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Paper 10
Date: July 19, 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.

IPR2023-00442
Patent 10,130,681 B2

Before JOHN G. NEW, SUSAN L.C. MITCHELL, and ROBERT A. POLLOCK, *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 2, "Pet.") seeking *inter partes* review of claims 1, 3–11, 13, 14, 16–24, and 26 of US Patent 10,130,681 B2 (Ex. 1001, the "'681 patent"). Patent Owner Regeneron Pharmaceuticals, Inc. ("Patent Owner") timely filed a Preliminary Response. Paper 7 ("Prelim. Resp."). With our authorization, Petitioner filed a Reply to the Preliminary Response (Paper 8 ("Reply")), and Patent Owner filed a Sur-Reply. Paper 9 ("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 '681 patent. We therefore institute *inter partes* review.

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.*, IPR2021-00880, IPR2021-00881, IPR2022-01225, and IPR2022-01226 as related matters. Pet. 6; Paper 5 at 2. Final Written Decisions were entered in both the IPR2021-00880 and -00881 *inter partes* reviews on November 9, 2022. Patent Owner has since appealed those decisions to the U.S. Court of Appeals for the Federal Circuit as *Regeneron Pharmaceuticals, Inc. v. Mylan Pharmaceuticals Inc.*, No. 2023-1395 (Fed. Cir.) and *Regeneron Pharmaceuticals, Inc. v. Mylan Pharmaceuticals Inc.*, No. 2023-1396 (Fed. Cir.), respectively. *See* Paper 5 at 3.

Furthermore, in IPR2022-01225, Mylan challenged the patentability of claims 1, 3–11, 13, 14, 16–24, and 26 of the '681 patent, the same patent and claims that Petitioner presently challenges in its Petition. *See* Paper 2, 6. Petitioner also sought, and was granted, joinder in IPR2022-01226 as a "silent partner" in that litigation. *See* IPR2022-00566, Papers 2, 10. Additionally, Celltrion, Inc. has similarly sought, and been granted, joinder with both IPR2022-001225 and -01226, and has also assumed a "silent partner" 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. 6. 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 Biotechnology Co. v. Regeneron*

Pharms., Inc., PGR2021-00035 (PTAB) (proceeding terminated). Paper 5 at 2–3.

C. The Asserted Grounds of Unpatentability

Petitioner contends that claims 1, 3–11, 13, 14, 16–24, and 26 of the '681 patent are unpatentable, based upon the following ground:

Ground	Claim(s) Challenged	35 U.S.C. §	Reference(s)/Basis
1	1, 3–11, 13, 14, 16–24, 26	103[1]	Dixon[2], CATT[3], MACTEL[4], PIER[5] (individually and collectively)

[1] 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 '681 patent issued has an effective filing date after that date, the AIA versions of §§ 102 and 103 apply.

[2] J.A. Dixon et al., *VEGF Trap-Eye for the Treatment of Neovascular Age-Related Macular Degeneration*, 18(10) EXPERT OPIN. INVESTIG. DRUGS 1573–80(2009) ("Dixon") Ex. 1006.

[3] NCT00593450, *CATT Patient Eligibility Criteria*, *available at*: www.clinicaltrials.gov/ct2/show/NCT00593450 (last visited July 5, 2023) ("CATT") Ex. 1031.

[4] NCT00685854, *Pilot Study of Intravitreal Injection of Ranibizumab for Macular Telangiectasia With Neovascularization (MACTEL 2)*, *available at*: https://clinicaltrials.gov/ct2/history/NCT00685854?V_1 =View#StudyPageTop (last visited July 5, 2023 ("MACTEL") Ex. 1032.

[5] 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. 1034.

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

D. The '681 Patent

The '681 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 col. 2, ll. 56–62.

E. Representative Claim

Claim 1 is representative of the challenged claims, and recites:

> 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 232-457 of SEQ ID NO:2;

wherein exclusion criteria for the patient include all of:

(1) active intraocular inflammation;

(2) active ocular or periocular infection;

(3) any ocular or periocular infection within the last 2 weeks prior to treatment.

Ex. 1001, col. 21, ll. 40–63.

F. Priority History of the '681 Patent

The '681 patent issued from U.S. Application Ser. No. 15/471,506 (the "'506 application") filed on March 28, 2017, and claims the priority benefit of, *inter alia*, US Provisional Application Ser. No. 61/432,245, which was filed on Jan. 13, 2011. Ex. 1001, code (60).

The claims of the '681 patent, including challenged claims 1, 3–11, 13, 14, 16–24, and 26, were allowed on July 26, 2018, and the patent issued on November 20, 2018. 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 an angiogenic eye disorder in a patient"

Petitioner initially accepts, for the purposes of this Decision, that the preamble of claim 1 is limiting, and agrees with the Board's previous rejection, in the related -00881 *inter partes* review, of Patent Owner's position that the preamble requires a particular level of efficacy. Pet. 19 (citing Ex. 1004, 18). According to Petitioner, the plain and ordinary meaning of the term "treating" does not require a specific level of efficacy, but only that the method be administered for the purpose of treatment of an angiogenic eye disease. *Id.* (citing Ex. 1002 ¶ 84).

Patent Owner disagrees, arguing that the recited "method for treating" requires "a high level of efficacy, i.e., efficacy noninferior to monthly ranibizumab." Prelim. Resp. 11. Patent Owner concedes, however, that it is

not necessary for the Board to resolve this dispute for purposes of resolving the arguments presented in its Preliminary Response. *Id.*

We agree with Patent Owner, and for the reasons we explain below (*see* Section C.1), that it is not necessary at this stage of the proceeding to resolve whether the language of the preamble requires, as Patent Owner argues, "a high level of efficacy, i.e., efficacy noninferior to monthly ranibizumab." *See Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) (providing claim construction only "to the extent necessary to resolve the controversy"). We consequently do not reach a construction of the preambular term "[a] method for treating an angiogenic eye disorder in a patient" at this stage of the proceeding.

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

Petitioner proposes that the claim terms "initial dose," "secondary dose," and "tertiary dose," be construed to refer to their temporal sequence of administration, consistent with the express definition in the Specification of the '681 patent. Pet. 22–23 (citing Ex. 1001, col. 3, ll. 31–38; Ex. 1002 ¶¶ 89–90.

Patent Owner provides no alternate construction for these claim terms. However, for the same reasons (*see* Section C.1, *infra*) that we conclude that it is unnecessary at this stage of this proceeding to construe the "method of treatment" language of the preamble, we similarly conclude that it is unnecessary to arrive at a construction of the claim terms "initial dose," "secondary dose," and "tertiary dose" in our determination of whether to institute this *inter partes* review. *See Nidec*, 868 F.3d at 1017. We consequently do not reach a claim construction of these terms at this time.

3. The exclusion criteria

The exclusion criteria limitation of challenged claim 1 recites:

[W]herein exclusion criteria for the patient include all of:

(1) active intraocular inflammation;

(2) active ocular or periocular infection;

(3) any ocular or periocular infection within the last 2 weeks prior to treatment.

Ex. 1001, col. 21, ll. 58–62.

Petitioner and Patent Owner agree that, for the purposes of this Decision, the exclusion criteria limitation is entitled to patentable weight, but offer no express claim construction of this limitation. Pet. 2, 4, 43; Prelim. Resp. 12. Consequently we need not provide an express construction of these terms at the present stage of the proceeding. *Nidec*, 868 F.3d at 1017

B. A Person of Ordinary Skill in the Art

Petitioner notes that, in the Final Written Decision in IPR2021-00881 (the "-00881 Decision"), 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. 17–18 (quoting Ex. 1004, 9–10). 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 disagrees with Petitioner's definition of a person of ordinary skill in the art, arguing that the skilled artisan is an ophthalmologist experienced in treating angiogenic eye disorders, including with VEGF antagonists. Prelim. Resp. 11. Patent Owner acknowledges, however, that the parties' differing definitions of a person of ordinary skill in the art do not affect any argument presented with respect to our present Decision to Institute. *Id.*

As we explain below, with the exception of the exclusion criteria, claim 1 of the '681 patent is identical to claim 1 of the '388 patent in the -00881 IPR. We again determine that our definition of a person of ordinary skill in the art is reasonable and consistent with the prior art of record at this stage of the proceeding. 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[6] that the claims are unpatentable. 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 ("POSA" or "POSITA"). *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;

[6] 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).

(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 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 above-stated principles.

B. Ground 1: Obviousness under 35 U.S.C. § 103 of claims 1, 3–11, 13, 14, 16–24, and 26 over Dixon (Ex. 1006), CATT (Ex. 1031), MACTEL (Ex. 1032), and PIER (Ex. 1034)

1. Background

Petitioner challenges claims 1, 3–11, 13, 14, 16–24, and 26 of the '681 patent as unpatentable under 35 U.S.C. § 103 as unpatentable in view of one or more of Dixon, CATT, MACTEL, and PIER. Pet. 48–52.

In the -00881 Decision, we determined that claim 1 of US 9,254,338 B2 (the "'338 patent") was unpatentable under 35 U.S.C. § 102 as being anticipated by Dixon. For the convenience of the reader, we present a claim

chart comparing independent claim 1 of the present challenged claims and claim 1 of the ’338 patent in the -00881 Decision:

IPR2022-01225 US 10,130,681 B2 Claim 1	**IPR2021-00881 US 9,254,338 B2 Claim 1 (unpatentable)**
1. A method for treating an angiogenic eye disorder in a patient,	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;	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 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	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 232–457 of SEQ ID NO:2.	comprising amino acids 130–231 of SEQ ID NO:2; and (3) a multimerization component comprising amino acids 232–457 of SEQ ID NO:2.
wherein exclusion criteria for the patient include all of: (1) active intraocular inflammation; (2) active ocular or periocular infection; (3) any ocular or periocular infection within the last 2 weeks.	

As should be readily apparent to the reader, challenged claim 1 of the present Petition and claim 1 of the ’338 patent are identical, with the sole exception in the ’681 patent of the additional limitation reciting the exclusion criteria. Because, in the -00881 Decision, we concluded that claim 1 of the ’338 patent is anticipated by Dixon, we incorporate here by reference and adopt our reasoning in the -00881 Decision with respect to the corresponding limitations of claim 1 of the ’681 patent. *See* -00881 Decision, 26–46. We therefore conclude that Petitioner has demonstrated sufficiently that those limitations of claim 1 of the ’681 patent are taught by Dixon.

Our Decision to Institute, then, must next consider whether Petitioner can demonstrate that the exclusion criteria are disclosed or obvious in view of the cited prior art (Ground 1). In the absence of any argument by either party that the exclusion criteria are not entitled to patentable weight (as in

the Decision to Institute in IPR2022-01225) we do not consider that issue in this Decision, but instead turn our attention to whether the cited art, Dixon, CATT, MACTEL, and PIER, teach or suggest the exclusion criteria.

2. Overview of the prior art

a. Dixon

Dixon was published in October, 2009, and is prior art to the '069 patent. Ex. 1006, 1573. Dixon discloses that a new drug for the treatment of age-related macular degeneration ("AMD") is aflibercept ("VEGF Trap-Eye"), a fusion protein that blocks all isoforms of VEGF-A and placental growth factors-1 and -2. *Id.*, Abstr. 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.*

In the '00881 Decision, we determined that Dixon anticipated the preamble and limitations of claim 1 of the '338 patent, which are identical to claim 1 of the '681 patent, with the exception that the former does not recite the exclusion criteria limitation recited in the latter. Petitioner does not depend upon Dixon as reciting the exclusion criteria, but rather relies on CATT, MACTEL, and PIER as reciting the exclusion criteria, either individually or collectively. *See* Pet. 24–25. We therefore direct our focus to whether CATT, MACTEL, and/or PIER teach or suggest the exclusion criteria.

b. CATT

The CATT Study was a University of Pennsylvania-sponsored study that evaluated the efficacy and safety of intravitreal injections of

bevacizumab relative to ranibizumab, the two major VEGF antagonist-treatments for angiogenic diseases at the time. *See* Ex. 1035. The web archive of the University of Pennsylvania's School of Medicine website provides a document (the "CATT Study") listing exclusion criteria for CATT as of July 13, 2010, and CATT is therefore prior art to the '681 patent under 35 U.S.C. § 102(a). *See* Ex. 1031.

CATT discloses a list of exclusion criteria for its study, including both "[a]ctive or recent (within 4 weeks) intraocular inflammation (grade trace or above) in the study eye." Ex. 1031, 6. It additionally lists "[a]ctive infectious conjunctivitis, keratitis, scleritis, or endophthalmitis in either eye" among its exclusion criteria. *Id.*

c. MACTEL

MACTEL discloses a clinical phase II study, NCT00685854, entitled: *Pilot Study of Intravitreal Injection of Ranibizumab for Macular Telangiectasia With Neovascularization (MACTEL 2)*. Ex. 1032, 1. According to ClinicalTrials.gov, which includes first posted information recorded with each study, an electronic document describing the MACTEL study was available on May 24, 2008 . *See id.* MACTEL is consequently prior art to the '681 patent under 35 U.S.C. § 102(b).

Among the exclusion criteria expressly listed in MACTEL are "[c]urrent acute ocular or periocular infection," and "[h]istory within the past 30 days of a chronic ocular or periocular infection…." Ex. 1032, 4.

d. PIER

The PIER study is summarized in an article published in The American Journal of Ophthalmology in February, 2008 and is prior art to the '681 patent under 35 U.S.C. § 102(b). Ex. 1034, 239. The purpose of the PIER study was "[t]o evaluate the efficacy and safety of ranibizumab administered monthly for three months and then quarterly in patients with subfoveal choroidal neovascularization (CNV) secondary to age-related macular degeneration (AMD)." *Id.*

PIER discloses, as exclusion criteria *inter alia*, "[a]ctive intraocular inflammation (grade trace or above) in the study eye" and "[i]nfectious conjunctivitis, keratitis, scleritis, or endophthalmitis in either eye." Ex. 1034, 248.e3.

3. Petitioner's argument

Petitioner argues that the CATT, MACTEL, and PIER Studies describe the exclusion criteria for clinical trials of the leading prior art anti-VEGF treatments— bevacizumab (Avastin®) and ranibizumab (Lucentis®). Pet. 42 (citing Ex. 1002 ¶¶ 99–110, 130–149). Petitioner notes that both of these prior art drugs are, like the claimed aflibercept, administered *via* intravitreal injection. *Id.* Petitioner's Table 1 compares the exclusion criteria of challenged claim 1 and the disclosures of the prior art, and is reproduced below:

Table 1	
Exclusion Criteria Recited in Independent Claims	**Prior Art Exclusion Criteria for Anti-VEGF Intravitreal Injections Relied on by Petitioner**
"(1) ***active intraocular inflammation***" – i.e. current inflammation within the eye. Ex. 1002, ¶¶ 91, 133.	"***Active*** or recent (within 4 weeks) ***intraocular inflammation*** (grade trace or below) in the study eye." Ex. 1031, CATT Study. "***Active intraocular inflammation*** (grade trace or above) in the study eye." Ex. 1034, PIER Study.
"(2) ***active ocular or periocular infection***" – i.e. a current infection anywhere on/in the eye (ocular) or surrounding it within its orbit (periocular). *Id.*	"***Current acute ocular or periocular infection***." Exs. 1032-33, MACTEL Study. "***Active*** infectious conjunctivitis, keratitis, scleritis, or endophthalmitis ***in either eye***." Ex. 1031, CATT Study. "***Infectious*** conjunctivitis, keratitis, scleritis, or endophthalmitis ***in either eye***." Ex. 1034, PIER Study.
"(3) any ***ocular or periocular infection within the last 2 weeks*** prior to treatment" – i.e. a ***recent*** infection anywhere on/in or surrounding the eye *Id.*	"***History within the past 30 days of a chronic ocular or periocular infection*** (including any history of ocular herpes zoster)" and "***[c]urrent acute ocular or periocular infection***." Exs. 1032-33, MACTEL Study. "Active or ***recent (within 4 weeks) intraocular inflammation*** (grade trace or below) in the study eye." Ex. 1031, CATT Study.

Pet. 43 (citing Ex. 1002 ¶ 133).

With respect to the first and second exclusion criteria, Petitioner points to the Declaration of Dr. Edward Chaum (the "Chaum Declaration, Ex. 1002), who testifies that the disclosed prior art exclusion criteria would

exclude the same patients as the first and second claimed exclusion criterion. Pet. 44 (citing Ex. 1002 ¶¶ 133–137).

With respect to the third exclusion criteria, Petitioner argues that MACTEL discloses the claimed exclusion criterion, excluding patients with a "[h]istory within the past 30 days of a chronic ocular or periocular infection (including any history of ocular herpes zoster)," as well as "[c]urrent acute ocular or periocular infection." Pet. 44–45 (citing Ex. 1032, 4). Petitioner argues that, because MACTEL excludes patients with a history of "chronic" ocular or periocular infection within the last 30 days (i.e., infections lasting for longer durations, such as four weeks or more, including ones have been recently symptomatic) or current "acute" ocular or periocular infection (i.e., infections that had the initial onset of symptoms within the last few weeks), it would exclude all of the patients excluded by the claimed third exclusion criterion, which is limited to fourteen days; whether their infection is chronic or acute. *Id.* at 45 (citing Ex. 1002 ¶¶ 140–144).

To clarify, Petitioner points to Dr. Chaum's testimony that a person of ordinary skill in the art would understand that "chronic" and "acute" are not generally given precise definitions in the art, but generally refer to the length of time an infection is present from presentation, and whether it has reoccurred. Pet. 45 (citing Ex. 1002 ¶¶ 142–143; *see, e.g.*, Exs. 1023–1024, 1063). Petitioner contends that excluding patients with a "history" of a chronic infection within the past 30 days would thus exclude any infection in the past 14 days that was present long enough to be considered "chronic" (or had otherwise reoccurred), and excluding current "acute" infections would

exclude any other infections that had presented within the weeks immediately before treatment (i.e., generally one to three weeks). *Id.*

Petitioner also argues that CATT expressly excludes from its study patients with "[r]ecent (within 4 weeks) intraocular inflammation (grade trace or below) in the study eye." Pet. 46 (citing Ex. 1002 ¶ 137). Petitioner again points to the testimony of Dr. Chaum, who opines that intraocular inflammation is a "hallmark" indicator for ocular and periocular infections, which cause such inflammation. *Id.* (citing Ex. 1002 ¶¶ 138–139; *see, e.g.*, Ex. 1018 (disclosing that endophthalmitis implicates both inflammation and infection – "endophthalmitis [is] defined as severe inflammation that was presumed infectious…"); Ex. 1017 ("[I]ntraocular inflammation that [was] reported as uveitis…was classified as presumed endophthalmitis because it was treated with systemic antibiotics"). Petitioner asserts that, by excluding patients with recent intraocular inflammation, CATT would also exclude patients with ocular or periocular infections within the past two weeks. *Id.* (citing Ex. 1002 ¶¶ 138–139).

Petitioner argues that, even if the prior art references do not disclose the third criterion *in haec verba*, it would have been obvious to modify them to apply to "any" ocular or periocular infection within the past two weeks. Pet. 46 (citing Ex. 1002 ¶¶ 140–144). According to Petitioner, a person of ordinary skill in the art, interpreting these prior art exclusion criteria, would understand that their purpose was to avoid complications from intravitreal injections into infected or recently infected eyes, as active and recent infections are associated with increased risks of adverse reactions. *Id.* at 47 (citing Ex. 1002 ¶¶ 55–66, 140–144). Petitioner contends that such a skilled artisan would have understood that it was routine practice to exclude any

ocular or periocular infections generally without reference to the specific timing of the infection at the time of the alleged invention. *Id.* (citing Ex. 1002 ¶ 144). By way of example, Petitioner points to the Lucentis® label, which states, as a contraindication, "ocular or periocular infections," without specifying further the timing of the infection. *Id.* (citing Ex. 1026).

Petitioner asserts that there is nothing novel about the claimed exclusion criteria: assessing for and excluding patients from treatment *via* intravitreal injection of anti-VEGF agent on the basis of current or recent infection or inflammation was part of the standard of medical care. Pet. 47 (citing Ex. 1006; Ex. 1059; Ex. 1026; Ex. 1034; Ex. 1040; Ex. 1041). The claimed exclusion criteria, argues Petitioner, merely reflect this practice. *Id.* (citing Ex. 1002 ¶¶ 145–149).

Petitioner next argues that a person of ordinary skill in the art would have been motivated to adopt the exclusion criteria from these studies in order to mitigate potential complications for intravitreal injections of aflibercept, which posed the same potential risks as prior VEGF antagonists that were administered intravitreally. Pet. 48 (citing Ex. 1002 ¶¶ 150–160). Petitioner contends that a skilled artisan would have understood that intravitreal injections involve penetration by a syringe needle into the eye, and there is thus a risk of introducing infectious agents from the eye, or the surrounding area, into the vitreous cavity, potentially causing endophthalmitis, a severe and potentially blinding condition, along with associated intraocular inflammation. *Id.* (citing Ex. 1002 ¶¶ 151–152).

According to Petitioner, endophthalmitis from intravitreal injections was acknowledged as a serious risk in the art; by way of example, Petitioner points to the 2006 label for Lucentis®, one of the two leading anti-VEGF

treatments at the time. *Id.* (citing Ex. 1026, 1). Petitioner also argues that skilled artisans were similarly aware of the risk of exacerbating intraocular inflammation with an injection of an anti-VEGF agent. *Id.* at 49 (citing Ex. 1034, 247; Ex. 1002 ¶¶ 152–154).

Petitioner notes that neither of these concerns were specific to the injection of aflibercept, but argues, rather, that persons of skill in the art would have known that injecting any anti-VEGF (or other) drug into an eye with an active or recent infection in or around the eye substantially increases the risk of endophthalmitis and associated inflammation. Pet. 49 (citing Ex. 1002 ¶¶ 152–153; Ex. 1041; Ex. 1006). Petitioner asserts that a skilled artisan would have known that the claimed exclusion criteria were routine and basic safety precautions for limiting the risks of endophthalmitis, intraocular inflammation, and other complications from intravitreal injections of any anti-VEGF agent. *Id.* at 50 (citing Ex. 1002 ¶¶ 146–147).

Finally, Petitioner argues that a person of ordinary skill in the art would have had a reasonable expectation of success in applying the prior art exclusion criteria to the Dixon dosing regimen. Pet. 53. Petitioner contends that the exclusion criteria are designed to address the known risks associated with intravitreal injections, the same route of administration as described in Dixon, and are common to all intravitreal injections, including injections of VEGF antagonists. *Id.* (citing Ex. 1002 ¶¶ 161, 156–158). According to Petitioner, a person of ordinary skill in the art would have therefore reasonably expected that the exclusion criteria developed for prior art VEGF antagonists could be successfully applied to aflibercept. *Id.* (citing Ex. 1002 ¶¶ 156–158).

4. Patent Owner's Preliminary Response

Patent Owner responds that Petitioner has failed to meet its burden because: (1) criterion three—and, in particular, the 2-week timepoint—is not disclosed in any of Petitioner's Ground 1 references; (2) Petitioner fails to demonstrate that a person of ordinary skill in the art would have been motivated to modify its references by adding the missing third criterion; and (3) Petitioner's contention that the exclusion criteria limitation is obvious regardless of the disclosures of the prior art fails as a matter of fact and law. Prelim. Resp. 13.

First, Patent Owner acknowledges that PIER teaches exclusion criteria including "active intraocular inflammation" in the subject eye, and certain active infections (conjunctivitis, keratitis, scleritis, or endophthalmitis) in either eye. Prelim. Resp. 13–14 (citing Ex. 1034, 13). Patent Owner asserts, however, that PIER does not disclose exclusion of subjects having prior (i.e., no longer active) ocular or periocular infection, let alone having had "any prior ocular or periocular infection within 2 weeks prior to treatment." *Id.* at 15 (citing Ex. 1034, 13–14).

Turning to MACTEL, Patent Owner notes that MACTEL discloses exclusion criteria including a "[h]istory within the past 30 days of a chronic ocular or periocular infection" and "[c]urrent acute ocular or periocular infection." Prelim. Resp. 15 (quoting Ex. 1032, 4). Patent Owner argues, however, that MACTEL does not exclude patients with "any prior ocular or periocular infection," let alone patients with any prior infection within the limited 2-week timepoint recited in criterion three. *Id.* at 15–16. According to Patent Owner, MACTEL's exclusion criteria are both broader and

narrower than criterion three. *Id.* at 16. Patent Owner contends that MACTEL's exclusion of patients with "history within the past 30 days of a chronic ocular or periocular infection," by virtue of its 30-day timepoint, would potentially exclude significantly more patients than criterion three of the challenged claims. *Id.* At the same time, argues Patent Owner, patients having acute (i.e., not chronic) ocular or periocular infection that resolved within the past 2 weeks prior to treatment, i.e., patients who would be excluded under Criterion 3, would still be eligible for treatment under the exclusion criteria of MACTEL. *Id.* Patent Owner asserts, therefore, that substituting the disclosures of MACTEL for criterion three would result in treatment of a different group of patients than the group that can be treated with the method of the challenged claims. *Id.* at 16–17.

With respect to CATT, Patent Owner acknowledges that the CATT exclusion criteria include, *inter alia*, "[a]ctive or recent (within 4 weeks) intraocular inflammation (grade trace or above) in the study eye." Prelim. Resp. 17 (quoting Ex. 1031, 6). Patent Owner notes that this CATT exclusion criterion differs from criterion three, not only in terms of its timepoint for excluding historic conditions (4 weeks in CATT versus 2 weeks in criterion three), but also in terms of the prior conditions it excludes (prior inflammation in the study eye in CATT, versus prior infection in either eye in criterion three). *Id.*

Patent Owner contends that CATT's exclusion criteria would result in administering injections to a different group of patients than those encompassed by criterion three. Prelim. Resp. 18. By way of example, Patent Owner hypothesizes that CATT would exclude more patients than criterion three in certain respects, i.e., excluding patients having had any

recent (within 4 weeks) intraocular inflammation regardless of the cause of that inflammation (CATT), versus excluding patients having had recent (within 2 weeks) inflammation only to the extent that inflammation was associated with infection, as with criterion three. *Id.* (citing Ex. 2120, 4).

Next, Patent Owner contests Petitioner's argument that exclusion of patients having current acute ocular or periocular infection includes exclusion of patients having prior ocular or periocular infection within the previous two weeks (as required by criterion three). Prelim. Resp. 19 (citing Pet. 45–46). According to Patent Owner, active ocular or periocular infection is not the same as prior infection; Patent Owner notes that active infection is separately addressed by criterion two of the challenged claims. *Id.* (citing, e.g., Ex. 1001, claim 1). Patent Owner contends that Petitioner's alleged proposal that current infection and prior infection are one and the same would therefore read criterion 3 out of the challenged claims altogether. *Id.*

Turning to its second argument, Patent Owner contends that Petitioner's analysis fails to explain why a person of ordinary skill in the art would look to the exclusion criteria of any of PIER, CATT, or MACTEL in the first place, rather than looking to the published exclusion criteria of the

VIEW[7], MARINA[8], or ANCHOR[9] studies. Prelim. Resp. 20. With respect to VIEW, Patent Owner argues that, although the VIEW results did not become available until after the priority date of the '681 patent, the VIEW study exclusion criteria were posted to clinicaltrials.gov prior to 2011. *Id.* (citing Ex. 2358; Ex. 2356). Patent Owner points out that, among the fifteen exclusion criteria listed for VIEW, neither of the VIEW clinicaltrials.gov publications include criterion three on their lists of exclusion criteria. *Id.* Patent Owner contends that Petitioner has failed to explain why a person of skill in the art would have ignored the published exclusion criteria of VIEW, which is the same study that is discussed in Dixon, but looks instead to PIER, CATT, and MACTEL. *Id.* at 20–21. Patent Owner particularly notes that MARINA did not exclude subjects with prior ocular infection, or subjects having had prior ocular infection within the specific 2-week time frame required by criterion three. *Id.* at 22.

Patent Owner further argues that, to the extent that a skilled artisan would have looked to the exclusion criteria of MARINA and ANCHOR, Petitioner has provided no explanation as to why a skilled artisan would deviate from them. Prelim. Resp. 22. According to Patent Owner, the prior art disclosed that MARINA was a safe trial, with very low rates of

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[7] Regeneron's Phase III VIEW studies are described in Example 4 of the '681 patent.

[8] NCT00061594, *A Study to Compare RhuFab V2 with Verteporfin Photodynamic in Treating Subfoveal Neovascular Macular Degeneration* ("MARINA") Ex. 2346.

[9] NCT00056836, *A Study to Evaluate RhuFab V2 in Subjects with Minimally Classic or Occult Subfoveal Neovascular Macular Degeneration* ("ANCHOR") Ex. 2345.

endophthalmitis reported. *Id.* (citing Ex. 1021, 6; Ex. 2347, 158). Patent Owner asserts that ANCHOR also disclosed "low rates of serious ocular adverse events," with only 2 cases of presumed endophthalmitis reported among 277 subjects in the ranibizumab treatment arms. *Id.* (citing Ex. 2108, 1, 10, table 3).

Patent Owner asserts that Petitioner's argument that the claimed exclusion criteria would have been employed in every prior art study, notwithstanding that all the prior art studies disclosed different exclusion criteria than those recited by the challenged claims, should be discounted. Prelim. Resp. 26 (citing Pet. 52). Furthermore, argues Patent Owner, neither Petitioner nor its expert explains why or how a person of ordinary skill in the art would arrive at criterion three (including its specific 2-week timepoint) absent any instruction or disclosure in the art. *Id.* at 26–27 (citing e.g., *Ex Parte Shelton IV*, 2020-001178, 2020 WL 5544305, at *2–3 (PTAB Sept. 14, 2020).

Patent Owner contends that the art at the time of filing reflected the understanding that both intentional investigator deviation from a clinical study protocol, and failure to apply stated inclusion or exclusion criteria, generally constituted protocol violations. Prelim. Resp. 27 (citing Ex. 2354, 1). Patent Owner maintains that such protocol violations could "lead to the exclusion of patients from eligibility analysis, and/or their discontinuation from the study." *Id.* Patent Owner notes that the post-priority EYLEA Medical Review reported that, during the VIEW study, patient results from one study site were excluded from the data analysis because it was "initially thought" that the investigator at that site "did not correctly follow inclusion/exclusion criteria." *Id.* at 27–28 (citing Ex. 2355, 159). Patent

Owner contends that this evidence undermines Petitioner's assertion that clinical investigators would apply the exclusion criteria of the '681 challenged claims, in "contravention" of the exclusion criteria of the prior art studies. *Id.* at 28.

Turning to its third argument, Patent Owner argues that Petitioner has not shown that there would have been any "need" or "pressure" to alter, supplement, or "upgrad[e]" the exclusion criteria disclosed in the prior art. Prelim. Resp. 29 (citing *KSR*, 550 U.S. at 421, 424). Patent Owner contends that, even if Petitioner had shown a motivation to modify the disclosed exclusion criteria, it has not shown that there were a finite set of predictable combinations that could have been used. *Id.* Patent Owner argues that, even assuming that a skilled artisan would have implemented a waiting period after any ocular or periocular infection resolved as an exclusion criterion for administration of intravitreal injection, there are virtually an infinite number of different possible time intervals and classifications of infection that could have been combined in such an exclusion criterion. *Id.* at 29–30.

Finally, Patent Owner argues that Petitioner's arguments are based on impermissible hindsight reasoning. Prelim. Resp. 30. Patent Owner alleges that Petitioner's arguments use criterion three as a template, then employ multiple, inconsistent approaches to force the prior art disclosures (or lack thereof) into its desired shape. *Id.*

5. Analysis

Based upon the evidence of record at this stage of the proceeding, we conclude that Petitioner has demonstrated a reasonable likelihood of prevailing at trial. We find that Petitioner has demonstrated on the record

before us that the combination of PIER, CATT, and MACTEL reasonably appear to teach or suggest each of the exclusion criteria of the challenged claims. Furthermore, Petitioner has presented evidence that a person of ordinary skill in the art would reasonably have been motivated to combine the references to arrive at the claimed invention, and would have had a reasonable expectation of success in so doing. The sole issue argued by Patent Owner with respect to the merits is whether criterion three of the exclusion criteria limitation of the challenged claims is obvious over CATT, MACTEL, and PIER.

As an initial matter, Patent Owner argues the alleged deficiencies of the three references individually, despite Petitioner's express intent that the references forming the basis of Ground 1 can be viewed both "individually and collectively." Pet. 8. We consequently form the basis of our analysis upon whether a person of ordinary skill in the art, viewing the references either individually or collectively, would have found criterion three to be obvious over their teachings and suggestions. *See In re Mouttet*, 686 F.3d 1322, 1333 (Fed. Cir. 2012) (stating "the test for obviousness is what the combined teachings of the references would have suggested to those having ordinary skill in the art").

Criterion three of claim 1 recites "wherein exclusion criteria for the patient include all of: … (3) any ocular or periocular infection within the last 2 weeks prior to treatment." Ex. 1001, col. 21, ll. 61–62. Challenged independent claim 14, the only other independent claim of the '681 patent, recites an identical exclusion criterion three. *Id.* at col. 23, ll. 22–23. Petitioner relies on the exclusion criteria disclosed in MACTEL and CATT as teaching or suggesting the third exclusion criteria. Pet. 26–30.

Relevantly, MACTEL teaches, among its exclusion criteria, persons having a "[h]istory within the past 30 days of a chronic ocular or periocular infection (including any history of ocular herpes zoster)." Ex. 1032, 4. CATT teaches, among its exclusion criteria, persons with "[a]ctive or recent (within 4 weeks) intraocular inflammation (grade trace or above) in the study eye." Ex. 1031, 6. Both of these references, then, exclude from their respective studies individuals who have, or have had, infection or inflammation of the eye or surrounding tissues (ocular or periocular) over the course of the previous month. Ex. 1031, 6; Ex. 1032, 4. We find that these references, at least in combination, would lead a person of ordinary skill in the art to understand that they include the set of patients to be excluded recited in exclusion criterion three of the challenged claims. We do not discern from the present record how culling out a subset of these individuals is inventive. We therefore conclude that Petitioner has demonstrated a reasonable likelihood that exclusion criterion three is obvious over the teachings of CATT and MACTEL.

Patent Owner makes multiple attempts to argue that, because the exclusion criteria taught by the references could select a different set of patients to be included or excluded that only partially includes those in exclusion criteria three, the references do not, individually, teach or suggest exclusion criteria three of the challenged claims. We do not find Patent Owner's contentions persuasive on the present record.

With respect to the temporal limitations of the exclusion criterion at issue, we note that both CATT and MACTEL exclude patients with a history of eye infection/inflammation over the course of the previous month/30 days, respectively, prior to initiation of the study and treatment. This

interval would obviously include individuals who had had "any ocular or periocular infection within the last 2 weeks prior to treatment," as recited in the challenged claims. The overlapping ranges of the exclusion criteria taught by the references and recited in the challenged claims is sufficient to establish the obviousness of the temporal aspect of exclusion criterion three. *See In re Peterson*, 315 F.3d 1325, 1329 (Fed. Cir. 2003) (holding that "[i]n cases involving overlapping ranges, we and our predecessor court have consistently held that even a slight overlap in range establishes a *prima facie* case of obviousness"); *see also Genentech, Inc. v. Hospira Inc.*, 946 F.3d 1333, 1341 (Fed. Cir. 2020) (same) (citing *In re Peterson*).

Exclusion criterion three also recites "any ocular or periocular infection" within the recited two weeks. The MACTEL exclusion criteria require exclusion of subjects having "chronic ocular or periocular infection (including any history of ocular herpes zoster)" within the prior 30 days. Ex. 1032, 4. CATT's exclusion criteria require exclusion of individuals who have had "intraocular inflammation (grade trace or above)" within the prescribed 4-week interval. Ex. 1031, 6. Taken together, then, the combined teachings of MACTEL and CATT exclude from their studies, both of which employ intraocular injection of a VEGF-antagonist, individuals who have had, within at least the preceding two weeks, a chronic ocular or periocular infection or intraocular inflammation.

Patent Owner argues that "patients having acute (i.e., not chronic) ocular or periocular infection that resolved within the past 2 weeks prior to treatment, i.e., patients who would be excluded under Criterion 3, would still be eligible for treatment under the exclusion criteria of MACTEL." Prelim. Resp. 16. We do not find this argument persuasive because MACTEL

additionally teaches, among its exclusion criteria, excluding individuals with "[c]urrent acute ocular or periocular infection." Ex. 1032, 4. Consequently MACTEL excludes both individuals with "chronic ocular or periocular infection" within the past 30 days as well as those with "[c]urrent acute ocular or periocular infection." *Id.* As Petitioner's declarant, Dr. Chaum, testifies, a person of ordinary skill in the art:

> [W]ould understand that "chronic" and "acute" do not generally have precise definitions in the art, the terms do not limit the type of ocular or periocular infection excluded, but rather generally refer to the length of time the infection is present. *See, e.g.*[,] Exs. 1023–24, Ex. 1063. Excluding patients with a "history" of a chronic infection within the past 30 days (as well as any history of herpes zoster) would thus exclude any symptomatic infection in the past 14 days that was previously present long enough to be considered "chronic" (or which otherwise reoccurred); and excluding current "acute" infections would exclude any infections that had otherwise presented within a few weeks (i.e., one to three weeks) of treatment.

Ex. 1002 ¶ 142. For the purposes of this Decision, we find this reasoning persuasive.

With respect to CATT, Patent Owner reasons that CATT would "exclude more patients than [c]riterion [t]hree in certain respects: i.e., excluding patients having had any recent (within 4 weeks) intraocular inflammation regardless of the cause of that inflammation (CATT), versus excluding patients having had recent (within 2 weeks) inflammation only to the extent that inflammation was associated with infection[, as with criterion three]." Prelim. Resp. 18 (citing Ex. 2120, 4). We find Patent Owner's reasoning in this respect, inapposite. CATT's exclusion criteria may very well, as Patent Owner suggests, exclude a broader group of potential

subjects than the challenged claims third exclusion criterion, but CATT's exclusion criteria would encompass all the subjects included in the challenged claims exclusion criterion three.

Furthermore, although CATT does not expressly include individuals with "any ocular or periocular *infection*" within the challenged claims' prescribed two-week interval, it does exclude subjects with prior "intraocular inflammation (grade trace or above)," and inflammation is an essential indicator of infection. *See* Ex. 1031, 6. As Dr. Chaum explains:

> A POSA would have understood that ocular or periocular infections were known to cause inflammation in or on the eye as a symptom because the hallmark of infection is inflammation, and inflammation (e.g., redness, edema, uveitis, and etc.) is a clinical indication for all infections. In other words, there are other causes of inflammation, but infection will always cause inflammation (with the exception of extremely immunocompromised individuals). Therefore, based on the teaching of the CATT Study, a POSA would have understood that excluding patients with recent intraocular inflammation would also result, in practice, in excluding patients who have had recent ocular infections within the last 2 weeks before treatment, as recited.

Ex. 1002 ¶ 138. Although Patent Owner may be correct that CATT's exclusion criteria might exclude individuals with ocular or periocular inflammation caused by noninfectious agents, but it would *include* those with ocular or periocular infections within the prescribed interval. Because the exclusion criterion of CATT would include the individuals excluded by exclusion criterion three of the challenged claims, we find on the record presently before us that Petitioner has demonstrated a reasonable likelihood of showing at trial that exclusion criterion three of the challenged claims are obvious.

Patent Owner also criticizes Petitioner for relying upon CATT and MACTEL and not VIEW, ANCHOR, or MARINA studies. *See* Prelim. Resp. 20. Patent Owner particularly notes that MARINA did not exclude subjects with prior ocular infection, or subjects having had prior ocular infection within the specific 2-week time frame required by criterion three. *Id.* at 22.

Patent Owner proffers two preliminary, and edited, versions of the protocol for the VIEW1 study (reviewed in Dixon) that were publicly available prior to the priority date of the '681 patent on clinicaltrials.gov as Exhibits 2356 and 2358. Neither of these publications recite, as exclusion criteria, *any* infection or inflammation, either prior or present, as exclusionary criteria for potential study subjects. *See* Ex. 2356, 10–11; Ex. 2358, 10–11. Both ANCHOR and MARINA disclose, among its exclusion criteria, "[a]ctive intraocular inflammation (grade trace or above) in the study eye," "[i]nfectious conjunctivitis, keratitis, scleritis, or endophthalmitis in either eye," and "[c]urrent treatment for active systemic infection." Ex. 2345, 4–5; Ex. 2346, 4–5.

With respect to ANCHOR and MARINA, we are persuaded on this record that the protocols for these studies are not inconsistent with either CATT or MACTEL. Both ANCHOR and MARINA expressly include, among their exclusion criteria, active infections of the eye ("[i]nfectious conjunctivitis, keratitis, scleritis, or endophthalmitis in either eye"). Ex. 2345, 4; Ex. 2346, 4. Both studies also recite "[a]ctive intraocular inflammation" as an exclusion criterion. *Id.* As Dr. Chaum explains, a person of ordinary skill in the art would understand that "the hallmark of

infection is inflammation." Ex. 1002 ¶ 138. Dr. Chaum further explains that:

> Excluding patients with a "history" of a chronic infection within the past 30 days (as well as any history of herpes zoster) would thus exclude any symptomatic infection in the past 14 days that was previously present long enough to be considered "chronic" (or which otherwise reoccurred); and excluding current "acute" infections would exclude any infections that had otherwise presented within a few weeks (i.e., one to three weeks) of treatment.

Ex. 1002 ¶ 142. We find Dr. Chaum's testimony to be sufficient here and conclude, for the purpose of the record as it presently stands, that a person of ordinary skill in the art would find the MARINA and ANCHOR exclusion criteria to be consistent with those of the references cited by Petitioner.

We can offer no explanation for the absence of even an active infection as an exclusion criterion in the preliminary VIEW protocols, although we note that these are evidently not the final protocols employed in the study. Nevertheless, this absence appears to be inconsistent with the prior art at the time of invention. As Petitioner points out, and as the prior art indicates, introduction of infectious agents into the vitreous chamber of the eye can lead to endophthalmitis, a serious and potentially debilitating complication. *See* Pet. 48. As one prior art reference relates:

> Endophthalmitis is an uncommon, but perhaps the most feared complication of ocular surgery. Endophthalmitis is defined as a microbial infection involving the vitreous cavity: organisms are often isolated from anterior chamber as well. Retinal, choroidal, and scleral invasion can also occur. Most cases of endophthalmitis occur after elective ocular surgery. In the first six weeks after operation, endophthalmitis is caused by microbes introduced into the eye during the time of the surgery or in the immediate postoperative period before the wound is securely

> sealed.…*The second most common cause of endophthalmitis is penetrating ocular trauma*.

Ex. 1040[10], 349 (emphasis added). We agree with Petitioner that a person of ordinary skill in the art would likely understand that a penetration of the eye by a syringe needle during intravitreal injection of a VEGF receptor antagonist, such as that recited in the challenged claims, would present at least a degree of penetrating ocular trauma and a concomitant potential risk of endophthalmic infection. Certainly Dixon, in reviewing the VIEW1/VIEW2 studies, states that "[e]ach [intravitreal] injection subjects patients to risks of cataract, intraocular inflammation, retinal detachment and *endophthalmitis*." Ex. 1006, 1577 (emphasis added). The label for the VEGF receptor antagonist ranibizumab (Lucentis®) expressly warns that; "Endophthalmitis and retinal detachments may occur following intravitreal injections. Patients should be monitored during the week following the injection." Ex. 1026, 2. And the PIER study states that endophthalmitis had a "hypothesized or documented relationship to ranibizumab, based on … the route of administration [i.e., intravitreal injection]." Ex. 1034, 247.

Summarizing, Dr. Chaum opines that a person of ordinary skill in the art "would have considered it the standard of care to assess for and exclude patients with active ocular/periocular infection from treatment via intravitreal injection of an anti-VEGF treatment, as intravitreal injections could introduce bacteria into the vitreous cavity and cause endophthalmitis, which can be a blinding complication of an injection." Ex. 1002 ¶ 153. We credit Dr. Chaum's testimony here on the record before us.

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[10] T.A. Meredith, *Endophthalmitis*, *in* INTRAOCULAR DRUG DELIVERY, 349–362 (G.J. Jaffe et al., eds. 2006) ("Jaffe") Ex. 1040.

Patent Owner also argues that the post-priority EYLEA Medical Review reported that during the VIEW study, patient results from one study site were excluded from the data analysis because it was "initially thought" that the investigator at that site "did not correctly follow inclusion/exclusion criteria." Prelim. Resp. 27–28 (citing Ex. 2355, 159). Patent Owner contends that this evidence undermines Petitioner's assertion that "clinical investigators would apply the [e]xclusion [c]riteria of the '681 [c]hallenged [c]laims, in 'contravention' of the exclusion criteria of the prior art studies." *Id.* at 28.

Patent Owner's argument is, at best, not persuasive. The EYLEA Medical Review reports that the reason certain subjects in the VIEW study were excluded was because it was thought that individual investigators who were part of the study did not correctly follow the study's protocols. Ex. 2355, 159. In other words, the alleged deviations from protocol were intra-study, and therefore potentially confounded the results hoping to be obtained by the VIEW study. This has nothing to do with inter-study variation in protocols between the challenged claims and the prior art. The investigators in one study were under no obligation to slavishly follow the exclusion criteria protocols of other studies; the guiding principle for all such studies are the particular objectives of that study and the general standards of medical care. As Dr. Chaum explains:

> [A] POSA would have understood that assessing for and excluding patients from treatment on the basis of these criteria was part of the standard of care. In my opinion, POSAs at the time understood that active intraocular inflammation and active or recent ocular or periocular infections made any intravitreal injection, such as those required by an intravitreally administered anti-VEGF dosing regimen, potentially unsafe. *See, e.g.*[,]

> Ex. 1026 (Lucentis Label). Thus, it was the standard of care at the time to assess for active and recent infections and inflammation and to ensure they were cleared before intravitreal injections of anti-VEGF agents. The exclusion criteria recited in the '681 Patent reflect this practice.

Ex. 1002 ¶ 146.

As we have explained above, Petitioner has argued that a person of skill in the art would have been motivated to adopt the exclusion criteria when administering aflibercept *via* intravitreal injection to minimize the risks of intravitreal infection and complications such as endophthalmitis and that adoption of these criteria reflected basic safety precautions developed to address the risks associated with intravitreal injections generally, regardless of the specific anti-VEGF agent injected. *See* Pet. 48–52. Petitioner has shown sufficient support on the record before us for such a view.

Patent Owner also argues that Petitioner: (1) has not shown motivation to modify the exclusion criteria of PIER by adding the third exclusion criterion; and (2) has not shown motivation to modify the exclusion criteria of CATT and/or MACTEL. We disagree. We have explained above why we conclude that a person of ordinary skill in the art would have found exclusion criterion three to be obvious over not CATT and MACTEL individually and together. *See KSR*, 550 U.S. at 416. Moreover, Petitioner has, as we have also explained, asserted a persuasive reason why a skilled artisan would have been motivated to adopt the teachings of MACTEL and CATT to reduce the risk of intravitreal infection subsequent to injection of a VEGF receptor antagonist, such as aflibercept.

Furthermore, Petitioner has persuasively argued that a person of ordinary skill in the art would also have had a reasonable expectation of

success in adopting the exclusion criteria to the studies disclosed by Dixon, *viz.*, that a person of ordinary skill in the art would therefore have reasonably expected that the exclusion criteria developed for prior art VEGF receptor antagonists could be successfully applied to aflibercept. Pet. 53 (citing Ex. 1002 ¶¶ 156–158).

Finally, we are not persuaded by Patent Owner's allegation that Petitioner's arguments impermissibly employ hindsight reasoning. *See* Prelim. Resp. 30. Certainly:

> Any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning, but so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made and does not include knowledge gleaned only from applicant's disclosure, such a reconstruction is proper.

In re McLaughlin, 443 F.2d 1392, 1395 (C.C.P.A. 1971). Patent Owner has not adduced persuasive evidence of record that Petitioner's arguments have relied upon knowledge that could have been gleaned *only* from the Specification of the '681 patent. We consequently conclude, for the purposes of this Decision, that Petitioner has not impermissibly relied upon hindsight analysis.

Having examined the arguments and evidence of record, we conclude, for the purposes of this Decision, that Petitioner has demonstrated a reasonable likelihood of prevailing at trial, and that Patent Owner's arguments to the contrary are not persuasive on the record before us.

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

Finally, Patent Owner urges us to exercise our discretion to deny institution of trial under 35 U.S.C. § 314(a) under the analysis set forth in *General Plastic Indus. Co. v. Canon Kabushiki Kasha*, IPR2016-01357, 2017 WL 3917706 (PTAB Sept. 6, 2017) (precedential). Prelim. Resp. 34. Under *General Plastic*, when exercising our discretion to deny institution, we may consider a number of factors:

1. whether the same petitioner previously filed a petition directed to the same claims of the same patent;
2. whether at the time of filing of the first petition the petitioner knew of the prior art asserted in the second petition or should have known of it;
3. whether at the time of filing of the second petition the petitioner already received the patent owner's preliminary response to the first petition or received the Board's decision on whether to institute review in the first petition;
4. the length of time that elapsed between the time the petitioner learned of the prior art asserted in the second petition and the filing of the second petition;
5. whether the petitioner provides adequate explanation for the time elapsed between the filings of multiple petitions directed to the same claims of the same patent;
6. the finite resources of the Board; and
7. the requirement under 35 U.S.C. § 316(a)(11) to issue a final determination not later than 1 year after the date on which the Director notices institution of review.

General Plastic, Paper 19 at 9–10. The purpose of the analysis thus established in *General Plastic* is to deny a Petitioner successive attacks on the claims of a single patent, and profiting from those prior attempts by

altering a petition's strategy in response to Patent Owner's and the Board's responses. *Id.*

Patent Owner argues that Petitioner did not file its Petition until after it had Patent Owner's Preliminary Response to IPR2022-01225 (filed by Mylan) challenging the identical claims of the '681 patent. Prelim. Resp. 33. Patent Owner alleges that Petitioner attempts to incrementally improve upon Mylan's '681 patent challenge, while leveraging the Final Written Decision in the -00881 *inter partes* review. *Id.* According to Patent Owner, if allowed to go forward, Petitioner's serial challenge will require the Board to adjudicate (and Patent Owner to defend against) multiple, staggered challenges to the same patent claims based on art and arguments that are either substantially overlapping (if obviousness of the exclusion criteria is at issue), or cumulative (if the exclusion criteria are not afforded patentable weight). *Id.*

1. *General Plastic* factor 1

With respect to *General Plastic* factor 1, Patent Owner contends that the fact that this is Petitioner's first challenge to the '681 patent does not preclude discretionary denial of institution of *inter partes* review. Prelim. Resp. 34. Patent Owner points to our precedential decision in *Valve Corp. v. Electronic Scripting Prods., Inc.*, IPR2019-00062 (PTAB Apr. 2, 2019) (precedential), in which we denied institution of trial, suggesting that the same reasoning should apply in the present case. *Id.* at 34–35.

Patent Owner contends that Petitioner is similarly situated with Mylan, a fellow biosimilar manufacturer that challenged the same claims of the '681 patent in July of 2022, using the same primary reference (Dixon,

Ex. 1006). Prelim. Resp. 35. Patent Owner also points out that Petitioner has joined another IPR challenge brought by Mylan (to related U.S. Patent No. 10,888,601), that is proceeding in parallel with the Mylan challenge to the '681 patent. *Id.* (citing *Mylan Pharms. Inc. v. Regeneron Pharms., Inc.*, IPR2022-01226, Paper 10, 8 (PTAB Mar. 22, 2023)). Patent Owner hints darkly that "there can be little doubt that Mylan and Samsung are coordinating in their respective challenges to the '681 patent," noting that one of Mylan's expert depositions was hosted at the offices of Samsung's counsel before Samsung was even a joinder party in the consolidated Mylan challenge to the related US 10,888,601 B2 in IPR2022-01226. *Id.* at n.19. Patent Owner urges us to follow the logic of *Valve Corp.* and consider the relationship between Mylan and Petitioner when weighing the *General Plastic* factors. *Id.* at 35.

Petitioner vehemently disputes Patent Owner's allegation that there is any working relationship between Mylan and itself, or that they are coordinating their challenges to the '681 patent. Reply 1. Petitioner asserts that neither it, Mylan, nor their respective counsel have ever had any conversations about the '681 patent or the IPR challenges to the '681 patent, either before or after the filing date of the present Petition. *Id.* Petitioner points out that Petitioner and Mylan are potential business competitors, and there has never been any coordination between the two. *Id.*

With respect to Mylan's use of one of Petitioner's conference rooms for a scheduled deposition, Petitioner asserts that the loan of a conference room is a common courtesy among law firms, and was appropriate in this instance because counsel for Mylan (with offices located in Chicago) had no facilities of its own on the West Coast, where the deposition took place.

Reply 2. Petitioner further states that "[n]o attorneys for Petitioner attended the deposition." *Id.* Additionally, Petitioner notes, Mylan's counsel's request for the conference room was made weeks after Petitioner filed the present Petition against the '681 patent and after Petitioner filed its petition and motion to join as to the '601 patent. *Id.*

In its Reply, counsel for Petitioner reaffirm, as they did in the Petition, that:

> (1) there have been no communications, written or oral, between Petitioner and Mylan relating to the '681 patent or the filing of this IPR, including the financing, preparing, editing, review, approval, or filing of the instant Petition, (2) no individuals acting for or on behalf of Mylan participated or assisted in any way with the filing of this IPR, including with financing, preparation, editing, review, approval, or filing; and (3) there were no payments or agreements by or between Mylan and Petitioner in connection with the Petition or the '681 patent.

Reply 2–3.

The purpose of the *General Plastic* analysis, as stated above, is to deny a Petitioner successive attacks on the claims of a single patent, and profiting from those prior attempts by altering a petition's strategy in response to Patent Owner's and the Board's responses. *General Plastic*, Paper 19 at 9–10. Patent Owner is quite correct, however, that, under *Valve Corp.*, we can consider the relationship between different parties bringing successive challenges to a given patent. *Valve Corp*., Paper 11, at 2, 9. However, the facts of the present Petition render this present situation readily distinguishable from the facts in *Valve Corp*.

In *Valve Corp.*, we found that the parties bringing successive challenges to the patent-in-suit were "named as co-defendants in that lawsuit

and were accused of infringing the '934 patent based on [co-defendant] HTC's VIVE devices that incorporate Valve's technology." *Valve Corp.*, Paper 11, at 9–10. Furthermore, in that litigation, Valve represented that "HTC's VIVE devices incorporate certain Valve technologies under a technology license from Valve," and that "Valve employees did provide HTC with technical assistance during the development of the accused VIVE devices." *Id.* at 10. The Board consequently concluded that "there is a significant relationship between Valve and HTC with respect to Patent Owner's assertion of the '934 patent. The complete overlap in the challenged claims and the significant relationship between Valve and HTC favor denying institution." *Id.*

No such facts obtain in the present instance. Petitioner is not a co-defendant with Mylan in the district court infringement action, *Regeneron Pharms., Inc. v. Mylan Pharms. Inc.*, 1:22-cv-00061-TSK (N.D.W. Va.).[11] There is no credible evidence of record that Petitioner and Mylan, potential business competitors, have developed any significant relationship, as in *Valve Corp*. Petitioner has joined the -01226 *inter partes* review as a "silent

[11] We acknowledge Patent Owner's point that the fact that Petitioner "is not a co-defendant in the pending district court litigation against Mylan is a function of the unique statutory provisions of the Biologics Price Competition and Innovation Act ("BPCIA")." Prelim. Resp. 35 n.17 (citing 42 U.S.C. § 262(l)). It nevertheless remains a fact that Petitioner is not a party to that litigation, and Patent Owner adduces no evidence that Petitioner has ever played any role in it. Moreover, even were Petitioner a party to the district court action, "two parties being sued for infringement of the same patent and participating in a joint-defense group, of itself, [does not] establish a significant relationship between the parties that counsels for denying institution." *Qualcomm Inc. v. Monterey Research, LLC*, IPR2020-01493, Paper 11 at 16 (PTAB March 8, 2021).

partner" and has represented that it will play a limited role in that litigation unless Mylan should withdraw from the case. *See* IPR2023-00566, Paper 2 (Motion for Joinder with IPR2022-01226), at 1. Petitioner has not similarly joined the -01225 *inter partes* review, electing to follow a generally different litigation strategy and theory of the case in its present Petition with regard to the exclusion criteria (i.e., obviousness *versus* printed matter doctrine). In the single ground of the -01225 *inter partes* review that seeks to prove that the exclusion criteria of the '681 patent are obvious over the prior art (Ground 5), Mylan relies on a different prior art reference than that relied upon by Petitioner in the present instance. *See* IPR2022-01225, Paper 2, at 64.

In summary, we conclude that Patent Owner has failed to establish that there is a significant relationship between Mylan and Petitioner. The lack of a significant relationship, and the fact that this is Petitioner's first challenge to the '681 patent "weighs especially heavily against a discretionary denial." *Unified Patents, Inc. v. Certified Measurement, LLC*, IPR2018-00548, Paper 7 at 7–8 (PTAB Sept. 5, 2018). Indeed, we frequently decline to exercise discretionary denial under *General Plastic* where there is no "significant relationship" between parties challenging the same patent. *See, e.g.*, *Netflix, Inc. v. Broadcom Corp.*, IPR2020-01423, Paper 7 at 5–6 (PTAB March 11, 2021); *Google LLC v. Uniloc 2017 LLC*, IPR2020-00396, Paper 11 at 11, 16–17 (PTAB Aug. 3, 2020).

As such, and following the reasoning set forth in *Valve Corp.*, we conclude *General Plastic* factor 1 weighs heavily in favor of not exercising our discretion to deny institution. Furthermore, in the absence of extenuating circumstances such as a showing of coordination between

petitioners, "[o]nce resolution of [*General Plastic*] factor 1 indicates that Petitioner had not previously filed a petition against the same patent, factors 2–5 bear little relevance…." *Alcatel-Lucent USA Inc. v. Oyster Optics, LLC*, IPR2017-02146, Paper 12 at 12 (PTAB Feb. 28, 2018); *see also Qualcomm*, IPR2020-01493, Paper 11 at 15–17; *Twitter, Inc. v. Palo Alto Research Center Inc.*, IPR2021-01458, Paper 11 at 33 (PTAB April 6, 2022).

With respect to *General Plastic* factors 6 and 7, Patent Owner argues that Petitioner's challenge would also needlessly tax the finite resources of the Board. Prelim. Resp. 40. According to Patent Owner, the Petition, if instituted, will result in the Board having to twice adjudicate substantially similar obviousness challenges to the same challenged claims of the '681 Patent. *Id.*

We do not find Patent Owner's argument sufficiently persuasive to warrant denial of institution. Petitioner's arguments with respect to the exclusion criteria in the related IPR 2022-01225 are generally based upon a different legal theory than the present Petition, and rely upon different prior art references, so the Board will not be required to repeat its legal analysis in this proceeding. Moreover, this case presents but a single ground for our analysis. We do not believe that instituting trial in this case will severely tax the resources of the Board.

Given that Patent Owner has adduced no substantive evidence of coordination between Mylan and Petitioner, and given that we find no significant relationship exists between the two, we similarly conclude that the remaining factors of the *General Plastic* analysis are indeed of little relevance to our § 314(a) analysis. We therefore conclude our analysis at

this point, and we deny Patent Owner's request to exercise our discretion under 35 U.S.C. § 314(a) to deny institution of *inter partes* review.

V. CONCLUSION

For the reasons we have explained, we conclude that Petitioner has demonstrated a reasonable likelihood of showing that at least challenged claim 1 of the '681 patent is unpatentable as being obvious over Dixon, CATT, MACTEL, and PIER. 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 '681 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 10,130,681 B2 is GRANTED with respect to all grounds in the Petition; and

FURTHER ORDERED that *inter partes* review is instituted.

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