

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

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

v.

REGENERON PHARMACEUTICALS, INC.,
Patent Owner.

Patent No. 10,888,601

Inter Partes Review No. IPR2023-00739¹

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

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

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I. INTRODUCTION

In Petitioner's Reply, Petitioner contends that "the primary question remaining in this IPR is whether the use of five monthly loading doses for DR/DME was obvious." (Reply 1 (Paper 48).) But Petitioner's articulation of the purported question highlights the flaws in Petitioner's approach to the obviousness inquiry. The question is not whether an individual limitation of the challenged claims is identified in the prior art, with the benefit of hindsight, but without regard to what else the challenged claims require. Instead, the proper question is whether the claimed dosing regimens as a whole would be obvious to persons of ordinary skill at the time of the invention. Importantly, the invention dates back to 2011, before aflibercept was approved and before anyone had demonstrated that a predetermined, fixed, and extended dosing regimen for treating DME or DR (which are distinct diseases) would be expected to be effective.

Against this backdrop, the Board should decline to endorse Petitioner's suggestion that the claims are obvious simply because a POSA might back into the same dosing intervals as claimed, through individualized, *pro re nata* (PRN) dosing strategies. The claims are not directed to individualized treatment approaches—they are directed to particular predetermined, fixed dosing regimens for aflibercept, which the prior art does not teach or suggest. Indeed, two of the three primary references relied on by Petitioner concern a different drug,

Lucentis™. It is only with the benefit of hindsight that Petitioner is able to identify which portions of those varied, lengthy disclosures are needed to supplement the bare-bones disclosure of the 2009 Press Release (the one primary reference that *is* about aflibercept) so as to arrive at the claims. Even if a POSA somehow followed the same path as Petitioner and considered the references relied upon by Petitioner, Petitioner still has not shown that the challenged claims are obvious. The claimed invention is not to five loading doses standing alone (though Regeneron's later clinical trials showed there was an unexpected benefit from exactly five loading doses). Instead, the claims reflect a particular predetermined and fixed dosing regimen that is effective for treating specific angiogenic eye disorders and that limits the treatment burden on patients. Patients previously had been subject to monthly doses, or at best PRN dosing, of Lucentis, but neither renders the claimed dosing regimen for aflibercept obvious, nor would the ongoing clinical trials of aflibercept. Only later did Regeneron publish the results of its DA VINCI, VIVID, and VISTA clinical trials demonstrating the excellent efficacy of the predetermined, fixed, extended dosing regimens set forth in the challenged claims of the '601 patent. Accordingly, for the reasons set forth in the Patent Owner's Response, as addressed below, the Board should affirm the patentability of the challenged claims.

II. THE BOARD SHOULD ADOPT PATENT OWNER’S PROPOSED PRIORITY DATE

The Reply does not dispute that the challenged claims of the ’601 Patent have a priority date of January 13, 2011 at the latest. Thus, the Board should adopt Patent Owner’s proposed priority date.

III. CLAIM CONSTRUCTION

A. The Claims Require a Fixed, Predetermined Dosing Regimen

Petitioner maintains that the claims are not limited to fixed, predetermined dosing regimens to suggest that a PRN strategy—which theoretically *might* result in the claimed dosing intervals²—would render the claims obvious. But neither Petitioner nor its expert dispute that there is a recognized difference between as-needed dosing regimens (on which Petitioner relies heavily for obviousness) and fixed, predetermined dosing regimens. (Reply 7-8; POR 19.) This distinction is repeatedly emphasized in the specification. And that distinction matters for claim construction here.

In Example 5, the specification distinguishes between fixed “every 8 weeks dosing (2Q8)”—as found in the claims—and the unclaimed “as needed dosing ... (PRN)).” (*Id.*) Example 7 distinguishes between fixed, predetermined “every X

² Petitioner offers no evidence that any such PRN strategy ever did result in the claimed dosing intervals.

weeks” schedules and individualized approaches, such as PRN. Thus, Petitioner is incorrect in suggesting that Example 2 is the only embodiment that describes predetermined, fixed dosing. (Reply 6.) Petitioner attempts to minimize the disclosures, (*id.*), but whether Example 7 reports “actual clinical trials or testing,” as Petitioner urges, (*id.*), is irrelevant to the claim construction issue. *See also Pacing v. Garmin*, 778 F.3d 1021, 1026 (Fed. Cir. 2015) (holding that “every claim does not need to cover every embodiment”). The challenged claims track the language in Examples 5 and 7 that corresponds to predetermined, fixed dosing regimens, which do not encompass PRN. (*Compare, e.g.*, Ex.1001 at 22:41-46 *with id.* at 14:18-41 *and id.* at 15:36-17:8.)

Petitioner asserts that Patent Owner is trying to improperly limit the claims to specific embodiments. (Reply 5-6.) But there is nothing improper about some claims corresponding to some embodiments. A predetermined, fixed dosing regimen is the embodiment that is expressly claimed here. As Patent Owner explained, the specification and claims signal this by reciting “every X weeks.” That language is used in the claims and specification to refer to predetermined, fixed dosing regimens, which are explicitly distinguished from PRN dosing regimens (which are described using different language). (*Compare e.g.*, Ex.1001 at 22:41-46 *with id.* at 14:18-41, *and id.* at 15:36-17:8; POR 18-19.)

Given this intrinsic evidence, Petitioner’s argument that the claims do not

recite a “dosing strategy or underlying theory,” (Reply 4) makes no sense. As Patent Owner showed, “every [X] weeks” is a particular strategy—the intervals are predetermined and fixed. If they are not, and dosing is provided on an as-needed basis, then the claim is not practiced.

Petitioner separately argues that Patent Owner’s construction is inconsistent with the exclusion criteria of claims 17, 25, and 33. (Reply at 4-5.) It is not. The fact that treatment may be stopped entirely if certain conditions arise is not inconsistent with a fixed, predetermined dosing strategy employed for the duration of treatment. (Reply 5.) Petitioner also points to dependent claims 12, 21, and 28 to argue against Patent Owner’s construction. But those claims simply add additional predetermined, fixed requirements to the underlying predetermined, fixed dosing regimen. They do not encompass individualized or PRN dosing regimens.

Petitioner’s expert, Dr. Chaum, supports Patent Owner’s construction. (POR 11 (citing Ex.2029, 220:4-221:7).) On reply, Petitioner argues that Dr. Chaum’s testimony was taken out of context. Not so. The full testimony is set forth below and illustrates Dr. Chaum’s view that the language in Example 7 corresponding to the claims refers to a predetermined dosing regimen, presuming that “predetermined” is being used in the question to mean “timing frequency,” which is the case:

Q. Do you consider that to be a predetermined dosing schedule?

[objection omitted]

THE WITNESS: If your definition of “predetermined” is based upon a timing frequency, then that could be considered predetermined.

Q. Okay. In your opinion as a clinician and as someone offering opinions from the perspective of a POSA in this case, is that dosing regimen at lines 23 to 26 of Column 16 of the '601 patent, [“VEGFT 2 mg (0.5 mL) as administered by intravitreal injection once every 4 weeks for the first 20 weeks, followed by 2 mg (0.05 mL) via intravitreal injection **once every 8 weeks**”], a predetermined dosing schedule?

[objection omitted]

THE WITNESS: I think that dosing schedule could be considered to be predetermined, based upon your definition.

(Ex.2029 at 220:8-25 (emphasis added). Ex.1001 at 16:23-26 & claims 10, 18, 26.)

Petitioner separately argues that the named inventor of the '601 patent, Dr. Yancopoulos “admitted that PRN regimens were within the scope of the [challenged] claims.” (Reply 8 (citing Ex.1066 at 231:4-24).) But the cited testimony is not specific to any claim, let alone the challenged claims. Instead, Dr. Yancopoulos was directed to the portion of Example 7 referring explicitly to PRN dosing and he testified as follows:

Q. It's right here on the screen, but it's at Column 17, lines 33 to 37, exhibit page 2.

A. Yes. It's one of the examples of regimens that could be used.

Q. Okay. So you claimed as your invention a dosing regimen that you called earlier today the dumbest dosing regimen ever?

A. I think the point is that they're within the scope of the present invention. Nowhere am I saying that this is the preferred. This would work and provide some benefit to patients, just not a -- it would not provide the best visual outcomes, as we now know.

(Ex.1066 at 231:4-24.) Thus, Dr. Yancopoulos was testifying about his overall invention, not the invention specifically claimed in the challenged claims of the '601 patent. As Patent Owner previously explained, some claims in related patents do explicitly claim PRN dosing regimens, but the challenged claims of the '601 patent do not.

Petitioner's assertion that "Patent Owner's expert admitted that ... 'fixed' or 'predetermined' regimens can involve individual assessments" does not suggest Patent Owner's construction is incorrect. (Reply 8.) Dr. Stewart was asked if there was a "possibility" that a predetermined regimen would "vary" "based on what you see." (Ex.1061 at 98:5-8.) Dr. Stewart explained that "you always have to be willing to change therapies if you have an unusual adverse event." (*Id.* at 98:5-15.) That is a statement about medical practices—a doctor who starts out

practicing a patent claim may very well stop if there is a medical imperative to do so—and not about claim construction.

Finally, the opinion from the Northern District of West Virginia court in a related case, on which Petitioner relies, (Reply 8 (citing Ex.1062)), does not compel Petitioner’s construction. The parties in the District Court litigation did not present this issue in the claim construction phase of the litigation, and the District Court only addressed it in the context of the parties’ obviousness arguments, without fulsome discussion of the portions of the specification differentiating between predetermined, fixed “every ___ weeks” dosing regimens and individualized, PRN dosing strategies. (*See, e.g.*, Ex.1062 at 51-52, 242-251, 256-311.) The Board has evidence that the District Court did not, namely Dr. Chaum’s admissions about these portions of the intrinsic record. Ex.2014; Ex.1062, 50-51, 259-260, 287. The District Court’s opinion is not controlling and is merely potentially persuasive authority. *See Pentair v. Hayward Indus.*, No. IPR2014-00190, 2014 WL 2601768, at *6 (P.T.A.B. May 29, 2014) (Petitioner’s “reliance on the district court order is not persuasive”); *Westinghouse Air Brake Techs.. v. Siemens Mobility*, No. IPR2017-00580, 2019 WL 164710, at *7 (P.T.A.B. Jan. 10, 2019) (rejecting petitioner’s reliance on district court construction).

B. The Claims Require Efficacy

Petitioner maintains that the challenged claims do not require any efficacy,

even though the claims expressly refer to a method of “treating” with an “effective amount,” and the specification refers to a goal of maintaining a “high level of efficacy,” *i.e.*, on par with monthly Lucentis or Avastin. (POR 11, 21-22.)

Patent Owner’s expert, Dr. Stewart, did not testify otherwise. (*Contra* Reply 9 (citing Ex.1061, 53:19-59:21; 60:4-63:7; 66:10-68:12; 112:11-113:18; 122:2-6; 148:10-24).) Instead, Dr. Stewart consistently testified that efficacy is required. Specifically, a POSA would understand the claims to require significant visual acuity gains on average, across the patient population. (Ex.1061, 55:20-56:1 (“Q. So your opinion is for Claim 10, the level of efficacy required is about eight letters of improvement in visual acuity, on average, for the patient population? A. On average. That the drug with the treated regimen needs to produce an improvement of about eight letters, on average, correct.”); *id.* at 54:11-24, 68:21-69:9.) This was what “treating” and “effective” meant in the context of the patent at the time, with Lucentis and Avastin setting the bar. (POR 21-22; Ex.2027 ¶¶72-77.)

C. The Claims Require An Intent To Specifically Treat DME Or DR

Petitioner does not dispute that the claims require at least an “intent to treat specific angiogenic eye disorders, namely DME and DR.” (POR 22.) Petitioner’s Reply does not address Patent Owner’s authority that “[t]o 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.” (POR 22-23 (citing *Eli*

Lilly v. Teva, IPR2018-01710, 2020 WL 1540364 (P.T.A.B. Mar. 31, 2020).)

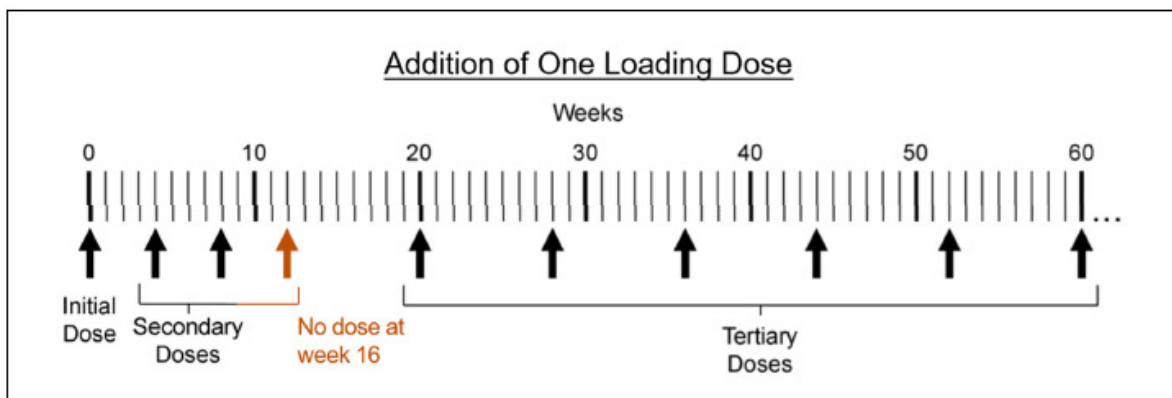
Accordingly, Patent Owner's proposed construction should be adopted.

IV. GROUNDS II, III, and VI FAIL

Petitioner has not met its burden of showing that the challenged claims are non-obvious based on Grounds II, III, or VI.

A. The 2009 Press Release Alone Does Not Render the Claims Obvious (Grounds II & VI – Claims 10-12, 17-19, 21, 25-28, and 33)

Petitioner does not dispute that none of the dosing regimens described in the 2009 Press Release employ more than 3 loading doses. (POR 26.) Petitioner maintains, however, that all that is needed to arrive at the claimed dosing regimen is one more loading dose. (Reply 12). That would not result in the claimed dosing regimen; it would result in a dosing regimen with four loading doses, as shown below:



In other words, even if a POSA were motivated to add a fourth loading dose as Petitioner suggests, it would not be followed by a fifth loading dose. Instead, the

POSA would recognize that there would be an eight-week interval, because the extended dosing phase begins as soon as the loading phase is over. Petitioner's suggestion that the claimed invention results from just adding a loading dose ignores that this would require modifying the loading dose phase set forth in the prior art *and* the extended dosing phase. Petitioner offers no rationale for why a POSA would have been motivated to add a single loading dose without pushing out the extending dosing portion of the regimen. There is no rationale in the prior art or the record beyond Petitioner's conclusory and hindsight-driven assertions.

Petitioner's arguments fail at the outset, as Petitioner fails to explain why a POSA would be looking to add loading doses at all, given that only three are proposed for one arm of the study reported in in the 2009 Press Release, and that no loading doses are employed in other arms (i.e., consistent monthly dosing). A POSA interested in reducing the number of injections to minimize treatment burden on patients would not be motivated to *increase* the number of initial injections as Petitioner contends. (See Ex.1002 ¶¶148-49.)

Petitioner's expert, Dr. Chaum, testified that even he was not relying on the 2009 Press Release alone for obviousness:

Q. Okay, I just want to be clear. If we go back to your declaration, on page 63, ... above paragraph 146, it refers to claims 10, 18, and 26, and you state that they're 'rendered obvious by the September 14, 2009 press release, either alone or in view of Shams.' Do you see that?

A. I – I do.

Q. And so is your testimony that you're not in fact relying on the press release alone?

A. I am not relying on the press release alone, rather in combination with Shams.

Ex.2029 at 266:4-16. Petitioner's attorney argument to the contrary should be rejected and its expert's testimony should be given effect.

Petitioner's reliance on *In Re Copaxone*, 906 F.3d 1013, 1017 (Fed. Cir. 2018) is also misplaced. (Reply 16.) There, the claims were directed to three injections of a 40mg dose of glatiramer acetate over seven days with at least one day between injections (i.e., for a total weekly dose of 120mg). *Copaxone*, 906 F.3d at 1017. The prior art, however, taught that 20mg and 40mg were the only available injections, that 40mg was an acceptable individual dose, that a total weekly dose of 140mg via daily 20mg injections was effective, and that less-than-daily injections were desirable and effective with fewer side effects. *Id.* at 1025. In view of these facts, a POSA would have limited dosing options to consider. As the court recognized, a POSA who was motivated to limit the number of injections would not choose 20mg with a day in between doses because that would yield a weekly dose of 60mg that was less than half of the known effective dose. *See id.* The POSA would not select 20mg to be injected four-six times a week because then there would not be a day in between doses. *See id.* So, the POSA was left with one option: try 40mg every other day to best approximate the current 140mg

weekly dose achieved by the 20mg daily dosing. *See id.* Thus, the Federal Circuit held that the claimed dose of 40mg three times per week for a 120mg/week dose was obvious to try. *Id.* at 1025-26.

Here, however, aflibercept was not yet approved. Regeneron itself continued to pursue different dosing amounts in clinical trials, and for any given dosing amount, there were multiple potential dosing regimens to consider and potentially pursue, each unproven. (POR 4, 34, 50-51.) Selecting the precise fixed-dosing regimen of the challenged claims when there was no established or approved dosing regimens for aflibercept required inventiveness far beyond the limited and standard dosing options at issue in *Copaxone*.

Genentech v. Sandoz, 55 F.4th 1368, 1371 (Fed. Cir. 2022), does not help Petitioner either. (Reply 14-15.) That case turned on the specifics of the prior art, what was known, and what was found by the district court to be standard medical practice—specifically, varying doses in response to certain side effects. *Id.* at 1376-77. That determination by the district court was supported by specific evidence, including drug labels. *Id.* Here, however, not only is there no similar evidence, but the evidence is the opposite: there were no standard regimens for aflibercept, because it had not yet been approved.

A more applicable decision is *Endo v. Custopharm*, 894 F.3d 1374, 1376-78 (Fed. Cir. 2018), where the Federal Circuit held that claims directed to extended

dosing regimens were nonobvious. There, the claimed method involved administering two initial injections and five subsequent administrations per year without “the need for doctors to personalize” the therapy. *Id.* at 1377. The prior art taught that existing therapies were undesirable in requiring injections every two or three weeks and “adjust[ments to] the dosage or intervals of administration for each patient.” *Id.* Even though the challenger presented evidence that a prior art injection presented a risk of overdosing, and even though the prior art disclosed that some patients in a study received prolonged injections at a similar rate to the intervals of the claimed method, the Federal Circuit held that the challenger “failed to meet its burden of showing that a skilled artisan would combine [a particular dose] with the injection schedule in the manner claimed.” *Id.* at 1386. The Board should follow this precedent and affirm the patentability of the challenged claims.

B. The 2009 Press Release and Shams Do Not Render the Claims Obvious (Ground II - Claims 10-12, 18-19, 21, 26-28)

Petitioner maintains that the various, undifferentiated dosing intervals disclosed by Shams, which can follow “any time schedule,” including “daily, weekly, biweekly, or monthly” doses that can be administered “before, during, or after the development of the disorder” for allegedly *any* VEGF antagonist and disorder (Ex.1010 at 22:30-35), would make the claimed method for treating DME or DR with aflibercept obvious in combination with the 2009 Press Release. But the only reason Petitioner is able to pull the claimed dosing regimen from the near

limitless number of possibilities listed in Shams is because Petitioner has the benefit of present day knowledge that the claimed dosing regimen worked in Regeneron's clinical trials. But this knowledge would not have been available to a POSA at the time of the invention and therefore, cannot provide the basis for an obviousness finding. *See, e.g., Purdue v. Depomed*, 643 F. App'x 960, 966 (Fed. Cir. 2016) ("Board therefore did not err in finding that [Petitioner] improperly relied on hindsight in formulating the problem to be solved."); *Insite Vision v. Sandoz*, 783 F.3d 853, 859 (Fed. Cir. 2015) ("Defining the problem in terms of its solution reveals improper hindsight in the selection of the prior art relevant to obviousness.").

While Shams does state a general preference for extending the dosing regimen (Ex.1010 at 21:27-35), that does not make the claimed dosing regimens obvious. Instead, "“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 Lab'ys v. Vanda Pharms., No. IPR2016-00690, 2016 WL 5226531 (P.T.A.B. Aug. 30, 2016) (quoting *In re Cyclobenzaprine*, 676 F.3d 1063, 1073 (Fed. Cir. 2012)); *In re Kubin*, 561 F.3d 1351, 1359 (Fed. Cir. 2009) ("where a defendant merely throws metaphorical darts at a board filled with combinatorial

prior art possibilities, courts should not succumb to hindsight claims of obviousness.”) (cited in Reply 3).³

Petitioner’s proposed combination of the 2009 Press Release with the general disclosures of Shams represents precisely the type of throw-everything-at-the-wall-and-hope-something-sticks approach to obviousness that the Federal Circuit has rejected. *See Cyclobenzaprine*, 676 F.3d at 1071. Petitioner’s approach is confirmed by its focus on broad, generalized disclosures in Shams, even though there are more specific disclosures in Shams that correspond to the extended dosing regimens actually pursued by Genentech in clinical trials for Lucentis. Petitioner does not explain why a POSA would rely on the broad, general disclosures of Shams instead of focusing on the specific dosing regimens actually pursued. And if, contrary to Petitioner’s arguments, a POSA focused on the Shams disclosures linked to clinical trials—a reasonable assumption—then those disclosures would steer the POSA away from an extended dosing regimen, because as Patent Owner showed, those clinical trials were regarded as a failure. (POR 6-7, 36-37.) Based on that information, a POSA would have no reason to be

³ Petitioner’s reliance on *Pfizer v. Apotex*, 480 F.3d 1348, 1368 (Fed. Cir. 2007), (Reply 11), is likewise unavailing because there is no “well-known problem-solving strategy” to apply to aflibercept.

motivated to try extended dosing ranges for a VEGF antagonist, particularly where sophisticated biopharmaceutical companies like Genentech had met with failures, and particularly where other dosing regimens had been shown to be effective. The path that Petitioner traces through Shams makes sense only with hindsight.

Petitioner's routine optimization theory fails as explained in Patent Owner's Response. (POR 4, 24, 31-37.) Petitioner pivots to contending that "monthly dosing intervals were the baseline 'result-effective variable.'" (Reply 15.) That argument does not cure the defect in Petitioner's combination: the 2009 Press Release and Shams do not disclose limited ranges that might support a routine optimization theory. (POR 32-33); *Genetics Inst. v. Novartis*, 655 F.3d 1291, 1306 (Fed. Cir. 2011) (quoting *In re Peterson*, 315 F.3d 1325, 1330 n.1 (Fed. Cir. 2003)). Dr. Stewart's testimony and Dr. Chaum's declaration do not satisfy Petitioner's new theory, which the Board should not consider in any event. *Telesign v. Twilio*, No. IPR2017-01976, 2019 WL 1085301, at *14 (P.T.A.B. Mar. 6, 2019) ("Because Petitioner's argument in the Reply (and at the oral hearing) is an improper new theory of unpatentability, this Decision does not consider that argument."). It would not have been obvious that increasing the number of loading doses from three to exactly five loading doses as part of a fixed, predetermined dosing regimen would have led to better outcomes in visual acuity, compared to other possible dosing regimens. (POR 26-27, 31.)

C. The 2009 Press Release and Elman Do Not Render the Claims Obvious (Grounds III & VI– Claims 12, 17-19, 21, 25-28, 33)

Using Elman instead of Shams does not help Petitioner because the focus of Elman is on individualized, PRN dosing, not a predetermined, fixed dosing regimen, as Petitioner concedes. (*Compare, e.g.*, POR 39-40, 43-44, 51-53 *with* Reply 18-20.) Petitioner tacitly concedes these points. (*Id.*)

Petitioner acknowledges, as it must, that Elman’s treatment protocols (which were always subject to physician discretion, (Ex.1006 at 16 (showing that treatment is “at ... discretion” and “can be skipped”))), required four initial monthly doses and allowed patients to receive more than five loading doses, both of which fall outside the claims. (POR 41.) Whether Elman teaches that 78% of patients received a fifth initial monthly dose does not mean it would have been obvious to treat DR/DME with aflibercept using exactly 5 initial monthly doses followed by fixed doses every 8 weeks on a predetermined basis. Nothing in Elman would steer a POSA toward this particular regimen, as opposed to others. (POR 43-44; Ex.2027 at ¶¶126-128; *Unigene Lab’s v. Apotex*, 655 F.3d 1352, 1361 (Fed. Cir. 2011) (“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.”)).

Even if a POSA were to consider Elman's treatment protocols, they relate to ranibizumab (Lucentis), not aflibercept. *See Allergan v. Sandoz*, 726 F.3d 1286, 1294 (Fed. Cir. 2013) ("we see no reason why the success of unrelated drugs would make it obvious to one of ordinary skill that" a dosing regimen for a different product would be effective). Beyond Dr. Chaum's present-day say-so, there is nothing in the 2009 Press Release or Elman that suggests increasing the number of loading doses for aflibercept from 3 to 5, while maintaining dosing every 8 weeks would be desirable or would "ensur[e] a greater likelihood of success" as opposed to the then-current dosing schedules. (Reply 20.)

Petitioner's argument, at bottom, is the type of appeal to "common sense" that the Federal Circuit has rejected, *see Arendi S.A.R.L. v. Apple*, 832 F.3d 1355, 1361-62 (Fed. Cir. 2016), and the Board should reject it as a basis for finding obviousness here.

D. The Prior Art Does Not Disclose an Intent to Treat DR (All Grounds – Claims 18-19, 21, 25-28, and 33)

Petitioner is wrong that Dr. Stewart testified that intending to treat DME necessarily includes an intent to treat DR. (Reply 22.) As Dr. Stewart explained in the passage cited by Petitioner:

Q. What is the difference between DR and DME?

A. So DR is changes to the retina. So DR is commonly believed to be a vasculopathy of the retina where you see microvascular changes related to diabetes, and it can occur anywhere in the

retina, be it the posterior pole, which is where DME exists, or it can be the more peripheral parts of the retina. DME is only confined to the macula; hence the name diabetic macular edema, and specifically it is swelling of the retina in the back center of the eye, the macula. DME may or may not have associated—I'm sorry, DR may or may not have associated DME. The two can coexist, but they do not necessarily coexist.

(Ex.1061 at 15:4-17.) Thus, Petitioner was wrong in its Petition when it argued that “treatment of DME via the dosing regimen disclosed in the 2009 Press Release would have necessarily been for the purpose of treating DR” and disclosure of a “DME dosing regimen” inherently anticipates a “DR dosing regimen.” (Pet. 32-33.) On reply, Petitioner attempts to distance itself from its prior argument that treating DME is the same as treating DR and argues for the first time that treating DME with aflibercept will necessarily treat any underlying DR. (Reply 22.) But even if Petitioner’s new argument is considered, it still fails to address the intent requirement of the claims. None of the prior art describing methods for treating DME disclose an intent to treat DR as well. Therefore, Petitioner has not satisfied its burden for challenged claims 18, 19, 21, 25, 26, 27, 28, and 33, each of which requires a specific intent to treat DR specifically, not just the chance that it might occur.

E. The Efficacy of the Claimed Dosing Regimen Is Not Disclosed In the Prior Art and Was Not Obvious (All Grounds – All Claims)

The Patent Owner Response explained that the prior art did not disclose the required efficacy. (POR 51-53.) Petitioner does not dispute that the claimed efficacy is not present in the 2009 Press Release, Shams, or Elman 2010.

Instead, Petitioner made a new obviousness argument about efficacy that is outside the permissible scope of reply. (Reply 9 n.3.) That argument is made in a footnote without any analysis. “It is of the utmost importance that petitioners in the IPR proceedings adhere to the requirement that the initial petition identify ‘with particularity’ the ‘evidence that supports the grounds for the challenge to each claim.’” *Intelligent Bio-Sys. v. Illumina Cambridge*, 821 F.3d 1359, 1369 (Fed. Cir. 2016) (quoting 5 U.S.C. § 312(a)(3)). Thus, a petitioner may not rely on new references and raise a new theory of unpatentability in reply. *Id.* (holding a reply brief and declaration exceeded the proper scope for a reply because they cited “a number of non-patent literature references which were not relied upon to support unpatentability in the Petition”); *Axonics v. Medtronic*, 75 F.4th 1374, 1383 (Fed. Cir. 2023); *Apple v. Andrea Elecs.*, 949 F.3d 697, 707 (Fed. Cir. 2020). Here, Petitioner newly relies on Major (Exhibit 1072), and cites Ground 4 of its Petition, which challenged only claims that Regeneron disclaimed. (*See* POPR at 1 n.1.) “Once the Board identifies new issues presented for the first time in reply, neither [the Federal Circuit] nor the Board must parse the reply brief to determine

which, if any, parts of that brief are responsive and which are improper.”

Intelligent Bio-Sys., 821 F.3d at 1369. Petitioner elected not to argue as part of Grounds 2-3 that the efficacy limitation is obvious. This belated obviousness combination is “entirely new.” *Id.* at 1370. Petitioner cannot now devise a new theory of unpatentability in a footnote in its Reply while depriving Patent Owner the opportunity to develop expert evidence to rebut the claim. Office Patent Trial Practice Guide, 77 FR 48756-01 (“Examples of indications that a new issue has been raised in a reply include new evidence necessary to make out a prima facie case for the patentability or unpatentability of an original or proposed substitute claim, and new evidence that could have been presented in a prior filing.”).

Regardless, the record shows that the claimed efficacy was unexpected and non-obvious. (POR 51-59.) Dr. Stewart’s testimony relates only to a POSA’s expectation of inter-patient variability, rather than efficacy on average across the population. (Ex.1061, 54:11-24; 55:20-56:1; 142:3-143:1.) Dr. Stewart was asked about the POSA’s expectations “in 2011” generally, which would have included the teachings in the ’601 patent itself given its January 13, 2011 priority date and additional public data from Regeneron’s clinical trials. (Ex.1061, 77:4-78:8, 142:20-143:1.) Virtually all of a POSA’s expectations “in 2011” is after the priority date. It is well-established that a drug cannot be expected to be successful from the mere fact that it has entered Phase III trials. *See Sanofi-Aventis U.S. v.*

Sandoz, No. 20-804-RGA, 2023 WL 4175334, at *14 (D. Del. Jun. 26, 2023) (cited in POR 52).

F. Objective Indicia of Non-Obviousness Weigh In Favor of Patentability (All Grounds – All Claims)

Although Petitioner includes a heading called “no commercial success,” Petitioner does not actually dispute that Eylea is commercially successful. *See Chemours Co. FC v. Daikin*, 4 F.4th 1370, 1377 (Fed. Cir. 2021) (reversing finding of unpatentability due to commercial success). Instead, it disputes whether there was an adequate showing that Eylea’s success is at least partially attributable to the claims. Thus, the only dispute is whether there is an adequate nexus.

Patent Owner established nexus. It demonstrated that the novel claimed dosing regimen is tied directly to Eylea’s sales. *Volvo Penta v. Brunswick*, 81 F.4th 1202, 1211 (Fed. Cir. 2023). Dr. Manning opined, relying on Dr. Stewart’s unrefuted testimony, that the claimed dosing regime is a significant driver of Eylea’s sales.⁴

Petitioner misreads *Novartis AG v. Torrent Pharms.*, 853 F.3d 1316, 1331 (Fed. Cir. 2017), by arguing that there can be no nexus if “the art discloses all of

⁴Patent Owner does not concede “the absence of unexpected results or a long felt need/failure of others.” (Reply 24.) The commercial success of Eylea due to the patented methods is sufficient to support the non-obviousness of the claims.

the claimed elements.” (Reply 25.) The *Novartis* court stated “[i]n evaluating whether the requisite nexus exists, the identified objective indicia must be directed to what was not known in the prior art—including patents and publications—which may well be the novel combination or arrangement of known individual elements.” *Novartis*, 853 F.3d at 1331. As the Federal Circuit has explained, *Novartis* does not stand for the proposition that commercial success has no bearing if “the art discloses all of the claimed elements” as Petitioner urges (Reply 25), because that reading “omits an important aspect of this principle: that ‘what was not known in the prior art ... may well be the novel combination or arrangement of known individual elements.’” *See Henny Penny Corp. v. Frymaster LLC*, 938 F.3d 1324, 1333 (Fed. Cir. 2019) (quoting *Novartis*, 853 F.3d at 1331). It is undisputed—as shown above—that the prior art does not disclose the claimed efficacy, the intent to treat DR, or 5 loading doses.

Finally, Petitioner’s argument overlooks that “there is a presumption of nexus for objective considerations when[, as here], the patentee shows that the asserted objective evidence is tied to a specific product and that product ‘is the invention disclosed and claimed in the patent.’” *WBIP v. Kohler*, 829 F.3d 1317, 1329 (Fed. Cir. 2016); (*see* POR 60 (explaining that Eylea practices the q8 dosing regimen)).

V. CONCLUSION

For the foregoing reasons and the reasons in the Patent Owner Response, 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.

Dated: June 14, 2024

Respectfully submitted,

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

I hereby certify that this PATENT OWNER’S SUR-REPLY TO PETITIONER’S REPLY TO PATENT OWNER’S RESPONSE has 5,598 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: June 14, 2024

By: /Adam R. Brausa/
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Certificate of Service (37 C.F.R. § 42.6(e)(4))

I hereby certify that the attached PATENT OWNER'S SUR-REPLY TO PETITIONER'S REPLY TO PATENT OWNER'S PRELIMINARY RESPONSE was served on the below date on the Petitioner via e-mail (by agreement) to the following counsel of record:

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