

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.

IPR2022-00796
Patent 10,392,434 B2

Before TIMOTHY G. MAJORS, 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 April 11, 2022, Eli Lilly and Company (“Petitioner”)¹ filed a Petition to institute *inter partes* review of claims 1–13 of U.S. Patent No. 10,392,434 B2 (Ex. 1045, “the ’434 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 1–13 of the ’434 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. 68; Paper 3, 1.

The parties also identify U.S. Patent Nos. 11,028,160 (“the ’160 patent”) and 11,028,161 (“the ’161 patent”) as relating to the ’434 patent. Pet. 68; Paper 3, 1–2. The ’434 patent, issued from U.S. Patent Application

¹ Petitioner identifies itself as the real party-in-interest. Pet. 68.

² Patent Owner identifies itself and Teva Pharmaceuticals USA, Inc. as the real parties-in-interest. Paper 3, 1.

No. 15/712,444 (“the ’444 application”), which claims priority to U.S. Provisional Patent Application Nos. 62/399,180 (“the ’180 provisional”) and 62/558,557 (“the ’557 provisional”). Ex. 1045, code (21), (60). The ’160 and ’161 patents both issued from applications filed as continuations of the ’444 application. IPR2022-00738, Ex. 1001, code (63); IPR2022-00739, Ex. 1002, 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 ’444 application. Pet. 68; Paper 3, 2.

The ’160 patent is challenged in IPR2022-00738 and the ’161 patent is challenged in IPR2022-00739. Pet. 68; Paper 3, 1.

B. The ’434 Patent

According to the ’434 patent, “[m]igraine is a prevalent neurological condition characterized by attacks of headache and associated symptoms, such as nausea, vomiting, photophobia, and/or phonophobia.” Ex. 1045, 1:14–16. 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 1:32–35. The ’434 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 1:36–42.

The ’434 patent teaches that calcitonin gene-related peptide (CGRP) “has been found to be involved in migraine processes, both centrally and peripherally.” *Id.* at 1:44–46. More specifically, the ’434 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 1:48–51. “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 1:53–55. According to the ’434 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 1:57–59. The ’434 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 1:64–66.

The ’434 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 14:36–40.

C. Challenged Claims

The ’434 patent includes 13 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 migraine in a subject, the method comprising:
selecting a subject who has an inadequate response to two or more different classes of preventative migraine treatment selected from the group consisting of beta-blockers, anticonvulsants, tricyclics, calcium channel blockers, angiotensin II receptor antagonists, onabotulinumtoxinA, and valproates; 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: 1 and the amino acid sequence of the light chain variable region set forth in SEQ ID NO: 2.

Ex. 1045, 173:26–42.

D. Asserted Grounds of Unpatentability

Petitioner asserts two grounds of unpatentability in the Petition (Pet. 17), which are provided in the table below:

Claim(s) Challenged	35 U.S.C. §	Reference(s)/Basis
1–13	103	Sun, ³ Teva Press Release ⁴
1–13	103	Bigal ⁵

Petitioner relies on the declaration of Dr. Stefan Evers, among other evidence. Ex. 1109. Patent Owner responds with a declaration from Dr. Pamela Blake, along with other evidence. Ex. 2001.

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

⁴ Teva Pharmaceutical Industries Ltd., *Teva to Present New Findings at the American Headache Society (AHS) Meeting – Analysis of Migraine Phase IIb Studies Provides Novel Insights into TEV-48125 Efficacy and Safety in Both Episodic & Chronic Migraine*, Press Release dated June 18, 2015 (Ex. 1041, “Teva Press Release”).

⁵ Bigal et al., US Patent Publication No. 2015/0266948 A1, published Sep. 24, 2015 (Ex. 1102, “Bigal”).

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

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

§ 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. 31-49. 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 Electromedizinische 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.*

⁶ Available at <https://www.uspto.gov/TrialPracticeGuideConsolidated>.

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 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 “effectively” all of the references relied upon by Petitioner – i.e., Sun, the Teva Press Release, and Bigal – were “previously considered by the Examiner during prosecution.” Prelim. Resp. 32. More specifically, Patent Owner contends that “[t]he two primary references, Sun and Bigal, were cited and considered” and that “[t]he Teva Press Release merely reports on two clinical trials that were themselves cited and considered by the Examiner.” *Id.*

We focus our discussion on Sun and the Teva Press Release because Petitioner’s discussion of these references in connection with Ground 1, by

itself, persuades us that we should not exercise our discretion to deny institution.

Patent Owner is correct that Sun was before the Office. *See* Ex. 1045, code (56) (listing Sun). Patent Owner also appears to be correct that the clinical studies disclosed in the Teva Press Release were cited and considered by the Examiner. *Id.* (listing Exs. 1023 and 1039 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. 35. More particularly, Patent Owner argues that Sun is cumulative of Zeller and that the Teva Press Release is cumulative to the clinical studies it describes. *Id.* at 35–43. We are not persuaded.

During prosecution of the ’444 application, the Examiner rejected the then-pending claims over Zeller. Ex. 2008, 233. 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.” *Id.* 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 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

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.

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 art asserted in this proceeding is cumulative of Zeller because, as discussed in more detail below, various disclosures of that art, including Sun, disclose 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.”).

Similarly, we are not persuaded that the analysis of clinical studies in the Teva Press Release is cumulative of the clinical studies themselves. Importantly, the analysis in the Teva Press Release states that “[t]he very fast onset of preventative response, seen after a single dose of therapy, along with impressive decrease in migraine days, amongst such highly refractory patients, may bring us a step closer to provide widespread relief to people who suffer from chronic and episodic migraine.” Ex. 1041, 2. This teaching

bears directly on the element that the Examiner found was missing from Zeller – treatment of refractory patients. Ex. 2008, 655–656

In sum, we determine that Sun is not cumulative of Zeller and the Teva Press Release is not cumulative of the clinical studies it analyzes. Nonetheless, Sun was considered by the Examiner. Accordingly, we determine that the first part of the *Advanced Bionics* framework is satisfied. We turn next to the second part of the *Advanced Bionics* 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 or Bigal, and therefore must have failed to appreciate the prior art.” Prelim. Resp. 46. 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 prior art.” *Id.* at 48–49. 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 47. 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 ’434 patent to suggest that the Examiner accounted adequately for Sun’s teachings in allowing the ’434 patent to issue. Given that this error in overlooking Sun’s teachings was central to allowance of the ’434 patent, we find that this error was material.

We recognize that Patent Owner disputes that Sun suggests treating the claimed “inadequate response” 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 “inadequate response” 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 claimed invention and the prior art must be such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention 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 ’434 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. 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. 11-12.

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 '434 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.*

Both parties identify the limitation “selecting a subject who has an inadequate response to two or more different classes of preventative migraine treatment” as in need of construction. Pet. 13–14; Prelim. Resp. 9–12. Patent Owner also argues that we should construe the preamble, which recites “[a] method of treating migraine in a subject.” Prelim. Resp. 8.

1. “A method of treating migraine in a subject”

The phrase “[a] method of treating migraine in a subject” appears in the preamble to claim 1. Ex. 1045, 173:27–28. Patent Owner argues 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.” Prelim. Resp. 8. On this preliminary record, which does not include opposing argument from Petitioner on whether any further interpretation of the preamble is appropriate, we agree that the preamble of claim 1 limits the claim for the reasons expressed by Patent Owner. *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 Pharm. 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”).

2. “Selecting a subject who has an inadequate response to two or more different classes of preventative migraine treatments”

We turn now to the meaning of the phrase “a subject who has an inadequate response.” The parties agree that the ’434 patent expressly defines the phrase “a subject who has an inadequate response.” Pet. 13–14; Prelim. Resp. 9–10. In this regard, the ’434 patent states:

Inadequate response is defined as: [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] or when treatment has to be interrupted because of adverse events that made it intolerable by the patient [3] 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 onabotulinumtoxinA, 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.

Ex. 1045, 45:63 (bracketed numbers added for reference). 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 judgment, 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.

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

D. Priority

Petitioner asserts that claims 1–13 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. 15. Patent Owner argues that “[t]here is no

⁸ In its briefing on claim construction, Patent Owner contests Petitioner’s assertion that “the ‘at least three months of therapy at a stable dose’ aspect of the definition was ‘among common criteria for evaluating migraine prophylactics.’” Prelim. Resp. 11 (citing Pet. 21, fn.8). 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.

basis for requiring Patent Owner to address, or for the Board to decide, the priority date to which the claims are entitled” because Sun, the Teva Press Release, and Bigal – 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. 12–13.

At this point in the proceeding, and in the absence of a challenge to the prior art status of any of the references asserted 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 Sun, the Teva Press Release, and Bigal, the Petition characterizes several references that help to support its arguments as “prior art.” *See e.g.*, Pet 24 (citing Ex. 1037, which the Petition describes as providing “prior-art results” of a Phase II study described in Sun and Ex. 1040, which the Petition describes as providing “prior art results” of a Phase III study described in Sun), 34 (citing Exs. 1038, 1039, 1057, and 1058 as evidence that fremanezumab was “known to be effective in patients with a history of preventative treatment failure”); 45 (citing Exs. 1102, 1039, and 1072 as “prior art references teaching success 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. 24. 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 2007/054809, which, according to Dr. Evers, discloses fremanezumab (Ex. 1109 ¶ 50), 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 “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 . . .

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.” Ex. 1006 ¶ 65. Lack of efficacy includes an “inability to tolerate the migraine prophylactic agent” or instances where the agent is contraindicated. *Id.* ¶ 66.

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. Teva Press Release

The Teva Press Release is titled “*Teva to Present New Findings at the American Headache Society (AHS) Meeting – Analysis of Migraine Phase IIb Studies Provides Novel Insights into TEV-48125 Efficacy and Safety in Both Episodic & Chronic Migraine.*” Ex. 1041. It is dated June 18, 2015 and Petitioner contends that it is prior art under 35 U.S.C. § 102(a)(1). *Id.*; Pet. 7.

The Teva Press Release analyzes the results of two Phase II studies of TEV-48125 (fremanezumab), one directed to high frequency episodic migraine (ClinicalTrials.gov Identifier: NCT02025556), the other directed to chronic migraine (ClinicalTrials.gov Identifier: NCT02021773). Ex. 1041. According to the Teva Press Release, “in both episodic and chronic migraine studies,” “[a] single administration of all tested doses of TEV-48125 . . . resulted in a statistically significant separation from placebo.” *Id.* at 1. After discussing the two clinical trials in greater detail, the Teva Press Release quotes Marcelo E. Bigal, Teva’s Head of Global Clinical

Development for Migraine and Headaches, who concludes that “[t]he collective data generated from these studies herald promise for millions of people who suffer from episodic and chronic migraines, a disease with substantial implications and unmet needs,” and that “[t]he very fast onset of preventive response, seen after a single dose of therapy, along with the impressive decrease in migraine days, amongst such highly refractory patients, may bring us a step closer to provide widespread relief to people who suffer from chronic and episodic migraine.” *Id.* at 2.

3. Bigal

Bigal is a U.S. patent publication published on September 24, 2015. Ex. 1102. Petitioner asserts that Bigal is prior art under 35 U.S.C. § 102(a)(1). Pet. 10. Bigal discloses “methods for preventing or treating CGRP associated disorders such as . . . migraine . . . by administering an anti-CGRP antagonist antibody.” Ex. 1102, Abstract.

Bigal discloses a clinical study on the prevention of chronic migraine comparing anti-CGRP antagonist antibody G1 (fremanezumab) to placebo. Ex. 1102 ¶¶ 409–418 (Example 17). Bigal also discloses a clinical study on the prevention of high-frequency episodic migraine comparing anti-CGRP antagonist antibody G1 to placebo. *Id.* ¶¶ 419–422 (Example 18). According to Patent Owner, these are “the same two clinical trials disclosed in [the] Teva Press Release.” Prelim. Resp. 27–28.

For the clinical trial on prevention of chronic migraine, subjects were permitted to “use up to two different daily migraine preventative medications . . . if the dose and regimen ha[d] been stable for at least 2 months prior to beginning the 28-day run in period.” Ex. 1102 ¶409. The exclusion criteria for the trial excluded subjects who “failed>2 medication categories or >3 preventive medications (within two medication categories)

due to lack of efficacy for prophylactic treatment of episodic or chronic migraine after an adequate therapeutic trial.” *Id.* ¶ 410. The results of the trial showed that both of the two doses tested provided a “significant decrease” in the number of headache hours, as well as a “statistically significant decrease” in number of headache days. *Id.* ¶¶ 412, 415. In addition, a “significant decrease in number of headache hours was . . . observed in subjects using prevention medications (e.g., topiramate and amitriptyline or propranolol) relative to a placebo group.” *Id.* ¶ 417.

For the clinical trial on preventing episodic migraine, the “[s]tudy design” was the same as that used for the trial on prevention of chronic migraine except that it used a different dosing schedule, and specified in the inclusion criteria that subjects “fulfill[] criteria for episodic migraine” rather than “chronic migraine.” *Id.* ¶ 419. The results of the trial showed a “statistically significant decrease” in number of migraine days and headache days relative to baseline. *Id.* ¶¶ 420, 421.

F. Ground 1, as relates to treating subjects who failed prior treatments

Petitioner asserts that claims 1–13 would have been obvious over the combination of Sun and the Teva Press Release because it would have been obvious to use fremanezumab to treat patients who failed prior migraine treatments.¹⁰ Pet. 17–41. In brief summary, Petitioner contends that Sun discloses treating patients with “inadequate response” using the anti-CGRP monoclonal antibody (“mAb”), erenumab. Pet. 19–25. To address the

¹⁰ Petitioner also argues that claims 1–13 would have been obvious over the combination of Sun and the Teva Press Release because it would have been obvious to use fremanezumab to treat patients who were contraindicated for other migraine treatments. Pet. 42–44. We address this argument *infra* § III.G.

requirement of the challenged claims to treat “inadequate response” patients with the anti-CGRP mAb, fremanezumab,¹¹ Petitioner argues that it would have been obvious to use fremanezumab in the method disclosed in Sun, in view of the Teva Press Release’s disclosure that fremanezumab was effective for treating migraine. Pet. 27-34. Petitioner also argues that the Teva Press Release discloses treating “inadequate response” patients with fremanezumab. Pet. 26-27. Patent Owner opposes, arguing, principally, that neither Sun nor the Teva Press Release discloses treating “inadequate response” patients, as that term is defined in the ’434 patent, and that the cited art does not provide a reasonable expectation of success. Prelim. Resp. 49–63.

We begin our analysis by considering whether Petitioner has sufficiently supported that Sun and the Teva Press Release disclose treating “inadequate response” patients. We next consider whether Petitioner has articulated sufficient rationale to support that a POSA would have had reason to use fremanezumab when treating “inadequate response” patients. Finally, we consider whether Petitioner has supported that the POSA would have a reasonable expectation of success in treating “inadequate response”

¹¹ There does not appear to be any dispute that fremanezumab is “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: 1 and the amino acid sequence of the light chain variable region set forth in SEQ ID NO: 2,” as recited in claim 1. Prelim. Resp. 6 (“The patent’s claimed methods involve administering . . . a monoclonal antibody . . . having the heavy chain variable region and light chain variable region amino acid sequences of fremanezumab.”); Pet. 1 (“The [claimed] method comprises two steps. . . . The second [step] involves administering fremanezumab.”).

patients with fremanezumab. On this preliminary record, we conclude that Petitioner has demonstrated a reasonable likelihood of prevailing in showing that claims 1–13 would have been obvious over the cited art.

1. Does Petitioner sufficiently support that Sun discloses treating subjects who have an “inadequate response” to prior treatment?

Petitioner contends that Sun supports the obviousness of treating a “subject who has an inadequate response to two or more different classes of preventative migraine treatment” in four ways. **First**, according to Petitioner, Sun provides direction to treat patients who failed treatment with multiple classes of migraine prophylactic agents. Pet. 20–21. **Second**, Sun provides direction to treat patients who were intolerant to treatment with multiple classes of migraine prophylactic agents. *Id.* at 21–22. **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 23 (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., inadequate response patients].” Pet. 23–24. We discuss each of these four positions, and Patent Owner’s arguments in response thereto, in turn.¹²

¹² 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.”).

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 “inadequate response” that was recited in the Specification of the ’434 patent (and adopted in our claim construction). Pet. 20–21. 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. 21, n.8 (citing Ex. 1109 ¶¶ 24–25, 102, n.13; Ex. 1011, 3; Ex. 1019, 2; Ex. 1020, 4–5; Ex. 1022, 2)).

Patent Owner argues that Sun does not disclose treating patients who showed “no clinically meaningful improvement,” as that phrase is used in the ’434 patent and in our claim construction, because Sun defines patients who failed or were intolerant to prior preventive medication as “different

from inadequate response subjects of the claimed method.” Prelim. Resp. 51. First, Patent Owner argues that “failure to respond” in Sun requires failure of only one preventative medication while “inadequate response” in the ’434 patent requires the failure of at least two preventative medications. *Id.* at 22. 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 prophylactic agents. 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 ’434 patent requires that treatment carry on for at least three months. Prelim. Resp. 22. 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. 1109 ¶ 24 (Dr. Evers’ testimony); Pet. 21, n.8 (citing evidence supporting a 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 . . . 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.’” Ex. 1109 ¶ 102.

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 ¶ 40 (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 ’434 patent’s “no clinically meaningful improvement” because the ’434 patent requires a “stable dose” while Sun’s definition requires a “standard therapeutic regimen.” Prelim. Resp. 22. 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. 1109 ¶ 24, 102; Pet. 21, n.8.

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 inadequate response 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 ’434 patent (and adopted in our claim construction). Pet. 21–22.

Patent Owner argues that “[w]hen discussing the ‘inability to tolerate’ the agent, Sun exclusively discusses *side effects*.” Prelim. Resp. 20. 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 20–21.

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,”¹³ Sun’s discussion of “side effects” is exemplary, and 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 (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 (CCPA 1968)). Here, Sun is 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.

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 ¶¶ 41, 77–82) 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.

¹³ 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.

- 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.

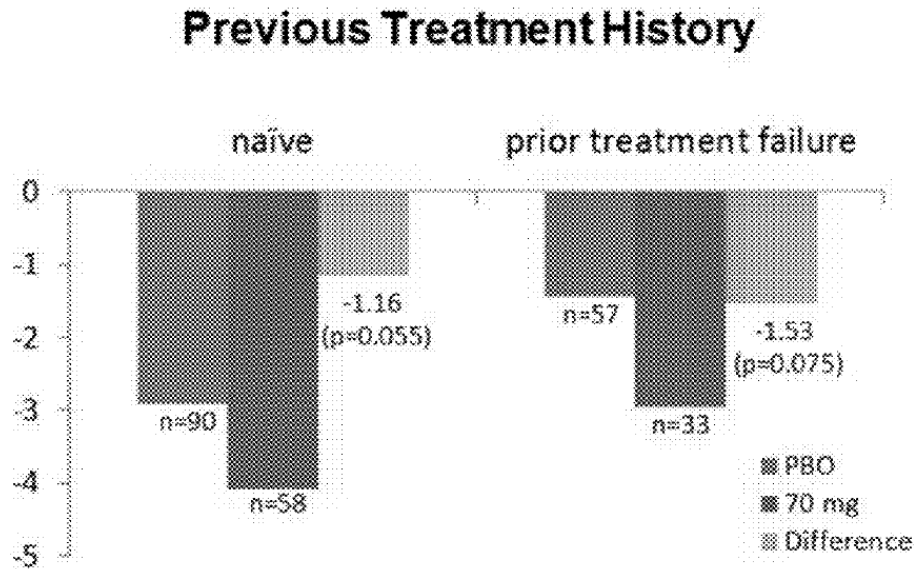


FIG. 7B

“FIG. 7B 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 ‘inadequate response’ subjects.” Pet. 23.

Patent Owner argues that the results of the Phase II trial reported in Sun do not suggest treating the claimed inadequate response patients,

repeating much the same argument it made 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 inadequate response of the claimed method," and that Sun does not disclose, for example "how many prior medications [patients] failed and under what conditions." Prelim. Resp. 53. 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 an inadequate response 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 trials 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. 24 (citing Exs. 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 contends 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., patients who had inadequate response].” Pet. 23–24.

Patent Owner argues that the planned clinical trials disclosed in *Sun* do not teach or suggest treating migraine in subjects who have an inadequate response because their inclusion criteria did not require inclusion of such subjects. *Id.* at 53–54. At this point in the proceeding, we do not find these arguments persuasive because Petitioner provides the prior-art results of *Sun*’s planned studies, which support treating patients with inadequate response. Ex. 1037, 432 (reporting efficacy in a patient population comprising “453 (68%) patients who had failed at least one previous preventive drug class because of lack of efficacy or poor tolerability and 327 (49%) who had failed at least two previous preventive drug classes,” and suggesting that “there could be efficacy in a treatment-resistant population”); Ex. 1040, 13–14 (reporting “[r]obust treatment effects . . . in subjects who had previously failed preventative migraine treatments”). Consistent with these results, *Sun* teaches stratifying the subjects by “prior treatment with migraine prophylactic medication (prior migraine prophylactic medication treatment vs. no prior migraine prophylactic medication treatment)” and states that the trials were expected to be successful. Ex. 1006 ¶¶ 291, 295.

On this preliminary record, we agree with Petitioner that these teachings provide additional motivation to treat the claimed patient population.

2. Does Petitioner sufficiently support that the Teva Press Release suggests treating subjects who have an “inadequate response” to prior treatment?

The Teva Press Release discusses two clinical of fremanezumab. After discussing the trials, the Teva Press Release states that “[t]he collective data generated from these studies herald promise for millions of people who suffer from episodic and chronic migraines, a disease with substantial implications and unmet needs.” Ex. 1041, 2. The Teva Press Release continues, “[t]he very fast onset of preventive response, seen after a single dose of therapy, along with the impressive decrease in migraine days, amongst such highly refractory patients, may bring us a step closer to provide widespread relief to people who suffer from chronic and episodic migraine.” *Id.* at 2. Petitioner contends that this disclosure teaches or suggests treating subjects who have “inadequate response” to prior treatments, as recited in claim 1. Pet. 26.

Patent Owner argues that the Teva Press Release does not “disclose any specific outcome in subjects of the claimed method.” Prelim. Resp. 56. According to Patent Owner, “later publications describing the same Phase II trials reported in the Teva Press Release make no mention of any inadequate response subject of the claimed method or any treatment outcome specific to such subject.” *Id.* Divorced of contextual data, Patent Owner argues, a POSA would not understand the phrase “highly refractory patients” in the Teva Press Release to refer to the claimed “inadequate response” patients. Instead, Patent Owner asserts, “a POSA would have understood ‘refractory’ in the phrase to have its plain English meaning, i.e., resistant to treatment,

and would have understood the phrase to mean highly resistant to treatment.” *Id.* at 26.

On this preliminary record, we are not persuaded that a POSA would have understood the term “refractory” as used in the Teva Press Release to mean only that patients were resistant to treatment. 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, the term “inadequate response” recited in the ’434 patent. *See*, Ex. 1109 ¶¶ 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, 513 (reporting results of a 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 ¶ 143 (testimony of Dr. Blake). As support, Patent Owner and Dr. Blake cite two dictionary definitions for the term “refractory.” *Id.* ¶ 46 (citing Exs. 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 “inadequate response” subjects. Prelim. Resp. 56; Ex. 2001 ¶¶ 92–115.¹⁴ 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

¹⁴ 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”).

“are effective for relatively refractory headaches” based on data from the fremanezumab clinical trial reflected in Exhibits 1038 and 1058)).

3. Has Petitioner articulated sufficient rationale to support that a POSA would have had reason to use fremanezumab to treat patients who had an “inadequate response” to prior treatment?

Petitioner argues that the “*Teva Press Release* directly provided motivation to treat the ‘selected’ ‘inadequate response’ patients.” Pet. 27, 28–31. In addition, Petitioner separately argues that a POSA “would have been motivated to substitute fremanezumab in the methods of treating ‘selected’ ‘inadequate response’ patients taught by *Sun*.” *Id.* 27, 31–34. We address each of these arguments in turn.

a) Motivation to treat the claimed patients based on the disclosure of the Teva Press Release

Petitioner contends that the POSA would have been motivated to use fremanezumab based on teachings in the *Teva Press Release*. Pet. 27–31. **First**, Petitioner argues that the “*Teva Press Release* expressly motivated treating patients with a history of treatment failure, disclosing an ‘impressive decrease in migraine days, amongst . . . highly refractory patients.’” Pet. 28 (quoting Ex. 1041, 2). **Second**, Petitioner argues that “the *Teva Press Release*’s disclosure that its ‘results were achieved in the presence of patients being allowed to remain on existing migraine prevention therapy,’ suggests treating patients with inadequate response because a POSA would have understood that such patients remain on existing therapies included patients with only partial efficacy, i.e., no “‘clinically meaningful’ improvements.” *Id.* at 28–29. **Third**, Petitioner argues that the

Teva Press Release describes the results of studies in which the eligibility criteria allowed patients that had “inadequate response” to four classes of preventatives. *Id.* at 29–31.

With respect to Petitioner’s first argument, as discussed above, Patent Owner contends that the POSA would not have understood the phrase “highly refractory patients” in the Teva Press Release to suggest treating the claimed patient population. We do not find this persuasive for the reasons discussed *supra* § III.F.2.

With respect to Petitioner’s second argument, Dr. Blake testifies that “a POSA would have understood that the subjects who were actively using other migraine preventive therapy were included in the clinical trial and that these subjects who continued to use other treatment(s) would typically be experiencing an adequate response to the treatment for them to continue it.” Ex. 2001 ¶ 94. This testimony has some appeal, but is at odds with Dr. Evers testimony that “a POSA would have understood that [subjects continuing therapy with other preventative drugs] included patients having an ‘inadequate response’ to medications whose effect did not rise to a ‘clinically meaningful’ level.” Ex. 1109 ¶ 143. The testimony of both experts has some appeal. On the one hand, allowing patients to remain on an existing therapy would seem to suggest that the existing therapy has some benefit. On the other hand, if the existing therapy were fully successful, it is not apparent why one would need additional treatments. Resolution of this factual dispute is not necessary to our decision and, in any event, would be better resolved on a more fully developed record.

With respect to Petitioner’s third argument, Patent Owner argues that “[t]he fact that a claimed species is encompassed by a prior art genus is not sufficient by itself to establish a *prima facie* case of obviousness.” Prelim.

Resp. 57. Patent Owner then asserts that “Petitioner does not—and cannot—point to any disclosure in the Teva Press Release identifying the inadequate response subjects of the claimed method for treatment.” Prelim.

Resp. 57. On the current record, we do not find this argument persuasive because Petitioner does not rely on the genus defined by the eligibility criteria in the Teva Press Release studies to create a *prima facie* case that it would have been obvious to treat a species of patients falling within that criteria. Rather, Petitioner uses the fact that the eligibility criteria encompass the claimed patients as one of several reasons why a POSA would have been motivated to treat such patients. *See e.g.*, Ex. 1109 ¶ 141 (“The motivation to treat both patients within the ’434 Patent’s population of ‘select[ed]’ ‘inadequate response’ patients was reinforced by the eligibility criteria of the studies described by *Teva Press Release*.”). On the current record, the fact that patients with “inadequate response” were not excluded from the studies described in the Teva Press Release lends some modest support to the motivation to treat such patients.

b) Motivation to substitute fremanezumab for erenumab in the method disclosed in Sun

Petitioner contends that the POSA would have been motivated to substitute fremanezumab for erenumab in the methods disclosed in Sun. Pet. 31–34. **First**, Petitioner asserts that “*Sun* expressly motivated using fremanezumab in its methods, disclosing combination treatment with ‘an anti-CGRP antibody... in *WO 2007/054809*’ (EX1006, [250]), which disclosed fremanezumab as SEQ ID Nos. 1 and 2.” *Id.* at 31. **Second**, according to Petitioner, the Teva Press Release described studies in which the eligibility criteria defined patients that “overlap with those disclosed by *Sun*.” *Id.* Petitioner argues “the efficacy of both drugs in these studies with

this common eligibility criteria would have motivated the substitution of fremanezumab – one of only four clinically proven anti-CGRP antibodies . . . – for *Sun*’s erenumab in *Sun*’s specifically-disclosed subjects.” *Id.* at 32.

Third, Petitioner contends that a POSA would have understood the Teva Press Release to teach that “fremanezumab 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.* According to Petitioner, this “motivation to substitute [fremanezumab 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 (fremanezumab)—would be similarly effective.” *Id.*

Petitioner’s assertions that a POSA would have had reason to use fremanezumab 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 fremanezumab in place of erenumab, 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 fremanezumab. *See generally*, Prelim. Resp. 49–63. On this preliminary record, Petitioner has articulated sufficient reasoning with rational underpinning to support that a POSA would have had reason to use fremanezumab to treat the claimed patient population.

4. Has Petitioner sufficiently supported that a POSA would have had a reasonable expectation of success in using fremanezumab to treat “inadequate response” patients?

Petitioner contends that a POSA would have had a reasonable expectation of success in using fremanezumab to treat “inadequate response” patients. Before turning to Petitioner’s contentions as to why the POSA would have expected success, we briefly consider what is meant by “success” in context of the ’434 patent. The ’434 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. 1045, 19:60–20:4 (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 their response to migraine treatment.

We now consider the multiple reasons why, according to Petitioner, the POSA would have expected success in treating the claimed “inadequate response” patients. **First**, Petitioner argues that the Teva Press Release “demonstrated fremanezumab was effective in migraineurs with a history of treatment failure, noting ‘the impressive decrease in migraine days, ***amongst such highly refractory patients.***’” Pet. 35 (citing Ex. 1041, 1). **Second**, Petitioner contends that the success of other anti-CGRP antibodies – like

erenumab and galcanezumab – support an expectation that fremanezumab, which similarly affects the CGRP pathway, would be similarly efficacious. *Id.* at 36–38. **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 fremanezumab to “treat migraineurs independent of whether they used or failed conventional treatments that targeted non-CGRP pathways.” *Id.* at 39. **Fourth**, Petitioner argues that plans for “numerous clinical trials that allowed for inclusion of patients that failed two preventives for numerous anti-CGRP mAbs further reinforced the reasonable expectation of success in treating the ‘select[ed]’ ‘inadequate response’ patients with fremanezumab.” *Id.* at 40. We discuss each of these four positions, and Patent Owner’s arguments in response thereto, in turn.¹⁵

a) *Teachings in the Teva Press Release regarding the effectiveness of fremanezumab*

The Teva Press Release reports the results of two clinical trials of fremanezumab, stating that fremanezumab is “the first investigational treatment to meet all efficacy endpoints in trials of both chronic and episodic migraine across multiple doses.” Ex. 1041, 1. After discussing the two clinical trials further, the Teva Press Release states that “[t]he collective data generated from these studies herald promise for millions of people who suffer from episodic and chronic migraines, a disease with substantial implications and unmet needs,” and that “[t]he very fast onset of preventive

¹⁵ 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 evidence as a whole.

response, seen after a single dose of therapy, along with the impressive decrease in migraine days, amongst such highly refractory patients, may bring us a step closer to provide widespread relief to people who suffer from chronic and episodic migraine.” *Id.* at 2.

Petitioner argues, based on these teachings, that there is “no need to speculate on an *expectation* of success” because the “*Teva Press Release* had already demonstrated fremanezumab was effective in migraineurs with a history of treatment failure.” Pet. 35. Further, according to Petitioner, in one of the studies described in the *Teva Press Release*, “more than a quarter of patients had ‘[d]iscontinued past preventive drug use owing to absence of efficacy.’” *Id.* at 35–36 (citing Ex. 1039, 5). Petitioner asserts that a “POSA would have thus reasonably expected at least the same efficacy using fremanezumab in the claimed patients with prior treatment failures.” *Id.* at 36 (citing Ex. 1109, ¶¶163–164). Finally, Petitioner points to the teaching in the *Teva Press Release* that its “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.” *Id.* (citing Ex. 1041, 2). According to Petitioner, this provides evidence that “fremanezumab provided an additional benefit beyond then-available medications.” *Id.* (citing Ex. 1009 ¶¶ 165–167; Ex. 1038, 5–7).

Patent Owner argues that “[a] POSA would not have understood the *Teva Press Release*’s mere disclosure of a chronic or episodic migraine patient with migraine that is difficult to treat to mean, or even include, the inadequate response subject of the claimed method.” Prelim. Resp. 60. We do not find these arguments persuasive for the reasons discussed *supra* § III.F.2. We find that, the preliminary record tends to support an expectation that 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 differences between the patients described in the Teva Press Release and the claimed “inadequate response” patients materially effects the expectation of success in treating those patients. On this preliminary record, the expectation of success fostered by the Teva Press Release, and the fremanezumab studies described therein, 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.” Ex. 1006 ¶¶ 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 preventative 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 fremanezumab targets the CGRP ligand while erenumab targets the receptor, Petitioner argues that the POSA would expect the

success of erenumab to extend to fremanezumab because the prior art teaches that targeting both the ligand and the receptor would be effective. *Id.* at 37 (citing Ex. 1034, 2, 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.”). Petitioner also cites the testimony of Dr. Evers that “a POSA would have expected that blocking the CGRP pathway with erenumab (targeting the CGRP receptor) or fremanezumab (targeting the CGRP ligand) would provide similar efficacy in like populations. Ex. 1109 ¶ 171 (cited at Pet. 37); *see also, id.* ¶ 170 (quoting the Teva Press Release as acknowledging that “CGRP signaling may be disrupted by *targeting the ligand itself or its receptor.*”).

Relatedly, Petitioner cites an abstract from Headache, The Journal of Head and Face Pain, that teaches that galcanezumab was effective in patients with a “history of failure to preventative treatments.” Ex. 1072, 74 (“the Headache Abstract”). According to Petitioner, the Headache Abstract “demonstrated a ‘statistically significantly greater treatment effect’ (Ex. 1072, 74) in patients that had failed prior treatments, further suggesting that fremanezumab . . . would at least ‘treat’ such patients.” Pet. 37–38.

Petitioner argues that “the clinical success of erenumab and galcanezumab in patients with a history of treatment failure further provided a reasonable expectation that clinically successful fremanezumab—which operated by the same overall anti-CGRP mechanism—would likewise be effective within the claimed method.” Pet. 36 (citing Ex. 1109 ¶ 168).

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 “inadequate response” subjects. Prelim.

Resp. 60–61. 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. 60. 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 fremanezumab and erenumab to have similar efficacy. Ex. 1034, 887; Ex. 1053, 647; Ex. 1109 ¶ 168–173.

With respect to galcanezumab, Patent Owner argues that the Headache Abstract “changes nothing because, like the Teva Press Release, [it] fails to disclose treating migraine in inadequate response subjects of the claimed method.” Prelim. Resp. 61. Patent Owner continues “mere disclosure of a patient with ‘a history of treatment failure,’ as purportedly in [the Headache Abstract], would not have conveyed to a POSA the inadequate response subjects of the claimed method.” *Id.*

We recognize that patients identified in the Headache abstract as having a “history of failure to preventative treatments” may not align perfectly with “inadequate response” patients, 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 “inadequate response” patients, such issue is best resolved on a fully developed record. On this preliminary record, the expectation of success fostered by the success of erenumab and galcanezumab, when considered with the additional evidence discussed herein (§§ 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 ‘selecting’ limitation.” Pet. 39. Because they have a different mechanism of action, according to Petitioner, “a POSA would have expected that fremanezumab 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.* (citing Ex. 1109 ¶¶ 177–178).

Patent Owner argues that “no evidence” supports the expectation that fremanezumab would be successful in treating the claimed patient population because anti-CGRP antibodies have a distinct mechanism of action. Prelim. Resp. 62. Instead, according to Patent Owner, “[t]he outlook for these subjects was poor because multiple previous treatments were unsuccessful.” *Id.* More specifically, Patent Owner argues that for “inadequate response” patients, “trying a new drug with a potentially different mechanism of action would not have created an expectation of

success.” *Id.* (citing Ex. 2001 ¶¶ 148–149). 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. 38–39 (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 “inadequate response” patients.

Petitioner also cites the “clinically effective small-molecule CGRP antagonist telcagepant.” Pet. 39. For example, one reference cited by Petitioner studied “whether migraine patients who cannot be adequately helped with triptans might benefit from treatment with telcagepant,¹⁶ as might be predicted given that triptans and CGRP receptor antagonists have different mechanisms of action.” Ex. 1060, 65. Based on that study, the reference concluded that “patients who respond poorly to/did not take

¹⁶ According to the reference, “[t]elcagepant is a novel, orally available CGRP receptor antagonist.” Ex. 1060, 70.

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 fremanezumab’s distinct mechanism of action, when considered with the additional evidence discussed herein §§ III.3.a-b and d, is sufficient to support institution.

d) Clinical trials that did not exclude “inadequate response” patients

Petitioner argues that plans for “numerous clinical trials that allowed for inclusion of patients that failed two preventives for numerous anti-CGRP mAbs further reinforced the reasonable expectation of success in treating the ‘select[ed]’ ‘inadequate response’ patients with fremanezumab.” Pet. at 40. As support Petitioner references the “eligibility criteria for completed fremanezumab, erenumab, and galcanezumab trials.” *Id.* at 40–41. Petitioner also cites 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. 1109 ¶ 183.

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

Resp. 63. Patent Owner presents the testimony of Dr. Blake, who notes that “none of Sun (EX1006), EX1037, EX1038, and EX1039 teaches or suggests treating in an effort to relieve signs or symptoms of migraine in the inadequate response subjects of the claimed method.” Ex. 2001 ¶ 151.

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.

5. 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 and the Teva Press Release. Pet. 19–27. For the reasons discussed *supra* § III.F.1–2, we are not persuaded by Patent Owner’s argument that Sun and the Teva Press Release do not disclose or suggest treating the claimed patient population. Prelim. Resp. 50–58. 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 fremanezumab. Pet. 27–34. Patent Owner does not challenge certain of the reasons why Petitioner contends a POSA would have been so motivated and, on the present record, we find Petitioner’s reasoning persuasive. *See supra* § III.F.3.b. As to the motivations Patent Owner does challenge, we are not persuaded for the reasons discussed *supra* § III.F.3. Prelim. Resp. 55–58. Finally, Petitioner provides reasons why the POSA would reasonably have expected treating the claimed “inadequate response” migraine patients to be successful. Pet. 34–41. For the reasons discuss *supra* § III.F.4, we are not persuaded by Patent Owner’s argument that the POSA would not reasonably have expected success. Prelim. Resp. 59–63. 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 and the Teva Press Release.

Petitioner contends that the limitations added in dependent claims 2–13 are taught or suggested in the prior art, and that these claims would have been obvious over the combination of Sun and the Teva Press Release. Pet. 45–51. Petitioner’s contentions with respect to these dependent claims are, at this stage, uncontested by Patent Owner. *See generally*, Prelim. Resp. We have considered Petitioner’s showing with respect to dependent claims 2–13 and find that it is backed by documentary and testimonial support sufficient to support institution.

G. Ground 1, as relates to contraindicated patients

Petitioner argues that claims 1–13 would have been obvious over the combination of Sun and the Teva Press Release because it would have been obvious to use fremanezumab to treat patients who were contraindicated for other migraine treatments. Pet. 42–44.¹⁷

Petitioner contends that “[t]he challenged claims extend beyond subjects that *failed* treatment to include subjects merely ‘contraindicated’ from at least two conventional medication classes.” Pet. 42. According to Petitioner, these patients are common and include, for example, patients with hypotension and obesity. *Id.* Such patients “need not have failed (or even taken) prior preventatives” and “would not have been considered ‘refractory’ migraineurs.” *Id.*

¹⁷ As discussed *supra* § III.C.2, we construed the phrase “a subject who has an inadequate response” in claim 1 to include patients for whom the drug is “contraindicated or not suitable for the patient.”

Sun discloses treating patients who have an “inability to tolerate the migraine prophylactic agent.” Ex. 1006 ¶ 66. As an example, Sun explains that “migraine prophylactic agents having a side effect of teratogenicity would be contraindicated in a pregnant patient.” *Id.* Petitioner thus argues that Sun’s intended patients include those “contraindicated from multiple treatments, such as anticonvulsants, betablockers, tricyclics.” Pet. 42–43. Petitioner contends that a POSA would have been motivated to treat such patients with fremanezumab for the reasons discussed *supra* § III.F.1.3, and would reasonably have expected success for the reasons discussed *supra* § III.F.4.

Petitioner then argues that “the expectation of success for using fremanezumab would have been even higher for these ‘contraindicated’ patients than other ‘inadequate response’ subjects because, in terms of migraine treatment, they were physiologically indistinguishable from the broader migraine population successfully treated in the *Sun* and *Teva Press Release* clinical trials.” *Id.* at 43–44 (citing Ex. 1109 ¶ 194). According to Petitioner, when evaluating non-contraindicated drugs for patients contraindicated for certain medications, POSAs “typically relied upon efficacy as evaluated in the general migraine population as opposed to the specific comorbid subpopulation.” *Id.* at 44 (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 fremanezumab as patients unaffected by hypotension, and 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. at 44 (citing Ex. 1109 ¶¶ 194–196).

Patent Owner argues that Sun uses the word “contraindicated” only once and, “even then[,] Sun uses ‘contraindicated’ in the context of discussing *side effects*.” Prelim Resp. 54. Patent Owner further argues that the condition Sun identifies as contraindicated – i.e., teratogenicity – is disclosed in Sun to be a side effect. *Id.* at 55. According to Patent Owner, this distinguishes treatment of migraine patients with teratogenicity from treatment of the claimed “inadequate response” patients. *Id.* In addition, Patent Owner argues that Sun’s contraindicated patients are “contraindicated only for ‘at least one’ ‘migraine prophylactic agent’ – not ‘two or more different classes of preventative migraine treatment selected from the group consisting of beta-blockers, anticonvulsants, tricyclics, calcium channel blockers, angiotensin II receptor antagonists, onabotulinumtoxinA, and valproates,’ as claimed.” *Id.* On this preliminary record, we do not find Patent Owner’s arguments persuasive.

Sun discloses treating patients who failed to respond to prior therapy. The parties dispute whether Sun’s disclosure of what it meant by “failure to respond” teaches or suggests treating contraindicated patients. The disclosure at issue reads as follows:

Failure to respond to prior treatment with a migraine prophylactic agent can also include inability to tolerate the migraine prophylactic agent. 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. In such embodiments, the side effects associated with the agent may exacerbate or may be incompatible with another medical condition which the patient has. ***By way of illustration, migraine prophylactic agents***

having a side effect of teratogenicity would be contraindicated in a pregnant patient.

Ex. 1006 ¶ 66 (emphasis added).

We agree with Patent Owner that the discussion of contraindicated patients in Sun occurs in the context of discussing side effects. However, on the current record, we are not persuaded by Patent Owner's argument that the identification of teratogenicity as a "side effect" distinguishes Sun's exemplary pregnant patients from the claimed contraindicated patients.

Simply put, it does not matter how one categorizes the property of teratogenicity so long as that property causes a drug to be contraindicated for a particular patient. In the example Sun provides, teratogenic migraine prophylactic drugs are contraindicated for pregnant patients regardless of the fact that Sun describes teratogenicity as a "side effect." Sun's pregnant patients are thus patients for whom migraine prophylactics are "contraindicated or not suitable for the patient," as recited in our construction of "inadequate response."

Similarly, we are not persuaded by Patent Owner's argument that Sun's contraindicated patients would be "contraindicated only for 'at least one' 'migraine prophylactic agent.'" Prelim. Resp. 55. Sun's pregnant patients are taught to be contraindicated for "migraine prophylactic agents having a side effect of teratogenicity." Ex. 1006 ¶ 66. Importantly, the word "agents" is plural, which is consistent with the expectation that a pregnant patient would be contraindicated for any teratogenic drug. Moreover, Sun's disclosure of contraindicated pregnant patients occurred in the context of a definition. Specifically, Sun defined patients who have

“failed prior treatment with a migraine prophylactic agent” to include, for example, contraindicated pregnant patients. *Id.* After defining “failed prior treatment” to include, for example, contraindicated pregnant patients, Sun discloses that “[i]n some embodiments, the patient has failed or is intolerant to treatment with two different classes of migraine prophylactic agents.” *Id.* ¶ 68. On the current record, this supports treating patients who are contraindicated for two different classes of migraine prophylactic agents.

Accordingly, the current record tends to support that Sun discloses treating contraindicated patients. As discussed *supra* § III.F.1.3 the current record also tends to support that a POSA would have been motivated to treat Sun’s patients with fremanezumab, and, as discussed *supra* § III.F.4, the current record supports that a POSA would reasonably have expected success in doing so. 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 and the Teva Press Release.

Petitioner contends that the limitations added in dependent claims 2–13 are taught or suggested in the prior art, and that these claims would have been obvious over the combination of Sun and the Teva Press Release. Pet. 45–51. 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 2–13 and find that it is backed by documentary and testimonial support sufficient to support institution.

H. Ground 2

Petitioner asserts that claims 1–13 would have been obvious over Bigal. Pet. 51–65. In brief summary, Petitioner contends that Bigal discloses “a successful clinical study of fremanezumab . . . in [chronic

migraine] patients employing eligibility criteria that included patients that had failed or were still taking two different preventive treatment classes.” Pet. 51. According to Petitioner, “[t]he success of fremanezumab in this ‘intended patient population’ rendered obvious its use in ‘select[ed]’ ‘inadequate response’ patients as recited by claim[] 1.” *Id.* at 51–52. Patent Owner opposes, arguing, principally, that Petitioner’s argument fails as a matter of law because “the fact that a claimed species is encompassed by a prior art genus is not sufficient by itself to establish a *prima facie* case of obviousness.” Prelim. Resp. 63–64.

We begin our analysis by considering whether Petitioner has sufficiently supported that Bigal discloses treating “inadequate response” patients. We next consider whether Petitioner has articulated sufficient rationale to support that a POSA would have had reason to use fremanezumab when treating Bigal’s patients. Finally, we consider whether Petitioner has supported that the POSA would have a reasonable expectation of success in treating Bigal’s patients with fremanezumab.

1. Does Petitioner sufficiently support that Bigal discloses treating subjects who have an “inadequate response” to prior treatment?

As discussed *supra* § III.E.3, Bigal discloses two clinical trials reporting the efficacy of fremanezumab, one focusing on prevention of chronic migraine, the other focusing on prevention of high-frequency episodic migraine. Ex. 1102 ¶¶ 409–422 (Examples 17 and 18). Both studies allowed – but did not require – inclusion of patients that had failed two prior treatments and patients that remained on preventative treatments during the study. *Id.* ¶¶ 409, 410, 419. Petitioner contends that Bigal

teaches or suggests treating “inadequate response” patients in four ways, each of which is summarized below.

First, Petitioner contends that allowing patients who failed two prior treatments “would have directed a POSA to select and treat patients that had ‘*no clinically meaningful improvement*’ per treating physician’s judgment after at least three months of therapy at a stable dose considered appropriate for migraine prevention according to accepted country guidelines,” as recited by the Patent’s ‘inadequate response’ definition.” Pet. 53 (citing Ex. 1109 ¶¶ 253–254). **Second**, Petitioner contends that allowing patients to remain on preventative treatments “suggest[s] treating migraineurs concurrently taking preventives that had a *partial* effect but failed to provide a ‘clinically meaningful’ response.” *Id.* at 54 (citing Ex. 1039, 8; Ex. 1109 ¶¶ 257–259). **Third**, Petitioner argues that Bigal’s recognition that some patients were “relatively resistant” to treatment with topiramate coupled with recognition in the prior art of a need for treatment for “inadequate response” patients would have reinforced the motivation to treat such patients. *Id.* at 56 (citing Ex. 1102 ¶ 9; Ex. 1027, 2; Ex. 1042, 8; Ex. 1109 ¶ 264). **Fourth**, Petitioner asserts that the motivation to treat “inadequate response” patients was “further reinforced by numerous other reports of successful use of anti-CGRP mAbs – including fremanezumab – in treating patients that failed multiple classes of migraine preventatives.” *Id.* (citing Ex. 1009 ¶¶ 266–68; Ex. 1041, 2; Ex. 1006, ¶ 268; Ex. 1072, 74; Ex. 1038, 5; Ex. 1037, 8; Ex. 1040, 15–16).

Patent Owner focuses its argument on the first of Petitioner’s arguments as to why Bigal teaches or suggests treating the claimed “inadequate response” patients. Prelim. Resp. 63–64. Patent Owner begins

by citing case law that disclosure of a genus does not, by itself, render obvious a species within that genus. *Id.* Patent Owner then argues:

Petitioner does not—and cannot—cite any disclosure in Bigal identifying the inadequate response subjects of the claimed method. EX2001, ¶¶153-162. Nor does Petitioner provide any reason for selecting these subjects. And even if the inadequate response subjects of the claimed method were included in Bigal’s study, Bigal does not separately report any results or data for those patients. EX2001, ¶127. A POSA therefore would not have known (a) whether the subjects of the claimed method were even included in the trial at all; and (b) if those specific subjects were responders or non-responders.

Id. at 64. We address each of the four ways that Petitioner contends Bigal discloses “inadequate response” patients in sequence.

With respect to the first way, we tend to agree with Patent Owner that, considered in isolation, the reasoning Petitioner provides for selecting the claimed “inadequate response” patients from within Bigal’s genus of test subjects – i.e., that Bigal allows them to participate – is weak. We further agree with Patent Owner that the absence of results (whether in the form of data or commentary) specific to “inadequate response” patients diminishes the weight of any teaching Bigal provides to treat the claimed “inadequate response” subjects.

With respect to the second way – i.e., that Bigal allowed patients to remain on existing therapies during the study – we addressed a similar argument *supra* § III.F.3.a. There, as here, we noted the seemingly contradictory testimony of Drs. Evers and Blake. *Compare* Ex. 1109 ¶ 259 (“It was often the case, however, that patients would take preventive treatment based on partial efficacy or perceived modest improvements in their migraines or other quality of life improvements that fell short of the IHS definition. In fact, the use of preventive medications even without what

would be considered ‘clinically meaningful improvement’ continues to this day.”), *with* Ex. 2001 ¶ 94 (“[A] POSA would have understood that the subjects who were actively using other migraine preventive therapy were included in the clinical trial and that these subjects who continued to use other treatment(s) would typically be experiencing an adequate response to the treatment for them to continue it.”). There, as here, we determine that this factual dispute better resolved on a more fully developed record.

With respect to the third way – i.e., that Bigal and other cited art taught a need for new treatments of “inadequate response” patients – Petitioner’s cited evidence (Ex. 1102 ¶ 9, Ex. 1027, 2, and Ex. 1042, 8) supports that there was a need for new treatments of “inadequate response” patients. We agree that this may support a motivation to treat such patients. *See, KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 420 (2007) (“Under the correct analysis, any need or problem known in the field of endeavor at the time of the invention and addressed by the patent [or application at issue] can provide a reason for combining the elements in the manner claimed.”). However, all Bigal says in this regard is that some patients respond to topiramate while “others are relatively resistant to its effects.” Ex. 1102 ¶ 9. On the current record, the connection between disclosing that some patients that are “relatively resistant” to the effects of topiramate and treating the claimed “inadequate response” patients seems tenuous. That said, Exhibits 1027 and 1042 provide a comparatively clearer connection between their disclosures and a need to treat the claimed “inadequate response” patients. Ex. 1027, 444 (“patients who are refractory to conventional treatment . . . are not rare and represent a wake up call for the development of new compounds in migraine therapy”); 1042, 27 (“partially refractory [patients], having

failed a number of preventives . . . stand[] to benefit the most from a novel, migraine-specific mechanism”).

With respect to the fourth way – i.e., the success of anti-CGRP mAbs in treating patients that failed multiple classes of migraine preventatives – Petitioner relies entirely on references other than Bigal. Pet. 56–57. We have already discussed each of the references that Petitioner relies upon – including, for example, Sun (Ex. 1006), the results of the clinical studies proposed in Sun (Exs. 1037 and 1040), the Teva Press Release (Ex. 1041), and the Headache Abstract (Ex. 1072) – in connection with Ground 1. We incorporate our prior discussion of these references here. To summarize, each of these references supports using an anti-CGRP antibody – erenumab for Sun, galcanezumab for the Headache Abstract, and fremanezumab for the Teva Press Release – in patient populations that are the same as, or very similar to, the claimed “inadequate response” patients. Collectively, these references provide some support for a general motivation to treat “inadequate response” patients with an anti-CGRP antibody.

On the current record, we find the success of anti-CGRP mAbs in treating patients that failed multiple classes of migraine preventatives to be Petitioner’s most persuasive argument. Indeed, Petitioner’s strongest evidence would appear to be found in its secondary references rather than in Bigal. Patent Owner’s opposition focuses its argument on Petitioner’s primary reference, Bigal. We find that we would benefit from a more fully developed record in resolving the question of whether Bigal, when considered with Petitioner’s additional cited evidence, supports treating the claimed inadequate response patients. In this regard, we note that for the reasons discussed *supra* § III.F and G, 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.”); *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”).

2. Has Petitioner articulated sufficient rationale to support that a POSA would have had reason to use fremanezumab to treat patients who had an “inadequate response” to prior treatment?

Bigal discloses a method of treating headache by administering “a therapeutically effective amount of an anti-CGRP antagonist antibody.” Ex. 1102 ¶ 90. More specifically, Bigal discloses a clinical study on the prevention of chronic migraine comparing two different doses of anti-CGRP antagonist antibody G1 (fremanezumab) to placebo. Ex. 1102 ¶¶ 409–418 (Example 17). The results of the trial showed that the two doses tested both showed a “significant decrease” in the number of headache hours, as well as a “statistically significant decrease” in number of headache days. *Id.* ¶¶ 112, 115. In addition, a “significant decrease in number of headache hours was . . . observed in subjects using prevention medications (e.g., topiramate and amitriptyline or propranolol) relative to a placebo group.” *Id.* ¶ 417.

Petitioner contends that these disclosures support a motivation to treat the claimed “inadequate response” patients with a therapeutically effective amount of fremanezumab. Pet. 57–59. Although Patent Owner disputes that Bigal teaches or suggests treating “inadequate response” patients, it does not otherwise contest that Bigal supports treating patients with fremanezumab. *See generally*, Prelim. Resp.

The preliminary record tends to support Petitioner's position that Bigal discloses treating patients with fremanezumab. As to whether those patients are "inadequate response" patients, we refer back to our prior discussion. *See supra* § III.H.1.

3. Has Petitioner sufficiently supported that a POSA would have had a reasonable expectation of success in using fremanezumab to treat "inadequate response" patients?

Petitioner contends that the POSA would reasonably have expected that fremanezumab would treat the claimed "inadequate response" patients for "at least the same reasons discussed above for Ground 1." Pet. 59. We incorporate here our discussion of reasonable expectation of success for Ground 1. *See supra* § III.F.4. Petitioner also contends that "the planning and successful results of *Bigal*'s [chronic migraine] study, which allowed for patients that had an 'inadequate response' to two classes of preventatives, alone provided a reasonable expectation of success." Pet. 60. The strength of this argument appears to rest on whether Bigal suggests treating the claimed "inadequate response" patients, as to which, we refer back to our discussion *supra* § III.H.1.

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 1–13 based on the grounds asserted in this Petition; and

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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