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Paper 21
Date: November 10, 2021

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MYLAN PHARMACEUTICALS INC.,
Petitioner,

v.

REGENERON PHARMACEUTICALS, INC.,
Patent Owner.

IPR2021-00881
Patent 9,254,338 B2

Before ERICA A. FRANKLIN, JOHN G. NEW, and SUSAN L. C. MITCHELL, *Administrative Patent Judges.*

FRANKLIN, *Administrative Patent Judge*.

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

I. INTRODUCTION

Mylan Pharmaceuticals, Inc. ("Petitioner") filed a Petition requesting an *inter partes* review of claims 1, 3–11, 13, 14, 16–24, and 26 of U.S. Patent No. 9,254,338 B2 (Ex. 1001, "the '338 patent"). Paper 1 ("Petition" or "Pet."). Regeneron Pharmaceuticals, Inc. ("Patent Owner") filed a Preliminary Response to the Petition. Paper 10 ("Prelim. Resp."). With our authorization, Paper 13, Petitioner filed a Reply to the Preliminary Response, and Patent Owner filed a Sur-reply to address further issues involving 35 U.S.C. § 325(d). Paper 16 ("Reply"); Paper 19 ("Sur-reply").

We have authority to determine whether to institute an *inter partes* review. 35 U.S.C. § 314 (2018). Upon considering the parties' arguments and evidence, we determine that Petitioner has demonstrated a reasonable likelihood that it would prevail in showing the unpatentability of at least one claim challenged in the Petition. Accordingly, we institute an *inter partes* review of claims 1, 3–11, 13, 14, 16–24, and 26 of the '338 patent.

A. Real Parties in Interest

Petitioner identifies itself, Viatris Inc., Mylan Inc., Momenta Pharmaceuticals, Inc., Janssen Research & Development LLC, and Johnson & Johnson as the real parties-in-interest. Pet. 3, Paper 18 (Petitioner's Amended Mandatory Notices). Patent Owner identifies itself as the real party-in-interest. Paper 5, 2.

B. Related Proceedings

Petitioner and Patent Owner identify *Mylan Pharms. Inc. v. Regeneron Pharms., Inc.*, IPR2021-00880 (PTAB May 5, 2021) ("the -880 petition") as a related matter. Pet. 3; Paper 5, 2. The -880 petition challenges claims of U.S. Patent No. 9,669,069 B2 ("the '069 patent"). The parties further identify *Chengdu Kanghong Biotechnol. Co. v. Regeneron*

Pharms., Inc., PGR2021-00035 (petition dismissed and proceeding terminated, Paper 8 (PTAB June 25, 2021)) challenging the claims of U.S. Patent No. 10,828,345 B2 ("the '345 patent"), which is related to the '338 patent and the '069 patent. Pet. 4; Paper 5, 2.

Petitioner identifies additional patents and patent applications that claim priority to the '338 patent, namely: U.S. Patent Nos. 10,130,681 B2, 10,857,205 B2, 10,828,345 B2, and 10,888,601 B2; and U.S. Application Serial Nos. 17/072,417, 17/112,063, and 17/112,404. Pet. 4.

C. The '338 Patent

The '338 patent relates to methods for treating angiogenic eye disorders. Ex. 1001, 1:63–64. Angiogenic eye disorders include age-related macular degeneration ("AMD") and diabetic macular edema ("DME"). *Id.* at 1:24–34. According to the Specification, "[r]elease of vascular endothelial growth factor (VEGF) contributes to increased vascular permeability in the eye and inappropriate new vessel growth. Thus, inhibiting the angiogenic-promoting properties of VEGF appears to be an effective strategy for treating angiogenic eye disorders." *Id.* at 1:44–48.

The Specification describes inhibiting the angiogenic-promoting properties of VEGF by administering a VEGF antagonist. *Id.* at 4:37–42. VEGF antagonists may include "VEGF receptor-based chimeric molecule(s), (also referred to herein as a 'VEGF-Trap' or 'VEGFT'). An exemplary VEGF antagonist . . . is a multimeric VEGF-binding protein comprising two or more VEGF receptor-based chimeric molecules referred to herein as 'VEGFR1R2-FcΔC1(a)' or 'aflibercept.'" *Id.* at 2:30–37. "VEGFR1R2-FcΔC1(a) comprises three components: (1) a VEGFR1 component comprising amino acids 27 to 129 of SEQ ID NO:2; (2) a VEGFR2 component comprising amino acids 130 to 231 of SEQ ID NO:2;

and (3) a multimerization component [] comprising amino acids 232 to 457 of SEQ ID NO:2." *Id.* at 4:58–5:3 (citing U.S. Patent No. 7,396,664 B2).

The Specification discloses that, despite the known methods for treating eye disorders using VEGF antagonists, "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.* at 1:53–61. The Specification discloses that

> [t]he present inventors have surprisingly discovered that beneficial therapeutic effects can be achieved in patients suffering from angiogenic eye disorders by administering a VEGF antagonist to a patient at a frequency of once every 8 or more weeks, especially when such doses are preceded by about three doses administered to the patient at a frequency of about 2 to 4 weeks.

Id. at 2:3–10. The Specification describes this dosing regimen as sequentially administering initial, secondary, and tertiary doses. *See id.* at 1:62–2:3. The Specification refers to "sequentially administering" as "each dose of VEGF antagonist is administered to the patient at a different point in time, e.g., on different days separated by a predetermined interval (e.g., hours, days, weeks or months)." *Id.* at 3:22–26. The Specification refers to the "initial dose" as "the dose which is administered at the beginning of the treatment regimen;" the "secondary doses" as "the doses which are administered after the initial dose;" and the "tertiary doses" as "the doses which are administered after the secondary doses." *Id.* at 3:31–38.

D. Illustrative Claims

Petitioner challenges claims 1, 3–11, 13, 14, 16–24, and 26 of the '338 patent. Claims 1 and 14, the only independent claims, are set forth below and are illustrative of the claimed subject matter.

> 1. A method for treating an angiogenic eye disorder in a patient, said method comprising sequentially administering to the patient a single initial dose of a VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonist;
>
> wherein each secondary dose is administered 2 to 4 weeks after the immediately preceding dose; and
>
> wherein each tertiary dose is administered at least 8 weeks after the immediately preceding dose;
>
> wherein the VEGF antagonist is a VEGF receptor-based chimeric molecule comprising (1) a VEGFR1 component comprising amino acids 27 to 129 of SEQ ID NO:2; (2) a VEGFR2 component comprising amino acids 130–231 of SEQ ID NO:2; and (3) a multimerization component comprising amino acids 232–457of SEQ ID NO:2.

Ex. 1001, 23:2–18.

> 14. A method for treating an angiogenic eye disorder in a patient, said method comprising sequentially administering to the patient a single initial dose of a VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonist;
>
> wherein each secondary dose is administered 2 to 4 weeks after the immediately preceding dose; and
>
> wherein each tertiary dose is administered at least 8 weeks after the immediately preceding dose;
>
> wherein the VEGF antagonist is a VEGF receptor-based chimeric molecule comprising VEGFR1R2-FcΔC1(a) encoded by the nucleic acid sequence of SEQ ID NO:1.

Id. at 24:2–15.

E. Asserted Grounds of Unpatentability

Petitioner asserts that claims 1, 3–11, 13, 14, 16–24, and 26 are unpatentable on the following grounds:

Claims Challenged	32 U.S.C. §	Reference(s)
1, 3–11, 13, 14, 16–24, 26	102	Dixon[1]
1, 3–11, 13, 14, 16–24, 26	102	Adis[2]
1, 3–11, 13, 14, 16–24, 26	102	Regeneron 2008[3]
1, 3–11, 13, 14, 16–24, 26	102	NCT-795[4]
1, 3–11, 13, 14, 16–24, 26	102	NCT-377[5]
1, 3–11, 13, 14, 16–24, 26	103	Dixon, Papadopoulos,[6] Dix[7]

Petitioner also relies upon the Declarations of Thomas Albini M.D. (Ex. 1002), and Mary Gerritsen Ph.D. (Ex. 1003). In the Preliminary Response, Patent Owner relies on the Declaration of Diana V. Do, M.D. (Ex. 2001).

[1] James A. Dixon et al., "VEGF Trap-Eye for the treatment of neovascular age-related macular degeneration," 18(10) *Expert Opin. Investig. Drugs* 1573–1580 (2009) (Ex. 1006, "Dixon")).
[2] Adis Data Information BV, "Aflibercept," 9(4) *Drugs R&D* 261–269 (2008) (Ex. 1007, "Adis").
[3] Press Release, Regeneron, "Bayer and Regeneron Dose First Patient in Second Phase 3 Study for VEGF Trap-Eye in Wet Age-Related Macular Degeneration" (May 8, 2008) (Ex. 1013, "Regeneron 2008").
[4] Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Wet Age-Related Macular Degeneration (AMD) (VIEW1), NCT00509795, ClinicalTrials.gov (Apr. 28, 2009), https://clinicaltrials.gov/ct2/show/NCT00509795 (Ex. 1014, "NCT-795").
[5] VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD (VIEW2), NCT00637377, ClinicalTrials.gov (Mar. 17, 2008), https://clinicaltrials.gov/ct2/show/NCT00637377 (Ex. 1015, "NCT-377").
[6] Papadopoulos et al., US 7,374,758 B1, issued May 20, 2008, (Ex. 1010, "Papadopoulos").
[7] Dix et al., US 8,110,546 B2, issued Feb. 7, 2012 (Ex. 1033, "Dix").

II. ANALYSIS

A. Discretionary Denial under 35 U.S.C. § 325(d)

Patent Owner asserts that we should deny the Petition under 35 U.S.C. § 325(d). Prelim. Resp. 9–17. We have discretion to deny review when "the same or substantially the same prior art or arguments previously were presented to the Office." 35 U.S.C. § 325(d). In that respect, § 325(d) provides that the Director may elect not to institute a proceeding if the challenge to the patent is based on matters previously presented to the Office.[8] *Advanced Bionics, LLC v. Med-El Elektromedizinische Geräte GmbH,* IPR2019-01469, Paper 6 at 7 (PTAB Feb. 13, 2020) (precedential) ("*Advanced Bionics*").

In evaluating matters under § 325(d), the Board uses the following two-part framework: (1) determining whether the same or substantially the same art previously was presented to the Office or whether the same or substantially the same arguments previously were presented to the Office; and (2) if either condition of the first part of the framework is satisfied, determining whether the petitioner has demonstrated that the Office erred in a manner material to the patentability of challenged claims. *Advanced Bionics* at 8.

In applying the two-part framework, we consider several nonexclusive factors, including:

(a) the similarities and material differences between the asserted art and the prior art involved during examination;

[8] The Board institutes trial on behalf of the Director. 37 C.F.R. § 42.4(a); *Advanced Bionics*, Paper 6 at 7 n.7.

(b) the cumulative nature of the asserted art and the prior art evaluated during examination;

(c) the extent to which the asserted art was evaluated during examination, including whether the prior art was the basis for rejection;

(d) the extent of the overlap between the arguments made during examination and the manner in which petitioner relies on the prior art or patent owner distinguishes the prior art;

(e) whether petitioner has pointed out sufficiently how the examiner erred in its evaluation of the asserted prior art; and

(f) the extent to which additional evidence and facts presented in the petition warrant reconsideration of the prior art or arguments. *Becton, Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8 at 17–18 (PTAB Dec. 15, 2017) (precedential as to Section III.C.5, first paragraph) ("*Becton, Dickinson*").

Factors (a), (b), and (d) of the *Becton, Dickinson* factors relate to whether the art or arguments presented in the Petition are the same or substantially the same as those previously presented to the Office. *Advanced Bionics* at 10. Factors (c), (e), and (f) "relate to whether the petitioner has demonstrated a material error by the Office" in its prior consideration of that art or arguments. *Id.* Only if the same or substantially the same art or arguments were previously presented to the Office do we then consider whether petitioner has demonstrated a material error by the Office. *Id.* "[T]his framework reflects a commitment to defer to previous Office evaluations of the evidence of record unless material error is shown." *Id.* at 9.

1. Part One of the § 325(d) Analysis

We first consider whether Petitioner asserts the same or substantially the same art or arguments that previously were presented to the Office. *Advanced Bionics*, Paper 6 at 8. Patent Owner asserts that Petitioner relies on substantially the same art that was already considered by the Examiner during prosecution of the '338 patent. Prelim. Resp. 9. In particular, Patent Owner asserts that its VIEW1/2 dosing regimens, which form the basis of Petitioner's unpatentability challenges, "were before the Examiner and considered during prosecution of the '338 Patent." *Id.* In support of that contention, Patent Owner asserts that "[o]n October 18, 2013, [applicant] Regeneron presented a September 28, 2008, Regeneron Press Release ('9/28/2008 Press Release') to the Office in an IDS, which was marked considered by the Examiner." *Id*. (citing Ex. 1017, 60 and 277). Patent Owner asserts that "[t]he 9/28/2008 Press Release discloses the same VIEW1/2 prospective dosing regimen that Petitioner relies on in Grounds 1–5 of its Petition." *Id*. (citing Ex. 2007, 1). Specifically, Patent Owner asserts that each reference relied on for the five separate anticipation challenges, i.e., Dixon, Adis, Regeneron May 2008, NCT-795, and NCT-377, "are essentially identical to the disclosure of the 9/28/08 Press Release." *Id.* at 12. To illustrate that point, Patent Owner provides the following table identifying the dosing regimen disclosed in each of those references:

9/28/08 Press Release (Ex. 2007, 1)	**Dixon (Ex. 1006, 1576)**	**Adis (Ex. 1007, 263)**	**5/8/08 Press Release (Ex. 1013)**	**NCT-795 & NCT-377 (Ex. 1014, 8; Ex. 1015, 6)**
"In [VIEW1/2], …VEGF Trap-Eye [will be] dosed 0.5 mg every 4 weeks, 2 mg every 4 weeks, **or 2 mg every 8 weeks (following three monthly doses)**…."	"[Phase 3] will evaluate the safety and efficacy of VEGF Trap-Eye at doses of. . . **2.0 mg at an 8 week dosing interval (following three monthly doses)**."	"The non-inferiority, [VIEW1] . . . study will evaluate the safety and efficacy of intravitreal aflibercept at . . . **2.0 mg at an 8-week dosing interval** . . . ."	VIEW2 "will evaluate the safety and efficacy of VEGF Trap-Eye at . . . **2.0 mg at an 8-week dosing interval, including one additional 2.0 mg dose at week four.**"	"**2.0 mg VEGF Trap-Eye administered every 8 weeks (including one additional 2.0 mg dose at week 4)** during the first year."

Id. at 13. Patent Owner's table includes five columns setting forth the disclosed dosing regimen for VEGF Trap-Eye or aflibercept. *Id.* According to Patent Owner, because the asserted references for these grounds are cumulative of the 9/28/08 Press Release provided to the Examiner in the IDS during the prosecution of the '338 patent, the Petition asserts substantially the same prior art that was previously presented to the Office. *Id.*

As for Petitioner's obviousness ground, Patent Owner asserts that "the 9/28/08 Press Release" also discloses the same CLEAR-IT 2 clinical trial results as Dixon, which Petitioner relies upon to show a reasonable expectation of success. *Id.* at 14 (citing Pet. 64; Ex. 2007, 1; Ex. 1006, 1576). Patent Owner further asserts that the same teachings of the secondary references, Papadopoulos and Dix, were provided to the Office in an IDS listing Daly.[9] *Id.* at 15 (citing Ex. 1017, 66, 112). Patent Owner asserts that

[9] Daly et al., US 2006/0058234 A1, published Mar. 16, 2006 (Ex. 2009, "Daly").

Daly "contains the same amino acid sequence that Petitioner identifies as the VEGF Trap-Eye sequence in" Papadopoulos and Dix. *See id.* at 15 (citing Ex. 2009, SEQ ID NO:7; Ex. 1010, Figs. 24A–C; Ex. 1033, SEQ ID NO:3). Therefore, Patent Owner asserts that substantially the same prior art relied upon by Petitioner for the obviousness ground was also previously presented to the Office. *Id.*

Petitioner contends that neither the same nor substantially the same art or arguments were previously considered by the Office during the prosecution of the '338 patent. Reply 2. Specifically, Petitioner asserts that the document, Exhibit 2007, that Patent Owner refers to as the "9/28/2008 Press Release," is actually "a 2012 (i.e., post-art) printout of a 'Thomson Reuters' website." *Id.* at 5.[10] Petitioner asserts that the actual 9/28/2008 press release, Ex. 1056, was not applied against the claims or discussed by the Examiner during prosecution of the '338 patent. *Id.* Therefore, according to Petitioner, the Thomson Reuters document, Ex. 2007, listed on the IDS, "is post-art and thus is not, and cannot be, the 'same or substantially the same *prior art*.'" *Id.* at 7 (citing 35 U.S.C. §325(d)).

Petitioner asserts also that its grounds rely on additional disclosures not in the Thomson Reuters document. *Id.* Specifically, Petitioner asserts that "Dixon discusses Lucentis extended dosing regimens and the problems with monthly intravitreal injections"; "Adis and Dixon disclose that VEGF Trap-Eye is aflibercept"; and "Regeneron (8-May-2008) includes efficacy

[10] Petitioner refers to a priority date of January 2011 for the '338 patent. *Id.* at 5 n.5.

endpoints for the VIEW trials and PO/inventor statements about the claimed regimens." *Id.* at 7 (citing Ex. 1006, 1573, 1574, 1577; Ex. 1007, 261; Ex. 1013). Additionally, Petitioner contends that the secondary references cited in the obviousness challenge (Ground 6) were not presented to the Examiner and include non-cumulative disclosures. *Id.* at 7–8.

Further, Petitioner asserts that its reliance on Dr. Albini's opinions and analysis in the Petition also weigh against § 325(d) denial. *Id.* at 9.

In Patent Owner's Sur-reply, Patent Owner asserts that "[t]he IDS clearly identifies the title of the press release, the source as Thomas [sic] Reuters Integrity, and the date as September 28, 2008." Sur-reply 2 (citing Ex. 1017, 60). According to Patent Owner, "[n]othing on the IDS suggests a 2012 date. Rather, the IDS and the face of the '338 Patent report the document's date as September 28, 2008." *Id.* Additionally, Patent Owner asserts that Exhibit 2007 "identifies the 'Reference' as 'Regeneron Pharmaceuticals Press Release 2008, September 28' and the 'Title' as 'VEGF Trap-Eye final phase II results in age-related macular degeneration presented at 2008 Retina Society Meeting." *Id.* at 3. According to Patent Owner, that information makes clear that the press release was available on September 28, 2008. *Id.* Patent Owner notes also that the footer of the Thomson Reuters Integrity printout indicates that it was obtained from a Thomson website in 2012. *Id.*

Patent Owner does not disagree with Petitioner's assertion that the actual press release includes disclosures not found in Exhibit 2007. *Id.* at 5. Instead, Patent Owner asserts those differences are not relevant, as the issue is whether Exhibit 2007 contains substantially the same disclosures as Petitioner's cited art. *Id.* In terms of the differences between Exhibit 2007 and Petitioner's cited art, Patent Owner contends that Petitioner does not

rely on the additional disclosures in its cited art for the anticipation grounds. *Id.* Patent Owner asserts that Petitioner also does not rely on Dixon's discussion about problems with monthly dosing of Lucentis. *Id.* Additionally, Patent Owner asserts that Petitioner's reliance on Dixon and Adis as disclosing that VEGF Trap-Eye is aflibercept "rests on the flawed premise that these terms are synonymous." *Id.* at 5–6.

According to Patent Owner, Petitioner's secondary references, Papadopoulos and Dix, relied upon in the obviousness challenge, are also substantially the same as what was presented to the Office during the '338 prosecution. *Id.* In particular, Patent Owner asserts that Daly, which was presented to the Office, expressly incorporates by reference the entirety of Papadopoulos. *Id.* Additionally, Patent Owner asserts that Dix is cumulative of Daly, inasmuch as Petitioner relies upon Dix for the obviousness ground. *Id.*

To begin, we find that Patent Owner has shown persuasively that, during the prosecution of the '338 patent, the Examiner was presented with the information disclosed in the 2008 Press Release for "VEGF Trap-Eye final phase II results in age-related macular degeneration presented at 2008 Retina Society Meeting." Applicant included the Thomson Reuters description of the press release on the IDS, Ex. 1017, 60–61, along with the submission of the Thomson Reuters publication, Ex. 2007, referenced therein. The Thomson Reuters publication expressly identified the press release by name and date as the "Reference" for the information described in the publication, as well as by the title of the press release. Ex. 2007. Importantly, the Thomson Reuters publication also provided a summary description of the contents of the press release, in a form that resembles an abstract. The contents of the Thomson Reuters publication provides the

information from the 2008 press release that describes the same dosing regimen for VEGF Trap-Eye as each of the cited references relied upon by Petitioner for its anticipation and obviousness challenges.

However, Patent Owner has not shown that the Office was presented with the additional information disclosed in Petitioner's cited art that Petitioner relies upon for its claim challenges. In particular, Petitioner relies upon a teaching in Dixon that "VEGF Trap-Eye and aflibercept (the oncology product) have the same molecular structure." Pet. 40 (citing Ex. 1006, 1575). Petitioner relies, in part, on that teaching to reach the limitations in the challenged claims reciting characteristics of the VEGF antagonist. *Id.* We note that the Thomson Reuters publication includes the term "[a]flibercept," but it does not discuss or describe it as having the same molecular structure as VEGF Trap-Eye. Instead, the term is presented with a parenthetical number next to it, i.e., "Aflibercept (303153)," without any further mention or explanation. Ex. 2007.

Patent Owner has not adequately accounted for the additional teaching in Dixon that "VEGF Trap-Eye and aflibercept have the same molecular structure" by merely asserting that Petitioner's reliance on that teaching in Dixon "rests on the flawed premise that these terms are synonymous." Sur-reply 5–6. The additional teaching in Dixon, relied upon by Petitioner to reach a claim limitation, is sufficient, under Part One of the § 325(d) analysis, to distinguish the Dixon ground presented by Petitioner here from what was before the Office during prosecution.

Thus, we do not find that Dixon is cumulative to the information presented to the Office in the Thomson Reuters publication. For the same reasons, we find that Adis is not cumulative to the information presented to

the Office in the Thomson Reuters publication, as Petitioner similarly relies on a disclosure in Adis that VEGF Trap-Eye is aflibercept. Pet. Reply 7.

Because we determine that the same or substantially the same prior art or arguments previously were not presented to the Office, we need not proceed to step two of the *Advanced Bionics* framework.

2. Conclusion

Based on the foregoing analysis, we decline to exercise our discretion to deny the Petition under § 325 (d).

B. Person of Ordinary Skill in the Art

The level of skill in the art is a factual determination that provides a primary guarantee of objectivity in an obviousness analysis. *Al-Site Corp. v. VSI Int'l Inc.*, 174 F.3d 1308, 1323 (Fed. Cir. 1999) (citing *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966)); *Ryko Mfg. Co. v. Nu-Star, Inc.*, 950 F.2d 714, 718 (Fed. Cir. 1991)).

Petitioner asserts that 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. 22 (citing Ex. 1002 ¶¶ 26–28; Ex. 1003 ¶¶ 20–24). Patent Owner does not address Petitioner's description of the level of ordinary skill in the art, or propose its own description, in the Preliminary Response.

Because Petitioner's definition of one of ordinary skill in the art is reasonable and consistent with the '338 patent and the prior art of record, we adopt Petitioner's definition for purposes of this Decision.

C. 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). 37 C.F.R. § 100(b) (2019). 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) (quoting *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996)). "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).

Petitioner proposes constructions for several claim terms. *See* Pet. 11–22. In the following discussion, we address those proposed constructions and Patent Owner's challenges to them.

1. "A method for treating an angiogenic eye disorder in a patient"

Petitioner asserts that "[t]he 'method for treating' preamble of independent claims 1 and 14 is 'merely a statement of purpose or intended' use for the claimed dosing regimen and is non-limiting." Pet. 17 (citing *Bristol-Myers Squibb Co. v. Ben Venue Lab'ys, Inc.*, 246 F.3d 1368, 1375

(Fed. Cir. 2001)). Petitioner further asserts that the preamble provides no antecedent basis for any other claim element, nor results in a manipulative difference in the steps of the claims. *Id.* at 20 (citing *In Re: Copaxone Consol. Cases*, 906 F.3d 1013, 1023 (Fed. Cir. 2018)).

Petitioner asserts that even if the Board determines that the preamble is limiting, the plain and ordinary meaning of the "method of treating an angiogenic eye disorder" does not require a therapeutically effective treatment. *Id.* at 20. Rather, Petitioner asserts that the plain and ordinary meaning requires "administering a therapeutic to a patient, without a specific degree of efficacy required." *Id.* at 20–21 (citing, Ex. 1002 ¶ 43).

Patent Owner disagrees with Petitioner's proposed construction. Prelim. Resp. 32–37. Patent Owner asserts that the preamble is limiting because it "sets forth the essence of the invention." *Id.* at 32 (citing Ex. 1001, Abstract, 2:3–22). According to Patent Owner, the Specification confirms "that treatment of an angiogenic eye disorder is the entire purpose of the claimed invention." *Id.* at 33 (citing Ex. 1001, 1:18–21, 63–66, 3:19–20, 7:15–19). Patent Owner asserts that the preamble provides utility to the claims and "makes clear that the recited dosing regimen must *treat* a patient with an angiogenic eye disorder." *Id.* at 34 (bolding omitted).

Additionally, Patent Owner asserts that the preamble is limiting because it provides an antecedent basis for "the patient" recited in the bodies of the independent claims and "angiogenic eye disorders" in dependent claims 6, 7, 18, and 20. *Id.* at 34–35. Patent Owner asserts that "[w]ithout the preamble, it would be unclear *who* is receiving sequentially administered doses, *i.e.*, being treated for an angiogenic eye disorder." *Id.* at 35 (bolding omitted).

Further, Patent Owner contends that the result of a limiting preamble is "that the recited method steps produce an effective method of treatment." *Id.* at 36. Patent Owner further asserts that "the method steps of the body of the claim that require administering an initial dose and one or more secondary doses must result in efficacy, which is maintained with the 'tertiary dose(s).'" *Id.*

Having considered the arguments and the evidence, we find, based on the current record, that the preamble reciting "[a] method for treating an angiogenic eye disorder in a patient" is limiting. Although we agree with Petitioner that the preamble sets forth "'a statement of purpose or intended' use for the claimed dosing regimen," the Federal Circuit has recently articulated that its case law does not support a "binary distinction between statements of mere intended purpose on the one hand and limiting preambles on the other." *Eli Lilly and Company v. Teva Pharms. Int'l GmbH,* 8 F.4th 1331, 1340 (Fed. Cir. 2021). Indeed, the Federal Circuit reiterated that "there is no 'litmus test' for determining whether a preamble is limiting." *Id.* (citing *Bicon, Inc. v. Straumann Co.*, 441 F.3d 945, 952 (Fed. Cir. 2006) and *Catalina Mktg. Int'l, Inc. v. Coolsavings.com, Inc.*, 289 F.3d 801, 808 (Fed. Cir. 2002)). As the Court instructed, we determine whether to treat a preamble as a claim limitation based upon "the facts [in this] case in light of the claim as a whole and the invention described in the patent." *Id.* (quoting *Storage Tech. Corp. v. Cisco Sys., Inc.*, 329 F.3d 823, 831 (Fed. Cir. 2003)). With that said, the Court explained that "while there is no bright-line rule, it is instructive that this court has not hesitated to hold preambles limiting when they state an intended purpose for methods of using a compound." *Id.* at 1342.

Here, the claims are directed to methods of administering, i.e., using, a VEGF antagonist for the specific purpose of treating an angiogenic eye disorder in a patient. The Specification repeatedly characterizes the method as one that is useful for treating angiogenic eye disorders in patients. *See* Ex. 1001, 1: 18–20, 63–66, 2:23–27; 3:19–20; 5:11–13. Apart from the preamble, the independent claims do not elsewhere recite or indicate the usefulness of the method steps. Thus, we agree with Patent Owner that the preamble sets forth the essence of the invention. Prelim. Resp. 32. In *Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corp.*, 320 F.3d 1339 (Fed. Cir. 2003), the Federal Circuit explained that "preamble language will limit the claim if it recites not merely a context in which the invention may be used, but the essence of the invention without which performance of the recited steps is nothing but an academic exercise," and that this principle frequently holds true for method claims. *Id. at* 1345 (citing *Griffin v. Bertina*, 285 F.3d 1029, 1033 (Fed. Cir. 2002)).

We also agree with Patent Owner that the preamble provides antecedent basis for claim terms "the patient" recited in the body of each independent claims, and "angiogenic eye disorders" recited in dependent claims 6, 7, 18, and 20. Prelim. Resp. 34–35. As Patent Owner asserts, without the preamble, it would be unclear to whom the doses of VEGF are administered. *See id.* at 35.

Thus, in view of Federal Circuit case law regarding statements of intended purpose in claims directed to method of using compositions, and in view of the evidence of record, namely, the claim language and the written description of the '338 patent, we preliminarily find that the preambles of claims 1 and 14 are limiting.

In addition to asserting that the preamble in claims 1 and 14 are limiting in terms of "treating an angiogenic eye disorder," Patent Owner further asserts that "[t]he preamble requires that the recited methods steps produce an *effective* method of treatment." Prelim. Resp. 36 (emphasis added). In support of that assertion, Patent Owner contends that the recitation of "tertiary dose(s)" in the claims "require[s] maintaining the efficacy gain of the initial and secondary doses." *Id.*

As discussed in our analysis of the claim term "tertiary dose" below, we disagree with Patent Owner that it requires maintaining any such efficacy. Patent Owner does not direct us to any other portion of the claims or written description in the '338 patent that supports finding that the claimed method for treating an angiogenic eye disorder requires such treatment method to have any particular level of effectiveness. Instead, as Petitioner asserts, the claim preamble recites treating and method steps recite administering, without requiring any "specific degree of efficacy." *Id.* at 20–21 (citing, Ex. 1002 ¶ 43).

Indeed, we note that the Specification states that "[t]he amount of VEGF antagonist administered to the patient in each dose is, *in most cases*, a therapeutically effective amount." Ex. 1001, 6:48–50 (emphasis added). The Specification explains that its use of the phrase, "'therapeutically effective amount,' means 'a dose of VEGF antagonist that results in a detectable improvement in one or more symptoms or indicia of an angiogenic eye disorder, or a dose of VEDF antagonist that inhibits, prevents, lessens, or delays the progression of an angiogenic eye disorder.'" *Id.* at 6:50–55. In tandem, those disclosures reveal that the claimed methods for treating an angiogenic eye disorder may or may not involve a dose that results in such a "detectable improvement in one or more symptoms or

indicia of an angiogenic eye disorder," or that "inhibits, prevents, lessens, or delays the progression of an angiogenic eye disorder," as the administered dose amount is described as being therapeutically effective "in most cases," as opposed to requiring it to be therapeutically effective in *all* cases.

That determination is unchanged upon considering the testimony of Patent Owner's declarant, Dr. Do, who draws our attention to the Specification statement that the inventors have "surprisingly discovered that beneficial therapeutic effects can be achieved in patients suffering from angiogenic eye disorders by administering a VEGF antagonist to a patient," in the manner claimed. *See* Ex. 2001 ¶¶ 39–40, 45–48; Ex. 1001, 2:3–10. Without more, we do not find the disclosure that such effects "can be achieved" demonstrates adequately that the claims *require* any particular level of efficacy.

Thus, based on the consideration of the current record, we find that the preambles of the independent claims do not require the recited method steps to provide an *effective* treatment.

2. "Initial dose," "Secondary Dose," and "Tertiary Dose"

Petitioner asserts that the Specification provides express definitions for these terms, specifically that "'initial dose' means 'the dose which is administered at the beginning of the treatment regimen'; 'secondary dose(s)' means 'the dose(s) which are administered after the initial dose'; and 'tertiary dose(s)' means 'the dose(s) which are administered after the secondary dose(s).'" Pet. 12–13 (citing Ex. 1001, 3:31–45; Ex. 1002 ¶ 41).

Patent Owner does not challenge Petitioner's assertions regarding the meaning of "initial dose" or "secondary dose." Prelim. Resp. 36. As for the "tertiary dose(s)," Patent Owner agrees only that it occurs after the secondary doses, but contends that description in the Specification "does not

provide a complete definition of 'tertiary dose.'" *Id.* at 38, 42. Instead, Patent Owner contends that "the prosecution history confirms that the "'tertiary dose' connotes a specific level of efficacy." *Id.* at 40. In that regard, Patent Owner asserts that it relied upon alleged unexpected results of the claimed invention to overcome a double patenting rejection. *Id.* (citing Ex. 1017, 288–291, 315). According to Patent Owner, its argument during prosecution that "less frequent, tertiary dosing 'once every 8 weeks' was surprisingly efficacious" resulted in issuance of the challenged claims. *Id.*

Additionally, Patent Owner asserts that the Specification demonstrates that "[t]he disclosed dosing regimens were a significant advance over existing therapies because they enabled less frequent dosing while maintaining a high degree of therapeutic efficacy." *Id.* at 39–40 (Ex. 1002, 1:55–59, 2:3–10, 2:15–22). According to Patent Owner, when the Specification is considered as a whole, "it is clear that the term 'tertiary dose(s) means 'dose(s), administered after the initial and secondary doses, that maintain(s) the efficacy gain achieved after the initial and secondary doses." *Id.* at 43. Further, the Patent Owner asserts that the Specification description of "tertiary dose" as "the dose(s) which are administered after the secondary dose(s)" should not be viewed as a formal definition because, for example, that description does not follow the same linguistic format used to define other terms in the Specification. *Id.* at 41–46.

Based on our review of the Specification and consideration of the arguments and the evidence, we find that the Specification expressly defines the terms "initial dose," "secondary doses," and "tertiary doses." The Specification states,

> The terms "initial dose," "secondary doses," and "tertiary doses," refer to *the temporal sequence of administration of* the VEGF antagonist. Thus, the "initial dose" is the dose which is administered at the beginning of the treatment regimen (also referred to as the "baseline dose"); the "secondary doses" are the doses which are administered after the initial dose; and the "tertiary doses" are the doses which are administered after the secondary doses.

Ex. 1001, 3:31–38 (emphasis added). Based on those express definitions, we do not find cause to construe the terms differently. In particular, we do not find that the Specification requires the "tertiary doses" to maintain any efficacy gain achieved after the initial and secondary doses, or that the term "connotes a specific level of efficacy" for the reasons urged by Patent Owner. *See* Prelim. Resp. 38–46. The Specification unequivocally states that "[t]he terms 'initial dose,' 'secondary doses,' and 'tertiary doses,' refer to the *temporal sequence of administration* of the VEGF antagonist," and that "the 'tertiary doses' are the doses which are administered after the secondary doses." Ex. 1001, 3:31–38 (emphasis added). Patent Owner has not directed us to any portion of the Specification that teaches differently or adds any efficacy requirement to that definition.

3. "4 weeks" and "8 weeks"

Petitioner contends that "[a] skilled artisan would understand the phrase "'4 weeks'—as it appears in the Challenged Claims—to be synonymous with monthly administration" and "'8 weeks' . . . to be synonymous with bi-monthly (or every-other-month administration)." Pet. 16 (citing Ex. 1001, 7:54–56, 14:41–52; Ex. 1002 ¶ 42). Patent Owner does not challenge this construction. Based on the current record, we determine that express construction of these claim terms is unnecessary for purposes of rendering this Decision. *See Wellman, Inc. v. Eastman Chem.*

Co., 642 F.3d 1355, 1361 (Fed. Cir. 2011) ("[C]laim terms need only be construed 'to the extent necessary to resolve the controversy.'") (quoting *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999)).

4. "VEGFR1 Component," "VEGFR2 Component," and "Multimerization Component"

Petitioner contends that "VEGFR1 Component," "VEGFR2 Component," and "Multimerization Component" all refer to separate amino acid domains of SEQ ID NO:2. Pet. 16–17. Petitioner contends that "[a] skilled artisan would understand these terms to collectively refer to aflibercept (a/k/a VEGF Trap or VEGF Trap-Eye or VEGFR1R2-FcΔC1(a))." *Id.* at 17 (citing Ex. 1001, 2:32–37; Ex. 1002 ¶ 44). Patent Owner does not address Petitioner's contention or these terms in its claim construction analysis. As Petitioner's contention does not appear to be a proposed claim construction for the term, we find it more appropriate to address such contention and these terms below, in the context of our anticipation and obviousness analysis.

D. Anticipation

Petitioner asserts that claims 1, 3–11, 13, 14, 16–24, and 26 are anticipated by each of Dixon, Adis, Regeneron, NCT-795, and NCT-377. Pet. 37–61. Patent Owner disagrees. Prelim. Resp. 17–49.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Schering Corp. v. Geneva Pharms*, 339 F.3d 1373, 1379 (Fed. Cir. 2003) (quoting *Verdegaal Bros., Inc. v. Union Oil Co. of Cal.*, 814 F.2d 628, 631 (Fed. Cir. 1987)).

1. Dixon

Dixon describes a review of clinical trial data regarding administering VEGF Trap-Eye to treat neovascular AMD. Ex. 1006, 1573. Dixon discloses that "VEGF Trap-Eye is a novel anti-VEGF therapy, with Phase I and II trial data indicating safety, tolerability and efficacy for the treatment of neovascular AMD." *Id.* Dixon describes VEGF Trap-Eye as "a fusion protein of key binding domains of human VEGFR-1 and -2 combined with a human IgG Fc fragment." *Id.* at 1575. Dixon discloses that "VEGF Trap-Eye and aflibercept (the oncology product) have the same molecular structure, but there are substantial differences between the preparation of the purified drug product and their formulations." *Id.*

Dixon discloses that current therapy requires "frequent intraocular injections, as often, as monthly, without a defined stopping point," and that "[t]he time and financial burden of monthly injections has led to the initiation of studies to examine the efficacy of alternative dosing schedules." *Id.* at 1574, 1577. Dixon discloses that:

> [d]ue to its high binding affinity and the ability to safely inject high doses into the eye, VEGF Trap-Eye may have longer duration of effect in the eye. Two Phase III studies in wet AMD, VIEW 1 and VIEW 2, are currently under way and seek to compare monthly ranibizumab to monthly or bimonthly VEGF Trap-Eye.

Id. at 1577. Specifically, Dixon discloses that the Phase III trial initiated in August of 2007 "will evaluate the safety and efficacy of intravitreal VEGF Trap-Eye at doses of 0.5 and 2.0 mg administered at 4-week dosing intervals and 2.0 mg at an 8 week dosing interval (following three monthly doses), compared with 0.5 mg of ranibizumab administered every 4 weeks." *Id.* at 1576. Dixon discloses that in a Phase II trial, patients treated with monthly

doses of 2.0 or 0.5 mg VEGF Trap-Eye achieved improvements according to the Early Treatment of Diabetic Retinopathy Study ("ETDRS") scale. *Id.*

2. Adis

Adis discloses a research and development profile of aflibercept (VEGF Trap-Eye). Ex. 1007, 261. Adis discloses that "Aflibercept is a fully human recombinant fusion protein composed of the second Ig domain of VEGFR1 and the third Ig domain of VEGFR2, fused to the Fc region of human IgG_1." *Id.* Adis discloses that aflibercept is in clinical development for treating eye disorders because aflibercept's binding of VEGF-A isoforms can "prevent blood vessel formation and vascular leakage associated with wet age-related macular degeneration (AMD)." *Id.*

Adis discloses that Regeneron Pharmaceuticals and Bayer HealthCare "initiated a phase III trial of aflibercept in approximately 1200 patients with the neovascular form of wet AMD in August 2007," known as the VIEW1 study. *Id.* at 263. The VIEW1 study "will evaluate the safety and efficacy of intravitreal aflibercept at doses of 0.5 mg and 2.0 mg administered at 4-week dosing intervals, and 2.0 mg at an 8-week dosing interval, compared with 0.5 mg ranibizumab administered every 4 weeks." *Id.* "A second phase III trial (VIEW 2) in wet AMD began with the first patient dosed in May 2008." *Id.* "This study will evaluate the safety and efficacy of aflibercept at 0.5 mg and 2.0 mg administered at 4-week intervals and 2.0 mg at an 8-week dosing interval, including one additional 2.0 mg dose at week 4." *Id.* Adis discloses a completed study showing that dosing 0.5 or 2.0 mg monthly aflibercept or 0.5, 2.0, or 4.0 mg quarterly aflibercept resulted in statistically significant reduction in retinal thickness. *Id.*

3. Regeneron 2008

Regeneron 2008 is a press release announcing "that the first patient has been dosed in the VIEW 2 trial, a second Phase 3 clinical study in a development program evaluating VEGF Trap-Eye for the treatment of the neovascular form of Age-related Macular Degeneration (wet AMD)." Ex. 1013, 1. Regeneron 2008 discloses that the VIEW2 study "will evaluate the safety and efficacy of VEGF Trap-Eye at doses of 0.5 milligrams (mg) and 2.0 mg administered at 4-week intervals and 2.0 mg at an 8-week dosing interval, including one additional 2.0 mg dose at week four." *Id.*

Regeneron 2008 discloses that in a Phase 2 trial announced in October 2007, "VEGF Trap-Eye met both primary and secondary key endpoints: a statistically significant reduction in retinal thickness (a measure of disease activity) after 12 weeks of treatment compared with baseline and a statistically significant improvement from baseline in visual acuity (ability to read letters on an eye chart)." *Id.* at 1–2. The press release describes VEGF Trap-Eye as "fully human, soluble VEGF receptor fusion protein that binds all forms of VEGF-A . . . and VEGF-B. VEGF Trap-Eye is a specific and highly potent blocker of these growth factors." *Id.* at 2.

4. NCT-795[11]

NCT-795 discloses clinical trial information for the VIEW1 study. Ex. 1014, 1. NCT-795 describes the VIEW1 study as "a phase III, double-masked, randomized, study of the efficacy and safety of VEGF Trap-Eye in patients with neovascular age-related macular degeneration." *Id.* at 4. NCT-795 discloses Experimental Arm 3 which includes "2.0 mg VEGF

[11] Petitioner submits evidence to establish a reasonable likelihood that NCT-795 qualifies as prior art. *See* Pet. 32–34 (citing Ex. 1086; Ex. 1087). Patent Owner does not challenge the status of NCT-795 as prior art.

Trap-Eye administered every 8 weeks (including one additional 2.0 mg dose at week 4) during the first year. Thereafter a dose may be administered as frequently as every 4 weeks, but no less frequently than every 12 weeks." *Id.* at 8.

5. NCT-377[12]

NCT-377 discloses clinical trial information for the VIEW2 study. Ex. 1015, 1. NCT-377 describes the VIEW2 study as "phase III, double-masked, randomized, study of the efficacy and safety of VEGF Trap-Eye in patients with neovascular age-related macular degeneration." *Id.* at 5. NCT-377 discloses Experimental Arm 3 which includes "2.0 mg VEGF Trap-Eye administered every 8 weeks (including one additional 2.0 mg dose at Week 4) during the first year. Thereafter a dose may be administered as frequently as every 4 weeks, but no less frequently than every 12 weeks." *Id.* at 6.

6. Claim 1

Petitioner asserts that each of Dixon, Adis, Regeneron 2008, NCT-795, and NCT-377 inherently anticipates claim 1. *See* Pet. 37. Specifically, Petitioner asserts that "the Challenged Claims require only a dosing regimen without any particular efficacy or result . . . and therefore, 'proof of efficacy is not required in order for a [prior art] reference to be enabled for purposes of anticipation.'" *Id.* at 38 (quoting *Rasmusson v. SmithKline Beecham Corp.*, 413 F.3d 1318, 1326 (Fed. Cir. 2005)) (emphasis omitted). Petitioner's anticipation challenge based on Dixon is representative of the remaining anticipation challenges. Thus, for purposes

[12] Petitioner submits evidence to establish a reasonable likelihood that NCT-377 qualifies as prior art. *See* Pet. 35 (citing Ex. 1087). Patent Owner does not challenge the status of NCT-377 as prior art.

of this Decision, we focus on Petitioner's anticipation challenge based on Dixon.

Petitioner has identified the disclosures in Dixon that Petitioner asserts disclose each element of claim 1. *See* Pet. 39–41. Specifically, Petitioner asserts that Dixon discloses a method of treating an angiogenic eye disorder (neovascular AMD) in a patient, by administering a VEGF antagonist (VEGF Trap-Eye). *Id.* at 39–40 (citing Ex. 1006, 1573, 1577). In particular, Petitioner asserts that Dixon discloses a dosing regimen of sequentially administering an initial dose (day 0), two secondary doses (4 and 8 weeks), and at least one tertiary dose (every 8 weeks beginning at week 16). *Id.* at 40 (citing Ex. 1006, 1576; Ex. 1002 ¶¶ 119–128).

Petitioner asserts also that Dixon discloses the specific VEGF receptor-based chimeric molecule recited by the claim because Dixon discloses that VEGF Trap-Eye is "a fusion protein of binding domains of VEGF receptors-1 and -2 attached to the Fc fragment of human IgG" and has "the same molecular structure" as aflibercept. *Id.* (citing Ex. 1006, 1575–1576; Ex. 1002 ¶ 127). Petitioner further asserts that "[t]he amino acid sequence and structural information for VEGF Trap-Eye recited in the third 'wherein' clause was well-known and widely-published to skilled artisans." *Id.* (citing Ex. 1010, Fig. 24A–C, 10:15–17; Ex. 1033, ¶¶ 13–14, 30; Ex. 1002 ¶¶ 147–50).

Based upon our review and consideration of the current record, we determine that Petitioner has established a reasonable likelihood of successfully demonstrating that claim 1 is anticipated by Dixon. In particular, at this stage of the proceeding, we credit Dr. Albini's testimony that a person having ordinary skill in the art at the time of the invention would have known the molecular composition of Dixon's disclosed VEGF

Trap-Eye /aflibercept. Ex. 1002 ¶ 127. In reaching our determination, we considered Patent Owner's arguments that the Petition fails to show a likelihood of prevailing on this anticipation ground for a number of reasons. In many respects, Patent Owner addresses all five of Petitioner's anticipation challenges to the claims together. Here, we address those contentions as they relate to Dixon and claim 1 and explain why we find them deficient at this stage in the proceeding.

To begin, Patent Owner asserts that Dixon does not disclose the amino acid sequence of its VEGF antagonist, i.e., "VEGF Trap-Eye." Prelim. Resp. 18. Patent Owner asserts also that Petitioner has not established that the amino acid sequence of VEGF Trap-Eye was known to be the same as the amino acid sequence of aflibercept. *Id.* With respect to Dixon's disclosure that VEGF Trap-Eye and aflibercept have the same molecular structure, Patent Owner asserts that "the POSA would *not* have understood that VEGF Trap-Eye and aflibercept *necessarily* have the same amino acid sequence." *Id.* at 20 (bolding omitted). Rather, Patent Owner asserts that "[a]s of the priority date [of the '338 patent], the POSA would have been aware of inconsistent reports in the literature regarding the molecular weight of 'VEGF Trap-Eye.'" *Id.* at 24–25. Specifically, Patent Owner asserts that the molecular weight of VEGF Trap-Eye was separately reported as 110 kDa or 115 kDa, as compared to 115 kDa for aflibercept. *Id.* (citing Ex. 1075, 403; Ex. 2011, 667; Ex. 2012, 49; Ex. 2013, 144; Ex. 2015 ¶¶ 3, 10).

Although we agree with Patent Owner that Dixon does not expressly disclose the amino acid sequence of the VEGF antagonist that it describes, we find, based on the current record, that Petitioner has shown sufficiently for institution that it was known in the art that VEGF Trap-Eye and

aflibercept shared the same molecular structure and that the amino acid sequence of aflibercept was known. Pet. 40–41; Ex. 1002 ¶ 127. Dixon discusses the chemistry of VEGF Trap-Eye and expressly discloses:

> *VEGF Trap-Eye and aflibercept (the oncology product) have the same molecular structure*, but there are substantial differences between the preparation of the purified drug product and their formulations. Both aflibercept and VEGF Trap-Eye are manufactured in bioreactors from industry standard Chinese hamster ovary cells that overexpress the fusion protein. However, VEGF Trap-Eye undergoes further purification steps during manufacturing to minimize risk of irritation to the eye. VEGF Trap-Eye is also formulated with different buffers and at different concentrations (for buffers in common) suitable for the comfortable, non-irritating, direct injection into the eye.

Ex. 1006, 1575 (emphasis added). Thus, we find that Dixon expressly teaches that VEGF Trap-Eye has the same molecular structure as aflibercept. Further, as noted above, at this stage of the proceeding, we assign persuasive weight to Dr. Albini's testimony regarding what the skilled artisan would have understood about aflibercept's molecular structure, i.e., its amino acid sequence, and thus, the structure of VEGF Trap-EYE. Ex. 1002 ¶ 127. Dr. Albini's testimony appears to be based on sound reasoning, as it is supported by factual evidence. *Id.* Insofar as Patent Owner alleges that the skilled artisan "would *not* have understood that VEGF Trap-Eye and aflibercept *necessarily* have the same amino acid sequence," based on "inconsistent reports in the literature regarding the molecular weight of 'VEGF Trap-Eye,'" see Prelim. Resp. 20, 24, we find such contentions, based on the current record, to be insufficient to overcome the credible and currently unrebutted testimony of Dr. Albini.

Next, Patent Owner relies on its proposed claim construction to argue that none of the cited references expressly disclose the required efficacy

limitations because each reference discloses a prospective study that has not yet occurred. Prelim. Resp. 30 (citing Ex. 1006, 1576). Patent Owner asserts that "it is known that administration of aflibercept using the claimed dosing regimen will not result in an effective method for treating/tertiary dose for some patients." *Id.* at 47 (citing Ex. 2018, 1861). Accordingly, Patent Owner asserts that "the required efficacy is not inherent in the dosing regimen." *Id.* at 48. Patent Owner further argues that Petitioner does not account for other variables that relate to the preparation of VEGF Trap-Eye before administration. *Id.* at 48–49 (citing Ex. 1006, 1575; Ex. 1005, 2142). Patent Owner asserts that "[w]hat is needed to achieve the required efficacy is absent from any of Petitioner's allegedly anticipating references, and Petitioner makes no effort to show that the disclosed prospective dosing regimen of 'VEGF Trap-Eye' necessarily results in a 'method of treating' or a 'tertiary dose,' which require efficacy." *Id.* at 49.

As discussed above, we have not found that claim 1 requires any particular efficacy for the recited method of treating an antiogenic eye disorder in a patient. Thus, based on the current record, Patent Owner's arguments to the contrary lack merit.

Accordingly, based on the information presented at this stage of the proceeding, we determine that Petitioner has shown sufficiently that there is a reasonable likelihood that it would prevail in showing that independent claim 1 is anticipated by Dixon.

7. Claims 3–11, 13, 14, 16–24, and 26

Petitioner has also addressed the limitations in independent claim 14 and the challenged claims that depend from claims 1 and 14. Pet. 41–44. Patent Owner does not separately address or assert additional arguments regarding those challenges. *See* Prelim. Resp. 17–28, 30–49. Based on our

review of the current record, we determine that Petitioner has shown sufficiently for institution how Dixon further discloses each limitation of claims 3–11, 13, 14, 16–24, and 26.

Accordingly, based on the information presented at this stage of the proceeding, we determine that Petitioner has shown sufficiently that there is a reasonable likelihood that it would prevail in showing that claims 3–11, 13, 14, 16–24, and 26 are anticipated by Dixon.

E. Obviousness

Petitioner asserts that claims 1, 3–11, 13, 14, 16–24, and 26 would have been obvious over Dixon, alone or in combination with Papadopoulos or Dix. Pet. 62–69. Patent Owner disagrees. Prelim. Resp. 49–62.

A patent claim is unpatentable under 35 U.S.C. § 103(a) 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 the subject matter pertains. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007).

"An obviousness determination requires finding both '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.'" *CRFD Research, Inc. v. Matal*, 876 F.3d 1330, 1340 (Fed. Cir. 2017) (quoting *Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1367–1368 (Fed. Cir. 2016)).

Notwithstanding what the teachings of the prior art would have suggested to one with ordinary skill in the art at the time of the patent's invention, the totality of the evidence submitted, including objective

evidence of nonobviousness, may lead to a conclusion that the challenged claims would not have been obvious to one with ordinary skill in the art. *In re Piasecki*, 745 F.2d 1468, 1471–72 (Fed. Cir. 1984). Objective evidence of nonobviousness, so called "secondary considerations," may include long-felt but unsolved need, failure of others, unexpected results, commercial success, copying, licensing, and praise. *See Graham*, 383 U.S. at 17–18; *Leapfrog Enters., Inc. v. Fisher–Price, Inc.*, 485 F.3d 1157, 1162 (Fed. Cir. 2007).

1. Papadopoulos

Papadopoulos discloses isolated nucleic acid molecules encoding a fusion polypeptide capable of binding a VEGF polypeptide. Ex. 1010, 5:11–14. Specific molecules include a fusion polypeptide VEGFR1R2-FcΔC1(a), encoded by the nucleic acid (SEQ ID NO:15) and amino acid sequences (SEQ ID NO:16) set forth in Figures 24A–24C. *Id.* at 6:33–36; 10:15–17; 29:39–56. Papadopoulos discloses that the chimeric polypeptide may be useful in treating clinical conditions that are characterized by vascular permeability, for example, eye disorders such as age related macular degeneration and diabetic retinopathy. *Id.* at 15:50–16:6.

2. Dix

Dix discloses formulations for administering a soluble VEGF-specific fusion protein antagonist, i.e., VEGF trap protein. Ex. 1033 ¶¶ 5, 13–14. Dix discloses that the VEGF trap protein comprises the protein sequence of SEQ ID NO:4. Ex. 1033 ¶¶ 13–14, 30. Dix also discloses nucleic acid sequence of SEQ ID NO:3. *See id.* at 9.

3. Claim 1

According to Petitioner,

> Dixon [] renders the Challenged Claims obvious in light of the skilled artisan's (i) knowledge of the sequence and molecular structure for VEGF Trap-Eye; (ii) clear motivation—as expressly stated in Dixon—to explore less frequent dosing; and (iii) reasonable expectation of success found in Dixon's disclosure of the positive Phase 2 trial data for VEGF Trap-Eye.

Pet. 62–63 (citing Ex. 1002 ¶¶ 364–403). As in its anticipation challenge, Petitioner asserts here also that the sequence and domain architecture of the VEGF Trap-Eye disclosed in Dixon was known in the art. *Id.* at 63 (citing Ex.1010, Fig. 24A–C; 15:50-16:6; Ex.1033 ¶¶ 5, 13–14, 30). Based on that contention, Petitioner asserts that Dixon alone renders the challenged claims obvious based upon the same disclosures applied in its anticipation analysis. *Id.* at 63, 65.

Alternatively, Petitioner asserts that the combination of Dixon with Papadopoulos and/or Dix renders the challenged claims obvious. *Id.* at 63. Petitioner relies on each of those secondary references as setting forth the precise structure and sequence for VEGF Trap-Eye/aflibercept. *Id.* at 63.

As to the motivation to explore less frequent dosing, Petitioner asserts that Dixon describes frequent intraocular injections as a drawback to existing age-related macular degeneration therapy. *Id.* (citing Ex. 1006, 1577). Petitioner asserts that "Dixon discusses 'the initiation of studies to examine the efficacy of alternative dosing schedules'" which decrease the dosing intervals from the known monthly interval. *Id.* at 63–64 (citing Ex. 1006, 1577; Ex. 1002 ¶ 365) (bolding omitted). Petitioner asserts that Dixon "directly recommends using a dosing regimen featuring longer intervals to minimize the treatment burden, which would have motivated a

skilled artisan to adopt the disclosed Phase 3 regimen—an obvious solution to the need for less frequent injections." *Id.* at 64 (citing Ex. 1002 ¶ 366).

Petitioner asserts that a skilled artisan would have had a reasonable expectation of success in administering the VIEW1/VIEW2 dosing regimens because Dixon reported success from previous Phase 2 regimen (monthly dosing) and the initiation of a Phase 3 trial. *Id.* at 64–65. Petitioner further asserts that "Dixon reports that Phase 2 patients required (on average) *only 1.6 additional injections* after the four monthly loading doses during the year-long study—further confirming the skilled artisan's expectation of success with the VIEW1/VIEW2 dosing regimen." *Id.* at 65 (citing Ex. 1002 ¶¶ 367–368).

Patent Owner responds only to Petitioner's obviousness ground based on Dixon alone. Prelim. Resp. 50–57.[13] Thus, for purposes of this Decision, we focus on Petitioner's obviousness challenge based on Dixon alone.

Patent Owner asserts that Petitioner fails to show "that the POSA would have had a reasonable expectation of success." *Id.* Patent Owner contends that Regeneron's initiation of a Phase 3 clinical trial is not evidence that a "POSA would have expected the 8-week dosing regimen to be successful." *Id.* at 50–51. Patent Owner asserts that several Phase 3 clinical trials of VEGF inhibitors for angiogenic eye disorders previously

[13] Patent Owner asserts that Ground 6 does not meet the particularity requirement because it "is a 'catch-all' ground that alleges that the Challenged Claims are obvious over seven references under fifteen different theories." Prelim. Resp. 6–7. We disagree, as we recognize Petitioner's obviousness ground to present four clear alternatives, i.e., Dixon alone, Dixon in combination with Papadopoulos, Dixon in combination with Dix, or Dixon in combination with Papadopoulos and Dix, wherein Papadopoulos and Dix are each relied upon as disclosing the amino acid sequence of Trap-Eye/aflibercept. *See* Pet. 6, 62–66.

failed. *Id.* at 51–52 (citing Ex. 2020–2025). Patent Owner asserts that "the design of the VIEW1/2 trials demonstrates that Regeneron itself was hedging its bets on an extended 8-week dosing regimen." *Id.* at 52 (citing Ex. 1006, 1576).

Patent Owner further asserts that Dixon's disclosure of positive Phase 2 results (CLEAR-IT 2 trial), would not have provided a reasonable expectation of success as the "CLEAR-IT 2 trial results called into question the viability of an 8-week dosing regimen for VEGF Trap-Eye." *Id.* at 53. Specifically, Patent Owner asserts that the "CLEAR-IT 2 12-week primary endpoint data indicated that the therapeutic effect of VEGF Trap-Eye began to decrease between the week-4 and week-8 timepoints in the quarterly dosing arms, and the only treatment arms that were successful in sustaining therapeutic efficacy were the monthly treatment dosing arms." *Id.* at 53–55 (citing Ex. 2028). Apart from the CLEAR-IT 2 Trial, Patent Owner asserts that other trial failures led to "great uncertainty in the art regarding extended dosing." *See id.* at 55–56 (citing Ex. 1006, 1574, 1577; Ex. 1018, 2537; Exs. 2029–2032).

Finally, Patent Owner asserts that Dixon itself acknowledges that "The most effective dosing regimen and monitoring program for anti-VEGF therapy has yet to be firmly established." *Id.* at 56 (quoting Ex. 1006, 1576–1577) (emphasis omitted). Petitioner asserts that Dixon teaches "the durability of VEGF Trap-Eye and its adoption in clinical practice will only be known after Regeneron's Phase 3 clinical trial results are reported." *Id.* at 56 (citing Ex. 1006, 1577).

We have considered each of Patent Owner's arguments, *see* Prelim. Resp. 49–57, and do not find them sufficient at this stage of the proceeding to deny the Petition.[14] As explained for the anticipation ground, on this record, we have determined that Petitioner has shown sufficiently for institution that Dixon discloses each limitation of the challenged claims. As the Federal Circuit has observed, "it is well settled that 'a disclosure that anticipates under § 102 also renders the claim invalid under § 103, for 'anticipation is the epitome of obviousness.'" *Realtime Data, LLC v. Iancu*, 912 F.3d 1368, 1373 (Fed. Cir. 2019) (quoting *Connell v. Sears, Roebuck & Co.*, 722 F.2d 1542, 1548 (Fed. Cir. 1983) (quoting *In re Fracalossi*, 681 F.2d 792, 794 (CCPA 1982))).

Accordingly, based on the information presented at this stage of the proceeding, we determine that Petitioner has shown sufficiently that there is a reasonable likelihood that it would prevail in showing that claim 1 is rendered obvious by at least Dixon alone.

4. Claims 3–11, 13, 14, 16–24, and 26

Petitioner also refers to its anticipation challenge to address the limitations in independent claim 14 and the challenged claims that depend from claims 1 and 14. Pet. 65. Patent Owner does not separately address or assert additional arguments regarding those challenges. *See* Prelim. Resp. 49–62. Based on our review of the current record, we determine that Petitioner has shown sufficiently for institution how Dixon also discloses each limitation of claims 3–11, 13, 14, 16–24, and 26.

[14] At this stage of the proceeding, Patent Owner does not present evidence of objective indicia supporting nonobviousness of the challenged claim. *See* Prelim. Resp. 57–62 (concluding that it will present such evidence "[i]n the unlikely event it is required").

Accordingly, based on the information presented at this stage of the proceeding, we determine that Petitioner has shown sufficiently that there is a reasonable likelihood that it would prevail in showing that claims 3–11, 13, 14, 16–24, and 26 are rendered obvious by at least Dixon alone.

III. CONCLUSION

For the foregoing reasons, we conclude that Petitioner has established a reasonable likelihood of prevailing on its assertion that at least one claim of the '338 patent is unpatentable. In *SAS Institute Inc. v. Iancu*, the Supreme Court held that the Board's final written decision in an instituted *inter partes* review must address every claim challenged by a petitioner. 138 S. Ct. 1348, 1354 (2018). In light of *SAS*, the "the Board will either (1) institute as to all claims challenged in the petition and on all grounds in the petition, or (2) institute on no claims and deny institution." Patent Trial and Appeal Board Consolidated Trial Practice Guide 64 (Nov. 2019), *available at* https://www.uspto.gov/sites/default/files/documents/tpgnov.pdf.

Accordingly, we institute an *inter partes* review of all of the challenged claims on all asserted grounds.

Our determination in this Decision is not a final determination on either the patentability of any challenged claims or the construction of any claim.

IV. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that pursuant to 35 U.S.C. § 314(a), an *inter partes* review of claims 1, 3–11, 13, 14, 16–24, and 26 of the '338 patent on all grounds set forth in the Petition is instituted, commencing on the entry date of this decision; and

FURTHER ORDERED that pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4, notice is hereby given of the institution of review.

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