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Paper 9
Date: October 20, 2023

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SAMSUNG BIOEPIS CO. LTD,
Petitioner,
v.

REGENERON PHARMACEUTICALS, INC.,
Patent Owner.

IPR2023-00739
Patent 10,888,601 B2

Before JOHN G. NEW, ROBERT A. POLLOCK, and RYAN H. FLAX, *Administrative Patent Judges*.

NEW, *Administrative Patent Judge*.

DECISION
Granting Institution of *Inter Partes* Review
35 U.S.C. § 314

I. INTRODUCTION

Petitioner Samsung Bioepis Co. Ltd. ("Petitioner") has filed a Petition (Paper 1, "Pet. ") seeking *inter partes* review of claims 10–12, 17–19, 21, 25–28, and 33[1] of U.S. Patent 10,888,601 B2 (Ex. 1001, the "'601 patent"). Patent Owner Regeneron Pharmaceuticals, Inc. ("Patent Owner") timely filed a Preliminary Response. Paper 6 ("Prelim. Resp."). With our authorization (*see* Ex. 3001), Petitioner filed a Reply to the Preliminary Response (Paper 7 ("Reply")), and Patent Owner filed a Sur-Reply. Paper 8 ("Sur-Reply").

Under 35 U.S.C. § 314, the Board "may not authorize an *inter partes* review to be instituted unless … the information presented in the petition … and any response … shows that there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." Upon consideration of the Petition, Preliminary Response, Reply, Sur-Reply, and the evidence of record, we determine that the evidence presented demonstrates a reasonable likelihood that Petitioner would prevail in establishing the unpatentability of at least one challenged claim of the '601 patent. We therefore institute *inter partes* review of the challenged claims.

[1] Petitioner originally challenged claims 10–33, 46, and 47 of the '601 patent. Pet. 1. Patent Owner states that claims 13–14, 22, and 29–30 were disclaimed on July 11, 2022, before the Petition was filed. Prelim. Resp. 1, n.1 (citing Ex. 2001). Patent Owner also states that, subsequent to the filing of the Petition, claims 15, 16, 20, 23, 24, 31, 32, 46 and 47 were also disclaimed. *Id.* (citing Ex. 2002). Consequently, only claims 10–12, 17–19, 21, 25–28, and 33 of the '601 patent remain challenged by Petitioner.

II. BACKGROUND

A. Real Parties-in-Interest

Petitioner identifies Samsung Bioepis Co. Ltd. as the real party-in-interest. Pet. 6. Patent Owner identifies Regeneron Pharmaceuticals, Inc. as the real party-in-interest. Paper 5 at 2.

B. Related Matters

Petitioner and Patent Owner identify *Mylan Pharms. Inc. v. Regeneron Pharms., Inc.*, IPR2022-01226, as challenging different claims of the '601 patent. Pet. 6–7, Paper 4, 1. Petitioner confirms that, in *Samsung Bioepis Co., Ltd. v. Regeneron Pharms., Inc.*, IPR2023-00566, it filed a "copycat" petition, seeking joinder in IPR2022-01226, and proposing to join Mylan's *inter partes* review as a "silent understudy." *Id.* at 7 (citing IPR2023-00566, Papers 2, 3). Joinder of IPR2022-01226 and IPR2023-00566 was granted on March 22, 2023 in IPR2023-00566. *Id.* (citing IPR2023-00566, Paper 10).

The parties also identify *Mylan Pharms. Inc. v. Regeneron Pharms.*, *Inc.*, IPR2021-00880 and *Mylan Pharms. Inc. v. Regeneron Pharms., Inc.*, IPR2021-00881, challenging claims of US 9,254,338 and US 9,669,069, respectively, both of which are in the same family as the '601 patent. Pet. 7, Paper 4, 2. Final Written Decisions were entered in both IPR2021-00880 and -00881 on November 9, 2022, finding all challenged claims of both patents unpatentable. *Id.* Patent Owner has since appealed those decisions to the U.S. Court of Appeals for the Federal Circuit as *Regeneron Pharms, Inc. v. Mylan Pharms. Inc.*, No. 2023-1395 (Fed. Cir.) and *Regeneron*

Pharms., Inc. v. Mylan Pharms. Inc., No. 2023-1396 (Fed. Cir.), respectively. *Id.*

Furthermore, in *Mylan Pharms. Inc. v. Regeneron Pharms., Inc.*, IPR2022-01225, Mylan challenged the patentability of claims 1, 3–11, 13, 14, 16–24, and 26 of US 10,130,681. Pet. 7. Petitioner has separately challenged the patentability of the same claims of that patent in in *Samsung Bioepis Co., Ltd. v. Regeneron Pharms., Inc.*, IPR2023-00442, institution of which was granted on July 19, 2023. *See* IPR2023-00442, Paper 10. Celltrion, Inc. has similarly sought, and been granted, joinder with both IPR2022-001225 and -01226, and has also assumed a "silent understudy" posture in those cases. *See* IPR2023-00532, Papers 3, 7; IPR2023-00533, Papers 3, 7.

The parties further identify *Regeneron Pharms., Inc. v. Mylan Pharms. Inc.*, 1:22-cv-00061-TSK (N.D. W. Va.) as a related matter. *See, e.g.*, Pet. 8. Petitioner also identifies as a related matter *United States v. Regeneron Pharms., Inc.*, No. 1:20-cv-11217-FDS (D. Mass.). *Id.* Patent Owner also identifies *Chengdu Kanghong Biotechnol. Co. v. Regeneron Pharms., Inc.*, PGR2021-00035 (PTAB) (proceeding terminated). Paper 4, 2.

C. The Asserted Grounds of Unpatentability

Petitioner contends that claims 10–12, 17–19, 21, 25–28, and 33 of the '601 patent are unpatentable, based upon the following grounds:

Ground	Claim(s) Challenged	35 U.S.C. §	Reference(s)/Basis
2[2]	10–12, 18, 19, 21, 26–28	103[3]	2009 Press Release[4], Shams[5]
3	10–12, 18, 19, 21, 26–28	103	2009 Press Release, Elman[6]
6	17, 25, 33	103	2009 Press Release, Elman, CATT[7], PIER[8]

[2] Grounds 1, 4, and 5 of the Petition challenged claims that have been disclaimed by Patent Owner. *See* n.1, *supra*; Pet. 11. We therefore do not address those Grounds in this Decision.

[3] The Leahy-Smith America Invents Act ("AIA"), Pub. L. No. 112–29, 125 Stat. 284 (2011), amended 35 U.S.C. §§ 102 and 103, effective March 16, 2013. Because the application from which the '601 patent issued has an effective filing date after that date, the AIA versions of §§ 102 and 103 apply.

[4] Press Release, Regeneron, Enrollment Completed in Regeneron and Bayer HealthCare Phase 3 Studies of VEGF Trap-Eye in Neovascular Age-Related Macular Degeneration (Wet AMD) (September 14, 2009) (the "2009 Press Release") Ex. 1009.

[5] Shams (WO 2006/047325 Al, May 4, 2006) ("Shams") Ex. 1010.

[6] M.J. Elman et al., *Randomized Trial Evaluating Ranibizumab Plus Prompt or Deferred Laser or Triamcinolone Plus Prompt Laser for Diabetic Macular Edema*, 117(6) OPHTHALMOLOGY 1064–1077.e35 (2010) ("Elman") Ex. 1006.

[7] CATT Patient Eligibility Criteria, *retrieved from*: https://web.archive.org/web/20100713035617/http:/www.med.upenn.edu/cpob/studies/documents/CATTEligibilityCriteria_000.pdf ("CATT") Ex. 1018.

[8] C.D. Regillo et al., *Randomized, Double-Masked, Sham-Controlled Trial of Ranibizumab for Neovascular Age-related Macular Degeneration: PIER Study Year 1*, 145(2) AM. J. OPHTHALMOL. 239–48 (2008) ("PIER") Ex. 1004.

Petitioner also relies upon the Declaration of Dr. Edward Chaum (the "Chaum Declaration," Ex. 1002).

D. The '601 Patent

The '601 patent is directed to methods for treating angiogenic eye disorders by sequentially administering multiple doses of a vascular epithelial growth factor ("VEGF") antagonist to a patient. Ex. 1001, Abstr. These methods include the administration of multiple doses of a VEGF antagonist to a patient at a frequency of once every 8 or more weeks, and are useful for the treatment of angiogenic eye disorders such as, *inter alia*, age related macular degeneration. *Id.*

In an exemplary embodiment, a single "initial dose" of VEGF antagonist ("VEGFT") is administered at the beginning of the treatment regimen (i.e., at "week 0"), two "secondary doses" are administered at weeks 4 and 8, respectively, and at least six "tertiary doses" are administered once every 8 weeks thereafter, i.e., at weeks 16, 24, 32, 40, 48, 56, etc.). Ex. 1001, cols. 2–3, ll. 63–2.

E. Representative Claim

Claim 10 is representative of the challenged claims, and recites:

> 10. A method for treating diabetic macular edema in a patient in need thereof, comprising intravitreally administering, to said patient, an effective amount of aflibercept which is 2 mg approximately every 4 weeks for the first 5 injections followed by 2 mg approximately once every 8 weeks or once every 2 months.

Ex. 1001, col. 22, ll. 40–46.

F. Priority History of the '601 Patent

The '601 patent issued from U.S. Application Ser. No. 16/397,267 (the "'267 application") filed on April 29, 2019, and claims the priority benefit of, *inter alia*, US Provisional Application Ser. No. 61/432,245, which was filed on January 13, 2011. Ex. 1001, code (60).

The claims of the '601 patent, including challenged claims 10–12, 17–19, 21, 25–28, and 33 were allowed on November 12, 2020, and the patent issued on January 12, 2021. Ex. 1017, 5591; Ex. 1001, code (45).

III. ANALYSIS

A. Claim Construction

The Board applies the same claim construction standard that would be used to construe the claim in a civil action under 35 U.S.C. § 282(b). *See* 37 C.F.R. § 100(b) (2020). Under that standard, claim terms "are generally given their ordinary and customary meaning" as understood by a person of ordinary skill in the art at the time of the invention. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312–13 (Fed. Cir. 2005) (en banc). "In determining the meaning of the disputed claim limitation, we look principally to the intrinsic evidence of record, examining the claim language itself, the written description, and the prosecution history, if in evidence." *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 469 F.3d 1005, 1014 (Fed. Cir. 2006) (citing *Phillips*, 415 F.3d at 1312–17). Extrinsic evidence is "less significant than the intrinsic record in determining 'the legally operative meaning of claim language.'" *Phillips*, 415 F.3d at 1317 (quoting *C.R. Bard, Inc. v. U.S. Surgical Corp.*, 388 F.3d 858, 862 (Fed. Cir. 2004)).

1. "A method for treating...."

Petitioner initially accepts, for the purposes of this Decision, that the preamble of claim 1 is limiting, and agrees with the Board's prior rejection, in the related IPR2021-00881 Final Written Decision, of Patent Owner's position that the preamble requires a particular level of efficacy. Pet. 16 (citing Ex. 1002 ¶¶ 82–91). Specifically, Petitioner notes 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. *Id.* at 17 (quoting Ex. 1025, 19; and citing *id.* at 23; Ex. 1053, 9–10; Ex. 1054).

Patent Owner states that, for the purposes of this Decision only, it does not contest Petitioner's proposed construction. Prelim. Resp. 11.

Therefore, for the same reasons we explained in the Final Written Decision in related IPR2022-00881 concerning a related patent having claims with language similar to the presently challenged claims, and for the purposes of this Decision, we adopt Petitioner's proposed construction of "a method for treating…."

B. A Person of Ordinary Skill in the Art

In determining the level of skill in the art, we consider the type of problems encountered in the art, the prior art solutions to those problems, the rapidity with which innovations are made, the sophistication of the technology, and the educational level of active workers in the field. *See Custom Accessories, Inc. v. Jeffrey-Allan Industries, Inc.*, 807 F.2d 955, 962

(Fed. Cir. 1986*); see also Orthopedic Equip. Co. v. United States*, 702 F.2d 1005, 1011 (Fed. Cir. 1983).

Petitioner notes that, in the Final Written Decision in IPR2021-00881 and in the Decision to Institute in IPR2022-01226, the Board adopted the following definition of a person of ordinary skill in the art:

> A person of ordinary skill in the art at the time of the invention would have had (1) knowledge regarding the diagnosis and treatment of angiogenic eye disorders, including the administration of therapies to treat said disorders; and (2) the ability to understand results and findings presented or published by others in the field, including the publications discussed herein. Typically, such a person would have an advanced degree, such as an M.D. or Ph.D. (or equivalent, or less education but considerable professional experience in the medical, biotechnological, or pharmaceutical field), with practical academic or medical experience in (i) developing treatments for angiogenic eye disorders (such as AMD), including through the use of VEGF antagonists, or (ii) treating of same, including through the use of VEGF antagonists.

Pet. 14–15 (quoting Ex. Ex. 1025, 9–10). The Board found, in both proceedings, that this definition was consistent with the proper level of skill in the art. *See, e.g.*, Ex. 1025, 10. Petitioner urges us to adopt this definition as being consistent with the '681 patent, as well as the prior art cited by Petitioner. *Id.* at 18.

Patent Owner does not disagree with Petitioner's proposed definition for the purposes of the present decision Prelim. Resp. 11.

We again determine, at this stage of the proceeding, that our previous definition of the requisite level of ordinary skill in the art is reasonable and consistent with the prior art of record. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (holding that "the prior art itself [may] reflect[]

an appropriate level" as evidence of the ordinary level of skill in the art) (quoting *Litton Indus. Prods., Inc. v. Solid State Sys. Corp.*, 755 F.2d 158, 163 (Fed. Cir. 1985)). For the purposes of this decision, and for the sake of consistency, we adopt our prior definition, quoted above, as the definition of a person of ordinary skill in the art.

IV. ANALYSIS

A. Principles of Law

1. Burden of Proof

"In an [*inter partes* review], the petitioner has the burden from the onset to show with particularity why the patent it challenges is unpatentable." *Harmonic Inc. v. Avid Tech., Inc.*, 815 F.3d 1356, 1363 (Fed. Cir. 2016 (citing 35 U.S.C. § 312(a)(3) (requiring *inter partes* review petitions to identify "with particularity … the evidence that supports the grounds for the challenge to each claim")). Therefore, in an *inter partes* review, the burden of proof is on the Petitioner to show that the challenged claims are unpatentable; that burden never shifts to the patentee. *See* 35 U.S.C. § 316(e); *In re Magnum Oil Tools Int'l, Ltd.*, 829 F.3d 1364, 1375 (Fed. Cir. 2016) (citing *Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015)).

2. Obviousness

To ultimately prevail in its challenge to Patent Owner's claims, Petitioner must demonstrate by a preponderance of the evidence that the

claims are unpatentable.[9] 35 U.S.C. § 316(e); 37 C.F.R. § 42.1(d). A patent claim is unpatentable under 35 U.S.C. § 103 if the differences between the claimed subject matter and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying factual determinations including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of ordinary skill in the art; and (4) objective evidence of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

In determining obviousness when all elements of a claim are found in various pieces of prior art, "the factfinder must further consider the factual questions of whether a person of ordinary skill in the art would be motivated to combine those references, and whether in making that combination, a person of ordinary skill would have had a reasonable expectation of success." *Dome Patent L.P. v. Lee*, 799 F.3d 1372, 1380 (Fed. Cir. 2015); *see also WMS Gaming, Inc. v. Int'l Game Tech.*, 184 F.3d 1339, 1355 (Fed. Cir. 1999) ("When an obviousness determination relies on the combination of two or more references, there must be some suggestion or motivation to combine the references."). "Both the suggestion and the expectation of

[9] The burden of showing something by a preponderance of the evidence requires the trier of fact to believe that the existence of a fact is more probable than its nonexistence before the trier of fact may find in favor of the party who carries the burden. *Concrete Pipe & Prods. of Cal., Inc. v. Constr. Laborers Pension Tr. for S. Cal.*, 508 U.S. 602, 622 (1993).

success must be founded in the prior art, not in the applicant's disclosure." *In re Dow Chemical Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988); *see also In re Magnum Oil Tools*, 829 F.3d at 1381 (finding a party that petitions the Board for a determination of unpatentability based on obviousness must show that "a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so.") (internal quotations and citations omitted).

An obviousness analysis "need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *KSR*, 550 U.S. at 418; *see In re Translogic Tech, Inc.*, 504 F.3d 1249, 1259 (Fed. Cir. 2007). In *KSR*, the Supreme Court also stated that an invention may be found obvious if trying a course of conduct would have been obvious to a person of ordinary skill in the art:

> When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103.

550 U.S. at 421. "*KSR* affirmed the logical inverse of this statement by stating that § 103 bars patentability unless 'the improvement is more than the predictable use of prior art elements according to their established functions.'" *In re Kubin*, 561 F.3d 1351, 1359–60 (Fed. Cir. 2009) (citing *KSR*, 550 U.S. at 417).

We analyze the asserted grounds of unpatentability in accordance with the principles stated above.

B. Ground 2: Obviousness under 35 U.S.C. § 103 of claims 10–12, 18, 19, 21, 26–28 over the 2009 Press Release (Ex. 1009) and Shams (Ex. 1010)

Petitioner challenges claims 10–12, 18, 19, 21, 26–28 of the '601 patent as unpatentable under 35 U.S.C. § 103 as being obvious over the combination of the 2009 Press Release and Shams. Pet. 34–40.

1. Overview of the prior art

a. The 2009 Press Release

The 2009 Press Release was released by Patent Owner on September 14, 2009 and is prior art to the '601 patent. The 2009 Press Release announces the completion of patient enrollment in two randomized, double-masked, Phase 3 clinical trials evaluating VEGF Trap-Eye (aflibercept), its VEGF inhibitor, in the treatment of the neovascular form of age-related macular degeneration (also known as "wet AMD"). Ex. 1009, 1. The 2009 Press Release discloses that, in each study (respectively, VIEW-1 and VIEW-2), VEGF Trap-Eye was being evaluated for its effect on maintaining and improving vision when dosed as an intravitreal injection on a schedule of 0.5 mg every four weeks, 2.0 mg every four weeks, or 2.0 mg every eight weeks (following three monthly doses), as compared with intravitreal ranibizumab (Lucentis®) administered 0.5 mg every four weeks during the first year of the studies. *Id.* The 2009 Press Release further discloses that

as-needed ("PRN") dosing with both agents would be evaluated during the second year of each study. *Id.*

The 2009 Press Release further discloses that VEGF Trap-Eye was also in Phase 3 development for the treatment of Central Retinal Vein Occlusion (CRVO), another cause of blindness. Ex. 1009, 1. Patients in both studies would receive six monthly intravitreal injections of either VEGF Trap-Eye at a dose of 2 mg, or sham control injections. *Id.* At the end of the initial six months, patients would be dosed on a PRN basis for another six months. *Id.*

Additionally, the 2009 Press Release states that VEGF Trap-Eye was also in Phase 2 development for the treatment of Diabetic Macular Edema (DME) a type of diabetic retinopathy. Ex. 1009, 1. Patients would be administered VEGF Trap-Eye at 0.5 mg or 2 mg monthly, 2 mg every eight weeks after three monthly loading doses, or 2 mg on a PRN basis after three monthly loading doses, and would be compared to focal laser treatment, which was the then-current standard of care in DME. *Id.* The 2009 Press Release relates that patient enrollment had been completed, with initial data expected in the first half of 2010. *Id.*

b. Shams

Shams is WIPO International Application WO 2006/047325 A1, published on May 4, 2006, and is prior art to the '601 patent. Ex. 1010, codes (10), (43). Shams is directed to methods of administering to a mammal suffering from, or at risk for, an intraocular neovascular disorder, with regular dosing of a therapeutically effective amount of a VEGF

antagonist, followed by less frequent dosing of a therapeutically effective amount of VEGF antagonist. *Id.* at Abstr.

Specifically, Shams teaches methods of administering to a mammal a number of first individual doses of a VEGF antagonist, followed by a number of second individual doses of the antagonist, with the second individual doses administered less frequently than the first individual doses. Ex. 1010, 4–5.

Specifically, Shams teaches exemplary embodiments in which the first individual doses are administered at one-month intervals (e.g., about 3 individual doses), and the second individual doses are administered at three-month intervals (e.g., about 6 individual doses), with the second individual doses administered beginning three months after the number of first individual doses. Ex. 1010, 5. In another exemplary embodiment, the first individual dose is administered at months 0, 1 and 2. In another aspect, the second individual dose is administered at months 5, 8, 11, 14, 17, 20 and 23. *Id.*

Shams further teaches that "[t]he doses may be administered according to any time schedule which is appropriate for treatment of the disease or condition. For example, the dosages may be administered on a daily, weekly, biweekly or monthly basis in order to achieve the desired therapeutic effect and reduction in adverse effects." Ex. 1010, 22. In this respect, Shams discloses 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 within the method of the present invention. The time of administration of the number of first individual and second individual doses as

> well as subsequent dosages is adjusted to minimize adverse effects while maintaining a maximum therapeutic effect. The occurrence of adverse effects can be monitored by routine patient interviews and adjusted to minimize the occurrence of side effects by adjusting the time of the dosing. Any dosing time is to be considered to be within the scope of the present invention so long as the number of first individual doses of the VEGF antagonist is administered followed by a number of second individual doses, which are less frequently administered. For example, doses may be administered on a monthly schedule followed by subsequent quarterly or more dose schedule. Maintenance doses are also contemplated by the invention.

Id. at 22–23.

2. Petitioner's Argument

a. Independent claims 10, 18, and 26

Petitioner argues that independent claims 10, 18, and 26 recite treating diabetic retinopathy ("DR") and diabetic macular edema ("DME") by intravitreally injecting aflibercept using a dosing regimen of five initial injections of 2 mg (rather than two or more) that are spaced a month apart, followed by maintenance doses spaced eight weeks apart. Pet. 34 (citing Ex. 1001, 11).

The 2009 Press Release teaches that Regeneron, the Patent Owner and manufacturer of aflibercept, was beginning clinical trials studying the efficacy of aflibercept to treat DME *via* three different dosing regimens for 2 mg VEGF Trap-Eye (aflibercept), including the use of three initial injections of 2 mg that are spaced a month apart, followed by maintenance doses spaced eight weeks apart. Pet. 34–35 (citing Ex. 1009, 1; Ex. 1002 ¶ 147). Furthermore, argues Petitioner, the 2009 Press Release taught that a

regimen with more than three loading doses would be safe and tolerable and more likely to improve treatment for at least some patients. *Id.* at 35 (citing Ex. 1009, 1; Ex. 1002 ¶¶ 146–158).

Petitioner notes that the 2009 Press Release also discloses two alternative regimens for the Phase II clinical trial: (1) a regimen of 12 monthly doses of 2 mg aflibercept for the first year of treatment of DME—a standard and proven safe regimen for other anti-VEGF agents; and (2) a regimen of three initial loading doses followed by PRN dosing for treatment of DME. Pet. 35. According to Petitioner, the 2009 Press Release teaches that more than three initial doses would be safe and tolerable, and would suggest to a person of ordinary skill in the art that some patients might benefit from more than three loading doses, which could provide a reasonable expectation of success for such patients. *Id.*

Petitioner notes that Shams teaches that it was known in the art at the time of the '601 patent's filing that "monthly dosing of a therapeutically effective amount of VEGF antagonist, followed by less frequent dosing of a therapeutically effective amount of VEGF antagonist." Pet. 35, 2 (quoting Ex. 1010, 2; and citing Ex. 1002 ¶ 155). Petitioner also points to Shams' teaching "a treatment schedule comprising an initial interval of administration of a therapeutic compound [a VEGF antagonist], followed by a subsequent, less frequent interval of administration of the therapeutic compound" allows "one to decrease subsequent doses of the therapeutic compound, while at the same time maintaining the therapeutic efficacy." *Id.* at 36 (quoting Ex. 1010, 22). Petitioner also notes that Shams further explains that "[t]he specific time schedule [for administering doses] can be readily determined by a physician having ordinary skill in administering the

therapeutic compound by routine adjustments of the dosing schedule within the method of the present invention [i.e., loading and maintenance dosing]." *Id.* (quoting Ex. 1010, 23–24; and citing Ex. 1002 ¶ 155).

Petitioner contends that adjusting the 2009 Press Release protocol to administer 5 initial doses would be 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). According to Petitioner, a person of ordinary skill in the art would follow such a routine strategy when evaluating the appropriate dosing regimen for an individual patient, based on their clinical judgment, precisely as described in the art as early as 2006. *Id.* (citing Ex. 1002 ¶¶ 58–61, 146–158).

Petitioner also points to the Specification of the '601 patent, which, it argues, discloses no data specific to the efficacy of five monthly loading doses versus three monthly loading doses, or to any efficacy data on five monthly loading doses at all. Pet. 37. Petitioner notes that the Specification explains that "[t]he methods of the invention may comprise administering to the patient any number of secondary and/or tertiary doses of a VEGF antagonist" including "e.g. 2, 3, 4, 5, 6, 7, 8, or more." *Id.* (quoting Ex. 1001, col. 4, ll. 13–22). Furthermore, argues Petitioner, the use of five loading doses is disclosed by the Specification patent only as part of a list of twenty other variations on loading/maintenance dosing regimens that vary the number of initial doses, including from two to eight loading doses spaced four weeks apart. *Id.* (*see* Ex. 1001, cols. 15–17, ll. 40–8). Petitioner states that the Specification further discloses that "[a]ny of the foregoing

administration regimens may be used for the treatment of…" DME, among other angiogenic eye disorders. *Id.* (quoting Ex. 1001, col. 17, ll. 16–27).

Petitioner asserts that person of ordinary skill in the art would have therefore considered it obvious to vary the number of initial loading doses disclosed in the art for the treatment of DR/DME before moving to maintenance dosing for individual patients, including the use of five loading doses. Pet. 38 (citing Ex. 1002 ¶¶ 58–61, 146–158). Petitioner's Declarant, Dr. Chaum opines that such variation is a normal part of practice in treating DME and other angiogenic diseases. *Id.* According to Dr. Chaum, it was, and is, a routine clinical practice to continue monthly loading doses of anti-VEGF agents until the point at which the dosing interval can be reduced. *Id.*

Petitioner argues that varying the amount of secondary doses would have been part of the basic problem solving strategy a skilled artisan would undertake in treating a patient with DR/DME. Pet. 38 (citing Ex. 1002 ¶¶ 146–158). Petitioner contends that the motivation for making such routine adjustments to a dosing regimen for treatment of a patient "flows from the 'normal desire of scientists or artisans to improve upon what is already generally known.'" *Id.* at 38–39 (quoting *Pfizer*, 480 F.3d at 1368 (quoting *In re Peterson*, 315 F.3d 1325, 1330 (Fed. Cir. 2003)); also citing Ex. 1002 ¶¶ 145–158).

Petitioner contends that a person of ordinary skill in the art would also have had a reasonable expectation of success in using five initial loading doses instead of the three described in the 2009 Press Release. Pet. 39. Petitioner asserts that the 2009 Press Release's disclosure of a Phase II trial using loading and maintenance dosing of aflibercept to treat DME would have provided a skilled artisan with a reasonable expectation of success that

such a regimen would work, including the use of maintenance dosing. *Id.* Petitioner contends that the claimed combination merely adds an additional loading dose, which would only increase a POSA's expectation of success given the proven superiority of monthly dosing in general. *Id.*

Petitioner notes that prior initial testing of only a single injection of aflibercept for DME improved a patient's tested visual acuity, with a decrease of 79 μm in retinal thickness as measured by OCT, but then showed regression at six weeks without follow up. Pet. 39 (citing Ex. 1008; Ex. 1002 ¶¶ 146–158). Petitioner contends that a person of ordinary skill in the art would therefore have reasonably expected that continuing regular initial dosing beyond a single injection would increase the success of the treatment. *Id.* at 39–40 (citing Ex. 1002 ¶¶ 146–158).

b. Dependent claims 11, 19, and 27

Dependent claim 11 is representative of these claims and recites:

> 11. The method of claim **10**, wherein approximately every 4 weeks comprises approximately every 28 days or approximately monthly.

Ex. 1001, col. 22, ll. 47–49.

Petitioner argues that a person of ordinary skill in the art would have understood that 4 weeks consist of 28 days and that the term is used interchangeably with "monthly." Pet. 40 (citing Ex. 1006, 15; Ex. 1002 ¶¶ 180).

c. Dependent claims 12, 21, and 28

Dependent claim 12 is representative, and recites:

> 12. The method of claim **10**, further comprising, after 20 weeks, administering, via intravitreal injection, 2 mg of aflibercept once every 4 weeks.

Ex. 1001, col. 22, ll. 50–52.

Petitioner asserts that the language of the independent claims, including claim 10, requires dosing every 4 weeks for the first five injections followed by dosing every 8 weeks starting after week 16 (5 initial doses). Pet. 40. Petitioner argues that the language of claims 12, 21, and 28 requiring dosing every 4 weeks "after 20 weeks" is therefore facially inconsistent with the claims from which they depend. *Id.* (citing Ex. 1002 ¶¶ 181–184).

Petitioner argues that, to the extent that these claims should be read as requiring dosing every 4 weeks (monthly), the 2009 Press Release discloses such dosing as one arm of the VEGF Trap-Eye Phase 2 clinical trial for DME. Pet. 40 (citing Ex. 1009; Ex. 1002 ¶ 182).

Petitioner argues that, to the extent that these claims should be read as requiring dosing every 4 weeks through week 16, followed by 8 week intervals between doses, and then dosing every 4 weeks starting at a later point ("after 20 weeks"), such a regimen would be the result of routine experimentation, particularly in patients that show regression. Pet. 40–41 (citing Ex. 1006; Ex. 1008; Ex. 1045; Ex. 1002 ¶¶ 157, 183, 191).

3. Patent Owner's Preliminary Response

Patent Owner responds that each of the claims challenged upon this ground requires treating DR or DME using a fixed dosing regimen that consists of (a) five monthly initial injections of 2 mg each, followed by (b)

additional doses spread eight weeks apart, and argues that none of Petitioner's references discloses such a regimen. Prelim. Resp. 11. Patent Owner alleges that Petitioner use of different disclosures from the 2009 Press Release and Shams is impermissibly hindsight-driven and fails to cure this deficiency. *Id.*

Patent Owner contends that Petitioner's reliance on the 2009 Press Release suffers from two major flaws: (1) none of the four dosing regimens disclosed by the 2009 Press Release is the five-loading-dose regimen required by the challenged claims; and (2) the 2009 Press Release was issued before the disclosed clinical trials began and, therefore, the 2009 Press Release does not disclose the results of any of the four dosing regimens. Prelim. Resp. 12. With respect to (2), Patent Owner contends that there are consequently no results that would have motivated a person of ordinary skill in the art to modify one of the proposed regimens to add loading doses, despite the treatment burden, to arrive at the recited dosing regimen. *Id.* at 12–13.

Patent Owner contends that Petitioner "mixes and matches" the different regimens disclosed by the 2009 Press Release without providing a rationale for doing so. Prelim. Resp. *Id.* at 13. According to Patent Owner, Petitioner does not explain how the prospective regimens could provide any such motivation, given that the 2009 Press Release does not report the results for these regimens, which were unavailable. *Id.*

Patent Owner asserts that, even if, *arguendo*, results of the studies had been available, Petitioner does not explain why the 2 PRN regimen would suggest that some patients would benefit from more than three loading doses, much less five loading doses. Prelim. Resp. 13. The 2q8 regimen

involves three loading doses followed by doses at eight-week intervals, and so does the 2 PRN. *Id.* Patent Owner argues that combining them does not disclose or motivate, the administration of five loading doses. *Id.* Nor does the Petition explain why the 2 PRN regimen, which involves a switch from fixed dosing to individualized patient assessment after three doses, would provide a skilled artisan with motivation to achieve the claimed dosing regimen, which involves fixed dosing throughout the course of treatment. *Id.* at 13–14.

Patent Owner contends that Petitioner's reliance upon Shams does not cure these alleged deficiencies. Prelim. Resp. 14. According to Patent Owner, Shams concerns a different drug, Lucentis (ranibizumab), and does not disclose the recited dosing regimen, or any results that a person of ordinary skill in the art could reasonably expect from implementing such a regimen. *Id.* Patent Owner contends that Petitioner has not articulated any reason to modify the dosing regimens of the prior art beyond an alleged hindsight desire to arrive at the invention of the claims. *Id.* (citing *Life Spine, Inc. v. Globus Medical, Inc.*, IPR2022-01603, Paper 8 at 41 (PTAB June 12, 2023) (denying institution where record "d[i]d not reveal a reason for making the multiple modifications other than a desire to arrive at device [sic] with all the elements recited in claim").

Patent Owner argues that, despite Petitioner's reliance on Shams for the general concept of "a treatment schedule comprising an initial interval of administration of a therapeutic compound [an VEGF antagonist], followed by a subsequent, less frequent interval of administration of the therapeutic compound," Petitioner identifies nothing in Shams that would point the way specifically towards the recited dosing regimen. Prelim. Resp. 14 (citing

Pet. 36 (quoting Ex. 1010, 22)). Indeed, Patent Owner argues, Petitioner acknowledges that, by its own logic, "other dosing regimens with a different number of monthly doses—such as three, four, six, etc." were also obvious. *Id.* at 14–15 (quoting Pet. 38). Patent Owner contends that Petitioner's argument therefore ignores the law of obviousness. *Id.* at 15 (citing *KSR*, 550 U.S. at 421 (holding that that it is not "obvious to try" multiple possibilities unless "there are a finite number of identified, predictable solutions"); also citing *In re NTP, Inc.*, 654 F.3d 1279, 1299 (Fed. Cir. 2011); *In re Bell*, 991 F.2d 781, 784 (Fed. Cir. 1993)).

Patent Owner contends that Petitioner fails to identify a finite (let alone predictable) number of options for the numerous variables that can be varied to generate a dosing regimen from the prior art references, including: (1) the number of loading doses; (2) how far apart the extended doses are spaced; (3) the amount of each dose; and (4) the identity of the VEGF antagonist. Prelim. Resp. 15–16. Patent Owner contends that a claim is not obvious where one must "vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result." *Id.* at 16 (quoting *In re Kubin*, 561 F.3d 1351, 1359 (Fed. Cir. 2009); also citing *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1359 (Fed. Cir. 2007)).

Patent Owner contends that Petitioner points to no considerations that would lead a person of ordinary skill in the art to modify these various variables to arrive at the recited dosing regimen. Prelim. Resp. 16. On the contrary, argues Patent Owner the considerations that a skilled artisan would have to balance point in different directions. *Id.* By way of example, Patent Owner posits that adding more monthly loading doses to an extended dosing

regimen, as Petitioner suggests, would result in a greater treatment burden from visits and an increased risk of adverse events. *Id.* On the other hand, hypothesizes Patent Owner, abandoning monthly dosing in favor of extended dosing runs the risk of reduced efficacy and undertreatment. *Id.* at 16–17. Patent Owner argues that the lack of any guidance in the prior art on how to balance these various considerations to arrive at the specific regimen recited in the claims reflects the use of impermissible hindsight by Petitioner to arrive at the claimed inventions. *Id.* at 17 (citing *TWI Pharms, Inc. v. Merck Serono SA*, IPR2023-00050, Paper 8 at 21 (PTAB March 28, 2023)).

Patent Owner next argues that Shams teaches away from the claimed dosing regimen by disclosing dosing regimens in which the initial, more frequent doses are administered only three times, not five. Prelim. Resp. 17 (citing Ex. 1010, 24 (disclosing that "[t]he first dose may be administered, for example, one, two or three times, typically three times before the less frequent administration dose(s) is (are) administered" and "[i]n one aspect, the first individual dose is administered at month 0, 1 and 2").

Patent Owner adds that the sole example in Shams is a prophetic description of Genentech's Phase IIIb PIER study, which involved three monthly loading doses of a different VEGF antagonist (ranibizumab) followed by quarterly dosing. Prelim. Resp. 18 (citing Ex. 1010, 32–36). Patent Owner asserts that both the initial and second parts of this dosing regimen differ from the requirements of the challenged claims, as does the VEGF antagonist used in the study (ranibizumab is an antibody fragment, whereas aflibercept is a fusion protein). *Id.*

However, Patent Owner argues, even if Shams does not teach away from the challenged claims, a person of ordinary skill in the art would not

have had any motivation to adopt the regimen taught in Shams. Prelim. Resp. 18. According to Patent Owner, by the priority date of the challenged claims, the PIER study and its extended dosing regimen were known to be failures. *Id.* Patent Owner notes that, by 2011, the PIER dosing regimen disclosed in Shams was regarded as ineffective, "highly disappointing," and a "failure." *Id.* (citing Ex. 2005 ¶¶ 46–59). Therefore, Patent Owner argues, a skilled artisan would have been motivated to avoid, not adopt a similar regimen. *Id.*

In contrast, Patent Owner contends, by 2005, and based upon the results of Genentech's Phase 3 ANCHOR and MARINA trials, it was known in the art that monthly ranibizumab successfully produced visual acuity gains. Prelim. Resp. 19–20 (citing Ex. 2005 ¶¶ 32–38). Patent Owner asserts that there would thus have been little motivation to adopt PIER's extended dosing regimen when other treatments that could produce visual acuity gains were available. *Id.* at 20. Petitioner argues that the PIER data led Genentech to recommend that patients receive either monthly injections of ranibizumab, or have their retreatment schedules determined through individualized testing, reflecting an acknowledgment by Genentech that Shams' extended dosing regimen did not work well. *Id.* (citing Ex. 2004, 1).

Patent Owner contends that the recognized failure of Shams' PIER regimen is referred to in the Specification of the '601 patent. Prelim. Resp. 21. Patent Owner contends that the Specification, after citing the U.S. national phase application of Shams, states that "there remains 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." *Id.* (quoting Ex. 1001, col. 1, ll. 64–67). Patent

Owner asserts that Petitioner is not permitted to ignore these negative teachings of the prior art but, rather, "[w]hether the prior art teaches away from a reference may be dispositive of a challenge set forth in an *inter partes* review." *Id.* (citing *Apotex Inc. v. Novartis AG*, IPR2017-00854, 2018 WL 3414289, at *12 (PTAB July 11, 2018)).

Patent Owner next argues that Petitioner's argument that a person of ordinary skill in the art would be motivated to make "routine adjustments," based on exercising the artisan's "clinical judgment" during regular visits, fails to render the challenged claims obvious for at least two reasons. Prelim. Resp. 22.

First, Patent Owner contends, Petitioner does not show that making these "routine adjustments" to the dosing regimens disclosed in the 2009 Press Release or Shams would, in fact, result in the dosing regimen of the challenged claims. *Id.* Patent Owner asserts that Petitioner fails to point to disclosure of "routine adjustments" resulting in a single patient receiving five loading doses followed by a dose every eight weeks. *Id.* at 22–23. According to Patent Owner, this applies even if art involving VEGF antagonists other than aflibercept (such as Lucentis or Avastin) are considered. *Id.* at 23 (citing Ex. 1008, 5).

Second, Patent Owner asserts that the challenged claims are directed to methods for treating DME and DR using a fixed, extended dosing regimen, and not one based upon individualized patient assessments. Prelim. Resp. 23. Patent Owner asserts that a fixed approach provides for treatment on a predetermined schedule regardless of whether reaccumulated fluid has been detected, while assessment-based approaches take a fundamentally different approach by making injections conditional on

patient characteristics. *Id.* (citing Ex. 2009 1617–18, 1618; 643–44, 781). Patent Owner asserts that the '601 patent's achievement of the first fixed, extended dosing regimen was a departure from prior assessment-based approaches, rather than an obvious variant of them. *Id.* at 23–24.

Patent Owner argues that a major advantage of a fixed dosing regimen as compared to one based on individualized assessments is that monitoring visits are unnecessary. Prelim. Resp. 24. Patent Owner points to the 2009 Press Release, which explains that the regular monitoring visits necessary to implement Petitioner's "routine adjustments" dosing regimen would result in a significant burden as compared to a fixed dosing regimen, like the one reflected in the claims. *Id.* (citing Ex. 1009, 1; also citing Ex. 1002 ¶ 62).

Therefore, argues Patent Owner, even if Petitioner showed that a patient on PRN dosing were coincidentally administered PRN doses on a schedule approximating that recited in the claims, such a PRN dosing strategy is fundamentally different than the advantageous fixed, extended dosing regimen recited in the challenged claims. Prelim. Resp. 24–25. Patent Owner contends that such happenstance would not have motivated a person of ordinary skill in the art to pursue any particular fixed regimen except with the benefit of hindsight. *Id.* at 25.

4. Petitioner's Reply

Petitioner replies that, Patent Owner's arguments to the contrary notwithstanding, the challenged claims do not require "a fixed, extended dosing regimen." Reply 6.

Petitioner first argues that there is no claim language that supports Patent Owner's interpretation of the claims. Reply 6. Petitioner asserts that

the claims do not recite that the method of treatment is "fixed" or "predetermined" at the start, nor that "assessment based approaches" that are "conditional on patient characteristics" are excluded." *Id.* at 6–7. According to Petitioner, the claim does not require that the recited doses be "predetermined," and the claim would be practiced if a patient was assessed every month and only received doses according to the claimed dosing regimen. *Id.* at 7.

Petitioner further contends that the intrinsic evidence contradicts Patent Owner's position. Reply 7. Petitioner points again to the Specification of the '601 patent, which explains that "the frequency at which the secondary and/or tertiary doses are administered to a patient can vary over the course of the treatment regimen." *Id.* (citing Ex. 1001, col. 4, ll. 32–46). Petitioner notes that the Specification further discloses that these adjustments are based on an assessment of the patient's characteristics, stating that "[t]he 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.* Petitioner argues that, should such an adjustment result in extended 8-week dosing after five initial monthly doses—i.e., based on an assessment that the patient has improved after five doses such that bi-monthly injections are sufficient—those circumstances would fall within the scope of the challenged claims. *Id.* at 7–8.

Petitioner argues that dependent claims 12, 21, and 28 are similarly inconsistent with "a fixed, extended dosing regimen." Reply 8. Petitioner contends that these claims recite returning to monthly dosing after beginning the extended dosing. *Id.* Petitioner contends that such a course of treatment

makes no sense if predetermined, but would make sense if arrived at based on a clinical assessment of a patient that shows regression after trying extended dosing. *Id.* Petitioner asserts that a person of ordinary skill in the art would not interpret the recited method of treatment to exclude arriving at the claimed sequences of doses through a routine evaluation of the patient for improvement (or regression), consistent with clinical practice. *Id.* at 9.

Petitioner next argues that, even assuming, *arguendo*, that Patent Owner is correct that the claims require "fixed" dosing, Petitioner's grounds are based on the 2009 Press Release's disclosure of a regimen that, as Patent Owner acknowledges, is "fixed." Reply 9. Petitioner asserts that Patent Owner acknowledges that "the 2009 Press Release does disclose an arm with fixed eight-week dosing (after three initial monthly doses)." *Id.* (citing POPR at 34). Petitioner emphasizes that its argument, on all grounds of this *inter partes* review, is that a person of ordinary skill in the art would find the use of five initial monthly doses as claimed, rather than three as disclosed in the 2009 Press Release, to be obvious, based either on the 2009 Press Release alone, or in combination with Shams (Ground 2) or Elman 2010 (Ground 3). *Id.* Petitioner asserts that Patent Owner acknowledges that this is a disclosure of the sort of "fixed" dosing regimen it claims is required. *Id.* at 9–10.

5. Patent Owner's Sur-Reply

Patent Owner responds that Petitioner's arguments on reply are contradicted by its own evidence and by the disclosures of the '601 patent. Sur-Reply 7. Patent Owner points to the testimony of Petitioner's declarant, Dr. Chaum, who describes non-PRN dosing required by the labels of the

major VEGF antagonists (including the claimed schedule) as "fixed dosing schedules," contrasting them with administering the drugs "at frequencies that vary based on physician preference and individual patient response." *Id.* (citing Ex. 1002 ¶ 61). According to Patent Owner, Petitioner's preferred nomenclature is inconsistent with the patent itself, which refers to dosing on a particular schedule as "fixed interval" dosing, and reserves the terms "as needed" or "PRN" for dosing according to retreatment criteria. *Id.* (citing Ex. 1001, col. 8, ll. 39–44, col. 14, ll. 60–65, col. 15, ll. 29–34).

Patent Owner points to the language of claim 10, which requires dosing "approximately every 4 weeks for the first 5 injections followed by 2 mg approximately once every 8 weeks or once every 2 months," which stands in stark contrast to other claims in the same family of patents, which require dosing "on an as-needed/*pro re nata* (PRN) basis, based on visual and/or anatomical outcomes as assessed by a physician or other qualified medical professional." Sur-Reply 7–8 (quoting US 9,669,069 , col. 21, ll. 50–54). Patent Owner insists that it is giving the claim language its plain and ordinary meaning, and that no formal claim construction is needed to see that claim 10 would not be met by a physician who varied the label regime for Eylea to administer three initial monthly doses instead of five. *Id.* at 8.

Patent Owner contends that Petitioner implicitly recognizes that the dosing regimen disclosed in the 2009 Press Release is not the same as the regimen described in the challenged claims. Sur-Reply 9. According to Patent Owner, Petitioner argues either that the disclosure of three loading doses would make any number of loading doses obvious or, alternatively that it would be obvious to combine the 2009 Press Release with the very different class of references disclosing assessment-based dosing. *Id.* at 9–10

(citing Prelim. Resp. 11–37). Patent Owner contends that Petitioner has failed to articulate any motivation to combine these two different types of references. *Id.* at 10.

6. Analysis

Having considered the parties' arguments and the evidence of record as developed at this stage of the proceeding, we conclude that Petitioner has demonstrated a reasonable likelihood of prevailing at trial upon Ground 2.

As an initial matter, we acknowledge that neither the 2009 Press Release nor Shams expressly teaches the dosing regimen of "2 mg approximately every 4 weeks for the first 5 injections followed by 2 mg approximately once every 8 weeks or once every 2 months," as recited in the independent claims. However, the question guiding our analysis is not one of anticipation, but of obviousness. Specifically, the question is whether the differences between the claimed subject matter and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. *KSR*, 550 U.S. at 406. We therefore turn to that analysis.

The 2009 Press Release discloses a number of clinical trials employing aflibercept that were beginning or already underway. Most relevant of these studies is the disclosure that:

> VEGF Trap-Eye is also in Phase 2 development for the treatment of Diabetic Macular Edema (DME). VEGF Trap-Eye dosed at 0.5 mg or 2 mg monthly, *2 mg every eight weeks after three monthly loading doses*, or 2 mg on an as-needed (PRN) basis after three monthly loading doses is being compared to focal

> laser treatment, the current standard of care in DME. The primary efficacy endpoint evaluation is mean improvement in visual acuity at six months. Patient enrollment has been completed with initial data expected in the first half of 2010.

Ex. 1009, 1 (emphasis added). The 2009 Press Release thus teaches the use of aflibercept (VEGF Trap-Eye) in the clinical trial for the treatment of DME, and a dosage regimen that differs only from the regimen recited in the challenged claims in that there are only three initial monthly loading doses as opposed to five.

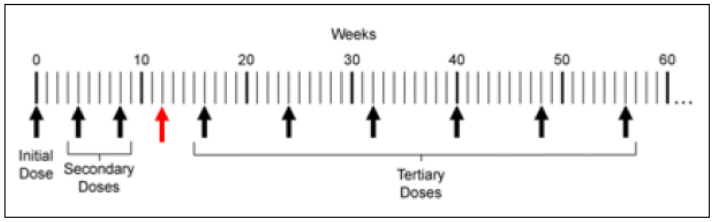
Petitioner's Declarant, Dr. Chaum, testifies that:

> A [person of ordinary skill in the art] 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. Dr. Chaum further opines that such a skilled artisan "would have also had a strong motivation to further optimize these dosing regimens to achieve the same two goals, especially given the success with other anti-VEGF agents in treating DME and knowledge from prior courses of treatment of DME with anti-VEGF agents." *Id.* at ¶ 149 (citing Ex. 1009).

Summarizing, Dr. Chaum opines that:

> In my opinion, including additional doses to treat DME would have been a matter of routine experimentation for a POSA. For instance, to arrive at the recited dosing regimen from the 2009 Press Release's disclosure of a regimen using three initial doses for DME, the only modification required is a *single* additional injection at week 12, as shown below in reference to the '601

> patent's sole figure, which discloses a regimen involving three initial doses as disclosed in the press release:
>
> 
>
>
> As can be seen above, the addition of a single dose at week 12 (red arrow) discloses the recited regimen

Ex. 1002 ¶ 152 (internal citation omitted, emphasis in original).

Shams is directed to a method "for administering to a mammal suffering from, or at risk for, an intraocular neovascular disorder with regular dosing of a therapeutically effective amount of VEGF antagonist, followed by less frequent dosing" of the same. Ex. 1010, Abstr. Specifically, Shams teaches "administering to a mammal a number of first individual doses of a VEGF antagonist, followed by administering to the mammal a number of second individual doses of the antagonist, wherein the second individual doses are administered less frequently than the first individual doses." *Id.* at 4–5. Shams further discloses:

> The doses may be administered according to any time schedule which is appropriate for treatment of the disease or condition. For example, the dosages may be administered on a daily, weekly, biweekly or monthly basis in order to achieve the desired therapeutic effect and reduction in adverse effects. The dosages can be administered before, during or after the development of the disorder. 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 within the method of the present invention. The time of administration of the number of first individual and second individual doses as well as subsequent dosages is adjusted to minimize adverse effects while maintaining a maximum

> therapeutic effect. The occurrence of adverse effects can be monitored by routine patient interviews and adjusted to minimize the occurrence of side effects by adjusting the time of the dosing. Any dosing time is to be considered to be within the scope of the present invention so long as the number of first individual doses of the VEGF antagonist is administered followed by a number of second individual doses, which are less frequently administered. For example, doses may be administered on a monthly schedule followed by subsequent quarterly or more dose schedule.

Id. at 22–23.

The disclosures of Shams are, in this regard, not limited to a single species of VEGF antagonist but, rather, Shams teaches that "[a]ny compound which binds to VEGF or a VEGF receptor and reduces the severity of symptoms or conditions associated with an intraocular neovascular disease may be used in this embodiment of the invention." Ex. 1010 26. These include "[o]ne category of polypeptide compounds, are compounds containing an antibody or a fragment thereof which immunologically recognize and bind to cell surface receptors or ligands," a genus expressly encompassing aflibercept. *See* Ex. 1010, 28, 6 ("VEGF antagonists include … fusions [sic] proteins, e.g., VEGF-Trap (Regeneron)."

We acknowledge that, in its exemplary embodiments, Shams generally teaches three initial doses followed by the secondary doses at greater intervals. *See, e.g.*, Ex. 1010, 5 ("the first individual doses are administered at one month intervals (e.g., *about 3 individual doses*)…. In another embodiment, the second individual doses are administered at three month intervals (e.g., about 6 individual doses"); *see also id.* at Example 1. Nevertheless, Shams expressly discloses that the scope of its disclosures includes "the doses … be[ing] administered according to *any time schedule*

which is appropriate for treatment of the disease or condition." *Id.* at 22 (emphasis added)

Petitioner's Declarant, Dr. Chaum, testifies that, with respect to the scheduling of dosage regimens in the treatment of DME and related diseases:

> DME is characterized by leakage of fluid and blood and swelling from damage to blood vessels at the back inner wall of the eye (retina). The principal way to treat DME effectively in the first instance therefore was to "dry" the liquid and stop the leakage with a series of anti-VEGF injections. VEGF-antagonists are relatively short-acting compared to focal laser treatment, thus a series of initial injections are required.
>
> Because there was a need to "dry" the retina before proceeding to reduce the frequency of injections, POSAs would have thus sought, through routine variation in the number of initial doses, to determine the optimal number of initial injections, before moving to eight-week dosing.
>
> ….
>
> In my opinion, including additional doses to treat DME would have been a matter of routine experimentation for a [person of ordinary skill in the art].

Ex. 1002 ¶¶ 150–152.

We conclude that, on the record as presently developed, Petitioner has demonstrated a reasonable likelihood of success in demonstrating that a person of ordinary skill in the art would have found it obvious to modify the dosage regiment of the 2009 Press Release by adding a single dose at week twelve, in view of the teachings of Shams, to arrive at the claimed invention. We find that a person of ordinary skill in the art would have considered this addition of a single dose to be routine optimization to ensure, as Dr. Chaum relates, "to determine the optimal number of initial injections, before moving

to eight-week dosing." Ex. 1002 ¶ 151. Furthermore, and at this stage of the proceeding, we agree with Petitioner that a person of ordinary skill in the art would have had a reasonable expectation of success in modifying the 2009 Press Release dosing protocol to include an additional dose at week twelve to ensure sufficient "drying" of the inner wall of the retina prior to increasing the interval of the doses two eight weeks/two months.

Patent Owner argues that Petitioner points to no considerations that would lead a person of ordinary skill in the art to modify the 2009 Press Release protocols to arrive at the claimed regimen, contending that adding more monthly loading doses to an extended dosing regimen would result in a greater treatment burden from visits and an increased risk of adverse events. Prelim. Resp. 16. We are not persuaded that the addition of but a single dose at week 12 would necessarily pose a significantly greater treatment burden or adverse risk to the patient. Moreover, we credit Dr. Chaum's testimony that a physician of ordinary skill would want to ensure sufficient "drying" of the retina before proceeding to increase the dosage interval. Ex. 1002 ¶ 151. We agree that this interest in maintaining the standard of care would provide motivation to add the single additional dosage at 12 weeks, and would not step outside the bounds of routine optimization of the regimen.

Shams further confirms this opinion, teaching that "[t]he doses may be administered according to any time schedule which is appropriate for treatment of the disease or condition" and 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 within the method of the present invention." Ex. 1010, 22–23.

Patent Owner also argues that Shams "teaches away" from the claimed method. A reference teaches away when "a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994). Patent Owner points to Shams' Example 1, which it cites as representing Genentech's PIER Phase IIIb study. *See* Prelim. Resp. 18. The PIER study, argues Patent Owner involved three monthly loading doses of a different VEGF antagonist (ranibizumab) followed by quarterly dosing, and, according to Patent Owner, was widely perceived as a failure. *Id.* Patent Owner contends that, based upon this single example, a person of ordinary skill in the art would have been discouraged from following the teachings of Shams. *Id.*

We disagree. As we have explained above, the disclosures of Shams encompass a larger variety of regimen options than merely that embodied in Example 1. Shams is directed expressly to "methods including administering … a number of first individual doses of a VEGF antagonist, followed by administering … a number of second individual doses of the antagonist, wherein the second individual doses are administered less frequently than the first individual doses." Ex. 1010, 4–5; *see also id.*, claim 1. Furthermore, Shams expressly teaches that "[t]he doses may be administered according to any time schedule which is appropriate for treatment of the disease or condition." *Id.* at 22. We find that these broad teachings of Shams would, rather than discouraging a skilled artisan from

following its teachings, encourage a person of ordinary skill in the art to optimize the number of first and second individual doses to maximize the therapeutic effect of the regimen of VEGF antagonist dosage administration. Shams places no express limits upon the number of first individual doses and, as we have explained above, the addition of a single additional dose at week twelve would fall well within the scope of Shams' disclosures.

Finally, Patent Owner argues that the challenged claims are directed to "fixed dosing throughout, with a transition from monthly to eight-week dosing after five fixed monthly loading doses." *See, e.g.*, Prelim. Resp. 3. Patent Owner asserts that a fixed approach is advantageous because it provides for treatment on a predetermined schedule regardless of whether reaccumulated fluid has been detected, while assessment-based approaches take a fundamentally different approach by making injections conditional on patient characteristics. *Id.* at 23. Patent Owner asserts that the '601 patent's achievement of the first fixed, extended dosing regimen was a departure from prior assessment-based approaches, rather than an obvious variant of them. *Id.* at 23–24.

We are not persuaded that Patent Owner's argument overcomes Petitioner's showing. The language of the challenged claims nowhere require that the doses required therein are "fixed" or "determined." *See, e.g.*, Ex. 1001, claim 10. Furthermore, the disclosures of the Specification of the '601 patent expressly undermine Patent Owner's argument that the doses of the VEGF antagonist aflibercept are "fixed" and invariable.

Specifically, the Specification of the '601 patent expressly teaches that:

> The methods of the invention may comprise administering to a patient any number of secondary[10] and/or tertiary doses of a VEGF antagonist. For example, in certain embodiments, only a single secondary dose is administered to the patient. In other embodiments, two or more (e.g., 2, 3, 4, 5, 6, 7, 8, or more) secondary doses are administered to the patient. Likewise, in certain embodiments, only a single tertiary dose is administered to the patient. In other embodiments, two or more (e.g., 2, 3, 4, 5, 6, 7, 8, or more) tertiary doses are administered to the patient.

Ex. 1001, col. 4, ll. 13–19. Furthermore, the Specification expressly contemplates that a physician of ordinary skill in the art might contemplate altering the amount of secondary or tertiary doses:

> For example, the amount of VEGFT and/or volume of formulation administered to a patient may be varied based on patient characteristics , severity of disease, and other diagnostic

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[10] The '601 patent defines "secondary dose" as those immediately following the "initial dose":

> In one exemplary embodiment of the present invention , a single initial dose of a VEGF antagonist is administered to a patient on the first day of the treatment regimen (i.e., at week 0), followed by two secondary doses, each administered four weeks after the immediately preceding dose (i.e., at week 4 and at week 8), followed by at least 5 tertiary doses, each administered eight weeks after the immediately preceding dose (i.e., at weeks 16, 24, 32, 40 and 48).

Ex. 1001, col. 4, ll. 1–8. As defined by the Specification, then, the language of the claims reciting "administering, to said patient, an effective amount of aflibercept which is 2 mg approximately every 4 weeks for the first 5 injections" encompasses an initial dose (at week 0) and 4 secondary doses (at weeks 4, 8, 12, and 16). There is no dispute between the parties with respect to this interpretation

> assessments by a physician or other qualified medical professional.

Ex. 1001, col. 11–15. In fact, the only reference to "fixed" doses is in Example II of the Specification, which describes a clinical study in which "[p]atients were dosed at a fixed interval for the first 12 weeks, after which they were evaluated every 4 weeks for 9 months, during which additional doses were administered based on pre-specified criteria." *Id.* at col. 8, ll. 39–42. This is not the dosing regimen recited in the challenged claims.

"[C]laims are interpreted in light of the specification and with the knowledge of one of ordinary skill in the art." *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996). We can discern no evidence in the language of the claims or the Specification of the '601 patent to indicate that a person of skill in the art would understand that the claimed regimen of five doses first administered at 4 week intervals was necessarily a "fixed" or "determined" dose. Moreover, Patent Owner adduces no evidence that providing the first five doses at the prescribed interval provided a surprising, or even superior result that would have been unexpected by those of ordinary skill in the art.

Consequently, at this stage of the proceeding, we conclude that Petitioner has demonstrated a reasonable likelihood of success in demonstrating that the challenged claims of Ground 2 are obvious over the 2009 Press Release and Shams. We also conclude that Patent Owner's arguments, as presently developed, are insufficient to overcome Petitioner's demonstration of a reasonable success in prevailing upon this ground.

Furthermore, because we determine that Petitioner has shown a reasonable likelihood of prevailing at trial in demonstrating that at least one

claim is unpatentable on at least one of the stated Grounds, we institute *inter partes* review of all challenged claims of the '601 patent, based on all of the remaining grounds identified in the Petition. *See SAS Inst., Inc. v. Iancu*, 138 S.Ct. 1348, 1359–60 (2018); *PGS Geophysical AS v. Iancu*, 891 F.3d 1354, 1360 (Fed. Cir. 2018) (interpreting the statute to require "a simple yes-or-no institution choice respecting a petition, embracing all challenges included in the petition"). Nevertheless, we provide our preliminary views with respect to remaining Grounds 3 and 6 below, based upon the parties' arguments and the evidence of record as presently developed.

C. Ground 3: Obviousness under 35 U.S.C. § 103 of claims 10–12, 18, 19, 21, 26–28 over the 2009 Press Release (Ex. 1009) and Elman (Ex. 1006)

Petitioner challenges claims 10–12, 18, 19, 21, 26–28 of the '601 patent as unpatentable under 35 U.S.C. § 103 as being obvious over the combination of the 2009 Press Release and Elman. Pet. 34–40.

1. Overview of Elman (Ex. 1006).

Elman is a 2010 article published in the peer-reviewed journal Ophthalmology entitled *Randomized Trial Evaluating Ranibizumab Plus Prompt or Deferred Laser or Triamcinolone Plus Prompt Laser for Diabetic Macular Edema*. Elman describes multicenter, randomized clinical trial to evaluate the efficacy of the treatment of subjects with diabetic macular edema (DME) with either intravitreal 0.5 mg ranibizumab (Lucentis® a VEGF-antagonist) or 4 mg triamcinolone combined with focal/grid laser compared with focal/grid laser alone. Ex. 1006, Abstr.

Relevantly, the treatment protocol described by Elman included a baseline (initial) treatment followed by intravitreal study drug or sham (i.e., control) injection retreatments every 4 weeks through the 12-week study visit (i.e., injections at weeks 0, 4, 8, and 12). Ex. 1006, 1066. From the 16-week (i.e., the fifth) study visit and thereafter, a retreatment algorithm for study drug injections and sham injections was designed to require retreatments unless a study visit was deemed a "success," at which point retreatment was at investigator discretion. *Id.* From the 24-week study visit and, thereafter retreatment was at investigator discretion if the study visit was deemed "no improvement." *Id.*; *see also id.* at 1077.e1. "Success" "improvement," and "no improvement" criteria were scored on the basis of visual acuity test performance or optical coherence tomography ("OCT") central subfield thickness measured at each visit from week 16 onwards. *Id.* at 1077.e11 (Table 1).

2. Petitioner's arguments

Petitioner repeats its arguments presented above, noting again that the only difference between its disclosure and that of the challenged claims is that the claims recite five initial loading doses, rather than three. Pet. 41.

Petitioner argues that Elman was the most significant study of the treatment of DR/DME *via* an anti-VEGF agent in the art prior to the filing date of the '601 patent. Pet. 42. Petitioner contends that Elman strongly suggests the use of five initial monthly loading doses, at least for some patients. *Id.* (citing Ex. 1002 ¶¶ 159–184). Petitioner asserts that, even if substantially less than 78% of patients required a fifth dose, the fact that Elman describes such doses after clinical evaluation would be sufficient to

suggest to a person of ordinary skill in the art, at least for the treatment of some patients, the use of five initial loading doses. *Id.* Petitioner asserts that that is all that the claims require. *Id.*

Petitioner contends that a person of ordinary skill in the art, reviewing the 2009 Press Release, would have found it natural to adopt, at least for some patients, teachings from the study of another anti-VEGF agent, ranibizumab, that five monthly loading doses were deemed desirable for at least 78% of patients. Pet. 43 (citing Ex. 1002 ¶¶ 164—172). According to Petitioner, modifying the dosing regimen disclosed by the 2009 Press Release would have required only ensuring a greater likelihood of success in treating at least some patients by adopting a dosing regimen with two additional monthly doses (in effect, a single dose administered between months 3 and 5). *Id.* (citing Ex. 1002 ¶¶ 146–158, 164–172; also citing Ex. 1001, 9).

Petitioner also argues that a skilled artisan would have been further motivated to take this step 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 (quoting Ex. 1005; also citing Ex. 1007; Ex. 1002 ¶¶ 164–172).

Petitioner also argues that one of ordinary skill in the art would have reasonably expected success in making and using the claimed combination. Pet. 44. Petitioner contends that the 2009 Press Release's disclosure of a Phase II trial using loading and maintenance dosing of aflibercept to treat DME would have provided an ordinarily skilled artisan with a reasonable expectation that such a regimen would work, including the use of

maintenance dosing. *Id.* (citing Ex. 1002 ¶¶ 173–179). Petitioner additionally argues that the dosing regimens taught by the 2009 Press Release suggests that additional initial loading doses (e.g., five, rather than three) would be safe and tolerable, because one of the Phase II trials disclosed was for monthly injections only—a standard and proven safe regimen for other anti-VEGF agents. *Id.* (citing Ex. 1002 ¶ 174–178).

3. Patent Owner's Preliminary Response

Patent Owner argues that the cited references forming the basis of Ground 3 do not disclose, and instead teach away from, the dosing regimen recited in the challenged claims. Prelim. Resp. 25.

First, argues Patent Owner, contrary to Petitioner's assertions, the dosing protocol disclosed by Elman did not involve five fixed monthly loading doses for any arm. Prelim. Resp. 27. According to Patent Owner, Elman does not disclose that the study included even a single patient who received five (and only five) initial monthly doses of ranibizumab. *Id.* Rather, Patent Owner argues, Elman's protocol provided for four initial monthly doses for all patients, and made it likely that patients would receive at least six initial monthly doses; and allowed for patients to receive even more monthly doses. *Id.* (citing Ex. 1006, 1066). Patent Owner summarizes the Elman 2010 protocol in the diagram below:

Diagram illustrating the protocol for injections as disclosed by Elman

Patent Owner disputes Petitioner's focus on Elman'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. Prelim. Rep. 28 (citing Pet. 25–26). According to Patent Owner, there is no disclosure that that 78% of patients received just five initial monthly doses, as the challenged claims require, nor any disclosure that five would have been a desirable number of doses. *Id.* at 28–29. Patent Owner contends that the 78% may also have included no such patients and consist only of patients who received six or more initial monthly doses. *Id.* at 29.

Patent Owner next argues that Elman does not disclose the subsequent fixed eight-week dosing required by the challenged claims.
Prelim. Resp. 30. Patent Owner contends that the design of the trial makes it unlikely that a patient who received five initial monthly doses would have subsequently received fixed eight-week doses. *Id.*

Patent Owner disputes Petitioner's contention that the recited dosing regimen would involve nine doses over the course of 52 weeks, and that Elman discloses that the median number of injections that the ranibizumab with deferred laser group received was also nine. Prelim. Resp. 31 (citing Pet. 26). Patent Owner asserts that the median number of doses disclosed by

Ellman is derived from *all* the patients in the deferred laser arm, including those who did not receive a fifth dose. *Id.*

Patent Owner next argues that even if Elman had disclosed that the median applied to the subgroup Petitioner contends is relevant (i.e., those who received a dose at week 16), that median figure says nothing about whether those patients received five initial loading doses. Prelim. Resp. 32. According to Patent Owner, receiving nine doses over the course of a year is consistent with receiving more than five initial monthly doses. *Id.*

Patent Owner argues further that, even if a patient received exactly five initial monthly doses, and even if that same patient received nine doses over the course of a year, that does not mean that they received any doses on an eight-week schedule. Prelim. Resp. 32.

Patent Owner additionally argues that, Petitioner's reliance on the median nine doses has no connection to the recited dosing regimen is misplaced, because only a small number of patients received nine doses over the course of a year. Prelim. Resp. 32–34 (citing Ex. 1006, Fig. 2). Patent Owner emphasizes that trial subjects receiving nine doses does not mean that they received any doses on an eight-week schedule, and that the small number of patients who received nine doses does not even make it likely that any received eight-week dosing by pure chance. *Id.* at 34.

Finally, Patent Owner argues that Petitioner has failed to demonstrate a reason for a person of ordinary skill in the art to combine the references. Prelim. Resp. 34. Patent Owner acknowledges that the 2009 Press Release discloses an arm with fixed eight-week dosing (after three initial monthly doses), however, it asserts that Petitioner does not provide any reason why a skilled physician would have been motivated to choose that particular arm

out of the three others disclosed. *Id.* Patent Owner argues that 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. *Id.* Patent Owner asserts that the 2009 Press Release does not disclose any results for the arms it discloses, and Elman does not contain data on the results (much less any difference in results) between using three initial monthly doses and five. *Id.*

Patent Owner notes that Petitioner's argument is based on two post-priority date articles (Ex. 1005,[11] Ex. 1007[12]) that one of ordinary skill 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…."' Prelim. Resp. 35 (quoting Pet. 43–44 (citations omitted)).

However, argues Patent Owner, both articles make this statement in the context of discussing the benefits of three initial monthly doses, not five, and neither suggests increasing the number of initial monthly doses would have been desirable. Prelim. Resp. 35. Patent Owner argues that Petitioner's argument is at best an argument that adding doses would have

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[11] J.S. Heier et al., *The 1-year Results of CLEAR-IT 2, a Phase 2 Study of Vascular Endothelial Growth Factor Trap-Eye Dosed As-needed after 12-week Fixed Dosing*, 118(6) OPHTHALMOLOGY 1098–106 (2011) ("Heier 2011") Ex. 1005.

[12] J.S. Heier et al., *Intravitreal Aflibercept (VEGF Trap-Eye) in Wet Age-related Macular Degeneration*, 119(12) OPHTHALMOLOGY 2537–48 (2012) ("Heier 2012") Ex. 1007.

been "obvious to try," but notes that "[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." *Id.* (quoting *Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1356 (Fed. Cir. 2013) (citations omitted)). More fundamentally, argues Patent Owner, even if a skilled artisan would have been motivated to add doses to the regimens disclosed in the 2009 Press Release, there are innumerable ways to add doses. *Id.* at 36.

4. Preliminary Analysis

At this stage of the proceeding, and based upon the record presently before us, we conclude that Petitioner has reasonably demonstrated that it is likely to prevail in proving that a person of ordinary skill in the art would have found the challenged claims obvious over the combination of the 2009 Press Release and Elman. Our preliminary reasoning in this regard mirrors our reasoning with respect to Ground 2.

The 2009 Press Release expressly discloses a trial protocol for the treatment of DME with a regimen comprising three initial four week loading doses, followed by maintenance doses at eight week intervals. As we have explained above, the addition of a fourth loading dose at week 12 would, with the week 16 dose disclosed by the reference, provide the regimen recited in the challenged claims.

Elman teaches an optional dose at week 12, depending upon the evaluation of the subject according to the retreatment algorithm disclosed in the study. A single patient, obtaining an "unsuccessful" score on the retreatment algorithm at week 12, and then receiving another dose at week

16, would meet the first requirement recited in the challenged claims (i.e., 5 initial doses at 4-week intervals). As we have explained with respect to Ground 2 above, we agree with Petitioner that a person of ordinary skill would have been motivated to perform the evaluative step at week 12, as Dr. Chaum explains, to ensure that the retina had "dried" prior to transitioning to the eight-week interval maintenance dose at week 18. This is strengthened by the fact that, whereas the 2009 Press Release and Elman relate to published protocols for clinical trials, the claims are not so restricted and that evaluation of the effectiveness of the loading doses before proceeding to maintenance doses would be within the standard of medical care of a practicing physician of ordinary skill. *See* Ex. 1002 ¶¶ 149–151.

Consequently, we agree, on the record as presently developed, that a person of ordinary skill would have found it obvious to provide an additional loading dose, if needed, at week 12 and, based upon the teachings of the references, would have had a reasonable expectation of success in doing so.

As we have explained above, we are not persuaded, at this stage of the proceeding by Patent Owner's argument that the protocol recited in the challenged claims requires a "fixed dose." We have explained why, based on the record as presently developed, this contention is not supported by the Specification of the '601 patent. *See Vitronics*, 90 F.3d at 1582. Nor, for the reasons we have explained, are we presently persuaded that the references teach away from the recited claims. *See Gurley*, 27 F.3d at 553. Moreover, Patent Owner's arguments with respect to the individual references do not yet, to our mind, sufficiently address what the combined references would teach or suggest to a person of ordinary skill in the art. *See In re Keller*, 642 F.2d 413, 425 (C.C.P.A. 1981) (holding that "the test for

obviousness is … what the combined teachings of the references would have suggested to those of ordinary skill in the art").

Furthermore, and at this stage of the proceeding, given the similarity of the VEGF inhibitor treatment protocols in the references cited by Petitioner, Patent Owner's arguments, citing *KSR*, that there are almost an infinite number of protocol variations possible, appear exaggerated and do not seem consistent with the level of skill in the art. *See KSR*, 550 U.S. at 420 (noting that "[a] person of ordinary skill is also a person of ordinary creativity, not an automaton"). Patent Owner may wish to further develop their arguments at trial.

D. Ground 6: Obviousness of claims 17, 25, and 33 over the 2009 Press Release alone or in view of Elman, CATT (Ex. 1018), and PIER (Ex. 1014).

Dependent claim 17 is representative of these claims, and recites:

> 17. The method of claim 10 wherein exclusion criteria for the patient include (1) active intraocular inflammation ; or (2) active ocular or periocular infection.

Ex. 1001, col. 2, ll. 65–67.

Petitioner argues that these limitations (the "exclusion criteria") are not entitled to patentable weight. Pet. 22.

In our Decision to Institute *inter partes* review in the related -01226 *inter partes* review, we agreed with Petitioner that identical claims 9 and 36 of the '601 patent were not entitled to patentable weight under the printed matter doctrine. IPR2022-01226, Paper 22, 11–15. Briefly, applying the analysis set forth by our reviewing court in *Praxair Distrib., Inc. v. Mallinckrodt Hosp. Prods. IP Ltd.*, 890 F.3d 1024, 1032 (Fed. Cir. 2018),

we concluded that, on the record as then-developed: (1) that the exclusion criteria are directed to informational content; and (2) that the exclusion criteria of the challenged claims are not functionally related to the rest of the claim, because "the claims do not expressly recite any positive step to be performed (or a negative step *not* to be performed) should a patient meet the exclusion criteria." *Id.* at 13–14 (emphasis in original).

We apply the same reasoning here, and conclude, on the record as presently developed, that identical claims 17, 25, and 33 are similarly not entitled to patentable weight. We also note that, in the related district court litigation, the court's *Markman* order arrived at the same conclusion with respect to the exclusion criteria. *Regeneron Pharms., Inc. v. Mylan Pharms. Inc.*, 1:22-cv-00061-TSK (N.D. W. Va.), Order on Claim Construction, 29–37 (April 19, 2023). Although our Decision to Institute was not binding upon the district court's *Markman* order, or *vice versa*, the reasoning and conclusion is nevertheless consistent in both decisions. *See Novartis AG v. Noven Pharms. Inc.*, 853 F.3d 1289, 1293–1294 (Fed. Cir. 2017) (holding that "the PTAB properly may reach a different conclusion based on the same evidence," for the PTAB and district courts function under different evidentiary standards and burdens of proof (preponderance of the evidence before the PTAB, clear and convincing evidence before the district court"). The Federal Circuit has recognized that "ideally" both district courts and the PTAB would reach the same results on the same record. *See In re Baxter Int'l, Inc.*, 678 F.3d 1357, 1365 (Fed. Cir. 2012). Such is the case in the present proceeding.

E. Discretionary Denial of Institution under 35 U.S.C. § 314(a)

Finally, Patent Owner urges us to exercise our discretion to deny institution of *inter partes* review under 35 U.S.C. § 314(a). Prelim. Resp. 37–44. Petitioner takes a contrary position, arguing that the Board should not deny institution. Pet. Reply 1–6. We address the parties' arguments below.

1. Legal standard

Under our precedential decision in *Apple Inc. v. Fintiv, Inc.*, IPR2020-00019, Paper 15 at 12–17 (PTAB May 13, 2020), the Board, in deciding "whether efficiency, fairness, and the merits support the exercise of authority to deny institution in view of an earlier trial date in the parallel proceeding," should consider a variety of factors, and, in evaluating these factors, "takes a holistic view of whether efficiency and integrity of the system are best served." *Fintiv*, Paper 11 at 5–6; *see also Samsung Elecs. Am., Inc. v. Uniloc 2017 LLC*, IPR2020-00117, Paper 11 at 7–11 (PTAB May 28, 2020) (same). According to Patent Owner, granting the Petition for *inter partes* review would be an inefficient use of Board resources and is contrary to Congress's intent in establishing IPR proceedings. Prelim. Resp. 17.

In *Fintiv*, the Board set forth six factors relating to whether efficiency, fairness, and the merits support the exercise of authority to deny institution in view of an earlier trial date in the parallel proceeding:

1. Whether the court granted a stay or evidence exists that one may be granted if a proceeding is instituted;

2. Proximity of the court's trial date to the Board's projected statutory deadline for a final written decision;
3. Investment in the parallel proceeding by the court and the parties;
4. Overlap between issues raised in the petition and in the parallel proceeding;
5. Whether the petitioner and the defendant in the parallel proceeding are the same party; and
6. Other circumstances that impact the Board's exercise of discretion, including the merits.

Fintiv at 21.

In our analysis, we are also guided by the USPTO's *Interim Procedure for Discretionary Denials in AIA Postgrant Proceedings with Parallel District Court Litigation*, June 21, 2022 available at: https://www.uspto.gov/sites/default/files/documents/interim_proc_discretionary_denials_aia_parallel_district_court_litigation_memo_20220621_.pdf (last visited September 24, 2023) (the "Guidance"). As stated by the Guidance, the Board will not rely on the *Fintiv* factors to discretionarily deny institution in view of parallel district court litigation when: (1) a petition presents compelling evidence of unpatentability; (2) a petitioner presents a stipulation (a "*Sotera* stipulation") not to pursue in a parallel proceeding the same grounds or any grounds that could have reasonably been raised before the PTAB[13]; and (3) if all other *Fintiv* factors weighing against exercising discretion to deny institution, or are neutral, the proximity

[13] *See Sotera Wireless, Inc. v. Masimo Corp.*, IPR2020-01019, Paper 12 (PTAB December 1, 2020) (precedential).

to trial should not alone outweigh all of those other factors.[14] Guidance at 1–8.

We consider these interrelated factors, as they apply to the facts of the Petition, as follows.

2. Analysis

a. *Fintiv* factor 1

Patent Owner first notes that the bench trial in the district court litigation concerning validity of claims 11 and 19 (the only claims at issue in the district court litigation) of the '601 patent took place from June 12 to June 23, 2023, and post-trial closing argument has by now taken place. Prelim. Resp. 40 (citing Ex. 2019). Patent Owner therefore argues that, given the advanced stage of the district court proceeding and the overlap of the challenged claims and prior art in both proceedings, five out of six *Fintiv* factors favor denial. *Id.*

With respect to *Fintiv* factor 1, Patent Owner asserts that the district court has not, and no longer can, stay the proceedings, and that factor 1 therefore favors denial. Prelim. Resp. 40.

We agree with Patent Owner that the issue of a stay of the proceedings in the district court litigation is now moot, trial having already taken place. *Fintiv* factor 1 therefore favors denial.

[14] The Guidance notes that the *Fintiv* factors do not apply to parallel litigation before the U.S. International Trade Commission (ITC). Guidance at 2–3, 5–7.

b. *Fintiv* factors 2 and 3

Patent Owner argues that *Fintiv* factor two weighs in favor of denial because any Final Written Decision will necessarily be after the trial. Prelim. Resp. 40. Furthermore, argues Patent Owner, an appeal of the district court's judgment is expected to proceed expeditiously. *Id.* (citing Ex. 2020, 20). Patent Owner contends that, because "the claims remain subject to further judicial review during the appeal of the district court's invalidity determination," the Board should "determine whether to exercise discretion to deny institution based on the parallel proceeding under *Fintiv*." *Id.* (quoting *Volvo Penta of the Ams., LLC v. Brunswick Corp.*, IPR2022-01366, Paper 15, 7–9 (PTAB May 2, 2023) (Director Review Decision).

With respect to factor 3, Patent Owner argues that Patent Owner and the district court's investment in the parallel proceeding has been extensive, as nearly all work, including statutory pre-litigation exchanges, claim construction, discovery, expert reports, substantive motions, pre-trial submissions, trial itself, and the bulk of post-trial briefing, has been completed. Prelim. Resp. 41. Patent Owner argues that this factor, too, favors discretionary denial. *Id.*

Petitioner responds that only claims 11 and 19 are at issue in the district court litigation and, accordingly, no matter what happens in that proceeding, the validity of ten of the twelve Challenged Claims will go unaddressed. Reply 1. Petitioner contends that there remains no risk of duplication of effort as to those ten challenged claims (*Fintiv* Factors 1–3) and the claims are not the same claims as presented in the district court (*Fintiv* Factor 4). Petitioner notes that the ten non-overlapping challenged claims recite, *inter alia*, a different dosing regimen (claims 12, 21, and 28)

than claims 11 and 19, as well as exclusion criteria (claims 17 and 25) that Patent Owner has argued render similar claims patentable. *Id.* at 2.

Petitioner also reasons that whether or not the district court invalidates claims 11 and 19, the remaining challenged claims will stand, and the district court litigation will do nothing to resolve the validity of the full set of challenged claims. Pet. Reply 2.

We find that, because certain of the challenged claims, including independent claim 26, are not expressly at issue in the district court litigation, *Fintiv* factor 3 favors institution. As an aside, however, we do not accept Petitioner's contention that independent claims 10 and 18 are not at issue at all in that litigation. Claim 11 depends directly from claim 10, and claim 19 depends directly from claim 18. As such, claims 11 and 19, which are at issue before the district court, incorporate all of the limitations of independent claims 10 and 18; the latter claims, therefore, are potentially at issue in the litigation. *See Monsanto Co. v. Syngenta Seeds, Inc.*, 503 F.3d 1352, 1357 (Fed. Cir. 2007) (holding that "[a] claim in dependent form shall be construed to incorporate by reference all the limitations of the claim to which it refers" (quoting 35 U.S.C § 112 ¶ 4 (2000)).

Furthermore, the district court, in its *Markman* Order, determined that dependent claims 17, 25, and 33, which recite the exclusion criteria, are not entitled to patentable weight. *See* Section IV.D, *supra*. Consequently, although the court's *Markman* ruling with respect to these claims may be appealed by Patent Owner, the claims will not play any significant role in the district court litigation's resolution.

Nevertheless, there remains independent claim 26, as well as dependent claims 12, 21, 27, and 28, which are challenged in the present

Petition, and are not at issue in the district court litigation. We see no reason why we should not address these claims in an *inter partes* review. We acknowledge that independent claim 26 is similar to the other independent claims (10 and 18) that are implicitly at issue in the district court litigation in terms of the dosing protocols cited in each. Nevertheless, the fact remains that claim 26 is not at issue in the district court litigation.

Because the district court action does not include all of the challenged claims within the scope of the litigation, we find that *Fintiv* factors 2 and 3 favors institution.

c. *Fintiv* factor 4

Fintiv factor 4 considers the overlap between issues raised in the petition and in the parallel proceeding. *See Fintiv* at 21. Patent Owner contends that claims 11 and 19, at issue in the district court litigation, are representative of claims 10–12, 18–19, 21, and 26–28 challenged in the Petition presently before us. Prelim. Resp. 42. Patent Owner asserts that these claims are all similar in scope. *Id.* Patent Owner asserts that Claims 10–12 and claims 18–19 and 21 are identical to claims 26–28, except that, whereas the former two sets require treatment of DR or DME, claims 26–28 require treatment of "diabetic retinopathy in a patient with diabetic macular edema" (i.e., the same two disorders as the claims tried). *Id.* at 42–43.

Patent Owner also points to Petitioner's reliance on the same primary prior art reference (the 2009 Press Release) in both the district court litigation and in Grounds 2, 3, and 6 of the present Petition. Prelim. Resp. 43 (citing Pet. 2, 10–11). Patent Owner asserts that both Petitioner and the district court defendants start with the point that the 2009 Press

Release discloses multiple aflibercept dosing regimens for DME, including "initial doses spaced 4 weeks/1 month apart, followed by extended dosing intervals, such as 8 weeks/2 months." *Id.* (citing Ex. 2018, 26; Pet. 34–35).

Petitioner responds that the district court litigation and the present Petition present different theories of unpatentability of the claims of the '601 patent. Pet. Reply 3. According to Petitioner, district court defendant Mylan's primary argument for unpatentability of claims 11 and 19 is based upon anticipation of claims 11 and 19 by the disclosure of the 2009 Press Release of three monthly loading doses followed by a PRN dosing regimen. *Id.* at 4 (citing Ex. 1058 at 14–17). In contrast, Grounds 2 and 3 of the present Petition challenge the claims on the basis of obviousness over the 2009 Press Release and either Shams (Ground 2) or Elman (Ground 3). *Id.* Petitioner asserts that its obviousness challenge is also based, in part, upon the 2009 Press Release's disclosure of three monthly loading doses followed by extended-interval maintenance doses at 8-week intervals, and not PRN dosing. *Id.* (citing Ex. 1009). Petitioner argues that, even putting aside the prior art combinations not argued by Mylan, Petitioner's fundamental argument is a substantially different and simpler obviousness theory than Mylan's anticipation and obviousness theories based on a PRN dosing regimen. *Id.* at 5.

We find that *Fintiv* factor 4 weighs in favor of institution. We agree with Petitioner that, although the district court litigation and the present Petition rely, in different degrees, upon the same reference (the 2009 Press Release) the theories of the case are different in each of the parallel actions and rely upon different disclosures of the reference (PRN maintenance dosing *versus* 8-week maintenance dosing). Furthermore, we also note that

Petitioner also relies, in at least Grounds 2 and 3 of the Petition, upon Shams and Elman, respectively; these references are not at issue in the district court action.

Given the differences with respect to the theories of unpatentability of the challenged claims of the '601 patent raised in the district court litigation and the present Petition, we find that *Fintiv* factor 4 weighs in favor of institution.

d. *Fintiv* factor 5

Patent Owner argues that *Fintiv* factor 5, which looks to whether Petitioner and the defendant in the parallel proceeding are the same party, is neutral. Prelim. Resp. 44. Patent Owner acknowledges that Petitioner is not a party to the district court litigation. *Id.* Patent Owner argues, however, that "[e]ven when a petitioner is unrelated to a defendant, … if the issues are the same as, or substantially similar to, those already or about to be litigated, or other circumstances weigh against redoing the work of another tribunal, the Board may, nonetheless, exercise the authority to deny institution." *Id.* at 44–45 (quoting *Fintiv* at 13–14; *Google LLC v. Personalized Media Commc'ns, LLC*, IPR2020-00724, 2020 WL 6530785, at *3 (PTAB November 5, 2020). Patent Owner asserts that Petitioner has offered no persuasive reason "why addressing the same or substantially the same issues would not be duplicative of the prior case." *Id.* at 45 (quoting *Fintiv* at 14).

We are not persuaded by Patent Owner's arguments. It is undisputed that Petitioner is not a party to the district court action. Furthermore, and as we have explained with respect to *Fintiv* factor 4 above, Petitioner is not advancing the same theory of the case as is the defendant in the district court

litigation, but is arguing a different theory of unpatentability of the challenged claims of the '601 patent, and using additional references to advance that argument. We find that *Fintiv* factor 5 weighs in favor of institution.

e. *Fintiv* factor 6

Fintiv factor 6 inquires into other circumstances that impact the Board's exercise of discretion, including the merits. Prelim. Resp. 44. Patent Owner argues that the merits of the Petition are weak, but a full merits analysis is not necessary to evaluate this factor. *Id.* Patent Owner argues that, even "if the merits of the grounds raised in the petition are a closer call," this factor "has favored denying institution when other factors favoring denial are present." *Id.* (quoting *Fintiv* at 15).

We disagree. As we have explained above, Petitioner has demonstrated a reasonable probability of success on the merits at least with respect to Ground 2. *See* Section IV.B, *supra*. Furthermore, for the reasons that we have explained above, we find that *Fintiv* factors 2–5 weigh in favor of institution. We consequently find that *Fintiv* factor 6 also weighs in favor of institution.

3. Conclusion

For the reasons we have explained above, we find that, although *Fintiv* factor 1 weighs against institution, *Fintiv* factors 2–6 weigh in favor of institution. We consequently decline to exercise our discretion to deny institution of *inter partes* review under 35 U.S.C. § 314(a).

V. CONCLUSION

For the reasons we have explained, we conclude that Petitioner has demonstrated a reasonable likelihood of showing that at least one of challenged claims 10–12, 18, 19, 21, 26–28 of the '601 patent is unpatentable as being obvious over the 2009 Press Release and Shams. Furthermore, because we determine that Petitioner has shown a reasonable likelihood of prevailing at trial in demonstrating that at least one claim is unpatentable on at least one of the stated Grounds, we institute *inter partes* review of all challenged claims of the '601 patent, based on all of the grounds identified in the Petition. *See SAS Inst., Inc. v. Iancu*, 138 S.Ct. 1348, 1359–60 (2018); *PGS Geophysical AS v. Iancu*, 891 F.3d 1354, 1360 (Fed. Cir. 2018) (interpreting the statute to require "a simple yes-or-no institution choice respecting a petition, embracing all challenges included in the petition"). We additionally deny Patent Owner's request that we exercise our discretion to deny institution under 35 U.S.C. § 314(a).

VI. ORDER

In consideration of the foregoing, it is hereby:

ORDERED, pursuant to 35 U.S.C. § 314(a), that the Petition for *inter partes* review of the challenged claims of US Patent 10,888,601 B2 is GRANTED with respect to all grounds in the Petition; and

FURTHER ORDERED that *inter partes* review is instituted.

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