Thus, to the extent Petitioner argues that the fixed regimen of the 2009 Press Release should be modified so that some patients receive five monthly loading doses if needed, that theory does not lead to the claimed dosing regimen, which must be predetermined. Ex.2027 ¶120.

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

Elman 2010's protocol required four initial monthly doses, made it likely that patients would receive at least six, and allowed patients to receive even more. Ex.1006, 3.

Petitioner focuses on Elman 2010's disclosure that 22% of patients did not receive a fifth dose at the 16-week visit to conclude that 78% of patients did receive five initial monthly doses. Pet. 25-26. But this is not a disclosure that 78% of patients received *only* five initial monthly doses, as the challenged claims require. Ex.2027 ¶121. In fact, there is no way to tell from the disclosures of Elman whether *any* patient received exactly five loading doses, or whether all patients in the 78% received six or more initial monthly doses. Ex.2027 ¶121. At most, Dr. Chaum concedes, some subjects "might" have received exactly five monthly doses. Ex.2029, 238:21-239:4.

Not only is there no disclosure of any patient receiving just five initial monthly doses, as the claims require, but such a scenario is unlikely, undermining

any motivation to cherry-pick five loading doses from Elman 2010 and combine them that with the 2q8 regimen of the 2009 Press Release. The criteria for administering a dose at weeks 16 (month 5) and 20 (month 6) are exactly the same: Patients who didn't meet specified success criteria received an injection.⁸ Ex.1006, 25; Ex.2027 ¶¶122-123. The results further show a worsening of visual acuity and retinal thickness at week 20 compared to week 16. Ex.2027 ¶123; Ex.1006, 6 Fig.3, 10 Fig.6. This makes it unlikely that subjects met the success criteria for the first time at week 20 and thereby became eligible to stop monthly doses after five. Ex.2027 ¶123. The change in dosing criteria in Elman 2010 comes not after five loading doses, but six. And treatment after the 20-week visit was discretionary, meaning that patients may have received still more monthly loading doses after the sixth loading dose. Ex.2027 ¶123. Thus, to the extent that Elman 2010 teaches any particular number of initial doses, it is six-plus, not five, as taught by the challenged claims. Ex.2027 ¶123. Samsung's attempt to read five loading doses into the reference is hindsight-driven.

⁸ The success criteria were “[e]ither visual acuity letter score ≥ 84 (20/20) or OCT central subfield thickness < 250 microns,” and those who did not meet the criteria could receive a dose at investigator discretion. Ex.1006, 25 Table 1.

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

The results reported in Elman 2010, which were not discussed pre-institution, further undermine Petitioner's contention that Elman 2010 would have led the POSA toward five loading doses. Even though 78% of subjects in the deferred laser group received a fifth monthly dose at week 16, there was no improvement in the average visual acuity gain or retinal thickness from week 16 to week 20. Ex.2027 ¶124. Figure 8 shows mean retinal thickness got slightly worse in this group from week 16 to week 20, and Figure 3 shows that visual acuity also got slightly worse. Ex.2027 ¶124; Ex.1006, 35 Fig.8, 6 Fig.3. What's more, nearly all the improvement in retinal thickness and visual acuity had been achieved by week 12, with only modest, slow gains thereafter. Ex.2027 ¶124; Ex.1006, 35 Fig.8, 6 Fig.3. Thus, although a large majority of subjects were administered a fifth monthly loading dose, Elman 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. Ex.2027 ¶125.

Elman does not even teach that exactly five loading doses would be helpful or appropriate "for some patients," Pet. 42. Beyond the data showing no improvement in retinal thickness or visual acuity on average, Elman 2010 provides no individual patient data to determine whether the fifth loading dose helped any individual subject. Ex.2027 ¶126; Ex.1006, 35 Fig.8, 6 Fig.3. Absent such

information, it is unclear why (other than hindsight) the POSA would view five loading doses as worthy of further consideration. Further, Elman 2010 is at best unclear about the conditions under which a patient should receive a fifth monthly dose. Ex.2027 ¶127. For subjects who met Elman's strict "success criteria," a fifth monthly dose could be administered at "investigator discretion." Figure 6 shows that at a minimum, about 37% of subjects had retinal thickness <250 microns, and thus achieved the success criteria, by week 16. Ex.1006, 10 Fig.6; Ex.2027 ¶127. Yet, all but 22% received a fifth dose. Dr. Chaum did not consider this aspect of the protocol. See Ex.2029, 241:19-242:2. This undermines Petitioner's contention that the POSA would have switched to less-frequent dosing based on whether a patient's retina was dry. Ex.1002 ¶165, see Ex.1002 ¶¶151-52, 157; Ex.2027 ¶128.

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

Even if Elman 2010 taught toward five loading doses of *ranibizumab*, the POSA would not be motivated to combine this teaching with the 2009 Press Release's teaching of a regimen of three monthly loading doses of *VEGF Trap-Eye* followed by doses every eight weeks.

a) The POSA would not expect the optimal ranibizumab and VEGF Trap-Eye dosing regimens to be exactly the same

Patent Owner does not dispute that the ranibizumab art would provide the POSA with some general guidance on the types of anti-VEGF dosing regimens that are appropriate for treating angiogenic eye disorders, *e.g.*, that many patients can tolerate a monthly regimen. Ex.2027 ¶130; *see* Ex.1002 ¶¶167-170. But the POSA would not expect VEGF Trap-Eye to have the exact same optimal loading dose schedule as ranibizumab absent data showing identical performance in drying the retina, which is missing here. Ex.2027 ¶131. Beyond the POSA's general understanding that different drugs have different pharmacokinetic and pharmacodynamic properties, the POSA would have reason to believe that VEGF Trap-Eye might dry the retina differently than ranibizumab. Ex.2027 ¶131. For one, Regeneron's VEGF Trap molecules (which include VEGF Trap-Eye) had been shown to have higher VEGF binding affinity than existing anti-VEGF therapies. Ex.1008, 5; Ex.2027 ¶132. Further, 2 mg of VEGF Trap-Eye contains more protein molecules than 0.5 mg of ranibizumab (the dose amounts used in the 2009 Press Release and Elman 2010). Ex.2027 ¶131. This evidence would make the POSA skeptical that ranibizumab and VEGF Trap-Eye regimens required the same number of loading doses. Ex.2027 ¶132. The POSA thus would not read

Elman 2010, a ranibizumab trial, Ex.2029, 237:1-8, as a disclosure of the optimal number of loading doses of VEGF Trap-Eye.

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

Even if a patient subject in Elman 2010 received five initial monthly loading doses, Elman 2010 does not teach combining that with dosing on a fixed eight-week interval. In fact, the design of the Elman 2010 trial makes it unlikely that a patient who received five loading doses would then have received subsequent doses every eight weeks. Ex.2027 ¶134. As discussed above, the next dose after five initial doses was most likely a sixth initial monthly dose. Ex.2027 ¶134.

Petitioner's sole attempt to locate any disclosure of or motivation to use a fixed eight-week dosing schedule after the initial doses in Elman is based on the median of nine injections over one year in the deferred laser arm. Pet. 26.

Petitioner notes that the recited dosing regimen would also involve nine doses over 52 weeks. Petitioner's suggestion that nine median doses corresponds with the recited regimen fails for numerous reasons.

First, as Petitioner concedes, that median number of doses is for all the subjects in the deferred laser arm, not just the subgroup Petitioner contends is

relevant: the 78% of subjects who received a dose at week 16. Ex.2027 ¶136; Ex.1006, 4. The median for that group is unknown. Ex.2027 ¶136.

Second, even if Elman 2010 had, contrary to fact, disclosed a median for those subjects who received a dose at week 16, the median says nothing about whether those subjects received five, and only five, initial loading doses. Ex.2027 ¶137. Receiving nine doses over the course of a year is consistent with receiving six or more initial monthly loading doses, *e.g.*, at weeks 0, 4, 8, 12, 16, 20, 28, 32, and 36. Ex.2027 ¶137; *see* Ex.2029, 260:6-10. Thus, there is no connection at all between receiving nine doses and receiving five initial monthly doses, as the claims require. What's more, the POSA would have expected that any patients who were a "success" at week 20 and did not need a sixth initial monthly dose would have received fewer than the median number of injections. Ex.2027 ¶137. According to the retreatment algorithm, these subjects "were not required to have continued injections unless visual acuity worsened or macular edema returned." Ex.1006, 11; Ex.2027 ¶134. The POSA would expect that subjects who had responded well to anti-VEGF treatment early on could then go longer than average without such a recurrence, meaning they would receive fewer than the median number of total doses. Ex.2027 ¶137.

Third, even if a subject received exactly five initial monthly doses (again, Elman 2010 does not disclose a single subject doing so), and even if that same

subject received nine doses over the course of a year, that does not mean that the subject received any doses on an eight-week schedule. Ex.2027 ¶138. For example, a subject who received injections at weeks 0, 4, 8, 12, 16, 28, 32, 36, and 48 would have both (1) received five initial monthly doses and (2) received nine doses total over the course of a year but would not have received a single dose that was eight weeks after the previous dose. Ex.2027 ¶138. Instead, only a small fraction of subjects received nine doses, making it unlikely that any subjects happened to receive exactly five monthly doses followed by eight-week dosing. Ex.2027 ¶140; Ex.1006, 28; *see* Ex.2029, 259:25-260:10. The POSA reviewing these results would therefore have no reason based on Elman 2010 to arrive at the recited dosing regimen. Ex.2027 ¶141.

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

Petitioner also fails to provide a reason to change the 2009 Press Release’s disclosure of three initial monthly doses to five based on Elman 2010, given that Elman 2010 not only does not teach any particular number of monthly loading doses, and if anything teaches more toward four, six, or more loading doses than five. Pet. 43-44. Indeed, nothing in either reference suggests that three loading doses was inadequate: The 2009 Press Release does not disclose results, and Elman 2010 shows no significant difference in retinal thickness or visual acuity after three monthly doses compared to (for most subjects) five or more monthly

doses. Ex.2027 ¶142. Thus, the 2009 Press Release and Elman 2010 do not provide any reason to add doses. *Id.*¶142.

Petitioner argues based on two post-priority-date articles that the POSA would have been motivated to “add” loading doses (presumably to the eight-week dosing arm described in the 2009 Press Release) “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 (citing Ex.1005 (published June 2011); Ex.1007 (available online October 17, 2012)); *see also* Ex.2029, 153:1-4. As an initial matter, to the extent that Petitioner argues that the prior art taught adding one loading dose, that does not result in the claimed regimen. Ex.2027, ¶82. Additionally, both articles on which Petitioner relies were discussing the benefits of three initial monthly doses, not five, and neither suggests that increasing the number of initial monthly doses would have been desirable. Ex.2027 ¶¶143-44. Petitioner otherwise provides no reason why the POSA would have modified the eight-week dosing arm described in the 2009 Press Release to require five, and just five, initial monthly loading doses. Indeed, the POSA’s motivation would have been the opposite—both the burden of intravitreal injections and the risk of rare but severe adverse events would have militated against increasing the number of loading doses. Ex.2027 ¶¶142, 180; Ex.1007, 1;

Ex.1002 ¶¶148-49 (arguing a POSA would seek to “minimiz[e] the number of injections so as to minimize potential complications from repeated intravitreal injections”).

Petitioner’s argument is at best an argument that adding doses would have been “obvious to try,” but as with Ground 2, “where the prior art, at best gives only general guidance as to the particular form of the claimed invention or how to achieve it, relying on an obvious-to-try theory to support an obviousness finding is impermissible.” *Roxane*, No. IPR2016-00690, 2016 WL 5226531 (quoting *In re Cyclobenzaprine*, 676 F.3d at 1073). And here, there is not even general guidance in favor of the modification that Petitioner asserts the POSA would have made.

More fundamentally, even if the POSA would have been motivated to add doses to the regimens disclosed in the 2009 Press Release (and there is no reason to believe she would have been), there are numerous ways to add doses that do not result in the claimed regimen. Ex.2027 ¶¶145, 147. The POSA could add one, or three, or four loading doses instead of two, or the POSA could have added monthly doses sometime after a period of every-eight-week dosing. Ex.2027 ¶145. The POSA could also have shortened the eight-week dosing interval (on a predetermined or individualized basis) rather than add monthly doses, as physicians began to do with “treat and extend” regimens around the time of the priority date of the ’601 Patent. Ex.2027 ¶145, 59; *see* Ex.2029, 209:17-19, 213:2-

12. The POSA might also, as Petitioner contends, have been motivated to make the maintenance dosing discretionary (as it was in Elman 2010 and other arms in the 2009 Press Release) rather than fixed. Ex.2027 ¶145. “When a field is ‘unreduced by direction of the prior art,’ and when prior art gives ‘no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful,’ an invention is not obvious to try.” *Unigene*, 655 F.3d at 1361 (citations omitted); *see also Ortho-McNeil Pharm., Inc. v. Mylan Lab’ys, Inc.*, 520 F.3d 1358, 1364 (Fed. Cir. 2008) (the number of alternatives must be “easily traversed, small and finite”). And 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. Ex.2027 ¶146, 104.

In short, Petitioner has not shown that the POSA would have combined the 2009 Press Release and Elman 2010, or that the POSA would have arrived at the dosing regimen of the challenged claims even if she had.

VII. THE PRIOR ART DOES NOT DISCLOSE THE REQUIRED EFFICACY (ALL CLAIMS AND GROUNDS)

Each of the independent claims includes the requirement of “an effective amount” in the dosing regimen, meaning that the regimen achieves a level of

efficacy at least as beneficial as the established standard of care in 2011. None of the asserted prior art discloses or renders obvious achieving this result with the claimed regimen. Ex.2027 ¶149. Rather, the art discloses trials with alternative approaches and no guarantees of efficacy.

Nothing in the 2009 Press Release discloses results or provides any other indication that any arms of the DA VINCI trial would be efficacious. Ex.2027 ¶¶150-153. Petitioner argues that the Press Release shows 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.” Pet. 34-35. But the fact that Regeneron was *beginning* clinical trials with multiple regimens does not mean that any one trial would be successful. *See Sanofi-Aventis U.S. LLC v. Sandoz, Inc.*, No. 20-804-RGA, 2023 WL 4175334, at *14 (D. Del. Jun. 26, 2023) (finding that the POSA would not “reasonably extrapolate from the fact that a Phase III trial had begun that a drug could be expected to be successful.”); Ex.2027 ¶151.

The 2009 Press Release notes that “[t]he primary efficacy endpoint evaluation is mean improvement in visual acuity at six months.” Ex.1009. This itself shows that the Press Release *could not* report whether the dosing regimens would reach the efficacy endpoint. Ex.2027 ¶152. The Press Release makes clear that initial efficacy data would not be available until at least the first half of 2010. Ex.1009; Ex.2027 ¶152.

Petitioner does not appear to rely on any reference except the 2009 Press Release to disclose the efficacy limitations of the challenged claims. Even if Petitioner attempted to rely on its secondary references, they do not teach or suggest the required efficacy.

As discussed above, Shams involves a different drug with a different disclosed dosing regimen. It therefore does not disclose any information about the effectiveness of a five loading-dose regimen using VEGF Trap-Eye to treat DR or DME. Ex.2027 ¶¶155-156.

As discussed above, Elman discloses information about a different drug and a range of possible dosing schedules. It reports efficacy results for the tested regimens, but it provides no indication of the efficacy of an eight-week dosing interval. Ex.2027 ¶¶157-158.

The PIER publication 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.2027 ¶159; Ex.1004, 5 Fig.1; *see also* Ex.2035 ¶¶22-31; Ex.2006, 2; Ex.2007, 2.

Petitioner's CATT reference discloses only inclusion and exclusion criteria and provides no information about efficacy. Ex.2027 ¶160; Ex.1018.

VIII. PETITIONER FAILS TO SHOW INTENT TO TREAT DIABETIC RETINOPATHY (CLAIMS 18-19, 21, 25-28, 33; ALL GROUNDS)

The 2009 Press Release discloses a clinical trial for DME. As discussed above in V.B.2, claims 18 and 26 require, at a minimum, an intent to treat DR. DR is a different condition than DME. Physicians can, and sometimes do, administer anti-VEGF agents for the purpose of treating DME rather than DR in patients with both conditions. Petitioner and Dr. Chaum can point to nothing in the 2009 Press Release to show that the investigators in that trial administered VEGF Trap-Eye for the purpose of treating DR. Instead, they assert that an intent to treat DME is tantamount to an intent to treat DR, but this assertion is unsupported and fails to address evidence such as the fact that the approved product labels list DR and DME as separate indications.

A. The record evidence distinguishes between DR and DME

The '601 Patent, Eylea® label, and Lucentis® label all distinguish between DR and DME, and so does Dr. Chaum. Ex.2027 ¶¶162. 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 separately list clinical trial data supporting the different indications. Ex.2034; Ex.1050; Ex.1016.

The distinction reflects differences in the definition and assessment of DR and DME. Ex.2027 ¶¶163-167. As discussed in II.A, DR is characterized by

various abnormalities in the retinal microvasculature, such microaneurysms, hemorrhages, and venous beading. Ex.2027 ¶163; Ex.2089, 6 Table 2; Ex.2091, 2. Its severity is assessed using composite scores based on the size and number of those abnormalities. Ex.2027 ¶¶164, 166. One such score is the Diabetic Retinopathy Severity Scale (DRSS). The Diabetic Retinopathy Study Research Group developed the DRSS to correspond to the risk of progression to vision-threatening proliferative DR. Ex.2027 ¶164; Ex.2091, 2. It is used to this day as a clinical trial endpoint for DR. Ex.2027 ¶164; Ex.2091, 8. Simpler classifications may be used in clinical practice. Like the DRSS, they grade DR based on the presence and quantity of various retinal abnormalities. Ex.2027 ¶166; Ex.2089, 6 Table 2; *see* Ex.2029, 225:18-226:4, 226:10-13.

DME is fluid buildup in the macula. Ex.2027 ¶163; Ex.1001, 1:41-44; Ex.2029, 30:24-31:15. Retinal thickness, as measured with optical coherence tomography, is a measure of the amount of edema (fluid buildup) in the eye. Ex.2027 ¶165; Ex.2029, 32:7-17.

DME can occur at any stage of DR and is not part of the definition of DR in clinical trials or clinical practice. Ex.2027 ¶¶165-67; Ex.2029, 25:7-13, 226:10-13. DME is not included on the DRSS or other standard scales of DR severity. Ex.2027 ¶¶165-66; Ex.2089, 6 Table 2; Ex.2091, 8.

In his own practice, Dr. Chaum, who “tr[ies] to be specific about what [he is] seeing in the patient,” uses the term “diabetic retinopathy” for patients without macular edema and adds “with macular edema” to describe the condition of a patient with both conditions. Ex.2029, 24:14-25:6.

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. Ex.2027 ¶168. DME has a more direct and immediate effect on vision than early stages of DR, and so treating DME is the foremost treatment objective in patients with both DME and mild to moderate DR. *Id.* In these patients, physicians often administer anti-VEGF drugs for the purpose of improving DME, *i.e.*, reducing fluid buildup in the macula, rather than improving DR, *i.e.*, improving the various microvascular abnormalities that define DR. *Id.*

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

Petitioner does not point to anything in the 2009 Press Release showing that VEGF Trap-Eye was administered for the purpose of treating DR specifically. The 2009 Press Release does not mention DR at all. Ex.2027 ¶169; Ex.1009. Instead, it states that VEGF Trap-Eye is “in Phase 2 development for the treatment of Diabetic Macular Edema (DME).” Ex.1009. From this disclosure, the POSA would understand that the focus of the trial was on testing VEGF Trap-Eye as a

drug to treat DME. Ex.2027 ¶169. There is no suggestion that the investigators were interested in testing the effects of the drug on DR, nor are any endpoints specific to DR, such as DRSS, mentioned. Ex.1009; Ex.2027 ¶169.

The comparison arm likewise fails to show any intent to treat DR. Ex.2027 ¶¶170-172. The press release states that the VEGF Trap-Eye arms were “being compared to focal laser treatment, the current standard of care in DME.” Ex.1009 at 1. Focal laser treatment, which involves intensive laser on or near the macula, had long been standard of care for DME, but would be unlikely to be used alone for DR. Ex.2027 ¶¶170-171; *see* Ex.2094, 3-4, 19. Whereas DME primarily affects the macula, DR affects the peripheral retina as well. Ex.2027 ¶171; Ex.2091, 2-5. Scatter laser photocoagulation, which involves laser treatment across the retina, sparing the macula, would be appropriate for proliferative DR and was used for severe non-proliferative DR as well. Ex.2027 ¶171; Ex.2095, 7; *see* Ex.2094, 4, Table 2, 17-19. A POSA would therefore recognize that focal laser treatment would be useful to evaluate the effectiveness of a drug on DME as compared to established therapies, but would not suggest that the investigators were interested in comparing the drug to established therapies for DR. Ex.2027 ¶172.

C. Petitioner's assertion that intent to treat DR is shown by intent to treat DME is unsupported and inconsistent with product labeling

Petitioner and Dr. Chaum assert that any treatment of DME is a form of treatment for the underlying DR and do not separately address the claims' requirement of an intent to treat DR. Ex.1002 ¶¶143-44 (“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.”); Pet. 30-31. This assertion is conclusory and unsupported—Dr. Chaum cites literature explaining that DME arises in DR patients, but not that treatment of DME counts as treatment of DR. Ex.1002 ¶¶143-44 (citing ¶¶137-139); *see* Ex.2027 ¶¶173-77. Petitioner's claim is therefore inadequate to support its conclusion that “treatment of DME via the dosing regimen disclosed in the 2009 Press Release would have necessarily been for the purpose of treating DR.” Pet. 33.

Petitioner also fails to grapple with the distinction drawn in product labels between DR and DME. The FDA recognizes a distinction between treating a single complication, symptom, or manifestation of a condition and treating the condition itself. Ex.2027 ¶174. In its regulations governing the indications and usage section of the label 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). FDA discussed in its later draft

guidance the circumstances under which “a broad disease indication may not be appropriate,” which include situations where “the drug may affect only certain signs, symptoms, or manifestations of the disease.” Ex.2096, 17.

This interpretation was borne out in the Eylea® label, which includes separate indications for DR and DME, and particularly in the Eylea® label approved in 2015, which distinguishes between “the treatment of ... Diabetic Macular Edema,” and “the treatment of Diabetic Retinopathy (DR) in Patients with DME.” Ex.1050, 2; Ex.2027 ¶175; *see* Ex.2029, 30:3-14 (Dr. Chaum testifying that he was unaware that FDA separately approved Eylea® for DR as compared to DME). Under Petitioner’s theory of the prior art, there would be no reason to include these separate indications (or separate claims in the ’601 Patent). Ex.2027 ¶175. Further, for the DR indication, the label provides DR-specific DRSS data and results from a DR-specific trial (PANORAMA). Ex.1016, 34-36. This supports an understanding that in the label, the indication “treatment of Diabetic Retinopathy” means treating underlying DR, not just DME. Ex.2027 ¶175.

In sum, nothing in the 2009 Press Release shows that Regeneron or the investigators were interested in the effect of VEGF Trap-Eye on subjects’ underlying DR, and any intent to treat DME would not be enough to meet the claim requirements.

IX. EYLEA'S COMMERCIAL SUCCESS IS AN OBJECTIVE INDICATOR OF NON-OBVIOUSNESS

A. Eylea® Has a Nexus to the Challenged Claims

There is a nexus between Eylea® and the challenged claims. *See Cont'l Can Co. USA v. Monsanto Co.*, 948 F.2d 1264, 1273 (Fed. Cir. 1991); *Volvo Penta of the Ams., LLC v. Brunswick Corp.*, 81 F.4th 1202, 1211 (Fed. Cir. 2023) (reversing finding of lack of nexus and vacating finding of obviousness).

Eylea's patented q8 dosing regimen is a key differentiator that has led to its commercial success. Ex.2043 ¶¶30-37; Ex.2027 ¶¶178-86. Patients and physicians value effective treatments that involve fewer needlesticks in the eye. *Id.*; Ex.2027 ¶¶180, 184. The dosing regimen makes that possible. Ex.2043 ¶¶30-37; Ex.2027 ¶¶181-84. Eylea® is administered because of the claimed dosing regimens for each indication in the challenged claims, DME, DR, and DR in patients with DME. Ex.2043 ¶¶14-15, 30-37; Ex.2027 ¶¶181-84. Physicians reported switching to Eylea® from competing products because of the dosing regimen. Ex.2043 ¶¶25-27, 34. Eylea's dosing regimen is considered a benefit over other anti-VEGF agents. Ex.2043 ¶¶34-35; Ex.2027 ¶¶180, 184. In a 2014 survey, 48% of physicians named dosing as a key benefit of Eylea® while only 16% named dosing as a key benefit of Lucentis®. Ex.2043 ¶¶34.

Thus, Eylea's commercial success has a nexus to the challenged claims.

B. Eylea® Is a Commercial Success

Significant market share and sales volume indicate the commercial success of the claimed embodiments in the challenged claims. *See Chemours Co. FC, LLC v. Daikin Indus., Ltd.*, 4 F.4th 1370, 1377 (Fed. Cir. 2021) (reversing finding of unpatentability due to commercial success).

Eylea® has grown to become the most common anti-VEGF treatment option for practitioners, with [REDACTED] using Eylea® more than other treatment options. Ex.2043 ¶29. Since 2012, Eylea's share of sales across all different indications has risen year-over-year, [REDACTED] Ex.2043 ¶28. A comparison of the change in market share from its launch until 2021 shows that it has gained [REDACTED] while Avastin® and Lucentis® have each lost [REDACTED]. *Id.*

For DME, Eylea® had a sales share of about [REDACTED] [REDACTED]. Ex.2043 ¶22. Eylea® also has the [REDACTED] [REDACTED] for the treatment of DME. *Id.* For DR without DME, sales share has increased since FDA approval for the indication [REDACTED] [REDACTED]. Ex.2043 ¶23.

Eylea® is the dominant option for second-line treatments, in which a patient switches to a new therapy because initial therapy doesn't work or stopped working. Ex.2043 ¶27. About [REDACTED] are in their second line of therapy.

Id. In terms of patient share of second line therapy, [REDACTED]

[REDACTED]. *Id.*

As for sales volume, the number of Medicare patients who have been treated with Eylea® and other treatments each year shows Eylea's commercial success.

From 2012 to 2021, the number of patients increased [REDACTED].

Ex.2043 ¶25. Over the same period, the number of Medicare patients [REDACTED]

[REDACTED] with fluctuations in between. *Id.*

The commercial success of Eylea® due to the claimed dosing regimen shows that the challenged claims are not unpatentable. Ex.2043 ¶16; *see also id.* ¶¶17-37.

X. CONCLUSION

For the foregoing reasons, the challenged claims 10-12, 17-19, 21, 25-28, and 33 of the '601 Patent are not unpatentable over Grounds 2, 3, and 6.

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Certification of Word Count (37 C.F.R. § 42.24)

I hereby certify that this PATENT OWNER’S RESPONSE has 13,930 words (as counted by the “Word Count” feature of the Microsoft Word™ word-processing system), exclusive of “a table of contents, a table of authorities, mandatory notices under § 42.8, a certificate of service or word count, or appendix of exhibits or claim listing.”

Dated: January 26, 2024

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CERTIFICATE OF SERVICE

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