

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SAMSUNG BIOEPIS CO., LTD.,
Petitioner,

v.

REGENERON PHARMACEUTICALS, INC.,
Patent Owner.

Case IPR2023-00739

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

**PETITIONER'S REPLY TO
PATENT OWNER'S RESPONSE**

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TABLE OF EXHIBITS

Exhibit(s)	Description
1001-1058	<i>Previously presented.</i>
1059	Declaration of Zachariah Summers In Support of Samsung Bioepis Co., Ltd.’s Unopposed Motion for Pro Hac Vice Admission
1060	Declaration of Elliot Choi Declaration In Support of Samsung Bioepis Co., Ltd.’s Unopposed Motion for Pro Hac Vice Admission
1061	Deposition Transcript of Michael W. Stewart, M.D. (March 29, 2024)
1062	Memorandum Opinion and Order Following Bench Trial, <i>Regeneron Pharms., Inc. v. Mylan Pharms. Inc.</i> , No. 22-cv-00061-TSK (N.D.W. Va. January 31, 2024) (ECF No. 692) (REDACTED)
1063	Final Written Decision in <i>Mylan Pharmaceuticals Inc. v. Regeneron Pharmaceuticals, Inc.</i> , IPR2022-01226 [Paper 101] (“601 FWD”)
1064	Final Written Decision in <i>Mylan Pharmaceuticals Inc. v. Regeneron Pharmaceuticals, Inc.</i> , IPR2022-01225 [Paper 96] (“681 FWD”)
1065	Order on Claim Construction, <i>Regeneron Pharms., Inc. v. Mylan Pharms. Inc.</i> , No. 22-cv-00061-TSK (N.D.W. Va. April 19, 2023) (ECF No. 427)
1066	Bench Trial Transcript (Vol. 1), <i>Regeneron Pharms., Inc. v. Mylan Pharms. Inc.</i> , No. 22-cv-00061-TSK (N.D.W. Va. April 19, 2023) (June 12, 2023) (“Yanco Trial Transcript”)
1067	Bench Trial Transcript (Vol. 8), <i>Regeneron Pharms., Inc. v. Mylan Pharms. Inc.</i> , No. 22-cv-00061-TSK (N.D.W. Va. April 19, 2023) (June 22, 2023) (“Csaky Trial Transcript”)
1068	Bench Trial Transcript (Vol. 4), <i>Regeneron Pharms., Inc. v. Mylan Pharms. Inc.</i> , No. 22-cv-00061-TSK (N.D.W. Va. April 19, 2023) (June 15, 2023) (“Albini Trial Transcript”)
1069	U.S. Patent No. 7,303,747
1070	Deposition Transcript of Richard Manning, Ph.D. (March 27, 2024)
1071	Deposition Transcript of David Brown, M.D. (April 3, 2024)

1072	Major JC et al., “DA VINCI: DME and VEGF Trap-Eye: Investigation of Clinical Impact: Phase 2 Study in Patients With Diabetic Macular Edema (DME), ARVO Annual Meeting Abstract (April 2010), Vol. 51, Issue 13, available at: https://iovs.arvojournals.org/article.aspx?articleid=2375028
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I. INTRODUCTION

Because Patent Owner disclaimed claims in response to the Petition in this matter, the remaining twelve claims are 10-12, 17-19, 21, 25-28, and 33 (the “Challenged Claims”). Grounds II, III, and VI of the Petition address these claims. Of the Challenged Claims, the three independent claims are 10, 18, and 26. These claims recite a dosing regimen of five monthly doses followed by doses administered every two months. The dependent claims recite trivial variations, none of which Patent Owner contends independently confer patentability. Accordingly, the primary question remaining in this IPR is whether the use of five monthly loading doses for DR/DME was obvious. It was.

The 2009 Press Release alone or in combination with Shams or Elman renders obvious five monthly loading doses. There is no special benefit taught in the ’601 patent to using five monthly doses. Ex.1061, 9:15-10:11; 29:3-30:6. Five monthly doses is simply the number that works for *some* patients, and, importantly, the claims do not require the dosing regimen to apply to all patient populations. *Id.*, 142:3-143:1. Indeed, there is no data in the patent supporting a conclusion that five doses is optimal to all patient populations. Ex.1061, 27:2-22, 29:22-30:2. It is not. There is thus no requirement that a POSA would have been motivated to adopt five initial loading doses for *all* patients.

The 2009 Press Release describes using three monthly loading doses followed by 8-week maintenance doses, among other regimens. Ex.1009. While three might be appropriate for some patients, a POSA would have understood that other patients would benefit from additional loading doses, including five monthly loading doses. This is reflected in the alternative dosing regimens described by the 2009 Press Release, which either did or could have resulted in more initial monthly doses. And if this is not enough for obviousness (it is), Shams (Ground II) taught the use of loading and maintenance periods for anti-VEGF regimens along with “adjust[ing] [doses] to minimize adverse effects while maintaining a maximum therapeutic effect.” Ex.1010, 22-24. And, if necessary, Elman (Ground III) specifically confirms the use of at least five monthly loading doses for DR/DME was known. In combination with the 2009 Press Release, these references render the Challenged Claims obvious.

In its Patent Owner Response (“POR”), Patent Owner’s primary tack is to treat the POSA like an automaton, insisting that because the art does not contain an explicit disclosure of exactly five monthly loading doses followed by 8-week dosing, a POSA could never find their way there, and would rigidly pursue “exactly” three monthly loading doses. But an obviousness analysis “can take account of the inferences and creative steps that a person of ordinary skill in the art would employ.” *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007). It is undisputed that a

standard “creative step” taken by POSAs was to evaluate the number of initial doses necessary to treat a patient. Thus, the claims are nothing more than predictable uses of prior art elements—monthly initial dosing, followed by extended 8-week dosing—according to established functions—drying the retina, reducing treatment burden to the extent possible. *In re Kubin*, 561 F.3d 1351, 1359-60 (Fed. Cir. 2009).

The remainder of Patent Owner’s resistance amounts to already-rejected or last-ditch claim construction positions that have no basis in the intrinsic evidence and violate the basic rule against reading in limitations from the specification. As it consistently has in prior decisions, the Board should reject Petitioner’s claim construction arguments here.

Accordingly, as set forth in the Petition and below, the Board should cancel the Challenged Claims as obvious.

II. CLAIM CONSTRUCTION

A. The Challenged Claims Are Not Limited to “Fixed,” “Predetermined” Dosing Without Patient Assessment

The Challenged Claims generally recite a method for treating DR/DME, including the intervals between doses. The claimed dosing schedule is not limited, however, by any particular dosing strategies (e.g., fixed, PRN, treat and extend, etc.), nor do the claims specify the regimen must be adopted in advance or exclude patient assessment. Based on the plain language, if administration of aflibercept to a patient

results in extended 8-week dosing after five initial monthly doses—regardless of the strategy used to arrive at it—it falls within the scope of the claims.

Patent Owner argues (at 3-4) that the Challenged Claims require the recited dosing schedule to be “fixed” or “predetermined” in advance of treatment, without patient assessment, and do not cover dosing regimens based on any other theory. It rests the bulk of its substantive arguments on this position. POR, 3-4, 11, 16-21, 23-59; Ex.2027, ¶¶58-70, 149-177. Patent Owner’s argument is so extreme that its expert contends that even if the prior art disclosed the exact regimen recited in the claims, that would not disclose the invention if the practitioner did not determine *in advance* to apply that regimen only, without individual assessment, or if the practitioner switched to PRN after some extended dosing. Ex.1061, 20:11-21:14, 23:3-24:13, 145:16-147:21. Nothing in the intrinsic evidence supports Patent Owner’s position.

First, all of the Challenged Claims simply recite the steps of the method without specifying *any* particular dosing strategy or underlying theory.¹ *Id.* Moreover, claims 17, 25, and 33, recite exclusion criteria based on an assessment of

¹ The *Mylan* Court “decline[d] to read [“fixed”] into the claims.” Ex.1062, 307. Its decision should be given collateral estoppel effect, or, at a minimum, should be considered persuasive.

the patient's ocular condition before, during, and after each treatment. *Id.*, claims 17, 25, and 33. The Challenged Claims cannot be limited to “fixed” or “predetermined” dosing if the claims explicitly contemplate that the decision to treat the patient requires assessment of their ocular conditions during the course of treatment. *See* Ex.1061, 83:2-84:16. Similarly, dependent claims 12, 21, and 28 recite “after 20 weeks, administering, via intravitreal injection, 2 mg of aflibercept once every 4 weeks,” indicating the practitioner can switch back, at a time after 20 weeks, to every 4 week dosing if necessary to treat the patient. Patent Owner nowhere explains how such a switch could be consistent with a rigorous, predetermined regimen that requires 8-week intervals only, without assessment, as Patent Owner alleges is recited in the independent claims. *See* Ex.1061 144:21-145:5.

Patent Owner's only hook in the claim language is its contention that “every [x] weeks” somehow rigorously denotes only time periods set in advance, because this language is allegedly limited to embodiments in the specification describing clinical trials where the dosing regimen was set in advance. There are numerous problems with this theory. First, it is black letter law that claims are not limited to individual embodiments described in a patent absent a clear indication in the intrinsic evidence. *Liebel-Flarsheim Co. v. Medrad, Inc.*, 358 F.3d 898, 913 (Fed. Cir. 2004). It would be error to read in a “fixed” limitation here, particularly where only one

embodiment (Example 2) is described as “fixed” in the specification, and it does not correspond to the claimed regimen of five monthly loading doses. Ex.1001, 8:39-42; Ex.1061, 103:20-104:13. Indeed, even in Example 2, patients “were evaluated every 4 weeks for 9 months, during which additional doses were administered based on pre-specified criteria.” *Id.* This is inconsistent with Patent Owner’s argument that such assessments are unnecessary in a “fixed” regimen.

Second, Example 7, which provides the only disclosure of a dosing regimen with five loading doses, definitively does not describe the type of “fixed” regimens Patent Owner argues are used in clinical trials—Patent Owner’s expert admitted Example 7’s examples teaching five initial monthly doses do not correspond to actual clinical trials or testing results in the patent. Ex.1061, 27:12-28:5. Indeed, Example 7 expressly contemplates that a POSA can vary the relevant regimens, including the amount of secondary or tertiary doses given. Ex.1001, 17:9-15; Ex.1061, 32:20-34:11.

Third, Patent Owner contends that a POSA would understand all of the relevant embodiments as “fixed,” but bases this argument on a gross mischaracterization of Dr. Chaum’s testimony. Patent Owner (at 17-21) asserts that “column 16, lines 23-26, the ’601 Patent describes the dosing regimen set forth in the challenged claims,” and that Petitioner’s expert Dr. Chaum allegedly “acknowledged at his deposition that this refers to a predetermined dosing schedule,

(Ex.2029, 220:4-221:7), decided upon before treatment has begun.”² Dr. Chaum did no such thing. The full context of his answer, just before the cited testimony, shows he stated: “predetermined can mean determined in advanced. But *predetermined can also be determined based upon, for example, the clinical exam . . .* then by . . . *that definition* . . . [the disclosed dosing regimens] could be predetermined for that feature, which is a change in the patient’s exam.” Ex.2029, 217:25-221:7.

Thus, put in context, Dr. Chaum was not agreeing any embodiments are limited to “predetermined” regimens, set only in advance, as Patent Owner uses that term. He was testifying the embodiments might be described as “predetermined” if that term is understood, as POSAs understood it at the time, to encompass dosing regimens based on patient assessment as well as those that are fixed entirely in advance. Ex.2029, 217:25-221:7; *see also* Ex.1061, 97:17-99:1.

Finally, Patent Owner (at 19-20) also faults Petitioner for allegedly “ignor[ing] . . . that . . . the specification [at 4:30-46] describes variable dosing regimens as an *alternative* to fixed, predetermined dosing ‘every [x] weeks.’” But even if the specification recognizes PRN as one dosing strategy, the specification does not make a clear distinction between “fixed” strategies and strategies that

² The section of the ’601 patent discussed in this testimony does not actually describe the use of five initial doses. Ex.1001, 16:23-26.

include some form of individual assessment—indeed, the specification only describes a single “fixed” regimen in passing—nor does the specification clearly indicate the claims should be so limited. Patent Owner’s argument requires artificially reading every example as either “fixed” or PRN (with nothing in between), and somehow connecting that artificial dichotomy to the claim language. But there is no basis for doing so, and the specification explicitly teaches that the disclosed dosing regimens, including variations thereof, “would be appreciated by persons of ordinary skill in the art and are also within the scope of the present invention.” Ex.1001, 17:9-16; Ex.1061, 32:20-34:11.

Notably, the district court in *Mylan* rejected Patent Owner’s artificial distinctions between regimens, finding PRN dosing renders the claims obvious. Ex.1062, 259-271. Indeed, the court there found the sole alleged inventor admitted that PRN regimens were within the scope of the claims, contrary to Patent Owner’s position the claims are limited to “fixed” regimens and necessarily exclusive of PRN. *Id.*, 259-260; Ex.1066, 231:4-24; Ex. 1068, 781:18-784:13 (discussing Ex.1009), 785:5-787:17 (discussing Ex.1069); Ex.1067, 1958:19-1961:24. Moreover, in this proceeding, Patent Owner’s expert admitted that, for instance, “fixed” or “predetermined” regimens can involve individual assessment. Ex.1061, 98:5-99:1.

B. Consistent with the Board's Prior Decisions, the Challenged Claims Do Not Require Efficacy

Patent Owner has had multiple opportunities to litigate the construction of the '601 patent preamble and the preambles of the '338 and '681 patents that are substantially identical. Patent Owner's arguments for a particular efficacy have been rejected by the Board at least twice already. *See, e.g.*, Exs.1025, 1063-1065. There is no reason for the Board to depart from its prior construction of the "treating" and "effective amount" terms in the '338 and '601 FWDs. Indeed, the record here is even stronger. Patent Owner's expert admitted that to fall within the scope of the claims a patient need not show any particular efficacy, such as 8 letter improvements, or any efficacy at all, because there is a variability in individual patients' responses.³ Ex.1061, 53:19-59:21, 112:11-113:18, 148:10-24; *see also id.*, 66:10-68:12, 122:2-6. He also admitted that under his "efficacy" construction, claim 13 would be broader than claim 10, despite depending from it, and that he was importing a "one year" timepoint for measuring efficacy. *Id.*, 60:4-63:7.

³ As set out in Section IX.B-D of the Petition, a POSA would have found the alleged efficacy requirement obvious and expected, regardless. *See, e.g.*, Pet., 34-50; Ex.1008, 3-5; Ex.1061, 77:4-78:8, 142:3-143:1; Ex.1072.

III. THE CHALLENGED CLAIMS ARE OBVIOUS

The primary reference for all Grounds of the Petition is the 2009 Press Release. The 2009 Press Release teaches that Regeneron was beginning Phase II clinical trials studying the efficacy of aflibercept to treat DME, a type of diabetic retinopathy, via three different dosing regimens for 2 mg VEGF Trap-Eye (aflibercept), including the use of three initial injections of 2 mg spaced a month apart, followed by maintenance doses spaced eight weeks apart.

It is undisputed that a POSA would have understood that while three initial monthly doses might be appropriate for some patients, other patients might benefit from additional monthly doses. Ex.1061, 37:21-39:9, 127:9-129:21, 142:20-143:1, 152:2-153:2; Ex.1002 ¶¶150-158.

Indeed, one of the alternative regimens disclosed by the 2009 Press Release for the Phase II clinical trial is a regimen of 12 monthly doses of 2 mg aflibercept for the first year of treatment. The disclosure of this alternative regimen would teach a POSA that more than three initial doses would be safe and tolerable, and further suggest that some patients might benefit from more than three loading doses. Similarly, the third regimen disclosed in the 2009 Press Release is three monthly loading doses followed by PRN (“as needed”) dosing, which could easily lead to five or more monthly loading doses. *See* Ex.1002, ¶ 148-158.

Using five monthly loading doses thus would have been a routine modification of the 2009 Press Release’s three monthly loading dose regimen: a product of a skilled artisan’s “routine adjustments” to the initial dosing schedule, i.e., a “routine application of a well-known problem-solving strategy.” Pet. 36 (citing, e.g., *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1368 (Fed. Cir. 2007); Ex.1002 ¶¶ 146-158). “A POSA reading the... 2009 Press Release would have understood that Regeneron was pursuing multiple different dosing regimens with 2 mg of aflibercept to optimize dosing frequency 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. They would have done the same.

Shams confirms this sort of routine adjustment would be have been part of a POSA’s normal problem solving process. It teaches that “monthly dosing of a therapeutically effective amount of VEGF antagonist, followed by less frequent dosing of a therapeutically effective amount of VEGF antagonist” was standard as early as in 2006. Ex.1010, 2; *see also* Ex.1002, ¶155. Shams further explains that loading and maintenance allows “one to decrease subsequent doses of the therapeutic compound, while at the same time maintaining the therapeutic efficacy.” Ex.1010, 22; *see also id.*, 5-6. And it confirms that “routine adjustments” to loading and maintenance schedules can be “readily determined by a physician having

ordinary skill.” *Id.*, 23-24; *see also* Ex.1002, ¶155. As Dr. Chaum explains and as Regeneron’s expert agrees, such variation was and is a normal part of practice in treating DME/DR and other angiogenic diseases. *Id.*; Ex.1061, 18:7-19:10, 30:16-34:11, 38:14-39:9, 78:19-79:24, 127:9-129:2, 133:11-135:3, 138:18-25, 152:2-153:2, 154:9-156:9. Thus, to arrive at the claimed invention, all that was needed was to add a single monthly dose, consistent with this standard practice. The alleged invention was obvious.

A. The 2009 Press Release Alone

Patent Owner (at 23-24) first contends “[t]here is no merit to Petitioner’s suggestion that arriving at the claim regimen requires the addition of only one dose to the loading phase.” This is chicanery. The claims do not recite a “loading phase” of five doses—they recite administering 2 mg of aflibercept “every 4 weeks for the first 5 injections,” followed by extended dosing. All that is needed to arrive at this regimen is the addition of one dose between the third initial dose and the first extended dose. This minimal modification would reassure a POSA that the treatment would likely be safe and effective, while limiting the treatment burden.

Relying on testimony from Dr. Chaum, Patent Owner (at 24-28) further contends that the 2009 Press Release is a “bare bones” disclosure that could not lead a POSA to use five loading doses and would only lead a POSA to use “exactly three

loading doses.” In doing so, Regeneron again mischaracterizes Dr. Chaum’s deposition testimony and the 2009 Press Release.

First, Patent Owner (at 25-26) alleges that Dr. Chaum testified that he found the 2009 Press Release insufficient to render the claims obvious by itself. This is false (Ex.1002, ¶146-154 (analyzing the Press Release alone)). The testimony cited by Patent Owner merely reflects Dr. Chaum’s consideration of the scope of the art as well (as required), including in evaluating how to modify the Press Release’s regimen and whether a POSA was enabled to do so. Ex.2029, 261:9-296:20; 265:21-272:13 (“Q. So you’re not relying on the Regeneron press release alone for obviousness purposes? A. I’m using the press release together with other documents as listed in the declaration.”); 267:2-9 (same).

Contrary to Patent Owner’s argument, Dr. Chaum never testified that he did not offer an opinion on the 2009 Press Release alone, or that the 2009 Press Release was insufficient as a “starting point” in an obviousness analysis. In fact, Dr. Chaum explained exactly the opposite: that the Press Release taught to five loading doses because “the concept that Regeneron was putting out in the press release that ... we are doing clinical trials in an attempt to modify the number of doses required for patients would suggest to a [POSA] that modification would be beneficial for patient and clinical care.” *Id.*, 267:11-272:13.

Second, Patent Owner (at 26-28) alternatively argues that the 2009 Press Release would teach “exactly three loading doses” and nothing else, because it allegedly teaches that “exactly three loading doses was ideal.” This is an inappropriately narrow, automaton-like reading of the Press Release. As set out above, a POSA would understand from the alternative dosing regimens disclosed in the Press Release that three may not be “ideal.” For instance, a POSA would understand the alternative PRN regimen may lead to five monthly loading doses, and would further understand from the alternative monthly regimen that some patients would be expected to respond better to more than three loading doses. Ex.1002, ¶¶146-158; *see also* Ex.1061, 142:3-143:1, 151:15-152:20, 154:9-156:9; Ex.1062, 260-268. None of the cited references suggest a limit of three on the number of initial doses.

Moreover, POSAs routinely make modifications to dosing regimens for a wide variety of reasons, and it was understood in the art that DME/DR “responds slower”/was more stubborn and may require more treatment for some patients but that extended dosing could be used as well. Ex.1061, 37:21-39:9, 78:19-79:24, 127:9-129:2, 138:18-25; 146:6-23, 151:15-152:20, 154:9-156:9; Ex.1002, ¶¶156-158. That is all that is required to reach the claimed regimen. As the Federal Circuit has explained, “well-known, standard medical practices” are obvious and thus “varying doses in response to the occurrence of [patient response] would seem to be

a well-established, hence obvious, practice.” *Genentech, Inc. v. Sandoz Inc.*, 55 F.4th 1368, 1376-78 (Fed. Cir. 2022). Modifying the disclosed regimen to use five loading doses “in the presence of [unfavorable patient responses],” “would have been obvious in view of the prior art.” *Id.* at 1378.

Patent Owner (at 31-35) argues that a POSA would not engage in such optimization because the art reflected only a “narrow range for the number of loading doses: ‘one, two or three’” and that, allegedly, there were too many possible variations. Patent Owner cites *Red Diamond, Inc. v. S. Visions, LLP*, 2020 WL 2046054, at *8 (P.T.A.B. Apr. 28, 2020) and *In re Sebek*, 465 F.2d 904, 907 as alleged support. Patent Owner ignores, however, that *Red Diamond* properly notes that optimization is obvious when the art “recognize[s] a parameter as a result-effective variable,” (2020 WL 2046054, at *7-8), and in both cases the variable fell outside the ranges taught in the art. Here, POSAs understood that monthly dosing intervals were the baseline “result-effective variable” and further understood that they could vary the number of initial doses—or reduce them from monthly doses—for better effect, followed by extended dosing. *See, e.g.*, Ex.1061, 37:21-38:23, 78:19-79:24, 95:2-18, 127:9-129:21, 142:20-143:1; 154:9-156:9. Indeed, as Dr. Chaum testified, “it was a routine clinical practice to continue injections of other anti-VEGF agents on a regular 4 week interval until drying [of the retina] was

complete, after which the dosing interval could be extended.” Ex.1002, ¶153. Dr. Stewart agreed. Ex.1061, 127:24-129:21, 34:12-38:23, 151:15-156:9.

Patent Owner’s “narrow range” argument also ignores the facts. For instance, in addition to the three monthly dose regimen, the Press Release taught a six monthly dose regimen and a 12 monthly dose regimen. Thus, to the extent Patent Owner contends there must be a “limited range” within which optimization can occur, five monthly doses was well within this range. Similarly, Patent Owner admits (at 41-42) that Elman taught a range of loading doses from four to up to “at least six” for the treatment of DME—five obviously fits squarely in that range.

Additionally, even if the ranges taught in the art were too narrow, as Patent Owner contends, a POSA would not want to vary the basic framework of monthly intervals in order to avoid patient confusion and increase compliance, as Patent Owner’s expert acknowledged. Ex.1061, 137:2-138:25. Thus there is a limited range for loading doses given that the rest of the parameters are set forth in the 2009 Press Release. Accordingly, the facts here are analogous to those in *In re Copaxone Consol. Cases*, 906 F.3d 1013, 1025-29 (Fed. Cir. 2018), where the Federal Circuit found dosing claims obvious over the prior art. In *Copaxone*, the Federal Circuit found that “[e]ven if there were multiple injection frequencies not yet tested in the prior art — 1x, 2x, 3x a week etc. — these still represent a limited number of discrete permutations” given the small number of other possible variables. *Id.*

Finally, Patent Owner (at 33-37) argues that a POSA would not know in advance the optimal treatment regimen or expect to achieve success using “fixed, extended dosing intervals,” relying on its misguided claim construction. But there is no need to show that other dosing regimens with a different number of monthly doses were not also obvious. And even if Patent Owner’s claim construction is adopted, its position is incorrect. Patent Owner’s expert admitted that a POSA would expect success using the Press Releases regimen, as modified, at least for some patients: “Q. If in 2011 a POSA thought of using five initial doses on a monthly basis followed by eight-week doses for a patient population, the POSA would expect success for some patients but not necessarily all of them, is that correct? A. That’s correct.” Ex.1061, 142:20-143:1; *see also* Ex.1002, ¶158. Indeed, Patent Owner’s expert testified that the data in Table 2 of the patent, which corresponds to the regimen disclosed in the 2009 Press Release and was in the prior art (*see* Ex.1072) “supports the idea of pursuing a regimen like that in Claim 10 in a prospective study.” Ex.1061, 30:34-32:19, 107:11-109:6. A POSA would have expected success, even if a “fixed” regimen is required.

B. The 2009 Press Release in Combination with Shams

Patent Owner (at 28-31) suggests that Shams was not a “dependable reference” because it discloses in Example 1, in part, the PIER regimen which Patent Owner contends was a “failure.” First, Patent Owner’s characterization of the PIER

regimen is revisionist. Patent Owner’s expert admitted that he was aware of no contemporaneous statements characterizing PIER as a failure. Ex.1071, 121:16-122:10; Ex.1061, 74:11-75:18. Instead, he admitted that PIER teaches that its extended regimen resulted in gains of over 15 letters for some patients, and that the study authors—including Patent Owner’s own witness—concluded in the paper that “ranibizumab administered monthly for three months and then quarterly *provided VA benefit* to patients with neovascular AMD and was well tolerated” and, rather than calling extended dosing a failure, merely taught in view of the results that “[m]onthly dosing may be necessary in some patients to achieve maximal treatment benefit from ranibizumab Ex.1004, 247; Ex.1071, 78:24-85:5.

Regardless, the Board need not resolve whether PIER was a failure to discard Patent Owner’s theory. As the Board noted in the Institution Decision (at 38), “the disclosures of Shams encompass a larger variety of regimen options than merely that embodied in Example 1,” the allegedly failed protocol. Patent Owner’s position ignores the real import of Shams: that POSAs understood that they could optimize the initial monthly doses and extended doses to maximize the therapeutic effect while minimizing the overall number of doses. Ex.1002, ¶155.

C. The 2009 Press Release in Combination with Elman

Additionally, a POSA would have found it obvious to treat at least some patients with DR/DME by administering five initial monthly loading doses of

aflibercept based on the Press Release in view of Elman. Ex.1002, ¶¶159-184. Among its findings, Elman reported that at least 78% of patients in the most relevant group received a fifth initial monthly dose. *Id.* Accordingly, a POSA would have found it obvious to treat at least some patients with DR/DME by administering five initial monthly loading doses. *Id.* Notably, the art taught aflibercept had been tested for treatment of angiogenic eye disorders via four monthly loading doses followed by PRN dosing and six monthly loading doses followed by PRN dosing, thus bracketing the use of five initial loading doses. *See* Ex.1011; Ex.1009 (discussing six monthly doses for CRVO). Elman suggests the use of five for at least some patients.

Patent Owner's primary argument (at 41-43) is that Elman does not identify any individual patients that received five doses, and that Elman would teach that most patients in fact received six doses. This misses the point of Elman. Even if substantially less than 78% of patients required a fifth dose, or even if, as Patent Owner contends, Elman taught toward the use of six doses, the fact that Elman describes such a narrow range would be sufficient to suggest to a POSA the use of five initial loading doses for the treatment of at least some patients based on routine variation in the number of initial doses, particularly in view of the teachings of the 2009 Press Release. Ex.1002, ¶¶159-184. Indeed, Patent Owner's primary contention that Elman teaches "six plus" doses of Lucentis supports the use of five

plus doses of aflibercept, which was understood to be more promising than Lucentis. *Id.*; Ex.1008, 5.

Patent Owner (at 43-44) argues that the visual acuity data in Elman allegedly showed no gain, on average, after the fifth loading dose. First, this assumes that maintenance of the gained benefit after four loading doses would not have been considered beneficial, even though stabilization was generally understood to be the point in drying the retina. More fundamentally, focusing on the average gain ignores Elman's teaching that, based on assessment, POSAs found a fifth dose necessary in most individual cases. That would teach a POSA that optimizing the 2009 Press Release by adding additional doses might be necessary for some patients, even if it only helped to maintain vision.

Finally, Patent Owner (at 44-51) contends that a POSA would not be motivated to combine the teachings of Elman with the 2009 Press Release. But a POSA reviewing the 2009 Press Release in view of Elman would have found it natural to adopt, at least for some patients, teachings from the study of another anti-VEGF agent, ranibizumab, that at least five monthly loading doses were deemed desirable for a large segment of patients. *See*, Ex.1002, ¶¶164-172. Modifying the dosing regimen disclosed by the 2009 Press Release based on Elman would have required the most obvious of steps: ensuring a greater likelihood of success in treating at least some patients by slightly increasing the number of initial doses. *Id.*,

¶¶146-158, 164-172. A POSA thus would be motivated to use additional initial monthly loading doses at least for some patients, particularly given that the Elman 2010 results reflected in-field assessments of DME patients during the course of treatment. *See generally*, Ex.1002, ¶¶164-172.

Patent Owner also argues that the Elman visual acuity results allegedly would defeat motivation. This is misguided and misunderstands the import of the data. For instance, Patent Owner argues nothing in Elman “suggests three loading doses was inadequate.” Putting aside the fact this ignores POSAs routine motivation to optimize treatment for an individual patient, Patent Owner itself argues (42, 48) that *on average*, patients allegedly showed some decline after the fifth dose, and that this teaches to “six-plus” doses—obviously suggesting three may not be adequate for some patients. Similarly, Patent Owner focuses on the data in Figures 3 and 8, which it alleges shows decline after week 16. This ignores the actual, substantial improvement reported for patients by week 16 (the fifth dose)—(1) >120 um reduction in OCT and (2) >7 letters gain by week 16—and the fact many patients still received an additional dose. This suggests that for a large number of patients, clinicians gave additional doses because of their desire to dry the retina, consistent

with the standard of care, and regardless of current visual acuity outcomes.⁴ It does not suggest that five doses would be viewed as a failure, as Patent Owner argues.

D. The Prior Art Discloses an “Intent” to Treat DR

As set out in the Petition, DME is a known symptom of DR, and treating DME necessarily addresses the underlying DR. *See also* Ex.1002, ¶¶137-140. In other words, treatment of DME via the dosing regimen disclosed in the 2009 Press Release necessarily would have been for the purpose of treating DR, and such treatment was known to be effective. *Id.*, ¶143. Patent Owner’s expert, Dr. Stewart, acknowledged that DR affects the entire retina, and DME is a manifestation of DR that occurs when the leakiness caused by DR affects central vision. Ex.1061, 14:17-15:14. Thus, a POSA would have recognized at the time of the alleged invention that a method for treating DME in a patient treats DR in the patient (and requires, in Patent Owner’s words, an “intent” to do so) because treatment for DME requires treating the underlying DR. Ex.1002, ¶¶43-44, 137-140.

⁴ Indeed, Patent Owner’s focus on Figure 6 allegedly showing that 37% of the patient met the “success” criteria but only 22% did not receive the dose at week 16 confirms POSAs added an additional dose for some patients to dry the retina based on discretion rather than stopping the treatment as soon as the success criteria were met.

Patent Owner (at 54-59) contends the prior art does not disclose an “intent” to treat DR, relying on artificial distinctions made for indications on a product’s label. First, the claims do not recite labeled indications. Instead, they recite a method for the treatment of the recited disorders—DR/DME—“in a patient in need thereof.” Nothing in the patent indicates the preambles are limited to indications on a product’s label. Instead, the ’601 specification states that DME is a complication of DR and that DR can be treated by administering anti-VEGF agents in the manner claimed for DME. Ex.1001, 1:36-45. That is because treating DME treats DR, regardless of the indications on a product’s label. Ex.1061, 14:17-15:14, 68:6-69:9; Ex.1002, ¶¶137-140.

To avoid this fact, Patent Owner tries to characterize DR as merely “various microvascular abnormalities,” in an attempt to argue DME can be treated without treating this aspect of DR. But this is directly contrary to the testimony of both experts, who recognized that DR is characterized by vascular leakiness that eventually manifests as DME, and that treatment with anti-VEGF agents addresses this leakiness. *Id.* That this treatment might not, as Patent Owner appears to contend, treat all aspects or effects of DR or be spurred by a specific diagnosis does not mean it does not reflect treatment (or intent to treat) DR.

IV. NO SECONDARY CONSIDERATIONS SUPPORT NON-OBVIOUSNESS OF THE CHALLENGED CLAIMS

Patent Owner did not establish secondary considerations that would support a finding of non-obviousness. Patent Owner does not contest the absence of unexpected results or a long felt need/failure of others. Patent Owner's argument concerning commercial success of Eylea fails to overcome the strong prima facie case of obviousness presented in Petitioner's briefing. *Wyers v. Master Lock Co.*, 616 F.3d 1231, 1246 (Fed. Cir. 2010); Ex.1002, ¶¶209-214.

No Commercial Success: For commercial success, Patent Owner cannot establish that the claimed dosing regimen is what drives Eylea sales. For instance, Patent Owner's expert did not analyze whether the reported Eylea sales were associated with the claimed dosing regimen, let alone apply Patent Owner's "fixed" or "predetermined" construction in his commercial success analysis. Ex.1070, 31:19-33:12; 35:8-36:9, 42:9-45:9, 79:23-100:1, 120:8-126:25; *see also* Ex.1061, 42:10-45:17, 86:13-87:5. Indeed, Patent Owner's own evidence shows the majority of the Eylea sales **were not** attributable to the claimed 8-week dosing regimen that require five initial monthly doses. Exs. 2082-2085, 2143-2159.

Accordingly, Patent Owner "has not sufficiently demonstrated that [Eylea's] 'tremendous success' can fairly be attributed to the claimed invention." *Pfizer Inc. v. Sanofi-Aventis Deutschland GmbH*, IPR2019-00979, FWD, 93 (P.T.A.B. Aug. 11, 2020).

No Nexus. Patent Owner failed to tie any of its purported secondary considerations to the aspects of the Challenged Claims it argues are novel and absent from the prior art: five “loading doses” spaced a month apart in the treatment of DME or DR. Patent Owner thus cannot establish nexus to the “merits of the claimed invention” of the ’601 patent because the art discloses all of the claimed elements. *Novartis AG v. Torrent Pharms. Ltd.*, 853 F.3d 1316, 1330-31 (Fed. Cir. 2017).

V. CONCLUSION

For the foregoing reasons, Petitioner respectfully requests the Challenged Claims of the ’601 patent be found unpatentable.

DATED: April 26, 2024

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CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. § 42.24(a) and (d), the undersigned hereby certify that the forgoing Reply to Patent Owner's Response complies with the type-volume limitation of 37 C.F.R. § 42.24(c) permitting a reply of up to 5,600 words because, exclusive of the exempted portions, it contains 5,598 words as counted by the word processing program used to prepare the paper.

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CERTIFICATE OF SERVICE

In accordance with 37 C.F.R. § 42.6(e), I hereby certify that on April 26, 2024, true and correct copies of Petitioner's Reply to Patent Owner's Response and Exhibits 1061-1072 were served via electronic mail to Patent Owner at the following email addresses of record:

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