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Paper 9
Entered: September 27, 2022

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

ELI LILLY AND COMPANY,
Petitioner,

v.

TEVA PHARMACEUTICALS INTERNATIONAL GMBH,
Patent Owner.

IPR2022-00739
Patent No. 11,028,161 B2

Before JAMES A. WORTH, DAVID COTTA, and JAMIE T. WISZ
Administrative Patent Judges.

COTTA, *Administrative Patent Judge*.

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

I. INTRODUCTION

On March 23, 2022, Eli Lilly and Company ("Petitioner")[1] filed a Petition to institute *inter partes* review of claims 1–30 of U.S. Patent No. 11,028,161 B2 (Ex. 1002, "the '161 patent"). Paper 1 ("Pet." or "Petition"). Teva Pharmaceuticals International GMBH ("Patent Owner")[2] filed a Preliminary Response. Paper 6 ("Prelim. Resp."). With our prior authorization, Petitioner filed a Reply to Patent Owner's Preliminary Response and Patent Owner filed a Sur-reply to Petitioner's Reply. Paper 7 ("Prelim. Reply"); Paper 8 ("Prelim. Sur-reply").

Under 35 U.S.C. § 314(a), *inter partes* review may not be instituted unless the Petition "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." Petitioner has established a reasonable likelihood of prevailing on its assertion that the challenged claims are unpatentable based on the grounds advanced here. We decline to deny the Petition on a discretionary basis as requested by Patent Owner. Thus, for reasons explained below, we institute *inter partes* review of claims 1–30 of the '161 patent.

A. Related Matters

The parties indicate that they are involved in a district court litigation in *Teva Pharmaceuticals International GmbH et al v. Eli Lilly and Company,* 1-21-cv-10954 (D. Mass.). Pet. 71; Paper 4, 1.

The parties also identify U.S. Patent Nos. 11,028,160 ("the '160 patent") and 10,392,434 ("the '434 patent") as relating to the '161 patent.

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[1] Petitioner identifies itself as the real party-in-interest. Pet. 71.
[2] Patent Owner identifies itself and Teva Pharmaceuticals USA, Inc. as the real parties-in-interest. Paper 4, 1.

Pet. 71–72; Paper 4, 1–2. The '434 patent, issued from U.S. Patent Application No. 15/712,444 ("the '444 application"), which claims priority to two provisional patent applications. Ex. 1045, code (21), (60). The '160 and '161 patents both issued from applications filed as continuations of the '444 application. Ex. 1001, code (63); IPR2022-00738, Ex. 1001, code (63). Thus, the '160, '161, and '434 patents all share substantially the same disclosure and claim priority from the same provisional patent applications. The parties also identify U.S. Patent Application No. 17/308,580, which is currently pending before the Office, as claiming priority from the applications that issued as the '161 and '434 patents. Pet. 71; Paper 4, 2.

The '160 patent is challenged in IPR2022-00738 and the '434 patent is challenged in IPR2022-00796. Pet. 71; Paper 3, 1.

B. The '161 Patent

According to the '161 patent, "[m]igraine is a prevalent neurological condition characterized by attacks of headache and associated symptoms, such as nausea, vomiting, photophobia, and/or phonophobia." *Id.* at 1:18–20. Preventative treatment may be appropriate "where frequency of attacks per month is two or higher, or where a patient's quality of life is severely impaired." *Id.* at 1:36–39. The '161 patent discloses that "a number of drugs from different pharmacological categories (e.g. beta blockers, anticonvulsants) have been approved for migraine prevention or have class A evidence to support their use," but explains that "response and tolerance to some of these medications varies, and compliance and adherence to these medications can be poor." *Id.* at 1:40–46.

The '161 patent teaches that calcitonin gene-related peptide (CGRP) "has been found to be involved in migraine processes, both centrally and peripherally." *Id.* at 1:48–49. More specifically, the '161 patent reports that

"[j]ugular levels of CGRP are increased during migraine attacks, and intravenous (iv) CGRP administration induces migraine-like headache in most individuals with migraine." *Id.* at 1:52–55. "CGRP is involved in the pathophysiology of migraine at all levels, peripherally (vasodilation, inflammation, and protein extravasation), at the trigeminal ganglion, and inside the brain." *Id.* at 1:57–60. According to the '161 patent, "[s]tudies have shown that inhibition of CGRP or antagonizing CGRP receptor has demonstrated efficacy in the treatment of EM [episodic migraine – i.e., migraine occurring less than 15 days per month]." *Id.* at 1:61–63. The '161 patent thus suggests that "[m]onoclonal antibodies that modulate the CGRP pathway . . . represent a class of promising therapeutic candidates for patients who failed prior preventative treatment for CM and EM." *Id.* at 2:1–4.

The '161 patent discloses "methods for preventing, treating, and/or reducing incidence of migraine in . . . a subject having refractory migraine by administering to the individual a therapeutically effective amount of an anti-CGRP antagonist antibody." *Id.* at 14:44–48.

C. Challenged Claims

The '161 patent includes 30 claims, all of which are challenged in the Petition. Claim 1, the only independent claim, is illustrative of the challenged claims and reads as follows:

> 1. A method of treating or preventing migraine in a subject having refractory migraine, the method comprising:
> selecting a subject who has been treated with two or more different preventative migraine treatments wherein at least one of the classes of preventative migraine treatments is selected from topiramate, carbamazepine, divalproex sodium, sodium valproate, valproic acid, divalproex, flunarizine, candesartan,

> pizotifen, amitriptyline, venlafaxine, nortriptyline, duloxetine, atenolol, nadolol, metoprolol, propranolol, bisopropol, timolol, onabotulmumtoxin A, lisinopril, and oxeterone; and
>
> administering to the subject a therapeutically effective amount of a humanized monoclonal anti-calcitonin gene-related peptide (CGRP) antagonist antibody comprising the amino acid sequence of the heavy chain variable region set forth in SEQ ID NO: 63 and the amino acid sequence of the light chain variable region set forth in SEQ ID NO: 62.

Ex. 1002, 173:1–19.

D. Asserted Grounds of Unpatentability

Petitioner asserts two grounds of unpatentability in this Petition (Pet. 13), which are provided in the table below:

Claims Challenged	35 U.S.C. §	Reference(s)/Basis
1–30	103	Sun,[3] Dodick,[4] Sharma[5]
1–30	103	Dodick, Sharma

Petitioner relies on the declaration of Dr. Stefan Evers, among other evidence. Ex. 1101. Patent Owner responds with a declaration from Dr. Pamela Blake, along with other evidence. Ex. 2001.

II. DISCRETION UNDER 35 U.S.C. § 325(D)

Patent Owner urges us to exercise our discretion under 35 U.S.C.

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[3] Sun et al., U.S. Patent Publication No. 2016/0311913 A1, published Oct. 27, 2016 (Ex. 1006, "Sun").

[4] Dodick et al., *Safety and efficacy of LY2951742, a monoclonal antibody to calcitonin gene-related peptide, for the prevention of migraine: a phase 2, randomized, double-blind, placebo-controlled study,* 13 Lancet Neurol., 885–92, published Aug. 11, 2014 (Ex. 1003, "Dodick").

[5] Sharma, International Patent Publication No. WO 2016/205037 A1, published Dec. 22, 2016 (Ex. 1007, "Sharma").

§ 325(d) to deny institution of review, on the basis that the prior art relied upon by Petitioner was previously considered by the Examiner. Prelim. Resp. 28–44. For the reasons discussed below, we decline Patent Owner's invitation to invoke our discretion to deny institution on this basis.

A. Standard for Exercising Discretion under Section 325(d)

Institution of *inter partes* review is discretionary. *Harmonic Inc. v. Avid Tech, Inc.*, 815 F.3d 1356, 1367 (Fed. Cir. 2016) ("[T]he PTO is permitted, but never compelled, to institute an IPR proceeding."). The Patent Office may, for example, deny institution under 35 U.S.C. § 325(d), which provides, in pertinent part, that "[i]n determining whether to institute or order a proceeding under this chapter . . . the Director may take into account whether, and reject the petition or request because, the same or substantially the same prior art or arguments previously were presented to the Office."

In evaluating whether the same or substantially the same prior art or arguments were previously presented to the Office, the Board has identified several non-exclusive factors for consideration. *Becton, Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8 at 17–18 (PTAB Dec. 15, 2017) (precedential as to § III.C.5, first paragraph) ("the *Becton, Dickinson* factors"). Those factors are as follows:

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

Id.; *see also* The Patent Trial and Appeal Board Consolidated Trial Practice Guide ("Trial Practice Guide") (Nov. 2019)[6] at 62–63 (discussing the *Becton, Dickinson* factors).

As further explained in *Advanced Bionics, LLC v. Med-El Electromedizinishe Geräte GmbH*, IPR2019-01469, Paper 6 at 10 (Feb. 13, 2020) ("*Advanced Bionics*") (precedential), factors (a), (b), and (d) from *Becton, Dickinson* relate to whether the art and arguments presented in the petition are the same or substantially the same as those previously presented to the Office. Factors (c), (e), and (f) "relate to whether the petitioner has demonstrated a material error by the Office" in its prior consideration of the 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 error. *Advanced Bionics* at 8–10. "If the petitioner fails to show that the Office erred, the Director may exercise his discretion not to institute inter partes review." *Id.* at 8–9 ("If a condition in the first part of the framework [i.e., substantially same art or arguments] is satisfied and the petitioner fails to make a showing of material error, the Director generally

[6] Available at https://www.uspto.gov/TrialPracticeGuideConsolidated.

will exercise discretion not to institute inter partes review"). "At bottom, this [§ 325(d)] framework reflects a commitment to defer to previous Office evaluations of the evidence of record unless material error is shown." *Id.* at 9. On the question of material error, "[i]f reasonable minds can disagree regarding the purported treatment of the art or arguments, it cannot be said that the Office erred in a manner material to patentability." *Id.*

B. Analysis

We begin our analysis by considering the first part of the *Advanced Bionic* framework, i.e., whether the art and arguments presented in the petition are the same or substantially the same as those previously presented to the Office. Patent Owner argues that all of the references relied upon by Petitioner – i.e., Sun, Dodick, and Sharma – were "previously presented to the Office during prosecution of both the parent patent, [the '434 patent], and the '161 patent." Prelim. Resp. 29. Patent Owner is correct that Sun, Dodick, and Sharma were before the Office. *See* Ex. 1002, code (56) (listing Sun, Dodick, and Sharma among the references cited).

Patent Owner further argues that the cited art is "entirely cumulative to art that was expressly discussed and distinguished." Prelim. Resp. 31. More particularly, Patent Owner argues that Sun, Dodick, and Sharma are cumulative of Zeller, which was the basis of a rejection during prosecution of the parent application. *Id.* at 31–41. We are not persuaded by Patent Owner's argument that the art cited in the Petition is cumulative of Zeller.

The rejection over Zeller occurred during prosecution of the '444 application, an application from which the '161 patent claims priority. Ex. 1002, code (63). In the rejection, the Examiner found that "Zeller t[aught] administering monoclonal anti-CGRP antagonist antibodies to treat migraine" but did not disclose treatment of the specifically claimed group of

subjects within the genus of "subjects with migraine." Ex. 2008, 233. The Examiner nonetheless rejected the pending claims as obvious, reasoning that "if a migraine subject was not responding to certain therapeutics, this provides clear motivation to one of ordinary skill in the art at the time of filing to select this species of the genus, i.e., to select for anti-CGRP therapy those who do not respond to alternative treatments with alternative targets/mechanisms." *Id.*

In response to the rejection over Zeller, Applicant amended the claims to recite that the claimed anti-CGRP peptide comprised specific amino acid sequences and to recite that the subject to be treated "has an inadequate response" to two or more different classes of treatments.[7] *Id.* at 241. Applicant then argued that the claims require "selecting and treating a particular subset of migraine patients having an inadequate response to two or more different classes of preventative migraine treatment" and that disclosure of a genus of treating migraine patients – as in Zeller – did not render the species of treating the specifically claimed migraine patients obvious. *Id.* at 245 (citing *In re Baird,* 16 F.3d 380, 382 (Fed. Cir. 1994)).

The Examiner evidently found Applicant's argument persuasive, issuing a Notice of Allowability. *Id.* at 654. In the Notice of Allowability, the Examiner explained that the pending claims were allowable because the prior art was silent as to the efficacy of using anti-CGRP antibodies to treat patients who had proven resistant to prior treatment:

> The rejection was predicated on the prior art's suggestion of treating migraine using anti-CGRP antibodies. In contrast, the instant claims are directed to a species of that genus, i.e., those

[7] Prior to the amendment, the claim required that the subject "does not respond favorably to two to four different classes of preventative migraine treatment." Ex. 2008, 241.

> subjects with migraines that have previously had an inadequate response (as defined by the specification) to two or more claimed classes of migraine treatment. While a species will anticipate a genus, a genus does not necessarily anticipate nor make obvious a species within that genus. . . . While the prior art discloses treatment of migraine using these antibodies, the art is silent regarding the efficacy of past treatments.

Id. at 655–656. The Examiner further reasoned that absent a teaching on treatment of refractory patients, the failure of prior treatments would have weighed against the expectation of success:

> It may be standard medical practice to terminate a therapy that is, in the physician's judgement, not working and to attempt alternatives but under the standards of obviousness, absent an explicit teaching, suggestion or motivation (which is not present in the prior art of record), the rationales for obviousness emphasize the need for "predictability" or a "reasonable expectation of success." While it might be obvious to try a new therapy when one or two do not work, this is relevant to a physician's mandate to treat a patient and not indicative of the legal standard of predictability. Rather, once two or more conventional therapies have been tried and failed, the Examiner considers this to weigh against any expectation that further therapies will work. Thus, as the prior art does not explicitly call out this species of migraine patients and there would be no predictable success when treating patients who have thus far proven resistant to other known treatments, the method as a whole is considered non-obvious.

Id. at 656.

We are not persuaded by Patent Owner's argument that the cited art is cumulative of Zeller because, as discussed in more detail below, various disclosures of the cited art, including Sun, discloses using anti-CGRP antibodies to treat refractory migraine. *See infra* § III.F.1. This is precisely the teaching that the Examiner found was missing from Zeller. Ex. 2008, 655–656 ("While the prior art discloses treatment of migraine using these

antibodies, the art is silent regarding the efficacy of past treatments."). Further, we are not persuaded that Dodick and Sharma are cumulative of Zeller because they disclose treatment with galcanezumab and Zeller does not.

Although we determine that Sun, Dodick, and Sharma are not cumulative of Zeller, as discussed above, they were considered by the Examiner. Accordingly, we determine that the first part of the *Advanced Bionic* framework is satisfied. We turn next to the second part of the *Advanced Bionic* framework, i.e., determining whether Petitioner has demonstrated material error by the Office.

Patent Owner argues that Petitioner did not identify any material error in the Examiner's analysis, and thus, its argument is essentially "that the Examiner did not issue a rejection based at least in part on Sun, Dodick, or Sharma, and therefore must have failed to appreciate the prior art." Prelim. Resp. 42. According to Patent Owner, given "Applicant's ability to overcome the rejection based on Zeller," there is "no plausible argument that [the] Examiner failed to appreciate teachings that appear over and over in the cited art." *Id.* at 44. Finally, Patent Owner argues that the failure to make a rejection is "not an identification of error as a matter of law" it is a "disagreement." *Id.* at 42. We are not persuaded.

In explaining why the claims of the '444 application were allowable, the Examiner stated that "the art is silent regarding the efficacy of past treatments" and, more specifically, that "the prior art does not explicitly call out" the species of migraine patients for whom "two or more conventional therapies have been tried and failed." Ex. 2008, 655–656. In making this statement, the Examiner appears to have overlooked Sun's suggestion to use an anti-CGRP antibody to treat refractory patients. *See e.g.,* Ex. 1006 ¶¶ 68

("In some embodiments, the patient has failed or is intolerant to treatment with two different classes of migraine prophylactic agents."); *see also, infra* § III.F.1. Patent Owner does not identify anything in the prosecution history of the '161 patent to suggest that the Examiner accounted for Sun's teachings in allowing the '161 patent to issue. Given that this error in overlooking Sun's teachings was central to allowance of the patent that issued from the '444 application, we find that this error was material.

We recognize that Patent Owner disputes that Sun suggests treating the claimed refractory patients, but, on this record, we do not find Patent Owner's arguments persuasive for the reasons discussed *infra* § III.F.1. On the current record, Petitioner has sufficiently demonstrated that the Examiner erred materially in finding that the prior art did not suggest using anti-CGRP antibodies to treat refractory patients. Accordingly, we choose not to exercise our discretion under 35 U.S.C. § 325(d) to deny institution on the basis that the prior art has already been considered during prosecution.

III. ANALYSIS

A. Legal Standards

"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*, 815 F.3d at 1363 (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")).

To show obviousness under 35 U.S.C. § 103 the differences between the subject matter sought to be patented and the prior art must be 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 that subject matter pertains. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406

(2007). The question of obviousness is resolved on the basis of underlying factual determinations including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of ordinary skill in the art; and (4) secondary considerations of nonobviousness when presented. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

B. Level of Ordinary Skill in the Art

In determining the level of skill in the art, we consider the problems encountered in the art, the art's solutions to those problems, the rapidity with which innovations are made, the sophistication of the technology, and the educational level of active workers in the field. *Custom Accessories, Inc. v. Jeffrey-Allan Indus., Inc.*, 807 F.2d 955, 962 (Fed. Cir. 1986).

Patent Owner identifies the skill level of a person of ordinary skill in the art ("POSA") as follows:

> A POSA with respect to the '161 patent would have possessed a strong understanding of migraine and its treatments. A POSA would typically have a Ph.D. in a relevant field (*e.g.*, neurobiology, neurology, or pharmacology) with several years of experience studying migraine or an M.D. with experience in a relevant field (*e.g.*, neurobiology, neurology, or pharmacology) with several years of experience studying migraine or treating migraine patients. EX2001, ¶¶22-23. A POSA may be part of a multi-disciplinary team, drawing upon his or her own skills and taking advantage of certain specialized skills of others in the team, to solve a given problem. *Id.* For example, such a team may be comprised of an M.D. specializing in treating migraine patients and a neurobiologist specializing in studying migraine.

Prelim. Resp. 6–7. Petitioner offers a similar definition of the POSA, with the principal differences being: 1) that Petitioner does not identify neurobiology and pharmacology as relevant fields for a POSA having an

M.D., and 2) that Petitioner does not propose that a POSA could also be part of a multi-disciplinary team. Pet. 11.

We find the additional exposition in Patent Owner's definition of the POSA helpful. Moreover, Patent Owner's definition appears to be consistent with the level of skill in the art reflected in the prior art of record and the disclosure of the '161 patent. Accordingly, for purposes of this Decision, we accept Patent Owner's proposed definition of the person of ordinary skill in the art. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) ("the prior art itself [may] reflect[] an appropriate level" as evidence of the ordinary level of skill in the art) (quoting *Litton Indus. Prods., Inc. v. Solid State Sys. Corp.*, 755 F.2d 158, 163 (Fed. Cir. 1985)). At this stage in the proceeding, the differences between Petitioner's and Patent Owner's identification of the POSA do not materially affect our decision with respect to institution. Put another way, we would reach the same decision under either definition.

C. Claim Construction

We interpret a claim "using 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. § 42.100(b) (2020). Under this standard, we construe the claim "in accordance with the ordinary and customary meaning of such claim as understood by one of ordinary skill in the art and the prosecution history pertaining to the patent." *Id.*

The parties identify two claim limitations as needing construction: "a subject having refractory migraine," and "selecting a subject who has been treated with two or more different classes of preventative migraine treatments." Pet. 12–16; Prelim. Resp. 7–13. We address each claim limitation in turn.

1. "A subject having refractory migraine."

The phrase "a subject having refractory migraine" appears in the preamble to claim 1. Ex. 1002, 173:2–3. The parties agree that the preamble is limiting because it provides context and antecedent basis for terms in the body of the claim. Pet. 12 ("Claim 1's preamble . . . should be construed as limiting at least because it provides context and antecedent [basis] for the claimed 'therapeutically effective amount.'"); Prelim. Resp. 8 ("The parties agree that the preamble . . . is limiting at least because it provides context and antecedent basis to the terms in the body of the claim, *e.g.*, 'administering to the subject a therapeutically effective amount' of the recited antibody."). We agree that the preamble of claim 1 limits the claim for the reasons expressed by the parties. *Rapoport v. Dement,* 254 F.3d 1053, 1059 (Fed. Cir. 2001) (finding that the phrase "treatment of sleep apneas" in the preamble of an interference count was limiting because it provided antecedent basis for the phrase "to a patient in need of such treatment" in the body of the interference count); *see also Eli Lilly Co. v. Teva Pharmas Int'l GmbH*, 8 F.4th 1331, 1340 (Fed. Cir. 2021) ("while there is no bright-line rule for determining whether a preamble is limiting, we have generally construed statements of intended purpose in such method claims as limiting").

We turn now to the meaning of the phrase "a subject having refractory migraine." The parties agree that the '161 patent expressly defines the phrase "a subject having refractory migraine." Pet. 13. Prelim. Resp. 9. In this regard, the '161 patent states:

> As used herein, refractory migraine patients (or "subject having refractory migraine") are considered refractory if they have a documented inadequate response (in a medical chart or by treating physician's confirmation) to at least two preventive

> medications (from a different cluster, defined below). Refractory migraine patients can also be considered refractory if they have a documented inadequate response (in a medical chart or by treating physician's confirmation) to two to four classes of prior preventive medications (from different cluster[s], as defined below), e.g., inadequate response to two classes of prior preventive medications, inadequate response to three classes of prior preventative medications, or an inadequate response to four classes of prior preventative medications.

Ex. 1002, 18:59–19:7. Thus, a "subject having refractory migraine" should be construed as: a migraine patient having a documented inadequate response (in a medical chart or by treating physician's confirmation) to at least two preventive medications from a different cluster. *Id.*

Our definition of "a subject having refractory migraine" includes the term "inadequate response." The Specification expressly defines this term as well. *Id.* at 19:8–26. The Specification states:

> Inadequate response is defined as: no clinically meaningful improvement per treating physician's judgement, after at least three months of therapy at a stable dose considered appropriate for migraine prevention according to accepted country guidelines, or when treatment has to be interrupted because of adverse events that made it intolerable by the patient or the drug is contraindicated or not suitable for the patient. The three-month period may not apply if the drug is intolerable or contraindicated or not suitable for the patient. For onabotulinumtoxin A, an inadequate response is defined as: no clinically meaningful improvement per treating physician's judgement, after at least six months of therapy at a stable dose considered appropriate for migraine prevention according to accepted country guidelines, or when treatment has to be interrupted because of adverse events that made it intolerable by the patient. Or, if onabotulinumtoxin A is a previous preventative medication, at least two sets of injections and three months should have passed since the last set of injections.

Id. Accordingly, the phrase "inadequate response" in our construction of "a subject having refractory migraine" should be understood to mean: 1) no clinically meaningful improvement per treating physician's judgement, after at least three months of therapy at a stable dose considered appropriate for migraine prevention according to accepted country guidelines, 2) treatment has to be interrupted because of adverse events that made it intolerable by the patient, or 3) the drug is contraindicated or not suitable for the patient.

Our definition of "a subject having refractory migraine" references medications from a "cluster." As used in our definition, the term "cluster" should be understood to refer to the "clusters" in the three sets of "clusters" set forth in the Specification. *Id.* at 19:27–35 (identifying a first set of clusters, including clusters A–E), 19:36–44 (identifying a second set of clusters, including clusters A–G), 19:52–62 (identifying a third set of clusters, including clusters a–e).

Patent Owner offers additional definitions, based largely on extrinsic evidence, for the terms "adverse event," "contraindicated," and "not suitable," as used in the Specification's definition of "inadequate response." Prelim. Resp. 10 (citing Exs. 1016, 2001, 2003, and 2004). At this point in the proceeding, we do not find it necessary to construe these terms. *See Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co. Ltd.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) ("[W]e need only construe terms 'that are in controversy, and only 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))); *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'").[8]

2. "Selecting a subject who has been treated with two or more different classes of preventative migraine treatments."

Claim 1 requires "selecting a subject who has been treated with two or more different classes of preventative migraine treatments." Ex. 1002, 173:4–5. Hereafter, we refer to this claim language as the "selecting limitation." Petitioner contends that the selecting limitation does not require an inadequate response to treatment with the two different classes of medication, but rather requires only selecting "a subject to whom [two] medication[s] ha[ve] been administered." Pet. 15–16, 45–46 ("the claimed 'selecting' step only requires having 'been treated with'—but not necessarily ***failed***—multiple conventional treatments."). Petitioner's construction has particular relevance in the context of contraindicated patients. A patient that is contraindicated for a particular medication would not be treated with that medication. Ex. 2001 ¶ 46. However, such a patient could be administered medications that are not contradicted. Thus, according to Petitioner, claim 1 encompasses selecting patients who are contraindicated for two migraine treatments – thus meeting our construction of the term "refractory" in the

[8] In its briefing on claim construction, Patent Owner contests Petitioner's assertion that a POSA would have known to "administer a preventative migraine medication for at least three months at an accepted stable dose before concluding that the treatment did not achieve a clinically meaningful improvement." Prelim. Resp. 10–11. This argument is directed not to what the claim terms mean, but whether they extend to obvious subject matter. Accordingly, we do not consider this argument as part of our claim construction analysis. We address it *infra* § III.F.1.a.

preamble – and are treated with, but do not have an inadequate response to, two different classes of preventative migraine medications.

Patent Owner argues that the selecting limitation should be interpreted to require failed treatment with two or more different classes of preventative migraine treatments. Prelim. Resp. 12–13. According to Patent Owner, the Specification defines a "subject having refractory migraine" in the preamble as falling into three groups: (i) a "no clinically meaningful improvement group"; (ii) an "adverse events group"; or (iii) a "contraindicated group." *Id.* at 12. Patent Owner asserts that the selecting limitation "carves out a narrower subset of subjects from the defined refractory migraine patients." *Id*. Thus, under Patent Owner's proposed construction, the selecting limitation "excludes the patients in group (iii), because contraindicated patients would have not received the preventative medication(s) as claimed." *Id.* at 12–13.

We begin by considering the language of the claims. The selecting limitation is, on its face, straightforward. It simply requires selecting a patient that has been treated with two or more different classes of preventative migraine medications. Ex. 1002, 173:4–5. The parties do not disagree. Prelim. Resp. 12 (arguing that the selecting limitation "should be accorded its ordinary and customary meaning: selecting a subject to whom two or more different classes of preventive migraine treatments have been administered."); Pet. 15 (arguing that the phrase "'a subject who has been treated with' a medication" as it appears in the selecting limitation "should be construed based on its ordinary meaning as: 'a subject to whom the medication has been administered'") (emphasis omitted).

On its face, the selecting limitation does not include language requiring failure of the "two or more different classes of preventative

migraine treatments." Ex. 1002, 173:4–5. Indeed, the language of the selecting limitation requires only that the subject have been "treated" with two medications. *Id.* At this stage in the proceeding Patent Owner does not direct us to support in the specification or in the prosecution history for construing the term "treated," as used in the selecting limitation, to require any particular result. Prelim. Resp. 12–13. On this preliminary record, we do not discern a basis for requiring that the "treated" patients in the selecting limitation have achieved, or failed to achieve, a particular response.

We recognize that claim 1 is directed to treatment of refractory migraine, which suggests that the patient treated is not responsive to other medications. Ex. 2003, 4 (medical dictionary, defining "refractory" as "resistant to treatment, as of a disease"). But, as discussed supra § III.C.1, Patent Owner expressly defined "subject having refractory migraine" to include patients that are contraindicated for two preventative medications. Such patients would not take the medications they are contraindicated for, but could take other migraine medications. Ex. 2001 ¶ 46 (Dr. Blake testimony that "a POSA would have understood that Group III (the contraindicated group) of the defined refractory migraine patients would not have received preventative medications because those patients should not receive the contraindicated or unsuitable medications"). Patent Owner's construction would exclude such patients from the meeting the definition of the term "refractory." On this preliminary record, Patent Owner does not direct us to, and we do not discern, support in the language of the claims, the specification, or the prosecution history for such a limiting construction.

Accordingly, we construe the selecting limitation to require selecting a subject that has been treated with two different classes of preventative migraine medications. We do not construe the selecting limitation to require

that the two preventative migraine medications achieve, or fail to achieve, any particular result when administered to the claimed subject.

D. Priority

Petitioner asserts that claims 1–30 are not entitled to an effective filing date earlier than the actual September 22, 2017 filing date because "the claims lack adequate § 112(a) support in the September 2016 '180 Provisional [application]." Pet. 16. Patent Owner argues that "[t]here is no basis for Patent Owner to address, or for the Board to decide, the priority date to which the claims are entitled" because Dodick, Sun, and Sharma – i.e., the prior art relied upon in Grounds 1 and 2 – "predate[] the earliest possible priority date for the challenged patent, making Petitioner's entire priority discussion irrelevant." Prelim. Resp. 14–15.

A this point in the proceeding, and in the absence of a challenge to the prior art status of any of the prior art relied upon by Petitioner, we accept Patent Owner's assertion that it is not necessary for us to decide the priority date to which the claims are entitled. In this regard, we note that in addition to Dodick, Sun, and Sharma, the Petition characterizes several references that help to support its arguments as "prior art." *See e.g.,* Pet 25 (citing Ex. 1037, which the Petition describes as providing "prior-art results" of a Phase II study described in Sun), 26 (citing Ex. 1040, which the Petition describes as providing "prior art results" of a Phase III study described in Sun), 36 (citing Exs. 1038, 1039, 1057, and 1058, which the Petition describes as "prior art studies" of fremanezumab). For purposes of this decision, we assume that Petitioner's characterization of these references as "prior art" is correct.

E. Overview of the Asserted Prior Art

1. Sun

Sun is a U.S. Patent Publication. Ex. 1006. Petitioner asserts that Sun is prior art under 35 U.S.C. § 102(a)(1) and (2). Pet. 9. Sun discloses "a method for preventing or reducing the occurrence of migraine headache in a patient in need thereof comprising administering to the patient an anti-CGRP receptor antibody or antigen-binding fragment thereof." Ex. 1006 ¶ 9. One anti-CGRP receptor antibody disclosed in Sun is AMG 334, which both parties identify as "erenumab." *Id.* ¶¶ 27–39, 254–295; Pet. 9; Prelim. Resp. 22. Sun discloses that its anti-CGRP receptor antibody "can be administered in combination with an agent that interferes with the binding of the CGRP ligand to the CGRP receptor to prophylactically treat migraine headache," such as an "anti-CGRP antibody." Ex. 1006 ¶ 250 (citing WO 2011/156324, which, according to Dr. Evers, discloses galcanezumab (Ex. 1101 ¶ 51), as evidence that "[a]nti-CGRP antibodies are known in the art"). Sun discloses that in some embodiments, its anti-CGRP receptor antibody may be administered to a patient that has "failed or is intolerant to treatment with two different classes of migraine prophylactic agents" and in other embodiments, "the patient has failed or is intolerant to treatment with three different classes of migraine prophylactic agents." *Id.* ¶ 68.[9]

Sun discloses a Phase II study to evaluate the safety and efficacy of erenumab for the prevention of episodic migraine. *Id.* ¶¶ 266–272. The

[9] Sun defines failure to respond as a "lack of efficacy of the prophylactic agent in reducing the frequency, duration, and/or severity of migraine headache in the patient following a standard therapeutic regimen of the agent" including an "inability to tolerate the migraine prophylactic agent" or instances where the agent is contraindicated. Ex. 1006 ¶¶ 65–66.

"results showed that AMG 334 when administered at a monthly dose of 70 mg, was efficacious in preventing episodic migraine, and AMG 334 had a safety/tolerability profile similar to placebo." *Id.* ¶ 272. "Subgroup analyses demonstrated that the efficacy of AMG 334 was similar regardless of . . . prior history of prophylactic medication use (FIG. 7B)." *Id.* ¶ 268. Sun discloses plans for a second Phase II study focusing on prevention of chronic migraine (*id.* ¶¶ 273–289), the results of which "are expected to show that in subjects with chronic migraine, AMG 334 dose-dependently reduces from baseline the monthly migraine days compared with placebo and the adverse event profile of AMG 334 is similar to placebo" (*id.* ¶ 281). Finally, Sun discloses plans for a Phase III study to evaluate the safety and efficacy of AMG 334 in migraine prevention in subjects with episodic migraine. *Id.* ¶¶ 290–295. "The phase 3 study results are expected to show that in subjects with episodic migraine, AMG 334 has a greater reduction from baseline in mean monthly migraine days compared to placebo." *Id.* ¶ 295.

2. Dodick

Dodick is a journal article published in the journal, Lancet Neurology. Ex. 1003. Petitioner asserts that Dodick is prior art under 35 U.S.C. § 102(a)(1). Pet. 7–8. Dodick discloses a "randomised, double-blind, placebo-controlled, phase 2 proof-of-concept study" to assess "the safety and efficacy of LY2951742 [galcanezumab][10] for the preventative treatment of migraine." Ex. 1003, 886. The study participants included "[m]en and women aged 18–65 years, with at least a 1-year history of migraine according to the International Classification of Headache Disorders (ICHD-

[10] There does not appear to be any dispute that LY2951742 is galcanezumab. Pet. 8; Prelim. Resp. 26.

II), and between four and 14 migraine headache days per month." *Id.* The study excluded patients who "fail[ed] to respond to more than two adequately dosed (ie, maximum tolerated dose by the patient for a sufficient duration) approved migraine prevention treatments." *Id.* Dodick reports that "LY2951742 was effective and generally well tolerated for the preventive treatment of migraine in patients with frequent attacks." *Id.* at 890. "Compared with placebo, LY2951742 significantly reduced the mean number of migraine headache days over the 3-month study period." *Id.*

3. Sharma

Sharma is an International Patent Publication. Ex. 1007. Petitioner asserts that Sharma is prior art under 35 U.S.C. § 102(a)(1) and (2). Pet. 10. Sharma discloses that "[a] phase [IIB], randomized, double-blind, placebo-controlled, dose-ranging study was conducted with 410 patients aged 18-65 years with 4 to 14 migraine headache days and at least 2 migraine attacks per month" to asses "whether at least one dose of LY2951742 was superior to placebo in the prevention of migraine headache." *Id.* at 23. "The results showed that all 4 dose arms were numerically superior to placebo on primary outcome measures at all-time points." *Id.* "One dose arm (120 mg) of LY2951742 met the primary objective (p = 0.004) with a significantly greater reduction compared to placebo in the number of migraine headache days in the last 28 day period of the week 12 treatment phase." *Id.*

F. Ground 1

Petitioner asserts that claims 1–30 would have been obvious over the combination of Sun, Dodick, and Sharma. In brief summary, Petitioner contends that Sun discloses treating patients with "refractory migraine" using the anti-CGRP monoclonal antibody ("mAb"), erenumab. Pet. 20–28. To address the requirement of the challenged claims to treat refractory

migraine with anti-CGRP mAb galcanezumab, Petitioner argues that it would have been obvious to use galcanezumab in the method disclosed in Sun, in view of Dodick's and Sharma's teachings that galcanezumab was effective for treating migraine. Pet. 28–33. Patent owner opposes, arguing, principally, that Sun does not disclose treating refractory migraine patients, as that term is defined in the '161 patent, and that the cited art does not provide a reasonable expectation of success. *See generally,* Prelim. Resp.

We begin our analysis by considering whether Petitioner has sufficiently supported that Sun discloses treating refractory migraine patients with erenumab. We next consider whether Petitioner has articulated sufficient rationale to support that a POSA would have had reason to use galcanezumab when treating refractory migraine patients. Finally, we consider whether Petitioner has supported that the POSA would have a reasonable expectation of success in treating refractory migraine patients with galcanezumab. On this preliminary record, we conclude that Petitioner has demonstrated a reasonable likelihood of prevailing in showing that claims 1–30 would have been obvious over the cited art.

1. Does Petitioner sufficiently support that Sun discloses treating refractory migraine patients?

Petitioner contends that Sun supports the obviousness of treating a "subject having refractory migraine" in four ways. **First**, according to Petitioner, Sun provides direction to treat patients who failed treatment with multiple classes of migraine prophylactic agents. Pet. 22–23. **Second**, Sun provides direction to treat patients who were intolerant to treatment with multiple classes of migraine prophylactic agents. *Id.* **Third**, Sun teaches that "efficacy 'was similar regardless of . . . prior history of prophylactic medication use' and [provides evidence showing] a numerically greater

reduction in headache days (relative to placebo) for patients with 'prior treatment failure' history." *Id.* at 24–25 (internal citations omitted). **Fourth**, Sun discloses "planned trials and subsequent results covering patients that had failed at least two preventatives" that, according to Petitioner, "further reinforced" "[t]he motivation to treat these patients [i.e., refractory migraine patients]." Pet. 25. We discuss each of these four positions, and Patent Owner's arguments in response thereto, in turn.[11]

a) Sun's direction to treat patients that failed treatment with multiple classes of migraine prophylactic agents

Sun discloses that in some embodiments, its anti-CGRP receptor antibody may be administered to a patient that has "failed . . . treatment with at least two different classes of migraine prophylactic agents." Ex. 1006 ¶ 68; *see also, id.* (disclosing that in other embodiments, "the patient has failed . . . treatment with three different classes of migraine prophylactic agents"). Sun defines the terms "failure to respond" and "treatment failure" to refer to "the lack of efficacy of the prophylactic agent in reducing the frequency, duration, and/or severity of migraine headache in the patient following a standard therapeutic regimen of the agent." *Id.* ¶ 65.

Petitioner contends that treating patients that have shown a "lack of efficacy" when administered prior therapies meets the definition of "no clinically meaningful improvement" that was recited in the specification of

[11] Although we discuss each of these positions individually, we do so purely for convenience, recognizing that our consideration of a prior art reference is not limited to any particular teaching. *In re Fritch*, 972 F.2d 1260, 1364–65, (Fed. Cir. 1992) ("It is well settled that a prior art reference is relevant for all that it teaches to those of ordinary skill in the art.").

the '161 patent (and adopted in our claim construction). Pet. 21–22. Petitioner addresses the requirement of our construction that "no clinically meaningful improvement" be determined "per treating physician's judgement, after at least three months of therapy at a stable dose considered appropriate for migraine prevention according to accepted country guidelines" by citing evidence that such criteria were standard for evaluating migraine prophylactics (Pet. 22 n. 9 (citing Ex. 1101 ¶¶ 24-25, 110, n.12; Ex. 1011, 3; Ex. 1019, 2; Ex. 1020, 4-5)).

Patent Owner argues that Sun does not disclose treating patients who showed "no clinically meaningful improvement," as that phrase is used in the '161 patent and in our claim construction, because Sun defines patients who failed or were intolerant to prior preventive medication "different[ly] from the claimed subjects having refractory migraine." Prelim. Resp. 46. First, Patent Owner argues that "failure to respond" in Sun requires failure of only one preventative medication while "no clinically meaningful improvement" in the '161 patent requires the failure of at least two preventative medications. *Id.* at 25. We do not find this persuasive because, regardless of how Sun defines "failure to respond," Sun expressly discloses treating patients who have failed treatment with multiple different classes of migraine. Ex. 1006 ¶ 68.

Patent Owner next argues that Sun's "failure to respond" does not require that therapy occur for any period of time before it is deemed a failure while the '161 patent requires that treatment carry on for at least three months. Prelim. Resp. 25. We do not find this argument persuasive.

We acknowledge that Sun does not define the term "standard therapeutic regimen" to require a stable dose over three months. However, Petitioner presents evidence that "[a] three-month evaluation period was a

commonly recommended minimum duration—i.e., in order to determine whether a given medication 'failed[,]' a patient needed to have taken the medication for at least three months at stable dose." Ex. 1101 ¶ 24 (Dr. Evers' testimony); Pet. 22 n. 9 (citing evidence supporting three month minimum to assess efficacy of migraine treatment). At this point in the proceeding, the preliminary record appears to support Dr. Evers' testimony that, "a POSA also would have understood that assessment of treatment failure in *Sun* suggested 'per treating physician's judgement, after at least three months of therapy at a stable dose considered appropriate for migraine prevention according to accepted country guidelines.'" *Id.* ¶ 109.

We recognize that Patent Owner has presented evidence that "[t]here was no requirement or understanding in the prior art to administer a preventive migraine medication for at least three months at a stable dose before concluding that the medication was unsuccessful." Ex. 2001 ¶ 42 (testimony of Dr. Blake (citing Ex. 1016, 3 and Ex. 1037, 3). To the extent that this evidence creates a factual dispute about what the POSA would have understood the phrase "standard therapeutic regimen" in Sun to mean, such dispute is best resolved on a fully developed record. At this point in the proceeding, Petitioner's evidence that Sun's disclosure meets the requirements for "no clinically meaningful improvement" is sufficient to support institution.

Patent Owner argues that Sun's "failure to respond" is distinguishable from the '161 patent's "no clinically meaningful improvement" because the '161 patent requires a "stable dose" while Sun's definition requires a "standard therapeutic regimen." Prelim. Resp. 25. We do not find this argument persuasive for the same reasons we are not persuaded by Patent Owner's argument that Sun's definition does not require treatment to last

any particular period of time in order to be deemed a failure. Namely, the preliminary record supports that a POSA would have understood the phrase "standard therapeutic regimen" to include treatment at a stable dose. *See* Ex. 1101 ¶¶ 24, 109; Pet. 22 n. 9.

Moreover, Petitioner's Ground 1 relies on obviousness, not anticipation. In this regard, Petitioner need only show that the cited art renders it obvious to treat the claimed patient population. On this record, Sun discloses treating a patient population that is, superficially, quite similar to the claimed patient population. Absent evidence of a material difference in how a POSA would perceive and/or treat Sun's patients as compared to the claimed patients, Sun's disclosure of treating patients who failed treatment with multiple classes of migraine prophylactics supports that it would have been obvious to treat the claimed refractory patients.

b) Sun's direction to treat patients that were intolerant to multiple classes of migraine prophylactic agents

Sun discloses treating patients that were intolerant to prior treatments. Ex. 1006 ¶¶ 66 ("Failure to respond to prior treatment with a migraine prophylactic agent can also include inability to tolerate the migraine prophylactic agent."), 68 ("In some embodiments, the patient . . . is intolerant to treatment with two different classes of migraine prophylactic agents."). Petitioner contends that treating patients that have shown an "inability to tolerate" prior therapy with a migraine prophylactic agent qualifies as treating a patient whose "treatment ha[d] to be interrupted because adverse events made it intolerable by the patient," thus meeting the definition of "inadequate response" recited in the specification of the '161 patent (and adopted in our claim construction). Pet. 22–23.

Patent Owner argues that "[w]hen discussing the 'inability to tolerate' the agent, Sun exclusively discusses *side effects*." Prelim. Resp. 23. Patent Owner then argues that "side effects" are different from and milder than "adverse events," and thus Sun does not disclose treating patients for whom "treatment ha[d] to be interrupted because adverse events made it intolerable by the patient" as recited in our definition of "inadequate response." *Id.* at 23–24.

On this record, we do not find Patent Owner's argument persuasive. Even if we credit Patent Owner's argument that "side effects" are different from and milder than "adverse events,"[12] Sun's discussion of "side effects" is exemplary, not limiting. *See e.g.,* Ex. 1006 ¶ 66 ("***For example***, in some embodiments, a patient who has failed prior treatment with a migraine prophylactic agent is a patient who cannot tolerate the side effects associated with the agent.") (emphasis added). A prior art reference is not limited to its exemplary embodiments. *In re Heck,* 699 F.2d 1331, 1332-33, 216 USPQ 1038, 1039 (Fed. Cir. 1983) ("The use of patents as references is not limited to what the patentees describe as their own inventions or to the problems with which they are concerned. They are part of the literature of the art, relevant for all they contain.") (quoting *In re Lemelson,* 397 F.2d 1006, 1009, 158 USPQ 275, 277 (CCPA 1968)). Here, Sun in not limited to patients who are intolerant to prior treatments because they suffered "side effects." Rather it encompasses the broader genus of patients who are unable to tolerate prior therapy for any reason.

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[12] At least one reference reporting results of a trial with erenumab describes "adverse events" as including seemingly mild effects like, for example, "injection-site pain" and "nausea." Ex. 1037, 425.

Moreover, the exemplary side effects disclosed in Sun are described as serious enough to cause the patient to "discontinue[] treatment with the migraine prophylactic agent." Ex. 1006 ¶ 66. To the extent the evidence submitted by Patent Owner (Ex. 2001 ¶¶ 43 75–77) creates a factual dispute as to whether Sun's patients who have discontinued treatment because of "side effects" are patentably distinct from the claimed patients, who have had their treatment "interrupted because adverse events made it intolerable," such dispute is best resolved on a fully developed record. At this point in the proceeding, Petitioner's evidence that Sun's disclosure meets the requirements for "treatment [that] had to be interrupted because adverse events made it intolerable" is sufficient to support institution.

c) Sun's teaching that efficacy was "similar regardless of . . . prior history of prophylactic medication use"

Sun provides the results of a randomized, double-blind, placebo-controlled, Phase II study to evaluate the efficacy and safety of erenumab for the prevention of episodic migraine. Ex. 1006 ¶¶ 266–272. Sun reports that "[s]ubgroup analyses demonstrated that the efficacy of [erenumab] was similar regardless of . . . prior history of prophylactic medication use." *Id.*

¶ 268. As support for this statement, Sun cites Figure 7B, which is reproduced below. (FIG 7B).

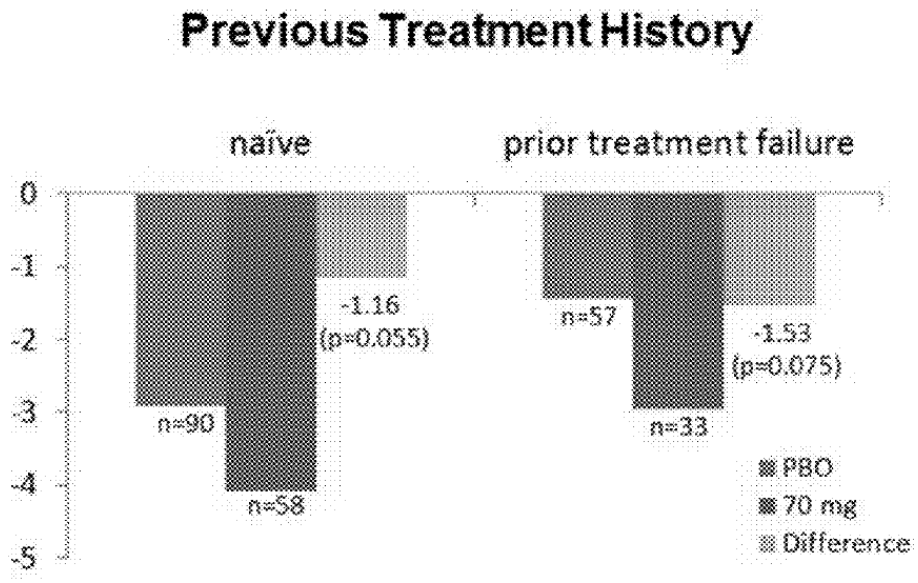

FIG. 7B

"FIG. 7B depicts the change from baseline in mean monthly migraine days in episodic migraine patients who were either treatment-naïve or failed prior prophylactic migraine treatment." *Id.* ¶ 36. Petitioner contends that based on these teachings, "[a] POSA would have been further motivated to treat the claimed [refractory migraine] subjects." Pet. 24.

Patent Owner argues that the results of the Phase II trial reported in Sun do not suggest treating the claimed refractory patients, repeating much the same argument it used in connection with Sun's direction to treat patients that failed treatment with multiple classes of migraine prophylactic agents. Patent Owner thus argues that "Sun defines patients that 'failed' prior medication as different from the subjects having refractory migraine of the claimed method," and that Sun does not disclose, for example "how many prior medications failed and under what conditions." Prelim. Resp. 48. According to Patent Owner, because of the differences in how failed

treatment is defined, "a POSA would not have viewed [the results of the Phase II trial reported in Sun] as teaching or suggesting treating a subject having refractory migraine of the claimed method." *Id.* At this point in the proceeding, we do not find this argument persuasive for the reasons discussed *supra* § III.F.1.a.

d) Sun's disclosure of two planned clinical trial and additional prior art disclosing the results thereof

Sun discloses two planned clinical trials: a proposed Phase II study focusing on prevention of chronic migraine (Ex. 1006, ¶¶ 273–289), and a proposed Phase III study to evaluate the safety and efficacy of erenumab in migraine prevention in subjects with episodic migraine (*id.* ¶¶ 290–295). Sun teaches that the planned Phase II trial was expected to show that erenumab "dose-dependently reduces from baseline the monthly migraine days compared with placebo" and the planned Phase III trial was expected to show that erenumab "has a greater reduction from baseline in mean monthly migraine days compared to placebo." *Id.* ¶ 281, 295.

Petitioner also provides prior art references describing the results of these planned trials. Pet. 25–26 (citing Ex. 1037 and 1040). For the planned Phase II trial, the actual results of the trial, in which 49% of the patients "had failed at least two previous drug classes," showed a reduction in monthly migraine days as compared to placebo. Ex. 1037, 425, 432. According to the reference, these results suggest that "there could be efficacy in a treatment-resistant population." *Id.* at 432. For the planned Phase III trial, the results showed "[r]obust treatment effects . . . in subjects who had previously failed preventive migraine treatments . . . suggest[ing] that erenumab may have particular utility in this subgroup of patients." Ex. 1040, 13–14. Petitioner alleges that "*Sun's* planned trials and

subsequent results covering patients that had failed at least two preventatives" "further reinforced" "[t]he motivation to treat these patients [i.e., refractory migraine patients]." Pet. 25.

Patent Owner argues that the planned clinical trials disclosed in Sun do not teach or suggest treating migraine in subjects having refractory migraine, as claimed, because they lack data and because their inclusion criteria did not require inclusion of the claimed subjects with refractory migraine. *Id.* at 48–49. At this point in the proceeding, we do not find these arguments persuasive because Petitioner provides data (i.e., the prior art references reporting the results of the clinical trials (Ex. 1037 and 1040)), and because, even without that data, Sun provides an expectation that the planned trials will be successful.[13] Ex. 1006 ¶¶ 281 ("The results are expected to show that in subjects with chronic migraine, [erenumab] dose-dependently reduces from baseline the monthly migraine days compared with placebo and the adverse event profile of [erenumab] is similar to placebo."), 295 ("The phase 3 study results are expected to show that in subjects with episodic migraine, [erenumab] has a greater reduction from baseline in mean monthly migraine days, compared to placebo."). With respect to the Phase III trial, Sun teaches stratifying subjects by "prior treatment with migraine prophylactic medication (prior migraine prophylactic medication treatment vs. no prior migraine prophylactic medication treatment)." *Id.* ¶ 291. On this preliminary record, we agree with Petitioner that these teachings provide additional motivation to treat the claimed patient population.

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[13] We discuss reasonable expectation of success in more detail *infra* § III.F.2.

2. Has Petitioner articulated sufficient rationale to support that a POSA would have had reason to use galcanezumab to treat refractory migraine patients?

Petitioner contends that the POSA would have been motivated to use galcanezumab to treat refractory migraine patients for several reasons. **First**, "Sun expressly motivated using galcanezumab in its methods, disclosing combination treatment with 'an anti-CGRP antibody… in… ***WO 2011/156324***' (EX1006, [250]), which disclosed galcanezumab as SEQ ID Nos. 19 and 24." *Id.* at 30. **Second**, according to Petitioner, Dodick's eligibility criteria – which expressly allowed treatment of patients who had failed two approved migraine treatments – "pointed to treating the same [refractory] patients taught by Sun." *Id.* at 30–31 (citing Ex. 1003, 886 (Dodick eligibility criteria)). **Third**, Petitioner contends that a POSA would have understood Dodick and Sharma to teach that "galcanezumab was clinically at least similarly efficacious to *Sun's* erenumab" such that it would have been obvious to substitute one for the other "to effectively treat migraine by blocking the CGRP pathway." *Id.* at 31–33. According to Petitioner, this "motivation to substitute [galcanezumab for erenumab] was reinforced by the expectation and evidence that blocking the CGRP pathway with clinically effective CGRP mAbs—whether by targeting the receptor (erenumab) or its ligand (galcanezumab)—would be similarly effective." *Id.* at 32.

Petitioner's assertions that a POSA would have had reason to use galcanezumab in place of, or in addition to, erenumab are supported by the cited prior art and by the testimony of its declarant, Dr. Evers. Patent Owner does not, at present, contest that a POSA would have had reason to use galcanezumab, focusing its arguments instead on whether the cited art

discloses treating the claimed patient population and whether the POSA would have had a reasonable expectation of success in treating the claimed patients with galcanezumab. *See generally,* Prelim. Resp. 44–56. On this preliminary record, Petitioner has articulated sufficient reasoning with rational underpinning to support that a POSA would have had reason to use galcanezumab to treat the claimed patient population.

3. Has Petitioner sufficiently supported that a POSA would have had a reasonable expectation of success in using galcanezumab to treat refractory migraine?

Petitioner provides multiple reasons why the POSA would have expected success in treating refractory migraine patients. **First**, Petitioner argues that Dodick "demonstrated galcanezumab was effective in migraineurs" and an abstract from Headache, The Journal of Head and Face Pain, reports that galcanezumab was effective in "patients with a history of treatment failure." Pet. at 35 (citing Ex. 1003, 1, 6–7; Ex. 1072, 74). **Second**, Petitioner contends that the success of other anti-CGRP antibodies – like erenumab and fremanezumab – support an expectation that galcanezumab, which similarly affects the CGRP pathway, would be similarly efficacious. *Id.* at 35–37. **Third**, according to Petitioner, anti-CGRP antibodies have a mechanism of action that is distinct from that of conventional non-anti-CGRP treatments such that a POSA would have expected an anti-CGRP treatment, like galcanezumab to "treat migraineurs independent of whether they used or failed conventional treatments that targeted non-CGRP pathways." *Id.* at 38. **Fourth**, Petitioner argues that plans for "numerous anti-CGRP mAbs clinical trials that allowed for inclusion of patients that failed two preventives further reinforced the reasonable expectation of success in treating the 'select[ed]' [refractory

migraine] patients with galcanezumab.'" *Id.* at 39. We discuss each of these four positions, and Patent Owner's arguments in response thereto, in turn.[14]

a) Teachings in the art that galcanezumab was effective in treating migraine

Dodick discloses a Phase II study of galcanezumab, the results of which showed that galcanezumab was "effective and generally well tolerated for the preventive treatment of migraine in patients with frequent attacks" and that galcanezumab "significantly reduced the mean number of migraine headache days over the 3-month study period." Ex. 1003, 890. Although Dodick does not disclose treating refractory migraine patients, it also does not exclude them from its study. *Id.* at 886 (Dodick's patient eligibility criteria, excluding patients who "fail[ed] to respond to more than two adequately dosed (ie, maximum tolerated dose by the patient for a sufficient duration) approved migraine prevention treatments").[15] A second reference, an abstract from *Headache*, The Journal of Head and Face Pain, addresses refractory patients, teaching that galcanezumab was effective in patients with a "history of failure to preventative treatments." Ex. 1072, 74 ("the *Headache* abstract").

Supported by the testimony of Dr. Evers Petitioner contends that Dodick and the *Headache* abstract support that a POSA would reasonably expect "efficacy using galcanezumab in the claimed patients with prior treatment failures." Pet. 35; Ex. 1101 ¶¶ 164, 165.

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[14] Although we discuss each of these positions individually, we do so purely for convenience, recognizing that expectation of success is determined based on consideration of the prior art as a whole.

[15] Sharma also discloses a study in which galcanezumab was effective in treating migraine. Ex. 1007, 23. Like Dodick, Sharma does not disclose that refractory migraineurs are excluded from its study. *Id.*

Patent Owner argues that Dodick does not disclose treating subjects having refractory migraine and that "a POSA would not blindly *assume* that Dodick included subjects having refractory migraine of the claimed method, just because Dodick did not expressly exclude them." Prelim. Resp. 53. According to Patent Owner, the *Headache* abstract "changes nothing because, like Dodick, [it] fails to disclose treating subjects having a refractory migraine of the claimed method." *Id.* at 53-54. More specifically, Patent Owner asserts that "[a] POSA would not have understood a mere disclosure of a patient with 'a history of treatment failure' [as in the *Headache* abstract] to mean, or even include, the claimed subjects having refractory migraine." *Id.* at 54. Patent Owner cites the testimony of Dr. Blake to support that Dodick and the *Headache* abstract do not disclose treating the claimed patient population. Ex. 2001 ¶¶107–108.

On this preliminary record, we do not find Patent Owner's arguments persuasive. As an initial matter, the '161 patent sets a relatively low threshold for success in "treating or preventing migraine," defining that phrase to mean:

> An approach for obtaining . . . ***improvement in any aspect*** of a refractory migraine, including lessening severity, alleviation of pain intensity, and other associated symptoms, reducing frequency of recurrence, reducing the number of monthly headache days or hours, increasing the quality of life of those suffering from refractory migraine, and decreasing dose of other medications (e.g., acute headache medication) required to treat the refractory migraine.

Ex. 1002, 19:65–20:9 (emphasis added). Thus, in considering whether Petitioner has sufficiently supported that a POSA would have had a reasonable expectation of success, we consider whether the POSA would have expected improvement in any aspect of refractory migraine.

On this preliminary record, Dodick supports an expectation that galcanezumab would be effective in treating a broad genus of patients suffering from migraine. Ex. 1003, 886 (Dodick eligibility criteria), 890 ("[Galcanezumab] was effective and generally well tolerated for the preventative treatment of migraine in patients with frequent attacks."). And the *Headache* abstract supports an expectation that galcanezumab would be effective in treating patients with a "history of failure to preventative treatments." Ex. 1072, 183 ("Compared with its respective counterpart, subgroups with statistically significantly greater treatment effect (galcanezumab vs placebo difference) at Month 3 included patients . . . [with a] history of failure to preventive treatments in the 300 mg dose group.").

We recognize that patients identified in the *Headache* abstract as having a "history of failure to preventative treatments" may not align perfectly with patients having refractory migraine, as that term is defined in our claim construction. To the extent the differences in patient populations create an issue of fact as to whether the POSA would have extrapolated the results of treating patients with a "history of failure to preventative treatments" to the claimed refractory migraine patients, such issue is best resolved on a fully developed record. *Compare* Ex. 1101 ¶ 166; Ex. 2001 ¶¶ 107–108, 116. On this preliminary record, the expectation of success fostered by Dodick and the *Headache* abstract, when considered with the additional evidence discussed *infra* §§ III.3.b–d, is sufficient to support institution.

b) Teachings in the art regarding the success of other anti-CGRP antibodies

As discussed above, Sun teaches that a monthly dose of 70 mg of the anti-CGRP antibody, erenumab, was "efficacious in preventing episodic

migraine" and that efficacy was "similar regardless of . . . prior history of prophylactic medication use." *Id.* ¶¶ 268, 272. In addition to these teachings, Sun also describes a prospective Phase II clinical trial and a prospective Phase III clinical trial. *Id.* ¶¶ 273–295. The results of the two prospective trials are described in separate, subsequent documents. Ex. 1037 (reporting on the Phase II trial); Ex. 1040 (reporting on the Phase III trial). As to the Phase II trial, in which 49% of the patients "had failed at least two previous drug classes," the results were described as suggesting that "there could be efficacy in a treatment-resistant population." Ex. 1037, 432. The results of the planned Phase III trial, are similarly described as showing "[r]obust treatment effects . . . in subjects who had previously failed preventive migraine treatments . . . suggest[ing] that erenumab may have particular utility in this subgroup of patients." Ex. 1040, 13–14.

Although galcanezumab targets the CGRP ligand while erenumab targets the receptor, Petitioner argues that the POSA would expect the success of erenumab to extend to galcanezumab because the prior art teaches that targeting both the ligand and the receptor would be effective. *Id.* at 36 (citing Ex. 1034, which states: "The expectation is that . . . antibodies against both the ligand and receptor would prevent CGRP-induced activation of sensitized central trigeminal pathways, therefore decreasing headache frequency over time."). According to Petitioner, the expectation that galcanezumab would be as effective as erenumab was further supported by the "recognition that "***mAbs targeting CGRP or its receptor*** hold the most promise for preventive treatment in [episodic, chronic and ***medically refractory] subgroups***." Pet. 37 (quoting Ex. 1053, 13).

Relatedly, two studies of another anti-CGRP antibody, fremanezumab, show that fremanezumab was effective as a migraine

prophylactic. Ex. 1038, 2 ("This study provides level 1b evidence (well conducted individual randomised controlled trial) that TEV-48125 is effective for the preventive treatment of chronic migraine"); Ex. 1039, 3 ("This study provides level 1b evidence (ie, a robust, randomized clinical trial) that two doses of TEV-48125, a monoclonal antibody against CGRP, are effective for the preventive treatment of high-frequency episodic migraine"); Ex. 1057, 6 (study characterized in Exhibit 1039); Ex. 1058, 5 (study characterized in Ex. 1038). A press release from Patent Owner ("the Teva Press Release") characterizes these two fremanezumab studies as showing an "impressive decrease in migraine days, amongst such highly refractory patients." Ex. 1041, 2.

Petitioner argues that "the clinical success of erenumab and fremanezumab in patients with a history of treatment failure further provided a reasonable expectation that clinically successful galcanezumab—which operated by the same overall anti-CGRP mechanism and had demonstrated similar efficacy—would likewise be effective within the claimed method." Pet. 35.

With respect to erenumab, Patent Owner argues that the results disclosed in Sun do not support an expectation of success because Sun does not disclose treating the claimed subjects having refractory migraine. Prelim. Resp. 54. We do not find this persuasive for the reasons discussed *supra* § III.F.1.c. Patent Owner further argues that Exhibits 1037 and 1040, which provide the results of the two prospective clinical trials disclosed in Sun, disclose nothing that was not already disclosed in Sun. Prelim. Resp. 54. We do not find this argument persuasive. On this preliminary record, Exhibits 1037 and 1040, support an expectation that erenumab would be effective in treating patients for whom prior treatments had failed. Ex. 1037,

432 (concluding that Phase II trial results "suggest[] there could be efficacy in a treatment-resistant population" because the study showed efficacy in a patient population where 327 patients (49% of the total study) "had failed at least two previous preventative drug classes"); Ex. 1040, 13–14 ("Robust treatment effects were observed . . . in subjects who had previously failed preventive migraine treatments . . . suggest[ing] that erenumab may have particular utility in this subgroup of patients."). The preliminary record also tends to support the POSA would reasonably have expected galcanezumab and erenumab to have similar efficacy. Ex. 1034, 887; Ex. 1053, 647; Ex. 1101 ¶ 167–171.

With respect to fremanezumab, Patent Owner argues that a POSA would understand the phrase "highly refractory patients" in the Teva Press Release to have its "plain English meaning . . . , i.e., migraines resistant to treatment, because there was no specific definition for refractory migraine in the art." Prelim. Resp. 55. As support, Patent Owner cites the testimony of Dr. Blake that various art cited by Petitioner used the term "refractory" to refer simply to migraines that are resistant to treatment. *Id.* (citing Ex. 2001 ¶¶ 111, 63–67). Patent Owner further argues that "neither of [the two fremanezumab studies characterized in the Teva Press Release] nor any of the publications referring to them discloses treating subjects having refractory migraine of the claimed method." *Id.* We do not find these arguments persuasive.

On this preliminary record, we are not persuaded that differences in how the term "refractory" is used in the Teva Press Release and the '161 patent adversely impact the expectations of the POSA with respect to the administration of fremanezumab to the claimed patient population. The present record tends to support that the term "refractory" was understood in

the art to have a definition similar to and, in some respects, more restrictive than, that recited in the '161 patent. *See,* Ex. 1101 ¶¶ 20–25 (testimony of Dr. Evers that refractory migraine was "generally recognized to describe patients that failed at least three drugs"); Ex. 1012, 13 ("There is no agreement on the number of drugs a patient should have received before being considered refractory, but it is common consensus that at least three or four drugs belonging to the four most effective pharmacological classes (beta blockers, anticonvulsants, calcium antagonists, tricyclic antidepressants) should have been adequately tested."); Ex. 1011, 3, table 1 (summarizing various approaches to defining "refractory," including requiring "failure of at least 4 classes" of treatments, failure "from at least 2 of 4 drug classes," and failure of "[t]he greatest possible number of drugs"); Ex. 1013, 778 (proposing to define "refractory migraine" to require that "patients fail adequate trials of preventative medicines, alone or in combination, from at least 2 to 4 drug classes . . . [p]atients must also fail adequate trials of abortive medicines . . . and *either* nonsteroidal anti-inflammatory drugs (NDAISs) *or* combination analgesic"); Ex. 1014, 509 (reporting results of survey distributed at the American Headache Society meeting in 2007, where 41% of respondents favored requiring more than 3 failed treatments in order for a patient to be consider refractory).

We recognize that Patent Owner provides evidence that the POSA would have understood the phrase "highly refractory patients" in the Teva Press Release to "include the plain English meaning of the word 'refractory,' *i.e.*, resistant to treatment." Ex. 2001 ¶ 111 (testimony of Dr. Blake). As support, Patent Owner and Dr. Blake cite two dictionary definitions for the term "refractory." *Id.* ¶ 51 (citing Ex. 2003, and 2006). On this preliminary record, we find Petitioner's evidence as to how the POSA would have

understood "refractory migraine" more persuasive because it cites articles specific to migraines while Dr. Blake cites generic dictionary definitions of the term "refractory" that are not specific to any medical condition.

We give some weight to Patent Owner's arguments that the Teva Press Release is based on clinical trials that do not stratify subjects having refractory migraine. Prelim. Resp. 55; Ex. 2001 ¶¶ 110-111.[16] However, we cannot completely discount Patent Owner's characterization of these studies as showing that fremanezumab is effective in "highly refractory patients" (Ex. 1041, 2), particularly where others appear to have echoed the same conclusion (*See, e.g.,* Ex. 1023, 7 (concluding that anti-CGRP antibodies "are effective for relatively refractory headaches" based on data from the fremanezumab clinical trial reflected in Exhibits 1038 and 1058)).

In sum, the preliminary record tends to support an expectation that erenumab and fremanezumab would be effective in treating patients for whom prior treatments were unsuccessful. At trial, Patent Owner will have the opportunity to develop its argument that the differences in how refractory patients are defined materially effects the expectation of success in treating those patients and that the statements in the Teva Press Release are not supported by the clinical trials on which they were based. On this

[16] The eligibility criteria for the fremanezumab clinical trials allowed subjects that failed two classes of migraine prophylactic. EX1038, 2; EX1039, 3 EX1057, 6; EX1058, 5. In addition, patients were allowed to stay on existing treatments. Ex. 1038, 7 (identifying the fact that the study "did not exclude individuals who used other preventative drugs" as a "strength of our study"); Ex. 1041 (Teva PR), 2 ("these results were achieved in the presence of patients being allowed to remain on existing migraine prevention therapy, an attribute not seen in other reported anti-CGRP studies").

preliminary record, the expectation of success fostered by the two fremanezumab studies, the Teva Press Release, Sun, and the two references describing the results of Sun's prospective clinical studies, when considered with the additional evidence discussed *infra* §§ III.3.a and c–d, is sufficient to support institution.

c. *Teachings in the art regarding the mechanisms of action of anti-CGRP antibodies and of other migraine treatments*

Petitioner contends that anti-CGRP antibodies have a mechanism of action that is distinct from that of the "commonly used preventative medications recited by the Patent's 'clusters' and 'selecting' limitation." Pet. 37–38. Because they have a different mechanism of action, according to Petitioner, "a POSA would have expected that galcanezumab would treat migraineurs independent of whether they used or failed conventional treatments that targeted non-CGRP pathways, e.g., topiramate (GABA inhibitor) or propranolol (beta blocker)." *Id.* at 38 (citing Ex. 1101 ¶¶ 177–178).

Patent Owner argues that "no evidence" supports the expectation that galcanezumab would be successful in treating the claimed patient population because anti-CGRP antibodies have a distinct mechanism of action. Prelim. Resp. 55–56. Instead, according to Patent Owner, "[t]he outlook for [refractory] subjects was poor because multiple previous treatments were unsuccessful." *Id.* at 56. More specifically, Patent Owner argues that for refractory patients, "trying a new drug with a potentially different mechanism of action would not have raised the expectation of success." *Id.* (citing Ex. 2001 ¶¶ 112–113). On the current record, we do not find this argument persuasive.

Contrary to Patent Owner's argument, Petitioner's position is supported by citation to evidence. For example, Petitioner cites two articles suggesting that medications targeting the CGRP pathway, as a class, may be successful where other treatments had failed. Pet. 37–38 (citing Exs. 1023 and 1059). One of these articles, states: "[f]or those who remain refractory to currently available treatments, the approach of a new generation of drugs targeted at CGRP, the lynchpin molecule of both migraine and cluster headache, holds out hope of improvement in the not too-distant future." Ex. 1059, 5. The other teaches that "monoclonal antibodies . . . against calcitonin gene-related peptide (CGRP) for the preventative treatment of episodic and chronic migraine deserve to be called a breakthrough . . . because they are effective for relatively refractory headaches." Ex. 1023, 7. Both of these articles support an expectation of success based on mechanism of action – i.e., that drugs that target the CGRP pathway will be successful in otherwise refractory patients.

Petitioner also cites the "demonstrated efficacy of a clinically effective small-molecule CGRP antagonist (telcagepant) in patients nonresponsive to other acute treatments" as evidence that treatments that target the CGRP pathway may be effective for treatment of patients that are refractory to other drug-types. Pet. 38. For example, one reference cited by Petitioner studied "whether migraine patients who cannot be adequately helped with triptans might benefit from treatment with telcagepant,[17] as might be predicted given that triptans and CGRP receptor antagonists have different mechanisms of action." Ex. 1060, 65. Based on that study, the

[17] According to the reference, "[t]elcagepant is a novel, orally available CGRP receptor antagonist." Ex. 1060, 70.

reference concluded that "patients who respond poorly to/did not take triptans might benefit from telcagepant and other CGRP antagonists." *Id.* at 70. This conclusion is echoed in other references cited by Petitioner. *See, e.g.,* Ex. 1027, 446 ("Further studies indicated that triptan non-responders would still benefit from the CGRP-RA [telcagepant]"); Ex. 1061, 6 ("Also exciting was the finding that patients who were unresponsive to the triptan class of acute medication could benefit from telcagepant.").

In sum, the preliminary record includes evidence that treatments targeting the CGRP pathway may be effective in treating migraine where other treatments have failed. On this preliminary record, the expectation of success fostered by galcanezumab's distinct mechanism of action, when considered with the additional evidence discussed *infra* §§ III.3.a-b and d, is sufficient to support institution.

d) Clinical trials that did not exclude refractory patients

Petitioner argues that plans for "numerous anti-CGRP mAbs clinical trials that allowed for inclusion of patients that failed two preventives further reinforced the reasonable expectation of success in treating the 'select[ed]' [refractory migraine] patients with galcanezumab.'" Pet. at 39. As support Petitioner references the "eligibility criteria for completed galcanezumab, erenumab, and fremanezumab trials." *Id.* Petitioner also cited Dr. Evers testimony that "A POSA would have understood that initiating a Phase II clinical trial requires that the study sponsor provide convincing rationale for the study and anticipated efficacy, from which a POSA would understand there to have been a reasonable expectation of efficacy." Ex. 1101 ¶ 184.

Patent Owner argues that "[n]one of the clinical trials teaches or suggests treating migraine in the subjects of the claimed method." Prelim.

Resp. 56. Patent Owner presents the testimony of Dr. Blake, who notes that "none of Dodick (EX1003), Sun (EX1006), EX1037, EX1038, and EX1039 teaches or suggests treating to relieve signs or symptoms of migraine in the refractory subjects of the claimed method." Ex. 2001 ¶ 115.

We have already discussed expectations fostered by each of the clinical trials referenced by Petitioner. *See supra* §§ III.F.3.a-b. We will not repeat that discussion here.

4. Conclusion

Petitioner shows, based on the present record, where each of the limitations of claim 1 is taught or suggested in the combination of Sun, Dodick, and Sharma. Pet. 21–30. For the reasons discussed *supra* §III.F.1 we are not persuaded by Patent Owner's argument that Sun does not disclose treating the claimed patient population. Prelim. Resp. 45–52. Petitioner also provides evidence-backed reasoning to support its argument that a skilled artisan would have had reasons for treating the claimed patient population with galcanezumab. Pet. 30–33. Patent Owner does not challenge that the POSA would have been so motivated and, on the present record, we find Petitioner's reasoning persuasive. *See generally,* Prelim. Resp. Finally, Petitioner provides reasons why the POSA would reasonably have expected treating the claimed refractory migraine patients to be successful. Pet. 33–40. For the reasons discuss *supra* § III.F.3, we are not persuaded by Patent Owner's argument that the POSA would not reasonably have expected success. Prelim. Resp. 52–56. Accordingly, we conclude that Petitioner has established a reasonable likelihood that it will prevail in showing that claim 1 would have been obvious over the combination of Sun, Dodick, and Sharma.

Petitioner contends that the limitations added in dependent claims 2–30 are taught or suggested in the prior art, and that these claims would have been obvious over the combination of Sun, Dodick, and Sharma. Pet. 42–45. Petitioner's contentions with respect to these dependent claims are, at this stage, uncontested by Patent Owner. We have considered Petitioner's showing with respect to dependent claims 2–30 and find that it is backed by documentary and testimonial support sufficient to support institution.

G. Ground 2

Petitioner asserts that claims 1–30 would have been obvious over the combination of Dodick and Sharma. In brief summary, Petitioner contends that claim 1 extends to patients who have not failed any migraine treatments but are merely contraindicated from conventional medications. Pet 45–46. For example, obese patients and patients with hypotension would be contraindicated for certain drugs within the classes of preventative migraine treatments recited in claim 1. *Id.* at 45, 48 (citing evidence that a migraine patient with hypotension would be contraindicated from beta-blockers and calcium channel blockers while an obese patient would be contraindicated from tricyclics and valproic acid).

Petitioner contends that it would have been obvious to administer galcanezumab to obese patients and patients who suffer from hypotension in view of "*Dodick* (EX1003) which demonstrated the effectiveness of galcanezumab using eligibility criteria that include the claimed 'contraindicated' and 'select[ed]' subjects, in view of *Sharma* (EX1007), which further disclosed galcanezumab formulations and effective doses." *Id.* at 46. Petitioner then argues that with respect to contraindicated medications, POSAs "typically relied upon efficacy as evaluated in the general migraine population as opposed to the specific comorbid

subpopulation." *Id.* at 53–54 (citing evidence). Thus, according to Petitioner:

> Migraine patients with comorbid hypotension— contraindicated for beta-blockers and calcium channel blockers—would be expected to experience the same clinical benefit from galcanezumab as patients unaffected by hypotension. [Ex. 1101] ¶255. Likewise, patients suffering from obesity—contraindicated from tricyclic antidepressants and valproic acid—would be expected to receive the same clinical benefit as non-obese patients. *Id.* ¶256.

Id. at 53.

As to the requirement of claim 1 for "selecting a subject who has been treated with two or more different classes of preventative migraine treatments," Petitioner asserts that Dodick's eligibility criteria allowed subjects that had been treated with multiple preventative treatments and that such patients were common, with the average migraine patient having used three or four treatments. *Id.* at 49 (citing Ex. 1015, 645 ("The mean number of prophylactic medications ever used was 2.92 for EM [episodic migraine] and 3.94 for CM [chronic migraine].")).

Patent Owner argues that Petitioner's arguments are "speculative" and "do not rise to the level of showing a reasonable likelihood of prevailing." Prelim. Resp. 57–58. According to Patent Owner, "just because Dodick did not expressly *exclude* contraindicated subjects" does not mean that Dodick somehow "directs a POSA to treat such 'contraindicated' patients." *Id.* To the contrary, Patent Owner asserts that Dodick's exclusion criteria expressly excluded patients with comorbidities, including:

> patients who had "evidence of significant active psychiatric disease" and who had "a *history or presence of any other medical illness* including but not limited to any cardiovascular, hepatic, respiratory, hematological, endocrine, psychiatric or

> neurological disease, or any clinically significant laboratory abnormality, that in the judgment of the investigator, indicates a medical problem that would preclude study participation."

Id. at 58 (quoting Ex. 1004, 3).

For the reasons discussed *supra* § III.C.2, on this preliminary record, we tend to agree with Petitioner that the claims do not exclude patients who are contraindicated for two preventative medications from among the classes of treatments recited in claim 1. On this preliminary record, the general obviousness theory relied upon in Ground II – i.e. that it would have been obvious to administer galcanezumab to obese patients with migraines or migraine patients who suffer from hypotension – has logical appeal. In addition, in the absence of evidence to the contrary, the factual components of Petitioner's theory appear to be generally supported by the evidence.

However, Patent Owner's argument that Dodick's exclusion criteria excludes patients with comorbidities may have merit, particularly as to patients suffering from hypotension, which we may well qualify as a "cardiovascular" illness under Dodick's eligibility criteria. In addition, we have some concern that the patient population Petitioner contends would have been obvious to treat is too attenuated from the disclosure of Dodick (or Sharma) to support a finding of obviousness. More specifically, the proposed obvious patient population is comprised of: 1) patients who are hypotensive or obese, 2) who have been treated with two or more different classes of preventative migraine treatments, and 3) who have not failed (and are thus not refractory to) the preventative migraine treatments with which they have been treated.

We find that we would benefit from a more fully developed record in resolving the questions of whether Dodick's exclusion criteria would

exclude the patient population that Petitioner contends would be obvious to treat and of whether that patient population is too attenuated from the disclosures of Dodick and Sharma to support a finding of obviousness. In this regard, we note that, for the reasons discussed *supra* § III.F, Petitioner's Ground 1 meets the reasonable likelihood standard for institution, and if trial is instituted, it must be instituted on all challenged claims and grounds. 37 C.F.R. § 42.108(a) ("When instituting . . . review, the Board will authorize the review to proceed on all of the challenged claims and on all grounds of unpatentability asserted for each claim."); and/or (b) *PGS Geophysical AS v. Iancu*, 891 F.3d 1354, 1359–60 (Fed. Cir. 2018) (interpreting the relevant statutory provisions, in light of *SAS*, to require "a simple yes-or-no institution choice respecting a petition, embracing all challenges included in the petition").

IV. CONCLUSION

On this preliminary record, Petitioner has established a reasonable likelihood of prevailing in showing that at least one of the challenged claims is unpatentable based on the grounds advanced in the Petition.

V. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that the Petition is *granted*, and we institute *inter partes* review of claims 1–30 based on the grounds asserted in this Petition;

FURTHER ORDERED that pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4, notice is given of the institution of trial, which will commence on the entry date of this Decision.

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