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Paper 45
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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 No. 10,392,434 B2

Before TIMOTHY G. MAJORS, DAVID COTTA, and JAMIE T. WISZ, *Administrative Patent Judges*.

COTTA, *Administrative Patent Judge*.

DECISION
Final Written Decision
Determining All Challenged Claims Unpatentable
Denying-in-Part and Dismissing-in-Part Patent Owner's Motion to Exclude
35 U.S.C. § 318; 37 C.F.R. § 42.64

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"). We instituted trial on October 14, 2022. Paper 9 ("Institution Decision" or "DI"). During trial, Teva Pharmaceuticals International GmbH ("Patent Owner")[2] filed a Patent Owner Response. Paper 21 ("PO Resp."). Later filings include Petitioner's Reply (Paper 26 ("Pet. Reply") and Patent Owner's Sur-reply (Paper 34 ("Sur-reply")). An oral hearing was held on July 19, 2023, and a transcript is entered in the record. Paper 44 ("Tr.").

We have jurisdiction under 35 U.S.C. § 6(b). After considering the parties' arguments and evidence, we determine that Petitioner has proved by a preponderance of the evidence that the challenged claims are unpatentable. *See* 35 U.S.C. § 316(e). Our reasoning is explained below, and we issue this Final Written Decision under 35 U.S.C. § 318(a)

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 No. 15/712,444 ("the '444 application"), which claims priority to U.S. Provisional Patent Application Nos. 62/399,180 ("the '180 provisional") and

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

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.[3]

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:

Claims Challenged	35 U.S.C. §	Reference(s)/Basis
1–13	103	Sun,[4] Teva Press Release[5]
1–13	103	Bigal[6]

[3] 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. PO Resp. 9 ("The method [of claim 1] further comprises administering to the subject a therapeutically effective amount of a humanized monoclonal anti-CGRP antagonist antibody (fremanezumab)."); Pet. 1 ("The [claimed] method comprises two steps. . . . The second [step] involves administering fremanezumab.").

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

[5] 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").

[6] Bigal et al., US Patent Publication No. 2015/0266948 A1, published Sept. 24, 2015 (Ex. 1102, "Bigal").

Petitioner relies on the declaration of Dr. Stefan Evers (Ex. 1109) and the declaration of Dr. Deborah Hay (Ex. 1239),[7] among other evidence. Patent Owner responds with a declaration from Dr. Brian M. Grosberg, along with other evidence. Ex. 2037.

II. 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, Inc. v. Acid Tech., Inc.*, 815 F.3d 1356, 1363 (Fed. Cir. 2016) (citing 35 U.S.C. § 312(a)(3) (requiring *inter partes* review petitions to identify "with particularity . . . the evidence that supports the grounds for the challenge to each claim")).

To show obviousness under 35 U.S.C. § 103 the differences between the subject matter sought to be patented and the prior art must be such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which that subject matter pertains. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying factual determinations including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of ordinary skill in the art; and (4) secondary considerations of

[7] The original version (Ex. 1233) of Dr. Hay's declaration was filed without an attestation under 18 U.S.C. § 1001. With our permission (Paper 2093, 22:12–23:8), Petitioner filed a corrected version (Ex. 1239) of Dr. Hay's declaration addressing this omission. We understand all citations to Ex. 1233 in the parties' pleadings to refer to Ex. 1239. Herein we refer to Ex. 1239 rather than Ex. 1233.

nonobviousness when presented.[8] *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. EX2037, ¶¶21-23. 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.

PO Resp. 7. Petitioner offers a similar definition of the POSA, with the principal differences being that: 1) Petitioner does not identify neurobiology and pharmacology as relevant fields for a POSA having an M.D., 2) Petitioner specifies that the POSA's experience also includes studying the

[8] Patent Owner does not direct us to objective indicia of nonobviousness in this case.

role of CGRP in migraine, and 3) 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. We do not see a need to specify that the POSA would have experience studying the role of CGRP in migraine. 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)). The differences between Petitioner's and Patent Owner's identification of the POSA do not materially affect our decision. 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; PO Resp. 7–15.

The parties agree that the '434 patent expressly defines the phrase "inadequate response." Pet. 13; PO Resp. 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, or **[2]** when 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. 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, 6:45–63 (bracketed numbers added for reference). Accordingly, the phrase "inadequate response" 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 ("Group I patients"), 2) treatment has to be interrupted because of adverse events that made it intolerable by the patient ("Group II patients"), or 3) the drug is contraindicated or not suitable for the patient ("Group III patients").

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."

PO Resp. 13–15 (citing Exs. 2003, 2004, 2005, and 2037). 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'").[9] Although we do not find it necessary to construe the term "adverse event," Patent Owner's arguments with respect to this term merit further discussion.

Patent Owner argues that we should also construe the term "adverse event," as that term is used in the Specification's definition of "inadequate response," proposing that we define it to mean: "a serious undesirable experience associated with the use of a treatment." PO Resp. 13.

Petitioner disagrees, asserting that Patent Owner's position that "the plain and ordinary meaning of 'adverse event' is a "***serious*** adverse event," and thus different from *Sun's* 'side effects' is facially implausible." Pet. Reply. 22. Petitioner asserts that "[t]he Patent only requires interruption due to 'adverse events that ***made it intolerable***,' not life threating." *Id.* at 23.

[9] In its briefing on claim construction, Patent Owner addresses whether three months of therapy is a standard in the art. PO Resp. 11. Similarly, Patent Owner addresses how the POSA would have understood the term "refractory migraine" *as used in the prior art. Id.* at 11–13. These arguments are directed not to what the claim terms mean, but whether they extend to obvious subject matter. Accordingly, we do not consider these arguments as part of our claim construction analysis. Instead, we consider these arguments in connection with applying the language of the claims to the cited art.

Thus, according to Petitioner, the plain and ordinary meaning of "adverse events" is "***any*** untoward medical occurrence associated with the use of a drug in humans." *Id.* at 23.

Neither party cites intrinsic evidence bearing on the construction of "adverse event" beyond the portion of the Specification defining "inadequate response" to include when "treatment has to be interrupted because of adverse events that made it intolerable." Ex. 1045, 6:45–52; PO Resp. 13–14 (acknowledging that "[t]he '434 patent does not provide an express definition of an 'adverse event'" and citing only extrinsic evidence); Pet. Reply 22–25 (citing only extrinsic evidence); PO Sur-Reply 18–19 (citing only extrinsic evidence). Like the parties, we do not find any other intrinsic evidence bearing on the construction of "adverse event." Accordingly, we turn to the extrinsic evidence provided by the parties.

Patent Owner provides the testimony of Dr. Grosberg, who testifies that "a POSA would have accorded the term its ordinary and customary meaning in the prior art: ***a serious undesirable experience*** associated with the use of a treatment." Ex. 2037 ¶ 42 (emphasis added). As support, Dr. Grosberg cites an FDA publication entitled "What is a Serious Adverse Event?" *Id.* The publication Dr. Grosberg cites plainly states that an adverse event is "***any undesirable experience*** associated with the use of a medical product in a patient." Ex. 2004, 1 (emphasis added).[10] It then specifies that "[t]he event is serious and should be reported to the FDA when the patient outcome is: [one of eight categories of outcomes, including, for example, death, life threatening conditions, and hospitalization]." *Id.* By

[10] All citations to exhibits in this opinion, other than those to patents and declarations, are to the page number added by the parties.

indicating that an "adverse event" is "any undesirable experience," and then specifying the conditions under which an adverse event is deemed "serious," the publication Dr. Grosberg cites makes clear that – contrary to Dr. Grosberg's and Patent Owner's proposed definition – not every adverse event is "serious."

The extrinsic evidence cited by Petitioner is consistent with the evidence cited by Dr. Grosberg that not every adverse event is a serious adverse event. For example, Petitioner cites a Guideline from the International Council for Harmonisation ("ICH") of Technical Requirements for Pharmaceuticals for Human Use. Pet. Reply 22 (citing Ex. 1210). Consistent with the evidence cited by Dr. Grosberg, it defines "adverse event" as: "[a]ny untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment." Ex. 2010, 8 (further explaining that an adverse event "can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product"). Similarly, an FDA document titled "Guidance for Industry and Investigators" states: "Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related." Ex. 1209, 6; *see also* Ex. 1208, 1 (FDA document entitled "IND Application Reporting: Safety Reports," using identical language to define "adverse event").

The preponderance of the evidence supports that the POSA would not understand the term "adverse event" to be limited to "serious" events. Ex. 2004, 1; Ex. 1208, 1; Ex. 1209, 6; Ex. 1210, 8. The only evidence to the contrary is the testimony of Dr. Grosberg. Ex. 2037 ¶ 42. Because

Dr. Grosberg's testimony is inconsistent with the evidence he relies upon, we decline to give it substantial weight. We recognize that the Specification of the '434 patent includes language imposing some degree of severity on the "adverse event." Specifically, the adverse event must be significant enough to cause treatment to be "interrupted" because the event made the treatment "intolerable by the patient." But, we find no support in the record for imposing an additional severity requirement by effectively limiting the term "adverse event" to "serious adverse events." Accordingly, we decline to construe the term "adverse event" to mean "a serious undesirable experience associated with the use of a treatment" as proposed by Patent Owner. PO Resp. 13. We do not find it necessary to further construe the term "adverse event" to resolve this dispute.

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. 16.

In its Preliminary Response, Patent Owner argued that "[t]here is no 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. 14–15.

In the Institution Decision, we accepted Patent Owner's assertion that it was not necessary for us to decide the priority date to which the claims are entitled. In doing so, we noted 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'" and explained that for purposes of the Institution Decision, we would "assume that Petitioner's characterization of these references as 'prior art' is correct." *See, e.g.,* DI 19 (citing, e.g., Exs. 1037–1040, 1057, and 1058).

Patent Owner's Response asserts that the Institution Decision correctly decided that it was not necessary to resolve Petitioner's priority challenge and that "[n]othing about the post-institution posture of this proceeding changes that assessment." PO Resp. 60–61 ("The Board correctly found that 'in the absence of a challenge to the prior art status of any of the prior art relied upon by Petitioner, . . . it is not necessary for us to decide the priority date to which the claims are entitled.'").

Given that Patent Owner continues not to challenge the prior art status of any prior art relied upon by Petitioner, we accept Patent Owner's assertion that it is not necessary for us to decide the priority date to which the challenged claims are entitled. For purposes of this decision, we assume that the references Petitioner characterizes as "prior art" are, indeed, prior art.

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; PO Resp. 5.

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.[11]

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 . . . 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

[11] 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.

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.

1. 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.

2. 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, Claim 1

Petitioner asserts that claims 1–13 would have been obvious over the combination of Sun and the Teva Press Release. Pet. 17–51. We focus first on Petitioner's arguments with respect to claim 1. In brief summary, Petitioner contends that Sun "teaches selecting and treating 'inadequate response' patients with anti-CGRP mAbs [monoclonal antibodies] and demonstrated erenumab's success in patients with a history of treatment failures." Pet. 18. To address the requirement of the challenged claims to treat "inadequate response" patients with the anti-CGRP mAb, fremanezumab, Petitioner argues that it would have been obvious to treat patients with fremanezumab, including in the method disclosed in Sun, in view of the Teva Press Release's disclosure that fremanezumab was effective for treating migraine among "highly refractory patients." Pet. 27–34. Patent Owner opposes, arguing that neither Sun nor the Teva Press Release discloses treating inadequate response patients, as that term is defined in the '434 patent, that a POSA would not have had reason to

modify Sun, and that the cited art does not provide a reasonable expectation of success. *See generally* PO Resp.

We begin our analysis by considering whether Petitioner has established that Sun discloses treating inadequate response patients.[12] We next consider whether Petitioner has articulated persuasive rationale to support that a POSA would have been motivated to use fremanezumab when treating "inadequate response" patients. We then consider whether Petitioner established, by a preponderance of the evidence, that the POSA would have a reasonable expectation of success in treating refractory migraine patients with fremanezumab. Finally, we consider whether using fremanezumab in Sun's methods meets the limitations of claim 1 for all three patient groups identified in our claim construction.[13] We conclude that Petitioner has demonstrated by a preponderance of the evidence that claims 1–13 would have been obvious over the cited art.

[12] Petitioner also contends that the Teva Press Release discloses treating inadequate response patients. Pet. 26–27. Because we find that Sun discloses the claimed patients, we need not separately address the disclosure of the Teva Press Release here. However, we do address whether the POSA would have understood the Teva Press Release to disclose treating the same patient population as disclosed in Sun in connection with our discussion of whether the POSA would have expected erenumab and fremanezumab to have similar efficacy. *See supra* § II.F.2.c.ii.

[13] Although Petitioner need only establish that it would have been obvious to treat one patient group, for completeness, this opinion addresses all three. *See* Tr. 7–8 (counsel for Petitioner agreeing that it is only necessary to show obviousness for one patient group), 43 (counsel for Patent Owner agreeing that it is necessary to show that each patient group would have been obvious, but arguing that Group III patients are excluded from the scope of claim 1).

1. Does Sun disclose or suggest treating the claimed patient population?

As discussed in connection with claim construction, the '434 patent defines three categories of refractory patients: 1) patients who experience 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 ("Group I patients"), 2) patients for whom treatment had to be interrupted because of adverse events that made it intolerable by the patient ("Group II patients"), and 3) patients from whom a treatment is contraindicated or not suitable ("Group III patients"). Petitioner contends that Sun discloses treating each of these three categories of patients. Patent Owner contends that Sun does not disclose Group I, Group II, or Group III patients. We discuss whether Sun discloses each of these three categories of patients in turn. For the reasons discussed below, we find that Sun discloses all three categories of refractory migraine patient.

a) Group I patients (no clinically meaningful improvement)

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

Petitioner contends that treating patients that have shown a "lack of efficacy" when administered prior therapies meets the definition of "no clinically meaningful improvement" that was recited in the Specification of the '434 patent (and adopted in our claim construction). Pet. 20–21; Pet. Reply, 9–12. Petitioner addresses the requirement of our claim 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 are "among common criteria for evaluating migraine prophylactics." Pet. 22 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 the cited art does not disclose treating Group I patients because "Sun does not specify the duration or dose at which the preventative medication is administered before the medication was deemed a failure." PO Resp. 22. Patent Owner contends that "the art taught a wide variety of different durations" for assessing efficacy, and thus three months of therapy is "not a defined standard in the art." PO Resp. 11 (citing prior art reflecting different treatment lengths as well as Dr. Grosberg's testimony that three months is not a defined standard). Petitioner also argues that "Sun does not specify any level of reduction in the frequency, duration, and/or severity of migraine headache below which the preventive medication is considered a failure." PO Resp. 22.

(i) The POSA's understanding of Sun's "standard therapeutic regimen"

We begin our analysis of whether Sun discloses treating Group I patients by considering how the POSA would have understood the phrase

"standard therapeutic regimen" in Sun's definition of the terms "failure to respond" and "treatment failure" as it relates to duration of treatment. We find that the POSA would have understood the phrase "standard therapeutic regimen" to refer to a treatment regimen of as few as six weeks (i.e., 1.5 months).

The evidence supports Petitioner's and Dr. Evers's position that three months was a common minimum treatment length for assessing efficacy of a prophylactic migraine treatment.[14] Ex. 1109 ¶¶ 24–25 (Dr. Evers's testimony that three months was a "commonly recommended minimum duration" for evaluating efficacy); Ex. 1011, table 1 (table including three definitions of "refractory," one which states that "[a] ***3-month treatment period is required*** to assess efficacy but it may be useful to continue for a further 3–6 months if there was some improvement during the first 3 months,"); Ex. 1019, 2 (explaining that when beta blockers are administered for migraine prevention, "[a]n ***adequate trial of 3 to 12 months*** with continued assessment of efficacy and tolerability is recommended"); Ex. 1020, 4-5 ("A migraine prophylaxis is regarded as successful if the frequency of migraine attacks per month is decreased by at least 50% ***within 3 months***."); Ex. 1228, 15 (guidelines for clinical trials of migraine

[14] Patent Owner argues that three months of therapy "is not a defined standard in the art." PO Resp. 11. However, we do not understand Petitioner to contend that three months is a "defined standard." Pet. 21 n.8 (asserting that three-month evaluation period was "among common criteria for evaluating migraine prophylactics"); Ex. 1109 ¶ 24 (Dr. Evers's testimony that "[a] three month evaluation period was a commonly recommended minimum duration"), ¶ 102, n.13 (Dr. Evers's testimony that "a period of three months at a stable dose was one of the commonly recommended treatment periods for evaluating the efficacy of the migraine prophylactic" and a "routine practice").

treatments recommending that "[t]reatment periods of at ***no less than 3 months*** in phase II RCTs [randomized controlled trials] and up to 6 months in phase III trials should be used"); Ex. 1224, 7 ("First, headache guidelines recommend assessing response to efficacy to prophylactic medications ***after 3 months of use***."); *see also* Ex. 1023, 5 ("Oral preventive medications must be titrated over weeks to effective doses, and then administered daily for ***approximately 3 months to establish efficacy***."); Ex. 1022, 2 (open-label study in which a patient was considered to have failed a prior treatment if that treatment was "***used in adequate doses for at least three months***").

However, the evidence also supports Patent Owner's and Dr. Grosberg's position that the "requirement of 'at least three months of therapy at a stable dose' for Group I . . . patients was not standard in the art" and Dr. Grosberg is correct that the prior art includes evidence showing patients were "evaluated for response to migraine medications after *less than three months* of therapy." Ex. 2037 ¶ 40 (Dr. Grosberg's testimony); Ex. 1011, table 1 (table including three definitions of "refractory," one which states that an adequate trial is "typically ***at least 2 months*** at optimal or maximum-tolerated dose, unless terminated early due to adverse effects."); Ex. 1016, 5 ("continuing treatment for ***at least 2 to 3 months*** after the target dose is achieved is important to determine maximal efficacy"); Ex. 1013, 4, ("An adequate trial is defined as a period of time during which an appropriate dose of medicine is administered, typically ***at least 2 months*** at optimal or maximum-tolerated dose, unless terminated early due to adverse effects."); Ex. 1021, 6 ("Give each drug an adequate trial. ***It may take 2 to 3 months to achieve clinical benefit***.").

Of particular importance in interpreting Sun, Tepper, a reference that reports the results of one of the prospective clinical trials described in Sun,

describes an "adequate trial" as "at ***least six weeks*** of treatment at generally accepted doses." Ex. 1037, 3.

The record regarding how the POSA would have understood Sun's "standard therapeutic regimen" stands in near equipoise. The evidence discussed above strongly supports that three months is a very common, but not standard, recommended minimum treatment length. However, in the context of Sun's disclosure, we give greater weight to Tepper's disclosure of an evaluation period of "at least six weeks" than to the many disclosed three-month evaluation periods because Tepper's disclosure reports the results of a trial discussed in Sun. With the greater weight accorded to Tepper, we find that the POSA would not have understood Sun's "standard therapeutic regimen" to refer to a minimum of three months of treatment. Ex. 2037 ¶ 111 (Dr. Grosberg's testimony that Tepper "describes 'at least 6 weeks of treatment' as an adequate trial period for determining whether a patient had a therapeutic response" and thus that a POSA would have understood Example 4 of Sun to disclose a "prior preventative medication a failure after *at least six weeks* of therapy, rather than *at least three months* of therapy"). Rather, we find that the POSA would have understood the phrase "standard therapeutic regimen," as used in Sun, to refer to treatment durations of at least six weeks.

(ii) Does Sun render treating Group I patients obvious?

Having determined that the POSA would not have understood Sun's "standard therapeutic regimen" to refer to at least three months of failed treatment with a migraine prophylactic, and thus that Sun does not expressly disclose treating Group I patients, we next consider whether Sun renders treating such patients obvious.

Patent Owner identifies two differences between Sun's patients who "failed . . . treatment with at least two different classes of migraine prophylactic agents" and the claimed Group I patients.[15] We address each in turn.

First, Patent Owner argues that "Sun also does not specify any level of reduction in the frequency, duration, and/or severity of migraine headache below which the preventive medication is considered a failure." PO Resp. 22. This argument is not persuasive because Sun expressly defines "failure to respond," as a subset of the claimed Group I patients:

> As used herein, "failure to respond" or "treatment failure" refers 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. For instance, in one embodiment, a patient who has failed prior treatment with a migraine prophylactic agent is a patient who experienced the same or a greater number of monthly migraine headache days following administration of the migraine prophylactic agent as compared to the number of monthly migraine headache days prior to treatment with the agent.

[15] In Patent Owner's Preliminary Response, Patent Owner argued that Sun's "failure to respond" is distinguishable from the '434 patent's "no clinically meaningful improvement" because the POSA would have understood Sun's "standard therapeutic regimen" to include "dose *adjustments*, such as a stepwise increase or decrease in dosage to find the optimum therapeutic dose." Prelim. Resp. 20. This argument is not included in Patent Owner's Response and is, thus, waived. Paper 12, 9 ("Patent Owner is cautioned that any arguments not raised in the response may be deemed waived"). Even if we were to consider this argument, the evidence of record supports that although dose may be adjusted to determine an optimum therapeutic dose, a POSA would have understood to determine efficacy after treatment with a stable dose. *See* Ex. 1023, 5; Ex. 1109 ¶ 24–25, 102 n.13; Ex. 2037 ¶ 89.

Ex. 1006 ¶ 65. The claimed Group I patients are only deemed a failure if their prior treatment does not reach the threshold of being "clinically meaningful." However, Sun defines failure to include an unqualified "lack of efficacy," thus encompassing patients that experience improvements that fall short of the claimed "clinically meaningful" improvements. Indeed, the patients in the embodiment who experienced "the same or a greater number of monthly migraine headache days" fall far short of a clinically meaningful improvement. Thus, at least with respect to the threshold for determining whether a prior treatment has failed, Sun defines a subset of the claimed patients. Ex. 2071, 80:21–81:6, 82:25–85:3 (Dr. Evers's testimony explaining "clinically meaningful" ≥50% reduction).

Second, the claimed Group I patients differ from Sun's patients who "failed . . . treatment with at least two different classes of migraine prophylactic agents" in how long the patients were administered treatments before those treatments were deemed failures; treatments of Sun's patients were administered for at least 6 weeks, while treatments of the claimed Group I patients must be administered for at least 3 months. The evidence does not support that this difference patentably distinguishes the claimed Group I patients from Sun's patients.

Petitioner argues that "it is immaterial whether three months at a stable dose was the ***only*** or 'a ***defined*** standard'" because Patent Owner's "few alternative evaluation periods—'at least two months,' 'two to six months,' 'two to three months,' 'at least six weeks' (POR, 29)—are at best 'a limited number of discrete permutations' that do not make 'at least three months' any less obvious." Pet. Reply. 10–11. We agree.

As discussed above, the evidence establishes that it was common practice to administer a drug for a minimum of three months. *See supra*

§ II.F.1.a.i. In addition, the prior art of record uniformly encompasses, in the various definitions of "refractory" or "patients who failed treatment," patients whose treatments were given longer than six weeks to show results. Ex. 1019, 2 (3 to 12 months); Ex. 1020 (within 3 months); Ex. 1228, 15 (no less than 3 months in phase II RCTs and up to 6 months in phase III trials); Ex. 1224, 7 (after 3 months of use); Ex. 1023, 5 (approximately 3 months); Ex. 1022, 2 (at least 3 months); Ex. 1016, 5 (at least 2 to 3 months); Ex. 1013, 4, (at least 2 months); Ex. 1021, 6 (2 to 3 months); Ex. 1011, table 1 (providing two definitions, one requiring 3 months, the other requiring at least 2 months). Even Tepper, whose definition set forth the lowest minimum treatment duration among the references identified by the parties, encompassed patients who failed treatments that were given more than six weeks to show results in defining "no therapeutic response" patients. Ex. 1037, 3 (excluding patients who had "no therapeutic response . . . with prophylaxis of more than three treatment categories . . . after an adequate trial (***at least*** six weeks of treatment at generally accepted doses) (emphasis added)).

These facts are analogous to those in *Prometheus Laboratories v. Roxane Laboratories*, 805 F.3d 1092 (Fed. Cir. 2015). In that case, the Federal Circuit affirmed the district court's finding that claims directed to a method for treating a species of patients were obvious over a prior art disclosure of a method for treating a genus encompassing that species. *Id.* More specifically, the claims at issue in *Prometheus* were directed to "treating a subset of those IBS [irritable bowel syndrome] patients — those who (1) are women (2) with IBS-D (3) who have experienced symptoms for at least six months and (4) who have had moderate pain" while the prior art disclosed treating the broader genus of patients with IBS. *Id.* at 1098. Of

particular relevance here, the Federal Circuit found it obvious to treat patients who had experienced symptoms for at least six months on the basis that "it was common practice at the time of the '800 patent to determine whether a patient had suffered symptoms for longer than six months." *Id.* at 1099. Here, as in *Prometheus,* the claim at issue recites a limitation that was "common practice" with the effect of narrowing a genus patient population to a narrower subset of patients within the claimed genus. *See supra* § II.F.1.a.i.[16]

Patient Owner argues that the claimed Group I patients are more difficult to treat than Sun's patients and thus "a POSA would have known that the patients in Sun's examples were different, and easier-to-treat, patients than the '434 patent's inadequate response patients who had no clinically meaningful improvement with prior medications after at least three months of therapy, given at a stable dose." PO Resp. 30. This issue is better discussed in connection with our discussion of reasonable expectation of success. *See infra* § II.F.3.b.i. For purposes of our discussion here, it is

[16] In *Prometheus,* the court also found that the claimed common practice of requiring patients to experience symptoms for longer than six months rather than just three months provided "a greater confidence in the diagnosis." *Id.* at 1099. Here, allowing patients to have more time to respond to treatment is similar in that it increases the confidence that they are truly refractory to that treatment. Ex. 2037 ¶ 39 (Dr. Grosberg testimony that "a patient who did not show improvement in a shorter evaluation period (e.g., 6 weeks) could still show improvement with the same medication after treatment for a longer period (e.g., 3 months) and perhaps was not even resistant to treatment in the first place."); *see also* Ex. 1013 (recognizing that an evaluation period longer than 2 months "would be preferrable," but concluding that such an evaluation period would "prolong the time necessary to meet refractory criteria" and thus "prevent patients receiving the appropriate level of care.").

sufficient to note: 1) that we do not agree with Patent Owner's position, and 2) that the evidence supports that the three-month observation period is not critical. Ex. 1196 ("Although there is no evidence on the optimal length of prophylactic treatments, 3 months is usually considered sufficient to assess prophylactic efficacy,"); Ex. 1234, 198:18–199:13 (testimony of Dr. Grosberg: I agree [with a statement in Ex. 1196] that there was no evidence in the optimal length of prophylactic treatments at the time").

Considering all of the evidence and argument of record, including Sun's and Tepper's disclosures, the evidence establishing 3 months as a very common minimum evaluation period, the evidence supporting that all of the minimum evaluation periods identified in the art encompass patients who fail treatment after three months, and the evidence supporting that the 3 month evaluation period was not critical, we find that Sun's disclosure of treating patients that "failed . . . treatment with two different classes of migraine prophylactic agents" (Ex. 1006 ¶ 68) suggests using erenumab to treat patients who had failed at least three months of treatment with migraine prophylactics.

(iii) Conclusion with respect to Group I patients

In sum, we find that the difference in how treatment failure is defined does not distinguish Sun's patients who "failed . . . treatment with at least two different classes of migraine prophylactic agents" from the claimed Group I patients. As to the difference in how long the patients were administered treatments before those treatments were deemed failures, Sun's disclosure of treating patients that "failed . . . treatment with two different classes of migraine prophylactic agents" renders obvious an evaluation period of at least three months.

b) Group II patients (treatment interrupted by adverse events)

Petitioner contends that Sun's disclosure of treating patients who are intolerant to treatment with a particular migraine prophylactic agent and who discontinue treatment with a migraine prophylactic agent is a disclosure of treating Group II patients under our construction of "a subject having refractory migraine." Pet. 21; Pet. Reply 22–24.

Patent Owner disputes that Sun discloses Group II patients (i.e., patients whose "treatment has to be interrupted because of adverse events that made it intolerable by the patient"), contending that Sun "deliberately used the term 'side effects' when defining its 'failure to respond' patients (despite using the term 'adverse events' elsewhere in the application)." PO Resp. 23. Patent Owner argues that "a POSA would have known that 'side effects' are quite different from 'adverse events.'," and asserts that "Dr. Evers agrees." *Id.* (citing Ex. 2071, 148:24–150:16). According to Patent Owner, "side effects" include "mild inconveniences such as morning grogginess, and even beneficial effects such as improved sleep" while adverse events "include serious events such as death, life-threatening circumstances, and permanent disability." *Id.* at 14. Thus, Patent Owner asserts, "Sun's purported 'side effects' criteria thus do not suggest treating the selected inadequate response subjects of the challenged claims." *Id.* at 24. We do not find this argument persuasive.

Sun discloses treating Group II patients. Sun discloses that in some embodiments, its anti-CGRP receptor antibody may be administered to a patient that has "failed . . . treatment with two different classes of migraine prophylactic agents." Ex. 1006 ¶ 68. Sun then discloses that "[f]ailure to respond to prior treatment with a migraine prophylactic agent can . . .

include inability to tolerate the migraine prophylactic agent," such as when a patient "cannot tolerate the side effects associated with the agent." *Id.* ¶ 66. And Sun discloses that, in some embodiments, "a patient who has failed prior treatment with a migraine prophylactic agent is a patient who discontinues treatment with the migraine prophylactic agent due to associated side effects." *Id.* Sun's side effects are, in relevant part, the same as the claimed adverse events; both cause treatment to become intolerable and both result in treatment being interrupted. Ex. 1006 ¶ 66; Ex. 1045, 6:45–52. We agree with Petitioner that Sun's disclosure meets the definition of Group II patients.

We are not persuaded by Patent Owner's argument (PO Resp. 30) that Sun does not disclose treating Group II patients because an "adverse event" is different from and more severe than Sun's "side effects." For the reasons discussed *supra* § II.C, we rejected Patent Owner's proposal that "adverse event" be construed as limited to "serious" events. The only requirement the claim imposes on the gravity of the adverse event is that it be severe enough to cause the patient to interrupt treatment. Sun's disclosure crosses that threshold.

We acknowledge Dr. Grosberg's testimony that "side effects were known in the art to be milder than adverse events." Ex. 2037 ¶ 42. We give this testimony some weight, but it does not persuade us that Sun's patients who cannot tolerate side effects do not qualify as Group II patients for two reasons. First, as discussed in connection with claim construction, Dr. Grosberg's testimony suggesting that "adverse events" must be "serious" is inconsistent with the evidence he cites to support his opinion. Ex. 2004, (defining "adverse event" as "***any undesirable experience*** associated with the use of a medical product in a patient" and explaining when an "adverse

event" is considered a "serious adverse event") (emphasis added). Second, his testimony that side effects include "mild inconveniences such as morning grogginess, and even beneficial effects such as improved sleep" (Ex. 2037 ¶ 42), even if true for some subset of "side effects" and some medical treatments, does not match the "side effects" at issue – those described in Sun's paragraph 66 (Ex. 1006 ¶ 66 (describing treating patients who "cannot tolerate the side effects" as well as patients who "discontinue[] treatment . . . due to the associated side effects"); *see also id.* ¶ 61 (defining the term "adverse side effect" as "any abnormality, defect, mutation, lesion, degeneration, harmful or undesirable reaction, symptom, or injury, which may be caused by taking the drug.")).

Patent Owner's argument that "Dr. Evers agrees" that "adverse events are more serious than side effects" (PO Resp. 23 (citing Ex. 2071, 148:23–150:16)) is unpersuasive because Dr. Evers's testimony says nothing of the sort. Rather, consistent with the evidence cited by both parties supporting that "serious adverse events" are a subset of "adverse events" (Ex. 2004, 1; Ex. 1208, 1–2; Ex. 1209, 6, 9; Ex. 1210, 8, 13), Dr. Evers's testimony addresses what adverse effects would be considered "serious adverse events" (Ex. 2071, 148:24–3 (explaining that "serious adverse event" is a "specific term" for when death occurs during a clinical trial), 150:3–151:11 (explaining that "[t]here is a list of serious adverse events in clinical trials, which comprises all events considered a serious adverse event," and providing examples)).

Patent Owner argues that Sun teaches that "intolerable side effects are those where the 'impact' is 'greater than the therapeutic benefit of the migraine prophylactic agent.'" PO Resp. 24. According to Patent Owner, "a POSA would not have considered such patients to have an inadequate

response of the claimed method because Sun's patients had a meaningful therapeutic benefit." *Id.* This argument is not persuasive because it conflates Group I and Group II patients. While our construction of "inadequate response" requires that Group I patients exhibit "no clinically meaningful improvement," our construction of Group II patients does not preclude patients from experiencing a benefit from the prior treatment; it requires only that patients have treatment "interrupted because of adverse events that made it intolerable by the patient." *See supra* § II.C.

Patent Owner and Dr. Grosberg point out that Sun uses both the term "adverse event" and the term "side effect." PO Resp. 23; Ex. 2037 ¶ 94. Based on this fact, Dr. Grosberg asserts: "[b]ecause Sun chose to use 'side effects' to define 'failure to respond' (despite using 'adverse events' elsewhere), a POSA would have concluded that 'failure to respond' to a prior preventive medication in Sun's patients was because of *side effects* and not because of *adverse events*." *Id.*

We do not find Patent Owner's inferences from Sun's usage of the terms "side effect" and "adverse events" persuasive because Sun's references to "adverse events" (Ex. 1006 ¶¶ 7, 61, 264, 268, 271, 281) do not diminish Sun's disclosure of treating Group II patients – i.e., patients who "cannot tolerate the side effects" of a migraine prophylactic treatment as well as patients who "discontinue[] treatment . . . due to the associated side effects" (Ex. 1006 ¶ 66). Moreover, in discussing that the present invention addresses the problem of poorly tolerated prior art therapies, Sun appears to use the terms "adverse events" and "adverse side effects" somewhat interchangeably. *Id.* ¶¶ 7, 8 (describing topiramate, a prior art anti-convulsant, as the most common migraine prophylactic, but teaching that there is "an urgent medical need for more effective and/or tolerable

treatment options" after explaining that topiramate is "poorly tolerated" and that treatment can cause "adverse events"), ¶ 9 (describing the "present invention" as providing a migraine treatment "with no or minimal adverse side effects"), ¶ 14 (explaining that the disclosed treatment "does not substantially cause an adverse side effect associated with . . . antiepileptics"), ¶ 40 (explaining that current therapies "have a poor risk-benefit profile due to adverse side effects" and teaching that "[t]he present invention addresses this problem"); *see also id.* ¶ 61 (referencing "the Common Terminology Criteria for Adverse Events v4.0" in the paragraph that defines "adverse side effect"). Thus, Sun's separate use of the terms "adverse event" and "side effect" does not support that Sun's disclosure of treating patients with intolerable side effects (Sun ¶ 66) is distinguishable from treating the claimed Group II patients.

In sum, we find that the evidence of record does not support the existence of a meaningful distinction between the Specification's definition of Group II patients and Sun's disclosure of treating patients who are unable to tolerate side effects. Accordingly, we find that Sun discloses treating Group II patients.

c) Group III patients (drug contraindicated or not suitable)

Sun discloses that in some embodiments, its anti-CGRP receptor antibody may be administered to a patient that has "failed . . . treatment with two different classes of migraine prophylactic agents." Ex. 1006 ¶ 68. Sun explains that the term "failure to respond" can include treating patients for whom the "side effects associated with the agent . . . may be incompatible with another medical condition which the patient has." *Id.* ¶ 66. Sun continues, "[b]y way of illustration, migraine prophylactic agents having a

side effect of teratogenicity would be contraindicated in a pregnant patient." *Id.*

Petitioner contends that Sun's disclosure of treating contraindicated patients meets the requirements of treating Group III patients under our claim construction. Pet. 42–43.

Patent Owner argues that "[w]hile Sun uses the term 'contraindicated' in its discussion of 'failure to respond' patients, it is only in the context of teratogenic side effects—not contraindications as a POSA would have understood the term in the '434 patent." PO Resp. 25. This argument is unavailing.

We agree with Patent Owner that Sun's disclosure about contraindicated patients is in the context of a discussion of side effects. In this regard, Sun states:

> 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). Regardless of its broader context, Patent Owner cannot seriously dispute that teratogenicity – the ability of a drug to cause fetal abnormalities or deformities – would cause a medication to be contraindicated for a pregnant patient. *See* PO Resp. 14 (proposing to construe "contraindicated" to mean "a medical reason (such as a symptom or condition) for not doing or using something (such as administering a

drug)"). The fact that Sun provides this example as part of a discussion of "side effects" does not somehow change the nature of the teratogenic side effect such that treatment with the drug would no longer be contraindicated in a pregnant patient. Indeed, Sun teaches that potential teratogenicity in a pregnant subject is why the drug is contraindicated. By disclosing treatment of patients that failed to respond to treatment, and by defining such failure to respond to include such contraindicated patients, Sun discloses treating Group III patients.

Patent Owner argues that "Sun clearly defines 'failure to respond' as an 'inability to tolerate' a preventive medication, indicating to a POSA that the patient must have been *previously administered* a preventive medication *before* ascertaining the patient's 'inability to tolerate' the medication." PO Resp. 25 (citing Ex. 2037 ¶ 98). Patent Owner contends that the "POSA would have known that Sun's "failure to respond" patients, even though described as having a preventive medication "contraindicated," had been previously administered the medication before the medication was deemed contraindicated." *Id.* According to Patent Owner, this distinguishes Sun's patients from the claimed Group III patients because "the [Group III] subjects of the claimed method who are contraindicated should not be administered the drugs in the first place." *Id.* (citing Ex. 2037 ¶ 43).

This argument is not persuasive for at least two reasons. First, we do not read Sun's use of the phrase "inability to tolerate the migraine prophylactic agent" to require that patients be treated with the intolerable drug. Ex. 1006 ¶ 66 ("Failure to respond to prior treatment with a migraine prophylactic agent can also include inability to tolerate the migraine prophylactic agent. . . . By way of illustration, migraine prophylactic agents having a side effect of teratogenicity would be contraindicated in a pregnant

patient.")). A patient could be unable to tolerate side effects based on prior knowledge of how they will react to that treatment. For example, they may know that they are allergic to one of its ingredients or cannot tolerate one of its known side effects. Second, even if Sun's "inability to tolerate" requires prior treatment, the challenged claims do not place a restriction on when a patient becomes contraindicated. Put another way, the claims encompass as Group III patients, patients who are treated with a drug but subsequently become contraindicated for that drug – for example by becoming pregnant or being newly diagnosed with an unrelated medical condition during treatment.

In sum, we agree with Petitioner that Sun discloses treating Group III patients. Ex. 1006 ¶ 66 ("[b]y way of illustration, migraine prophylactic agents having a side effect of teratogenicity would be contraindicated in a pregnant patient").

d) Conclusion regarding Sun's disclosure of the claimed patients

For the reasons discussed *supra* §§ II.F.1.a–c, we find that Petitioner has established, by a preponderance of the evidence, that Sun teaches or suggests treating each of Group I, Group II, and Group III patients.

2. Does the evidence support that a POSA would have had reason to use fremanezumab to treat inadequate response patients?

Petitioner contends that the POSA would have been motivated to use fremanezumab, as disclosed in the Teva Press Release, in Sun's methods for three reasons: 1) Sun discloses combination therapy with fremanezumab and erenumab, 2) Sun and the Teva Press Release disclose overlapping patient populations, and 3) the POSA would have expected fremanezumab and

erenumab to have similar efficacy. Pet. 31–34. Patent Owner contests each of the three motivations proffered by Petitioner and argues, more generally, that the POSA, "would not have had any reason to jettison that successful drug [erenumab] and replace it with a *different drug* (fremanezumab) directed to a *different target* (CGRP), for a *different patient population* (selected inadequate response patients of the claims), especially in view of the unpredictability surrounding the CGRP signaling pathway." PO Resp. 21. We address the evidence and the parties' arguments regarding motivation below. We find that Petitioner has established that the POSA would have been motivated to use fremanezumab in Sun's methods.

a) Sun's disclosure of combination therapy

Petitioner argues that the POSA would have been motivated to use fremanezumab in Sun's methods because Sun discloses "combination treatment with 'an anti-CGRP antibody . . . in . . . ***WO 2007/054809***'", which, according to Petitioner, disclosed fremanezumab. Pet. 31 (citing Ex. 1006 ¶ 250; Ex. 1109 ¶¶ 50, 147–149; Ex. 1103, 68, 72). Petitioner contends that a POSA would have "understood this to teach that the use of fremanezumab would be safe and effective in *Sun's* intended patients." *Id.* (citing Ex. 1092 ¶¶ 50, 150).

Patent Owner concedes that Sun "mentions fremanezumab" but argues that it does so "solely in the context of a hypothetical *combination* therapy with erenumab." PO Resp. 30. According to Patent Owner, Sun does not disclose a "therapeutically effective amount of fremanezumab, administered alone or in combination," and does not disclose a "patient population for which a POSA would have expected success in administering fremanezumab." *Id.* at 30–31. Patent Owner cites the testimony of Dr. Grosberg, who testifies that combination therapy could be dangerous:

> Although antagonist antibodies against the CGRP pathway were safe in general migraine patients studied in the clinical trials of the prior art, a POSA would have expected that targeting the CGRP pathway at multiple points with different medications could have deleterious synergistic effects resulting in severe adverse events that targeting the CGRP pathway at a single point by a single antagonist antibody would not have.

Ex. 2037 ¶ 225. Dr. Grosberg also testifies that "common knowledge in the prior art suggest[ed] using medications having different mechanisms of action in combination therapy." *Id.* ¶ 226. Thus, Patent Owner asserts, absent data or explanation, Sun's mention of combination therapy provides the POSA "no motivation to combine fremanezumab with erenumab because of safety concerns and the fact that both drugs act at the *same point* (receptor-ligand interaction) on the *same pathway*." PO Resp. 31.

Although Sun discloses that its anti-CGRP receptor antibody (erenumab) "can be administered in combination with" fremanezumab (Ex. 1006 ¶ 250), Patent Owner and Dr. Grosberg raise what appear to be valid concerns regarding the use of fremanezumab and erenumab together in combination therapy. *See, e.g.,* Ex. 2037 ¶¶ 223–227. As Petitioner does not persuasively address these concerns, the record does not support that the POSA would have been motivated to use fremanezumab and erenumab together in combination therapy.

That said, Patent Owner's argument appears to be somewhat of a red herring. The Petition relies on Sun's disclosure of combination therapy as teaching that "the use of fremanezumab would be safe and effective in *Sun's* intended patients." Pet. 31 (citing Ex. 1092 ¶ 50, 150). As Petitioner's counsel clarified at oral argument, Petitioner does not propose actually using fremanezumab in combination with erenumab.

> I think Teva has misconstrued our argument a little bit. . . . We rely on Sun's teaching of combination therapy as a rationale for why a person of ordinary skill would understand that galcanezumab is entirely suitable, same with galcanezumab [sic, fremanezumab] in Sun's methods. . . . Our proposal is not to take erenumab from Sun and move it into Dodick. What is being argued is that Sun teaches, here are types of patients that can be useful -- usefully treated with CGRP antibodies. Galcanezumab has similar properties. Galcanezumab and fremanezumab would be obvious to use, those in the same patient populations. There's no need to consider whether a combination per se is included or excluded in Dodick, in our view.

Tr. 20–21. Thus, Petitioner contends only that the disclosure of combination therapy in Sun is evidence that fremanezumab would be safe and effective in Sun's patients. On this point, we agree with Petitioner. Ex. 1006 ¶ 250 (Sun disclosing combination therapy with anti-CGRP antibodies known and described in WO 2007/054809); Ex. 1109 ¶¶ 149 (Dr. Evers's testimony explaining that WO 2007/054809 discloses fremanezumab), 150 (Dr. Evers's testimony that a POSA would understand Sun's disclosure as teaching that "fremanezumab would be effective in the patient populations it [Sun] disclosed").

b) Sun and the Teva Press Release's patient populations

Petitioner contends that the "*Teva Press Release* described studies in which the eligibility criteria pointed to treating the same 'select[ed]' 'inadequate response' patients taught by *Sun.*" Pet. 31. More specifically, Petitioner contends that the Teva Press Release "allowed for patients that failed two of the claimed common classes of preventives" and that "[t]hese patients overlap with those disclosed by *Sun*, which taught the use of

clinically-proven anti-CGRP mAbs to treat, e.g., patients that '***failed or [were] intolerant to treatment with***' both '***two***' and '***three different classes of migraine prophylactic agents***,' such as anticonvulsants, beta-blockers, and antidepressants." *Id.* at 31–32. In addition, the studies discussed in the Teva Press Release allowed patients to remain on two preventatives. Ex. 1038, 2; Ex. 1039, 2–3. According to Petitioner, this "would have included patients that used preventive treatments with some efficacy but would not rise to the level of a 'clinically meaningful' response" – i.e., patients encompassed within the claimed Group I patients. PO Resp. 30. Petitioner argues that this 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.

Patent Owner argues that "[n]either the Teva Press Release itself nor the underlying studies separately reports results in patients who would qualify as the inadequate response patients of the '434 patent." PO Resp. 33. Indeed, Patent Owner asserts "[n]o such patients were even identified as having participated." *Id.* As to Petitioner's claim that the clinical trials described in the Teva Press Release allowed certain of the claimed "inadequate response" patients, Patent Owner argues that those same trials excluded subjects who "failed >2 medication categories or >3 preventive medications" as well as "subjects with over 25 commonly observed comorbidities and contraindications." PO Resp. 34. As to Petitioner's claim that allowing patients to remain on two preventives suggests the claimed "inadequate response patients," Patent Owner asserts that "[l]ogically, a POSA would have understood that these patients were having

therapeutically meaningful improvements to these other preventives if they continued taking them in the trial." *Id.* at 33.

We agree with Patent Owner that none of the references discussing the fremanezumab clinical trials support that the claimed inadequate response patients were required by the inclusion criteria of the study. *See generally* Ex. 1023; Ex. 1038; Ex. 1039; Ex. 1041; Ex. 1057; Ex. 1058; Ex. 2012; Ex. 2015. The evidence of record does support that the fremanezumab clinical trials allowed some portion of the claimed patient groups to participate in the clinical trials and excluded some portion of the claimed patient groups from participation. *See* Ex. 2012, 2; Ex. 2015, 2. For example, patients that failed two treatment categories – potential Group I patients – could have participated in the trial, while patients that failed three treatment categories – also, potential Group I patients – would be excluded. *Id.* However, we agree with Patent Owner that there is no way of knowing how many, if any, Group I, II, or III patients participated in the fremanezumab clinical trials and, if they did participate, how they responded. PO Resp. 35. In this case, and under these circumstances, the absence of exclusion does not support an expectation that treating non-excluded patients would be successful. *Id.* For this reason, we are not persuaded by Petitioner's argument that the Teva Press Release's eligibility criteria "pointed to" treating the claimed refractory patients.

c) Expectation of similar efficacy

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," and, thus, it would have been obvious to substitute one anti-CGRP mAb (fremanezumab) for another (erenumab) to "effectively treat migraine by blocking the CGRP pathway." Pet. 32.

According to Petitioner, this motivation 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 asserts that "the similar efficacy of fremanezumab and erenumab" as well as the "potential for both to treat 'select[ed]' 'inadequate response' patients" was recognized in the art." *Id.* at 33.

Patent Owner disputes that similar efficacy provides motivation to use fremanezumab in Sun's methods, arguing that "Sun and the Teva Press Release disclose different patient populations *from each other*" and, thus, "a POSA would not have simply swapped out one drug for another and expected the same results – these were not simple, interchangeable substitutions." PO Resp. 39. Patent Owner argues that fremanezumab and erenumab are "different drugs, with different targets," and that the "mere fact that both drugs are monoclonal antibodies does not make them interchangeable." *Id.* Patent Owner contends that the differences between fremanezumab and erenumab are "underscored by the unpredictability of the CGRP pathway." *Id.* In particular, Patent Owner emphasizes that fremanezumab targets CGRP itself while erenumab targets its receptor. PO Resp. 19–21, 39–40.

We find that the expectation that erenumab and fremanezumab would have similar efficacy supports a motivation to substitute one for the other. We discuss the evidence and the parties' arguments below.

(i) Evidence supporting similar efficacy of fremanezumab and erenumab

The expectation that fremanezumab would be efficacious in treating the claimed population is supported by studies showing that erenumab and

fremanezumab have similar efficacy in the broader migraine population. *See* Pet. 32–34 (asserting that erenumab and fremanezumab have similar efficacy). For example, Sun discloses that erenumab is effective in treating migraine. Ex. 1006 ¶¶ 268–269 ("A statistically significant reduction in monthly mean migraine days was observed with AMG 334 70 mg (-3.40) vs placebo (-2.28). . . . Statistically significant reductions in monthly headache days (70 mg: -3.54 vs placebo: -2.39: P=0.022) and monthly acute migraine-specific medication use days (70 mg: -1.64 vs placebo: -0.69; P=0.004: FIG. 6) were also observed."). And the Teva Press Release teaches that fremanazumab is effective in treating migraine. Ex. 1041, 1 (reporting that "[a] single administration of all tested doses of [fremanezumab], in both episodic and chronic migraine studies, resulted in a statistically significant separation from placebo" and that in episodic migraine patients, fremanezumab reduced monthly migraine days by 2.81 for the 225 mg dose and by 2.63 for the 675 mg dose); *see also* Ex. 1038, 2 ("This study provides level 1b evidence (well conducted individual randomised controlled trial) that [fremanezumab] is effective for the preventive treatment of chronic migraine"); Ex. 1039, 3 ("This study provides level 1b evidence (ie, a robust, randomized clinical trial) that two doses of [fremanezumab], a monoclonal antibody against CGRP, are effective for the preventive treatment of high-frequency episodic migraine"). Dr. Evers testifies, that the efficacy results reported in the studies are "comparable" as are the side effect profiles. Ex. 1109 ¶¶ 156–157 (comparing responder rate and reduction in monthly migraine headache days as compared to placebo both erenumab and fremanezumab). This testimony is consistent with the references and credible.

Dr. Evers also testifies that "[t]he comparable efficacy of fremanezumab and erenumab in the treatment of migraine was recognized throughout the art." *Id.* ¶ 158; *see also* Pet. 32 (asserting that "[t]he similar efficacy of fremanezumab and erenumab . . . was recognized in the art, which addressed use of the clinically proven anti-CGRP mAbs collectively"). We credit Dr. Evers's testimony on this point because it is consistent with a wealth of prior art references addressing anti-CGRP mAbs as a class and supporting that, among the general migraineur population, all of the members of this class (which includes erenumab, galcanezumab, fremanezumab, and eptinezumab) have similar efficacy and safety. *See* Ex. 1230, 1 (teaching that the four mAbs that have been subject to clinical trials "have been almost similarly effective, tolerable and safe in phase 2 studies and are being studied in phase 3 trials for episodic and chronic migraine prevention."); Ex. 1074, 9 ("[B]ased on the results of 5 Phase II trials, this review and meta-analysis revealed a significant effect of CGRP-mAbs for migraine prevention with few adverse reactions"); Ex. 1231, 4 ("The present meta-analysis [of four phase II clinical trials] demonstrates that CGRP mAbs lead to improvement in decrease of monthly migraine days from baseline to week 1–4 or week 9–12 after CGRP mAbs administrated and well tolerated, as compared with placebo."); Ex.1232, 7 ("All four anti-CGRP mAbs investigated to date have led to significant reductions from baseline in either episodic and/or chronic migraine days per month compared with placebo."); Ex. 1037 ("Results from five other phase 2 studies have been published on the efficacy and safety of monoclonal antibodies targeting the CGRP pathway for migraine prevention, all of which showed efficacy, and none of which raised safety concerns."); Ex. 1049, 10 (discussing clinical trials of anti-CGRP mAbs, including

erenumab and fremanezumab, stating "[t]he numerous studies so far conducted with the available anti-CGRP monoclonal antibodies have shown satisfactory safety and efficacy outcomes in migraine prevention," and concluding that "the overall profile of anti-CGRP mAbs so far shown can be regarded as highly favorable" and that "in the forthcoming years, anti-CGRP mAbs will probably equal, in preventative treatment, the revolution introduced by triptans in acute treatment of migraine"); Ex. 1028, 2, 8 (article reviewing the "current state of development for mAbs targeting the CGRP pathway," concluding that "mAbs targeting the CGRP pathway are a promising new drug class that may provide a valuable new option for clinicians aiming to relieve the burden of individuals with episodic or chronic migraine."); Ex. 1025, 3 ("Overall, CGRP-mAbs look like promising options for migraine and chronic migraine prevention with impressive responder rates, improved safety and tolerability, absence of liver toxicity and long half-lives leading to infrequent dosing."); Ex. 1027, 5 ("Preliminary data showed positive results for all four mAbs."); Ex. 1042, 1 ("Monoclonal antibodies against CGRP or the CGRP receptor have a longer duration of action [that CGRP receptor antagonists] and have been investigated for migraine prevention. Four are in development and three have completed phase II and one phase III trials; every reported study has been positive. Furthermore, no safety issues have arisen to date, including hepatic or cardiovascular effects, and initial tolerability appears to be excellent."); Ex. 1036, 1–2, 6 (explaining that "[s]everal recent phase 2 studies with CGRP monoclonal antibodies [including fremanezumab and two other mAbs]. . . showed clinical benefit for migraine prevention, without hepatotoxicity concerns" and reporting that phase 2 studies of the mAb, erenumab, "showed a significant reduction in monthly migraine days from

baseline versus placebo"); Ex. 1029, 6, 7 (opining that "[f]ully humanized mAbs targeting CGRP or its receptor directly appear more promising [than CGRP receptor antagonists] for the prophylactic treatment of frequent episodic and chronic migraine" and that "CGRP-targeted mAbs could provide a possibility for successful therapy in this field"); Ex. 1025, 3 ("Overall, CGRP-mAbs look like promising options for migraine and chronic migraine prevention with impressive responder rates, improved safety and tolerability, absence of liver toxicity and long half-lives leading to infrequent dosing.")

In addition to supporting that mAbs have comparable efficacy among the general migraine population, the prior art also supports the recognition that both erenumab and fremanezumab have the potential to treat refractory migraine. For example, a *post hoc* analysis of the results of a phase II study of erenumab, concluded that "erenumab 70 mg and 140 mg reduced the number of monthly migraine days with a safety profile similar to placebo." Ex. 1037, 1. The study included "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," which the author found to suggest that "there could b[e] efficacy in a treatment-resistant population." *Id.* at 8; *see also* Ex. 1040, 14–15 (reporting that Phase III trial of erenumab 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."). Similarly, the Teva Press Release characterizes two phase II fremanezumab studies as follows:

> The 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," stated Marcelo E. Bigal, Teva's Head of Global Clinical Development for Migraine and Headaches [and a named inventor on the '434 patent]. "The ***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.

Ex. 1041, 2 (emphasis added). Consistently, at least one reference suggests that the entire class of mAbs may have efficacy in treating refractory migraine. Ex. 1023 ("No doubt, monoclonal antibodies (mAbs) against calcitonin gene-related peptide (CGRP) for preventative treatment of episodic and chronic migraine deserve to be called a breakthrough – not because they cure headache, but rather because they are effective for relatively refractory headaches"); *see also* Ex. 1053 (suggesting that "mAbs targeting CGRP or its receptor hold the most promise for preventive treatment" of patients in the "medically refractory subgroup[]").[17]

In sum, the evidence of record, including clinical trials of both erenumab and fremanezumab, Dr. Evers's credible testimony on the comparability of those clinical trials, and the wealth of prior art references

[17] A *post hoc* analysis of a phase II study of galcanezumab provides support for the proposition that entire class of mAbs may be effective in refractory patients by identifying another anti-CGRP mAb that may be effective in patients with a "history of failure to preventative treatments," galcanezumab. Ex. 1072, 74 (analysis of a phase II study of galcanezumab disclosing that the subgroup of patients with a "history of failure to preventative treatments" exhibited a "statistically significantly greater treatment effect (galcanezumab vs placebo difference) at Month 3," which the author found to suggest that this subgroup may be a "predictor[] of clinical response with greater treatment effects in episodic migraineurs.").

addressing anti-CGRP mAbs as a class and supporting that all members of that class have similar efficacy, provide strong evidence that the POSA would have expected erenumab and fremanezumab to have similar efficacy and tolerability.

(ii) Evidence regarding similarity of patient populations as between Sun and the Teva Press Release

Patent Owner argues that the POSA would not have expected erenzumab and fremanezumab to have similar efficacy because Sun and the Teva Press Release are not directed to the same patient populations:

> [N]either Sun nor Teva Press Release discloses treating the inadequate response patients of the '434 patent. *Id*. Also, Sun and the Teva Press Release disclose different patient populations *from each other*. *Id*. Sun's "failure to respond" patients are a different population with different criteria compared to the . . . the chronic migraine and episodic migraine patients disclosed in Teva Press Release. *Id.*, ¶¶234-235. Thus, a POSA would not have simply swapped out one drug for another and expected the same results—these were not simple, interchangeable substitutions.

PO Resp. 39.

We have already discussed Sun's failure to respond patients, finding them to align with the claimed "inadequate response" patients. *See supra* § II.F.1. Accordingly, we begin our analysis of Patent Owner's argument by discussing the "highly refractory patients" of the Teva Press Release. In particular, we address the dispute between the parties as to how the POSA would have understood the term "refractory" as used to describe migraine patients. We then apply that understanding to the Teva Press Release, taking into account that, as discussed *supra* § II.F.2.b, the clinical trials discussed in the Teva Press Release do not specifically require the inclusion of, or present

data on, "highly refractory patients." We find that the POSA would have understood "highly refractory patients," as used in the Teva Press Release, to be quite similar to Sun's "failure to respond" patients.

Petitioner contends that "[i]t was 'common consensus' that 'refractory' referred to failure of at least three classes of preventatives." Pet. Reply 19; *see also* Pet. 3. Patent Owner, argues that "[a] POSA would have understood 'refractory,' when not accompanied by any citation or reference to a specific proposed definition, to have its plain English meaning, i.e., 'resistant to treatment.'" PO Resp. 35.

We agree with Petitioner that the evidence of record supports that the term "refractory" was understood in the art to have a definition similar to and, in some respects, more restrictive than, that recited in the '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, 1 (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 (NSAIDs) *or* combination analgesic");

Ex. 1014, 5 (reporting results of a survey distributed at the American Headache Society meeting in 2007, where 42% of respondents agreed with a definition requiring failure of 2 of 4 preventative classes while 41% favored increasing the required number of failed preventatives); Ex. 1051, 35–37 (discussing the American Headache Society's Refractory Headaches Special Interest Section's proposed definition of "refractory," which requires that patients have "[f]ailed adequate trials of preventive medicines, alone or in combination, from at least 3 out of the following drug classes: a. Beta-blockers b. Anticonvulsants c. Tricyclics d. Calcium channel blockers"); Ex. 1053, 13 ("The EHF [European Headache Federation] recommends that refractory chronic migraine should be defined as ICHD-3 beta [International Classification of Headache Disorders] chronic migraine without medication overuse in patients who have failed to respond to treatment with at least three preventive medications at adequate dosages, each with trials of at least 3 months."); *see also* Ex. 2038, 2 (proposing definition for "intractable"[18] migraine headache to require "failure of at least four classes, where three should come from . . . β-Blockers . . . Anticonvulsants . . . Calcium channel blockers . . . [and] Tricylic antidepressants").

In connection with its discussion of claim construction, Patent Owner asserts that "[a]bsent a specific definition in the art, . . . a POSA would have understood the word 'refractory' (unaccompanied by a proposed definition) to generally mean 'resistant to treatment,' without any implied conditions or degree or severity." PO Resp. 11–12. As support, Patent Owner cites two

[18] Exhibit 2038 defines "intractable" to means "uncontrollable, refractory or unmanageable." Ex. 2053, 1; *see also* Ex. 1109 ¶ 20 n.1 (Dr. Evers's testimony equating refractory and intractable migraine: "refractory migraine, also known as 'treatment resistant' or 'intractable' migraine")

dictionary definitions for the term "refractory." *Id.* (citing Ex. 2003 and 2006); *see also* Ex. 2037 ¶¶ 48–49 (Dr. Grosberg's testimony on the meaning of the term "refractory"). 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 Patent Owner and Dr. Grosberg cite generic dictionary definitions of the term "refractory" that are not specific to any medical condition.

Patent Owner argues: "Petitioner wrongly asserts that a POSA recognized the word 'refractory' as describing patients that failed *at least three* drugs from four effective preventive treatment pharmacological classes." PO Resp. 12. Patent Owner supports this assertion with citation to references teaching that there was "no agreement on the number of drugs a patient should have received before being considered refractory," that there was an "unmet 'need for a consensus-based definition,' of 'refractory headache,'" and that there was "no worldwide consensus on any one definition." *Id.* (quoting Ex. 1012, 13 and Ex. 2010, 13).

Although Patent Owner is correct that the record does not support agreement on a single consensus definition, all of the definitions of "refractory" that the parties have identified require the failure of multiple preventative medications. Ex. 1011, 2, 3; Ex. 1012, 13; Ex. 1013, 1; Ex. 1014, 5; Ex. 1051, 35–37; Ex. 1053, 13; Ex. 2038, 2 (all discussed in parentheticals above). Even Exhibit 2010, which Patent Owner asserts "belie[s]" "Petitioner's purported 'consensus'" that "refractory" refers to failure of at least three or four drugs (PO Resp. 12), describes several existing and proposed definitions, all of which require the failure of multiple medications (Ex. 2010, 2–3 (discussing existing refractory definitions that require: "lack of responsiveness to multiple preventative medications," "one

would need to fail 4 different cluster or migraine preventative agents," "failed adequate trials of preventative medicines, alone or in combination, from at least 2 of 4 drug classes" and "failure of both acute and preventative agents"). Accordingly, we find that the POSA would have understood "highly refractory patients" in the Teva Press Release to refer to patients who failed multiple preventative treatments.

Patent Owner argues that we should not credit Dr. Evers's testimony on the meaning of the term "refractory" because in his deposition, Dr. Evers "admitted that he does not understand the teachings of the very references he relied upon for alleged definitions of refractory or inadequate response." PO Resp. 13. In the testimony at issue, Dr. Evers testifies that he does not know what the authors of three references were referring to when they used the term "refractory." Ex. 2071, 70:15–17 ("I do not know what he [the author of Ex. 1013] is referring to by 'refractory migraine' in this context."), 72:2–6 (discussing Exhibit 2014, stating "I was not a member of this group [the American Headache Society], and I cannot tell you what they mean with 'refractory migraine' in this context."), 75:2–10 ("I cannot conclude from this text what Schuster [Ex. 1053] is referring to, what is his definition for 'medically refractory subgroups.'"). We have reviewed this testimony and find that it does not cast doubt on Dr. Evers's testimony that "refractory" was "generally recognized to describe patients that failed at least three drugs" (Ex. 1109 ¶ 20), particularly as that testimony is consistent with all of the refractory migraine definitions of record. *See* Ex. 1011, 2, 3; Ex. 1012, 13; Ex. 1013, 1; Ex. 1014, 5; Ex. 1051, 35–37; Ex. 1053, 13; Ex. 2038, 2 (all discussed in parentheticals above). Indeed, even without Dr. Evers's testimony, we would have come to the same conclusion – i.e., that the POSA would have understood "highly refractory patients" in the Teva Press

Release to refer to patients who failed multiple preventative treatments – based on the references themselves.

As to the identity of treatments failed, we find that the POSA would have inferred that "refractory" patients had received typical preventative migraine treatments – i.e., those recited in claim 1. Ex. 1109 ¶¶ 136 (Dr. Evers's testimony that a POSA "would have understood that the 'highly refractory' patients described in Teva Press Release were 'refractory' as the term was used in the art and thus included those that had been treated with and failed at least three the most commonly prescribed migraine preventive classes, i.e., beta-blockers, anticonvulsants, and tricyclics, as recited by claim 1's 'selecting' limitation"); 111 n.16 (Dr. Evers's testimony that the medication recited in the clusters in our claim construction "include the most commonly prescribed migraine prevention treatments and treatment classes" and that in his own practice, "it would be exceedingly rare to see a patient that had *not* had an 'inadequate response' to at least two different medications selected from the Patent's defined 'clusters.'"); Ex. 1011, 3 (table with proposed definition of "refractory" requiring failure of treatment with drug classes overlapping with those recited in claim 1); Ex. 1012 (reporting that it is "common consensus" that refractory require failure with drugs from "the four most effective pharmacological classes" which it identifies as "beta blockers, anticonvulsants, calcium antagonists, [and] tricyclic antidepressants"); Ex. 1013 (proposing definition of refractory requiring, among other things failure of preventive medicines from "2 of 4 drug classes including: beta blockers, anticonvulsants, tricyclics, and calcium channel blockers").

As to length of treatment, the evidence of record also supports that the POSA would have inferred that "refractory" patients underwent a treatment

period of at least three months before being deemed to have failed treatment. Patent Owner argues that "a POSA would not have assumed from the mere use of the word 'refractory' that a patient had failed two or more different classes of preventive medications for at least three months at a stable dose appropriate according to accepted country guidelines." PO Resp. 49–50. But, as discussed *supra* § II.F.1.a.i, the evidence supports that three months was a very common minimum period for evaluating whether a treatment was successful. Absent a connection between the use of the word "refractory" and a reference suggesting a shorter evaluation period (like the tie between Sun and Tepper), we find that the POSA would have inferred a three-month evaluation period.[19]

Finally, as to the threshold for determining whether a treatment is successful, Dr. Evers testifies that "a preventative drug was considered clinically successful if it reduced migraine frequency and/or symptoms by at least 30% or 50%, depending on the criteria used." Ex. 1109 ¶ 23. To the extent Patent Owner's argument that Dr. Evers's testimony is not credible applies to this topic (PO Resp. 13), we do not find it persuasive because it does not call into question Dr. Evers's ability to speak to the criteria for determining success. This is particularly true where Dr. Evers's testimony is consistent with the evidence he cites. *See* Ex. 1016, 4 ("Success is defined as a 50% reduction in attack frequency or headache days, a significant decrease in attack duration, or an improved response to acute medication."); Ex. 1017, 8 ("Responder rates should be defined as either ≥ 30% or ≥ 50%

[19] Even if the POSA had inferred a shorter evaluation period, we find that it would not have impacted POSA's expectation of success for the reasons discussed *infra* § II.F.3.b.i. For the same reasons, it would not have adversely impacted a POSA's motivation to treat "refractory" patients.

reduction in (i) headache days with moderate or severe intensity, (ii) migraine days, or (iii) migraine episodes compared with the baseline period. Responder rates have been traditionally defined in migraine as ≥ 50% reduction, but in CM population, a ≥ 30% responder rate can be clinically meaningful."). Thus, we find that a POSA would have inferred that patients described as refractory did not meet this criteria for success.

Accordingly, the evidence supports that the POSA would have understood "refractory," as used in connection with migraine patients, to refer to a patient population that is very similar to the claimed Group I patients. We turn now to how the POSA would have understood the phrase "highly refractory patients," in the Teva Press Release, keeping in mind that, as discussed *supra* § II.F.2.b, the clinical trials referenced in the Teva Press Release do not require the participation of the claimed patient groups or separately report results for such patients, e.g., in a *post hoc* study.

We find that the POSA would have recognized a tension between how the term "refractory" is used in the migraine art and the absence of supporting data in the then-published documents. On the one hand, the absence of data in the underlying clinical trials lends support to Patent Owner's argument that the speaker quoted in the Teva Press Release intended to refer only to patients who were "resistant" or "difficult to treat" when using the phrase "highly refractory patients," particularly where the phrase describes participants in those very trials. On the other hand, the term "refractory" had a different, and understood, meaning in the migraine art. Moreover, the POSA would expect the quoted speaker, "Teva's Head of

Global Clinical Development for Migraine and Headaches" to be aware of that meaning.[20]

We find that the POSA would have given the term "refractory" in the Teva Press Release its ordinary meaning as used in the migraine art; the absence of supporting data would cause the POSA to give less weight to the Teva Press Release's statement suggesting efficacy in refractory patients, but would not cause the POSA to give the term "refractory" a meaning different than its ordinary use in the migraine art. In this regard, we note that a second reference draws the same conclusion from the same data. Ex. 1023, 7 (concluding that anti-CGRP antibodies "are effective for relatively refractory headaches" based on data from the fremanezumab clinical trial reflected in Exhibits 1038 and 1058). We acknowledge that Exhibit 1023 does not expressly define the term "refractory." However, we have already found that the POSA would have understood the word "refractory" when used to describe migraine patients to have a meaning similar to the claimed Group I patients, and two departures from the ordinary meaning of "refractory" seems somewhat unlikely. We further note that giving the word "refractory" its ordinary meaning when used in the Teva Press Release is consistent with multiple teachings in the art that anti-CGRP mAbs had the potential to treat refractory patients. Ex. 1037, 8 (teaching that a study that included patients that "failed at least two preventative drug classes" due to "lack of efficacy or poor tolerability" suggested efficacy in a

[20] The Teva Press Release attributes the "highly refractory patients" statement to Marcelo E. Bigal. Ex. 1041, 2. In addition to serving as "Teva's Head of Global Clinical Development for Migraine and Headaches" (Ex. 1041, 2), Dr. Bigal is also the lead author of multiple journal articles of record (Ex. 1022; Ex. 1023; Ex. 1028; Ex. 1034; Ex. 1038; Ex. 1039; Ex. 2011) and a named inventor on the '434 patent (Ex. 1045 code (72)).

"treatment-resistant population"); Ex. 1040, 14–15 (teaching that "[r]obust treatment effects were observed . . . in subjects who previously failed preventive migraine treatments"); Ex. 1040, 329 (disclosing that "[e]renumab 140 mg showed better efficacy in patients who had failed ≥1 or ≥2 prophylactic medications");[21] Ex. 1072, 74 (disclosing that patients with a "history of failure to preventive treatments" showed a "statistically significantly greater treatment effect . . . at Month 3"); *see also* Ex. 1053, 13 (teaching that "mAbs targeting CGRP or its receptor hold the most promise for preventive treatment" in "medically refractory subgroups").

In sum, we find that the POSA would have understood Sun's "failure to respond" patients to be quite similar to the patients suggested by the phrase "highly refractory patients."[22]

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[21] Ex. 1040 is a collection of abstracts. The abstract at pages 328–329 discusses the same underlying clinical trial as discussed in Ex. 1037. The abstract at pages 14–15 discusses a different clinical trial.

[22] Giving the phrase "highly refractory patients" the meaning suggested by Patent Owner would not change our determination with respect to motivation to combine. As discussed *supra* § II.F.2.c.i, fremanezumab and erenumab, indeed all of the anti-CGRP mAbs discussed *supra*, were recognized in the art as having similar efficacy and tolerability. This recognition does not depend solely on equating Sun's "failure to respond" patients and the Teva Press Release's "highly refractory patients." *See supra* § II.F.2.c.i. Recognition of similarity also includes evidence of similar efficacy among the general migraine population, evidence that the class of anti-CGRP mAbs were recognized to have similar efficacy, and evidence that other anti-CGRP mAbs were thought to have efficacy in treating a refractory population. *Id.* Treating the Teva Press Release as disclosing patients that were "difficult to treat" weakens the perceived similarity between fremanezumab and erenumab as relates to the claimed patients, but, even so, the evidence of record establishes motivation to use fremanezumab in Sun's methods by a preponderance of the evidence.

(iii) Evidence regarding CGRP pathway uncertainty and regarding differences between fremanezumab and erenumab in mechanism of action

Patent Owner argues "[f]remanezumab is an entirely different drug than erenumab" comprised of a "completely different antibody, directed against a different target." PO Resp. 19. According to Patent Owner, "[a] POSA would not assume fremanezumab's effectiveness in a particular patient population merely because erenumab demonstrated efficacy in that population." *Id.* (citing Ex. 2037 ¶¶ 228–231). Indeed, Patent Owner asserts, "a POSA would have considered the CGRP signaling pathway to be unpredictable in part due to CGRP's promiscuity with cellular receptors other than the CGRP receptor." Patent Owner explains:

> As Walker explained in 2013, "[t]he physiological and pathophysiological actions of CGRP could be mediated [through] multiple receptor subtypes, including the CGRP receptor, the AM_2 receptor and the AMY_1 receptor." EX2046, 3; *see also*, EX2047, Abstract (identifying the "presence of two CGRP-responsive receptors … AMY_1 … and the CGRP receptor."); CGRP's receptor promiscuity, coupled with "the complex nature of CGRP action," made "understanding [CGRP's] underlying biology and [signaling] mechanisms a distinct challenge." EX2046, 10. This unpredictability in the art is reflected in Petitioner's own references. For example, Dodick expressly discloses that "the site and mechanism of action of CGRP monoclonal antibodies is *unclear*." EX1003, 6. Teva Press Release discloses that "long-term total disruption to the normal physiological functions of the CGRP system … are *unknown*." EX1041, 3. And Tepper discloses that "the specific pathogenic mechanism of CGRP in migraine is *unknown*, including *uncertainty* with respect to its site of action." EX1037, 8; EX2037, ¶¶217-218.

Id. at 20–21.

We recognize that the evidence cited by Patent Owner, including two papers authored by Petitioner's witness, Dr. Hay, support the possibility that CGRP activity may be mediated through multiple receptor subtypes. Ex. 2046, 3; Ex. 2047, 2; *see also* Ex. 1239 ¶¶ 22–23 (testimony of author, Dr. Hay, acknowledging that articles she authored propose that there may be multiple CGRP receptors). We also recognize the evidence that there are aspects of CGRP's function – such as its "specific pathogenic mechanism . . . in migraine, including . . . its site of action" that were not known. Ex. 1037, 8; *see also* Ex. 1041, 3. However, we agree with Dr. Hay that any uncertainty created by the potential that there are multiple CGRP receptors and/or that CGRP has an uncertain mechanism of action would have been outweighed by the wealth of evidence (discussed *supra* § II.F.2.c.i) that erenumab and fremanezumab, indeed all the anti-CGRP mAbs discussed *supra*, have comparable safety and efficacy. Ex. 1239 ¶ 25 ("[A]ny inferences drawn from my papers in 2015 regarding potential differences in clinical properties among anti-CGRP pathway mAbs would have been outweighed by September 2017 by the clinical trial data showing that erenumab, galcanezumab, and fremanezumab were comparable in terms of efficacy, tolerability, and safety."); *see also* Ex. 1034, 2 ("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.") (emphasis added); Ex. 1035, 10 ("The introduction of ***mAbs targeting the CGRP neuroactive peptide and/or its main receptor*** appears to lay the foundation for a new class of prophylactic drugs that could finally overcome, even only partially, the efficacy, safety, tolerability, and adherence issues that often affect chronic migraineurs.") (emphasis added); Ex. 1053, 13 (suggesting that

"mAbs targeting ***CGRP or its receptor*** hold the most promise for preventative treatment" in specific subgroups of migraine patients, including the "medically refractory subgroup[]").

Patent Owner argues that "at the time of the invention, there were known advantages of targeting the CGRP receptor (as opposed to the ligand)." PO Resp. 21. As support, Patent Owner cites Dr. Grosberg's testimony that that "it was known that 'high selectivity' for blocking the CGRP receptor itself was advantageous because . . . if . . . other receptors are blocked by a less selective agent, undesired side effects could arise." Ex. 2037 ¶ 321 (citing Ex. 2049, 2); PO Resp. 21. Patent Owner and Dr. Grosberg also cite several references teaching that the "ability to block the CGRP receptor (as opposed to CGRP itself) might be advantageous since binding to the CGRP receptor might prevent receptor activation, independent of CGRP release." *Id.* (citing Ex. 2048, 3; Ex. 2075, 8; and Ex. 2076, 4). According to Patent Owner, a POSA would not have "expected to see these same advantages" using fremanezumab and thus, would have been "dissuaded . . . from switching drugs." PO Resp. 21.

We are not persuaded that a POSA would have perceived erenumab to be advantageous as compared to fremanezumab on the basis that fremanezumab is a "less selective agent" than erenumab. Patent Owner and Dr. Grosberg cite Shi 2016 (Ex. 2049) as teaching the "high selectivity" of erenumab for blocking the CGRP complex as compared to "less selective agents," and use this teaching to imply that fremanezumab is less selective than erenumab. PO Resp. 21; Ex. 2037 ¶ 321. But, as Dr. Hay explains, "[t]he 'less selective agents' that *Shi 2016* refers to are the [small-molecule CGRP receptor antagonists] Gepants," not fremanezumab. Ex. 1239 ¶ 30. We find Dr. Hay's testimony on this point persuasive, as it is consistent with

Shi 2016. *See* Ex. 2049, 2 (discussing concerns regarding small molecule CGRP antagonists that have prevented their approval and opining that "[a] monoclonal antibody may be a preferred modality to target the CGRP receptor"). Moreover, Shi 2016 concludes with a discussion of the advantages of the superior selectivity of mAbs as a class. Ex. 2049, 8 (discussing advantages of mAbs over small molecule CGRP-receptor antagonists, noting "[i]n addition to high potency and superior selectivity, which may provide the benefit of fewer off-target side effects, monoclonal antibodies provide advantages that make them better suited for preventive treatment compared with small molecules"); Ex. 1239 ¶ 32 (interpreting Shi as teaching that "antibodies as a class have limited off-target effects as compared to small molecules because they bind to fewer biological targets and are therefore considered more specific."). Accordingly, the evidence of record does not support that the POSA would have perceived erenumab to have a selectivity advantage over fremanezumab.

As to Patent Owner's argument that the POSA would have perceived erenumab to have the advantage that it "might prevent receptor activation, independent of CGRP release," we recognize that the references cited as support posit preventing receptor activation independent of CGRP release only as a theoretical advantage. *See* Ex. 2048, 3 ("***In theory***, the ability to block the CGRP receptor (as opposed to CGRP itself) ***might be*** advantageous since binding to the CGRP receptor ***might*** prevent receptor activation, independent of CGRP release."); Ex. 2075, 8 (similar); and Ex. 2076, 4 (similar); *see also* Ex. 1239 ¶¶ 33–37 (Dr. Hay testimony discussing absence of data supporting this advantage). Nonetheless we give this theoretical advantage some weight in considering whether a POSA

would have had reason to substitute fremanezumab for erenumab.[23] That said, we find that, like Patent Owner's evidence of uncertainty regarding the CGRP pathway, this theoretical advantage is outweighed by evidence from actual clinical trials (discussed *supra* § II.F.2.c.i) as well as suggestions in the art that targeting both the ligand or its receptor would be effective. *See* Ex. 1034, 2; Ex. 1035, 10; Ex. 1053, 13.

In sum, we are not persuaded by Patent Owner's evidence and argument that unpredictability in the CGRP pathway and differences between targeting the CGRP receptor as compared to its ligand materially detracts from the expectation that fremanezumab and erenumab would have similar efficacy or otherwise negatively impacts a POSA's motivation to substitute one for the other.

(iv) Conclusion with respect to similar efficacy

Taking into consideration all of the arguments and evidence of record bearing on Petitioner's assertion that similar efficacy provides a motivation to combine – including evidence regarding: efficacy in the general migraine

[23] In determining whether Petitioner has established motivation to use fremanezumab in place of erenumab, we consider this theoretical advantage together with all of the evidence of record, including the evidence, discussed above, that the comparable efficacy of fremanezumab and erenumab was "recognized throughout the art." We are not persuaded by Patent Owner's argument that Petitioner cannot "discount Patent Owner's evidence that blocking the CGRP receptor would have been thought superior to binding the ligand, by arguing that the evidence was eventually disproven through later clinical trials" because "[o]bviousness turns on what a POSA would have expected *ex ante*—not what is later proven by empirical evidence." Sur-reply 9–10. In this regard, we note that the relevant date is not the date of Patent Owner's evidence supporting that blocking the CGRP receptor would have been thought superior, but rather the priority date of the challenged claims, which we discussed *supra* § II.D.

population, efficacy in the refractory migraine population, differences in Sun's and the Teva Press Release's patient populations, uncertainty regarding the CGRP pathway, and differences between fremanezumab and erenumab in mechanism of action – we find that Petitioner has established, by a preponderance of the evidence, that the POSA would have expected erenumab and fremanezumab to have similar efficacy.

d) Conclusion regarding motivation to combine

We find that Petitioner has established, by a preponderance of the evidence, that a POSA would have been motivated to use fremanezumab in place of erenumab in Sun's method. This finding is supported by: 1) evidence showing that fremanezumab and erenumab have similar efficacy, 2) evidence showing that mAbs, including fremanezumab and erenumab, were treated as a class and recognized to have similar efficacy, and 3) evidence showing that prior art recognized both fremanezumab and erenumab, as well as mAbs in general, to have the potential to treat refractory migraine. *Aventis Pharma Deutschland GmbH v. Lupin, Ltd.*, 499 F.3d 1293, 1301 (Fed. Cir. 2007) (for motivation "it is sufficient to show… an expectation… [of] similar properties") (quotations omitted). Sun's disclosure of using fremanezumab in combination therapy provides further motivation to use fremanezumab in place of erenumab because it teaches that fremanezumab would be safe and effective in Sun's patients.

3. Does the evidence support 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 38–39. **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.[24] We conclude that Petitioner has established, by a preponderance of the evidence, that the POSA would have expected fremanezumab to be successful in treating each of the three claimed patient groups.

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

Two studies of the anti-CGRP antibody, fremanezumab, show that fremanezumab was effective as a migraine prophylactic. Ex. 1038, 2 ("This study provides level 1b evidence (well conducted individual randomised controlled trial) that [fremanezumab] is effective for the preventive treatment of chronic migraine"); Ex. 1039, 3 ("This study provides level 1b evidence (ie, a robust, randomized clinical trial) that two doses of [fremanezumab], a monoclonal antibody against CGRP, are effective for the preventive treatment of high-frequency episodic migraine"); Ex. 1057, 6 (study characterized in Exhibit 1039); Ex. 1058, 5 (study characterized in Ex. 1038).

[24] 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.

The Teva Press Release reports the results of these 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 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 [have] 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. 1109 ¶¶ 165–167; Ex. 1038, 5–7).

Patent Owner argues "Petitioner's cited references for fremanezumab all discuss the same two clinical trials: NCT02025556 episodic migraine . . . and NCT02021773 chronic migraine." PO Resp. 41 (citing Ex. 1023, Ex. 1038, Ex. 1039, Ex. 1041, Ex. 1057, and Ex. 1058). Patent Owner then asserts that the POSA "would not have understood these trials, . . . or references discussing these trials . . . , to teach or suggest that the patients in those trials were the inadequate response patients of the '434 patent." *Id.* According to Patent Owner, "[w]ithout that essential teaching—along with data showing success within this patient population alone—a POSA would have no basis to expect any success in the failure-prone patients of the challenged claims."

For the reasons discussed *supra* § II.F.2.c.ii, we find that the POSA would have understood the phrase "highly refractory patients" in the Teva Press Release to refer to patients very similar to those disclosed in Sun. By extension, such patients are also very similar to the claimed "inadequate response" patients. However, as discussed *supra* § II.F.b, none of the references discussing the fremanezumab clinical trials support that the claimed inadequate response patients were required by the inclusion criteria of the study. Nor do they separately report any data regarding the participation of inadequate response patients in those studies.

The absence of data supporting the statement that fremanezumab provided a "fast onset of preventive response" and an "impressive decrease in migraine days" among "highly refractory patients" diminishes the support it lends to the Petitioner's argument that the POSA would reasonably have expected to be successful in treating the claimed patients with

fremanezumab. However, we cannot completely discount Teva's own characterization of these studies as showing that fremanezumab is effective in "highly refractory patients" (Ex. 1041, 2), particularly where others appear to have echoed the same conclusion (*See, e.g.,* Ex. 1023, 7 (concluding that anti-CGRP antibodies "are effective for relatively refractory headaches" based on data from the fremanezumab clinical trial reflected in Exhibits 1038 and 1058)). Accordingly, we find that the Teva Press Release helps to support an expectation that fremanezumab would be successful in treating the claimed patients.[25]

b) Teachings in the art regarding the effectiveness of other anti-CGRP mAbs

Sun teaches that a monthly dose of 70 mg of the anti-CGRP antibody, erenumab, was "efficacious in preventing episodic migraine" and that efficacy was "similar regardless of . . . prior history of prophylactic medication use." *Id.* ¶¶ 268, 272. In addition to these teachings, Sun also describes a prospective Phase II clinical trial and a prospective Phase III clinical trial. *Id.* ¶¶ 273–295. The results of the two prospective trials are described in separate, subsequent documents: Tepper (Ex. 1037, reporting on the Phase II trial) and Goadsby (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

[25] This would be true even if we were to interpret the term "highly refractory" in the Teva Press Release to mean only "difficult to treat," because, even construed as Patent Owner suggests, the Teva Press Release supports that fremanezumab specifically, and mAbs by extension, may provide relief to patients who are more difficult to treat than the general migraine population.

suggesting that "there could be efficacy in a treatment-resistant population." Ex. 1037, 8. 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 and 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. Pet. 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.

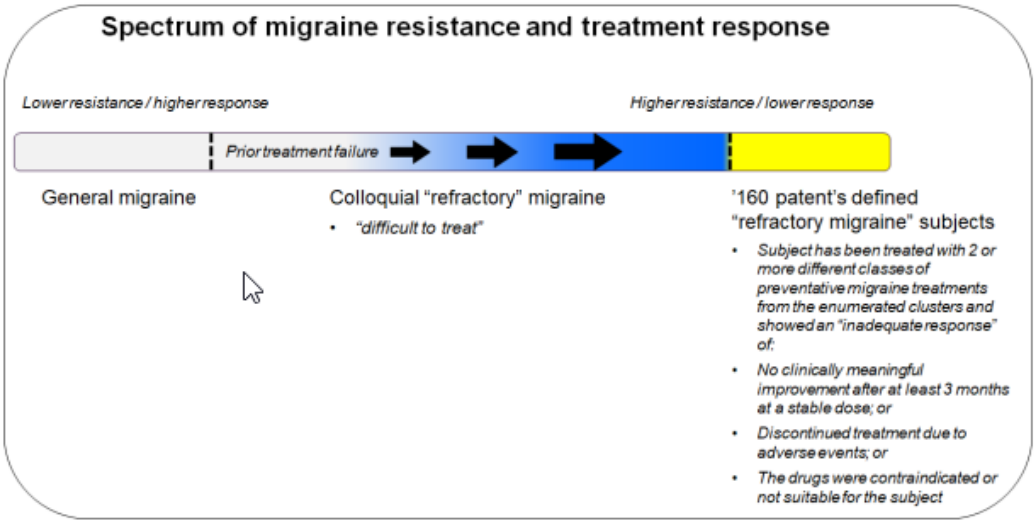
Petitioner argues that "the clinical success of erenumab and galcanezumab in patients with a history of treatment failure further provided a reasonable expectation that clinically-successful fremanezumab—which operated by the same overall anti-CGRP mechanism—would likewise be effective within the claimed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

Below, we address the arguments and evidence of record regarding whether the clinical trials of erenumab and of galcanezumab contribute to an expectation of success, as evidenced in each of Sun, Tepper, Goadsby, and the Headache Abstract (Ex. 1072).

(i) Evidence that the POSA would have expected success based on Sun's Example 3

Sun's Example 3 discloses 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. Petitioner argues that this helps to support an expectation of success. Pet. 36–37. Patent Owner argues that the results disclosed in Sun do not support an expectation of success because Sun does not disclose treating the claimed patients. More specifically, Patent Owner asserts that Sun does not support an expectation of success because the claimed Group I patients are more difficult to treat than Sun's inadequate response patients.

According to Patent Owner, "[a]t the time of the invention, migraine resistance to treatment was known to occur on a spectrum." PO Resp. 2. On this spectrum "more (or highly) 'refractory' migraine patients were known to be more difficult to treat than less (or partially) refractory migraine patients." *Id.* Patent Owner and Dr. Grosberg illustrate the spectrum in Figure 1, reproduced below.



Id. at 3; Ex. 2037 ¶ 56. Figure 1 depicts a "[s]pectrum of migraine resistance and treatment response" with "[l]ower resistance/higher response" on the left side of the spectrum and "[h]igher resistance/lower response" on the right side of the spectrum. *Id.* Figure 1 places "[g]eneral migraine" patients on the left end of the spectrum, indicating that they are the easiest to treat. *Id.* "Colloquial 'refractory' migraine" patients are the middle of the spectrum, and the "'434 patent's defined 'refractory migraine'" patients are on the right end of the spectrum, indicating that they are the most difficult to treat. *Id.*

Patent Owner argues that "[t]he selected inadequate response patients of the '434 patent are *more resistant to treatment and more prone to treatment failure* than the colloquial 'refractory' migraine patients in the

prior art." PO Resp. 4. More specifically, Patent Owner contends that in the clinical trials described in Sun, patients were deemed to have failed a preventive medication after six weeks of therapy rather than three months as required of Group I patients. *Id.* at 30. According to Patent Owner, "a POSA would have known that the patients in Sun's examples were different, and easier-to-treat, patients than the '434 patent's inadequate response patients who had no clinically meaningful improvement with prior medications after *at least three months* of therapy, given at a stable dose." *Id.* Patent Owner also cites Dr. Grosberg, who testifies that Figure 7B provides no indication that any of the patients with 'prior treatment failure' experienced failure of *two or more* prior medications, let alone failure of two or more *different classes* of medications." Ex. 2037 ¶ 102 (cited at PO Resp. 27). According to Dr. Grosberg, "the 'prior treatment failure' patients in Figure 7B could just be those who were treated with *only one* prior preventive medication or for *less than three* months—which a POSA would have known to be a different, and an easier-to-treat, patient group than the patent's defined inadequate response patients." *Id.* We are not persuaded that the evidence supports that the claimed patients would be more difficult to treat than Sun's patients.

The record includes evidence supporting that with anti-CGRP mAbs, failure of prior preventative migraine prophylactics is not predictive of how hard patients are to treat with anti-CGRP mAbs. For example, contrary to the expectation that they would be harder to treat, the Headache Abstract teaches that patients who failed to respond to prior preventative treatments showed a "statistically significantly greater treatment effect" than their counterparts when administered 300 mg of galcanezumab. Ex. 1072, 74. From this, the Headache Abstract concludes that failure to respond to

preventative treatments may be a "predictor[] of clinical response with *greater* treatment effect." *Id.* Similarly, Goadsby teaches that treatment of patients who failed prior treatments with 140 mg of erenumab had *greater* efficacy than the treatments in the overall trial population. Ex. 1040 ("Robust treatment effects were observed for both 70 mg and 140 mg erenumab in subjects who had previously failed preventative migraine treatments. For 140 mg, effects were numerically greater in this subpopulation than in the overall trial population."). And Sun itself reports that the efficacy of erenumab "was similar regardless of . . . prior history of prophylactic medication use." Ex. 1006 ¶ 268, Fig. 7B. These teachings are consistent with the evidence that anti-CGRP mAbs work by a different mechanism of action than other migraine prophylactics, and thus might be expected to succeed where other treatments had failed. *See infra* § II.F.3.c.

We weigh this evidence supporting that failure of prior treatment is not predictive of how hard patients are to treat with anti-CGRP antibodies against Dr. Grosberg's testimony – the only evidence offered by Patent Owner to support that Group I patients are more difficult to treat than the cited prior art patients. Dr. Grosberg testifies broadly that "a POSA would have concluded that the patients with migraine characterized as 'refractory' in [the] cited prior art are on the lower end of the resistance spectrum and are easier-to-treat (with lower resistance to treatment and higher response to treatment) compared to the defined refractory migraine patients of the '434 patent." Ex. 2037 ¶ 59. With respect to length of treatment, Dr. Grosberg asserts that patients who fail treatment after three months fall on the more resistant end of the spectrum of resistance to treatment than patients who fail treatment after only six weeks. Ex. 2037 ¶ 156 ("A POSA would have known that a patient who did not show clinically meaningful improvement

after a longer evaluation period with a medication was more resistant to treatment than a patient who did not show improvement after a shorter evaluation period with the medication."). Dr. Grosberg explains: "This is because, for example, a patient who did not show improvement in a shorter evaluation period (e.g., 6 weeks) could still show improvement with the same medication after treatment for a longer period (e.g., 3 months) and perhaps was not even resistant to treatment in the first place." *Id.*

We recognize that, logically speaking, requiring a patient to fail more treatments and giving a patient more time to respond to treatment before designating that treatment a failure will likely narrow the subset of patients deemed refractory. *Id.*; *see also* Ex. 1013 (recognizing that an evaluation period longer than 2 months "would be preferrable," but concluding that such an evaluation period would "prolong the time necessary to meet refractory criteria" and thus "prevent patients receiving the appropriate level of care."). However, Dr. Grosberg does not cite to any evidence to support a correlation between the time it takes to respond to treatment with one medication, or the number of prior treatments a patient has failed, and the likelihood that treatment with an anti-CGRP mAb that acts by a different mechanism of action will be successful. Ex. 2037 ¶ 56 (Dr. Grosberg's testimony lacking citation to evidence). Indeed, more generally, none of Dr. Grosberg's multiple invocations of a spectrum of resistance cite any evidence to support that such a spectrum was recognized in the art. *See* Ex. 2037 ¶¶ 52, 56, 59, 78, 124, 156, 158, 168, 175, 178, 179, 189, 219, 298, 311, 312, 319 (discussing spectrum of evidence without citation to evidentiary support). This significantly diminishes the persuasiveness of Dr. Grosberg's testimony. *Xerox Corp. v. Bytemark, Inc*., IPR2022-00624, Paper 9 at 15 (PTAB Aug. 24 ,2022) (precedential) (finding that conclusory

testimony that "does not cite to any additional supporting evidence or provide any technical reasoning to support [that testimony] . . . is entitled to little weight"); *see also* 37 C.F.R. § 42.65(a) ("Expert testimony that does not disclose the underlying facts or data on which the opinion is based is entitled to little or no weight.").

At oral argument, counsel for Patent Owner argued that Dr. Grosberg's spectrum of resistance testimony was supported by the use of adjectives to modify the word "refractory" in the prior art. Tr. 32–33. More specifically, Patent Owner argues that the uses of "partially" and "highly" to modify the word "refractory" in two articles confirms that "refractory" conditions exist on a spectrum along which treatment success and expectations of success vary. We agree that the use of adjectives to modify the term "refractory" lends support to the notion that there may be degrees of refractoriness. Ex. 1041, 2 ("The very fast onset of preventative 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.") (emphasis added); Ex. 1042, 8 ("Patients seen at specialty headache centers are often medically ***partially refractory***, having failed a number of preventives with limited remaining options.") (emphasis added). But such support is weak. And Dr. Grosberg does not cite these articles. More importantly, neither of these articles speaks to whether the length or number of treatments impacts degree of refractoriness. Nonetheless, we give these articles some weight as supporting that there are degrees of refractoriness.

In considering the evidence regarding Dr. Grosberg's spectrum of resistance as it relates to length of treatment, we also give some weight to

the evidence supporting that the evaluation period for determining whether a treatment is effective is not critical. Ex. 1196, 3 ("Although there is no evidence on the optimal length of prophylactic treatments, 3 months is usually considered sufficient to assess prophylactic efficacy,"); Ex. 1234, 198:18–199:13 (testimony of Dr. Grosberg: "I agree [with the statement in Ex. 1196] that there was no evidence in the optimal length of prophylactic treatments at the time").

Considering all of the evidence with respect to the impact of the treatment evaluation period, we are not persuaded that the difference between Sun's 6-week evaluation period and the claimed 3-month evaluation period would have a material impact on a POSA's expectation of success. Similarly, we are not persuaded that the difference between Sun's unspecified number of treatment failures (*see* Ex. 1006 ¶ 268, Fig. 7B) and the claimed inadequate response to at least two preventative medications would have a material impact on a POSA's expectation of success. We give some weight to Dr. Grosberg's testimony to the contrary (*see e.g.,* Ex. 2037 ¶ 102) but find that this testimony, even with the modest support lent by the use of adjectives "highly" and "partially" to modify "refractory," is outweighed by the evidence supporting that patients who had failed prior treatments responded to anti-CGRP treatment as well as, if not better than, patients who had not failed prior treatments. The evidence that there is no recognized optimal evaluation period further supports our conclusion with respect to the impact of length of treatment.

Having determined that the length and number of treatments would not materially impact a POSA's expectation of success, we are not persuaded that the POSA would have viewed the claimed narrower subset of patients as more difficult to treat with anti-CGRP mAbs than patients, like

those disclosed in Sun, who fail 6 weeks of treatment with an unspecified number of treatments. Put another way, the evidence of record does not support that a POSA would have different expectations for how, for example, a patient who failed to respond to six weeks of treatment with a beta blocker would respond to treatment with an anti-CGRP mAb than for a patient who failed to respond to three months of treatment with a beta blocker and an anti-convulsant. Thus, we are not persuaded by Patent Owner's argument that "[t]he selected inadequate response patients of the '434 patent are *more resistant to treatment and more prone to treatment failure*" than the patients in Sun's Example 3. PO Resp. 4, 30.

Patent Owner also argues that the post-hoc analysis in Figure 7B separates patient data from "prior history" into "naïve" and "prior treatment failure" patients and that these categories do not align with the claimed "inadequate response" patients. PO Resp. 27. We have already discussed the impact of length and number of treatments on expectation of success. Patent Owner argues that Figure 7B provides "no details as to how treatment was deemed a failure." *Id*. But, we see no reason why Sun's Figure 7B would depart from how Sun determines success, as disclosed in its definition of "treatment failure," which, as discussed above defines a subset of Group I's "clinically meaningful response." *See supra* § II.F.1.a.i; *see also* Ex. 1006 ¶ 65.

Patent Owner argues that Figure 7B relies on a post-hoc analysis and that "such data do not purport to be reliable for showing actual causal connections between prior treatment failure and success as the study was not blinded or randomized for that variable." PO Resp. 27 (citing Ex. 2037 ¶ 105). Although, a post-hoc analysis of a subgroup of refractory patients may not be a strong as, for example, an analysis in which this patient

subgroup was defined *a priori, post hoc* analyses were recognized and relied upon in the art. *See e.g.,* Ex. 1224, 7 ("post hoc analyses do play an important role in better understanding the benefits of any drug, including evaluation of subsets of patients that might experience particular benefit"). Moreover, the Federal Circuit has explained that "a person of skill in the present context *can* draw reasonable inferences about the likelihood of success even without a perfectly designed clinical trial showing a statistically significant difference in efficacy between a specific dose and placebo." *Acorda Therapeutics, Inc. v. Roxane Labs., Inc*., 903 F.3d 1310, 1333–34 (Fed. Cir. 2018) ("This Court has long rejected a requirement of '[c]onclusive proof of efficacy' for obviousness."). Accordingly, we do not disregard the data and conclusions relating to Sun's Figure 7B simply because they were generated post-hoc. Rather, we consider that Figure 7B was generated based on post-hoc data as one factor we weigh in assessing the weight to give a particular study.

Patent Owner argues that the data in Sun's Figure 7B "are not statistically significant." PO Resp. 27. As support, Patent Owner cites the testimony of Dr. Grosberg, who testifies that based on the p-value in Figure 7B, a POSA would have understood that "the data is not strong enough to suggest that erenumab was effective in patients with previous treatment history." Ex. 2037 ¶ 105. Dr. Grosberg's testimony that the POSA would not accord Figure 7B statistical significance is unrebutted and credible. This diminishes the weight we accord to Sun's teaching that the efficacy of 70 mg of erenumab, was "similar regardless of . . . prior history of prophylactic medication use." Ex. 1006 ¶ 268.

The weight we give Sun's teaching on efficacy is bolstered, to some extent, by that fact that it is consistent with other, similar statements in the

art supporting that prior treatment failures may not be predictive of whether treatment with an anti-CGRP mAb will be successful. *See e.g.,* Ex. 1072, 74 (discussed *supra* § II.F.3.a.iv); Ex. 1037 (discussed *infra* § II.F.3.b.ii); Ex. 1040, 16 (discussed *infra* § II.F.3.b.iii); and Ex. 1040, 329 ("Erenumab 140 mg showed better efficacy in patients who had failed ≥1 or ≥ 2 prophylactic medications.").[26] It is also bolstered, to some extent, by the evidence that anti-CGRP mAbs act through a different mechanism of action than conventional treatments. *See infra* § II.F.3.c.

Overall, we find that Sun's statement still carries some weight even though it was prepared post-hoc and lacks data supporting its statistical significance. We find that Sun's Example 3, which teaches that the efficacy of 70 mg of erenumab, was "similar regardless of . . . prior history of prophylactic medication use" (Ex. 1006 ¶¶ 268, 272), provides modest support for the expectation that erenumab would be successful in treating the claimed patient groups. This, in turn, helps to support an expectation that fremanezumab would be successful in treating the claimed patient groups. *See* Ex. 1092 ¶ 168–175 (Dr. Evers's credible testimony that a POSA would have reasonably expected that "*Sun*'s results for its receptor mAb would translate to *Dodick*'s ligand-targeting anti-CGRP mAb.").

[26] Exhibit 1040 is entitled Abstracts of the 18th International Headache Congress. Ex. 1041, 1. It is comprised of multiple abstracts, including the abstract referred to herein as "Goadsby." *Id.* at 15–16. The citation to page 329 of Exhibit 1040 is not to Goadsby, but to a different abstract within the same collection of abstracts. It appears the non-Goadsby abstract relates to the same clinical trial as is described in Tepper. *Compare id.* at 328-329 *with* Ex. 1037.

(ii) Evidence that the POSA would have expected success based on the results of Sun's proposed Phase II clinical as reported in Tepper

Sun describes a prospective Phase II clinical trial of erenumab, the results of which are described in a subsequently published reference, Tepper. Ex. 1006, ¶¶ 273–289; Ex. 1037; PO Resp. 27–30 (tying Sun's prospective clinical trials to Tepper and Goadsby). The published results show that, in the Phase II trial, "453 patients (68%) . . . had failed at least one previous preventive drug class because of lack of efficacy or poor tolerability and 327 (49%) . . . had failed at least two previous drug classes." Ex. 1037, 8. Tepper describes the results of the trial as suggesting that "there could b[e] efficacy in a treatment-resistant population." *Id*. Petitioner argues that this helps to support an expectation of success. Pet. 36–38.

Patent Owner argues that Tepper "fails to disclose any success in inadequate response patients that fit the definition of the '434 patent" and thus, according to Patent Owner, "a POSA would not have any basis to expect that the treatment described in Example 4 of Sun [and in Tepper] would succeed in the selected inadequate response patients of the challenged claims." PO Resp. 28 (citing Ex. 2037, ¶¶ 111-113). We disagree.

Tepper discloses that 49% of the patients in its Phase II trial failed "at least two previous preventive drug classes" either "because of lack of efficacy or poor tolerability." Ex. 1037, 8. As Petitioner points out, and Patent Owner does not dispute, the preventative classes of prior preventatives in this Phase II trial largely mirror those of the claims. Pet. Reply 18; *compare* Ex. 1223, 2 (listing prior preventives from Phase II study discussed in Ex. 1037), *with* Ex. 1045, 173:29-35 (claim 1, listing classes of preventatives). Moreover, even if the classes of treatments where not

enumerated, a POSA would have understood "preventives" to include typical preventative migraine treatments. Ex. 1109 ¶ 111 n.16 (discussed *supra* § II.F.3.c.ii).

As to length of treatment, we are not persuaded by Patent Owner's argument that Tepper "considered a preventive medication a failure if it failed after *at least six weeks* of therapy—far different from the *at least three months* of therapy required for the inadequate response patients of the claimed method." PO Resp. 30. For the reasons discussed *supra* § II.F.3.b.i, we are not persuaded that the difference between a 6-week evaluation period and the claimed 3-month evaluation period would have a material impact on a POSA's expectation of success.

As to how Tepper defined "lack of efficacy," Tepper states that "[r]eductions of headache frequency from baseline of more than 30% and by more than one day per month are generally thought to represent a clinically relevant change." Ex. 1037, 8. This is consistent with Dr. Evers's testimony that "a preventative drug was considered clinically successful if it reduced migraine frequency and/or symptoms by at least 30% or 50%, depending on the criteria used." Ex. 1109 ¶ 23; *see also* Ex. 1016, 4 ("Success is defined as a 50% reduction in attack frequency or headache days, a significant decrease in attack duration, or an improved response to acute medication."); Ex. 1017, 8 ("Responder rates should be defined as either ≥ 30% or ≥ 50% reduction in (i) headache days with moderate or severe intensity, (ii) migraine days, or (iii) migraine episodes compared with the baseline period. Responder rates have been traditionally defined in migraine as ≥ 50% reduction, but in CM population, a ≥ 30% responder rate can be clinically meaningful."). We find that a POSA would have inferred that patients who failed for "lack of efficacy" failed to meet this criteria for success.

As to Tepper's patients who fail for "poor tolerability," Tepper uses this phrase to describe a reason why patients failed treatment. Ex. 1037, 8 ("This study provided robust representation of . . . subgroups of patients . . . who had failed at least one previous preventive drug class because of . . . poor tolerability."); *see also id.* at 2 ("Oral preventive therapies available at present . . . are often . . . poorly tolerated, which can lead to low adherence rates."). Such patients are sufficiently similar to the claimed Group II patients (i.e., patients for whom adverse events made continued treatment intolerable) that Tepper helps to support an expectation of success in the claimed Group II patients.[27]

In sum, we find that the POSA would have understood Tepper's "patients who had failed at least two previous preventative drug classes" either "because of lack of efficacy or poor tolerability" to disclose patients very similar to those claimed. Relatedly, we find that the POSA would have understood Tepper's statement that these results "suggest[] there could b[e] efficacy in a treatment-resistant population" to suggest efficacy in a patient population very similar to that claimed, because, as Dr. Evers explains, "a POSA would have understood 'treatment-resistant' to refer to 'refractory.'"

[27] Patent Owner appears to question whether Tepper's "side effects satisfy Sun's definition of 'intolerable' (and therefore Sun's prior treatment failure) because they outweigh clinical improvement may depend on the severity of the migraine in the first instance, such that one of skill in the art would not have extrapolated from Sun Example 4 [the results of which are reported in Tepper] to the claimed method, which defines success, failure, and starting severity of migraine differently." PO Resp. 28. To the extent we understand this argument, we do not find it persuasive because it conflates Group I and Group II patients. As discussed *supra* § II.F.1.a.ii, our construction of Group II patients does not preclude patients from experiencing a benefit from a prior treatment or from weighing such benefit against side effects.

Ex. 1109 ¶ 108; *see supra* § II.F.2.c.ii (explaining how the POSA would have understood the term "refractory" when used in the migraine art).

Tepper thus provides strong support for the expectation that erenumab would be successful in treating the claimed patient groups. This, in turn, helps to support an expectation that fremanezumab would be successful in treating the claimed patient groups. *See* Ex. 1109 ¶ 169–173 (Dr. Evers's credible testimony that a POSA would have reasonably expected that "*Sun*'s results for its receptor mAb would translate to *Teva Press Release's* ligand-targeting anti-CGRP mAb.").

(iii) Evidence that the POSA would have expected success based on the results of Sun's proposed Phase III clinical trial as reported in Goadsby

Sun describes a prospective Phase III clinical trial of erenumab, the results of which are described in a subsequently published reference, Goadsby. Ex. 2006 ¶¶ 290–295; Ex. 1040, 15–16; PO Resp. 27–30 (tying Sun's prospective clinical trials to Tepper and Goadsby). Goadsby describes the results of the Phase III trial 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. Petitioner argues that this helps to support an expectation of success. Pet. 36–37.

Patent Owner argues that the clinical trial described in Goadsby "was not designed to test efficacy in refractory patients." PO Resp. 29. According to Patent Owner, the "data were assembled in post-hoc fashion, the analysis was not blinded, nor were the data statistically significant." *Id.* In addition, Patent Owner asserts that the clinical trial reported in Goadsby "considered a preventive medication a failure if it failed after at *least six*

weeks of therapy—far different from the *at least three months* of therapy required for the inadequate response patients of the claimed method." *Id.* at 29–30. Patent Owner's arguments are unavailing.

As discussed *supra* §§ II.F.3.b.i, the law does not require "'[c]onclusive proof of efficacy' for obviousness" and *post hoc* analyses are recognized and relied upon in the art. Ex. 1224, 7; *Acorda Therapeutics,* 903 F.3d at 1333–34. As also discussed *supra* § II.F.3.b.i, we are not persuaded that the difference between a 6-week evaluation period and the claimed 3-month evaluation period would have a material impact on a POSA's expectation of success. Thus, a six-week treatment length does not materially impact a POSA's expectation of success.

We recognize that Table 1 indicates that "[s]tatistical significance was not assessed in the subgroup analysis." Patent Owner correctly identifies this as a weakness in Goadsby's data. PO Resp. 29. This diminishes the weight we accord to Goadsby's teaching that erenumab showed "[r]obust treatment effects . . . in subjects who had previously failed preventive migraine treatments." Ex. 1040, 15. However, Goadsby interpreted its own data as "suggest[ing] that erenumab may have particular utility in this subgroup of patients." *Id.* at 16. In addition, the weight we give Goadsby's teaching on efficacy is bolstered, to some extent, by that fact that it is consistent with other, similar statements in the art. *See e.g.,* Ex. 1072, 74 (discussed *infra* § II.F.3.b.iii); Ex. 1006 ¶ 268 (discussed *supra* § II.F.3.b.i); Ex. 1037 (discussed *supra* § II.F.3.b.ii); Ex. 1040, 329 ("Erenumab 140 mg showed better efficacy in patients who had failed ≥1 or ≥ 2 prophylactic medications.").

In sum, we find that Goadsby provides modest support for the expectation that erenumab would be successful in treating the claimed

patient groups. This, in turn, helps to support an expectation that fremanezumab would be successful in treating the claimed patient groups. *See* Ex. 1092 ¶ 168–175 (Dr. Evers's credible testimony that a POSA would have reasonably expected that "*Sun*'s results for its receptor mAb would translate to *Dodick*'s ligand-targeting anti-CGRP mAb.").

(iv) Arguments relating to the Headache Abstract

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.

Patent Owner argues that the Headache Abstract provides a "post-hoc analysis" and "contains no definition of 'history of failure to preventive treatments,' and no information regarding the type or nature of 'failure,' or of the number of patients with 'history of failure' who were actually treated with galcanezumab.'" PO Resp. 47. According to Patent Owner, "[w]ithout details regarding the patient population and definition of "history of failure," such as duration of prior treatment that failed, the number of such patients, or actual efficacy data stratified by prior history of treatment failure, a POSA would not have known whether the patent's inadequate response patients were included in the analysis." *Id.*; *see also id.* at 42 (arguing that the Headache Abstract, "does not disclose that these patients had all the required characteristics of the groups of the inadequate response patients of the '434 patent").

Patent Owner's argument that the Headache Abstract does not support an expectation of success because it relies on a *post-hoc* analysis and does not provide details on number of patients or data stratified by prior history is not persuasive. As discussed *supra* §§ II.F.3.b.i, the law does not require "'[c]onclusive proof of efficacy' for obviousness" and *post hoc* analyses are recognized and relied upon in the art. Ex. 1224, 7; *Acorda Therapeutics,* 903 F.3d at 1333–34. Moreover, notwithstanding Patent Owner's criticisms, the variables analyzed were "pre-specified before study unblinding" and are described as "statistically significant." Ex. 1072, 73–74. Accordingly, although the Headache Abstract's may not be entitled to as much weight as a perfectly designed clinical trial designed to study galcanezumab in the claimed refractory patients, it may nonetheless help support an expectation that galcanezumab would be effective in treating patients with a "history of failure to preventative treatments."

We acknowledge that the Headache Abstract does not expressly define "history of failure to preventative treatments." Nonetheless, we do not agree with Patent Owner that this prevents the POSA from drawing inferences about the failed patients described in the Headache Abstract. We find that the POSA would have understood "history of failure to preventative treatments" to have the same meaning as "refractory" when used in the migraine art. *See supra* § II.F.2.c.ii (discussing how the POSA would have understood the term "refractory"). Consistent with this understanding, the Headache Abstract makes clear that its patients failed multiple treatments because: 1) the term "treatments" is plural, 2) the term "history" suggests more than one event, and 3) the evidence supports that the average migraineur has taken multiple prophylactic medications (Ex. 1015 ("The mean number of prophylactic medications ever used was 2.92 for EM

[episodic migraine] and 3.94 for CM [chronic migraine].”). Absent evidence to the contrary, we find that the POSA would have inferred that the patients in the Headache Abstract with a “history of failure to preventative treatments” would have: 1) typical preventative migraine treatments, 2) underwent a typical evaluation period of three months before being deemed to have failed treatment, 3) used a typical threshold for determining whether treatment is successful. *See supra* § II.F.2.c.ii (discussing typical treatments, evaluation periods, and success thresholds),

In sum, we find that the Headache Abstract provides strong evidence that galcanezumab would be successful in treating the claimed patient groups. This, in turn, helps to support an expectation that fremanezumab would be successful in treating the claimed patient groups. *See* Ex. 1092 ¶ 172 (Dr. Evers’s credible testimony the results of treatment with galcanezumab described in the Headache Abstract support an expectation that fremanezumab would be effective in the claimed patient population).

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. 38–39. 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 Petitioner "fails to provide an accurate account of the state of the art." PO Resp. 43. According to Patent Owner anti-CGRP mAbs were not the first treatment to impact the CGRP pathway. *Id.* To the contrary, Patent Owner asserts that "the art taught that many commonly used preventative migraine medications *did* affect the CGRP signaling pathway." *Id.* Thus, Patent Owner argues, because the "inadequate response patients of the '434 patent already did not have a clinically meaningful improvement with at least two different classes of preventative medications . . . [t]here is no basis to expect that they would respond to *yet a third treatment*." *Id.*

The evidence supports that anti-CGRP mAbs are unlike traditional treatments in the sense that they block the CGRP pathway by specifically binding CGRP or the CGRP receptor. In this regard, we credit the well-supported testimony of Dr. Evers explaining why certain traditional treatments are different from anti-CGRP mAbs:

> Although the importance of CGRP in migraine pathophysiology was long recognized, none of the prophylactic migraine treatments available as of the earliest possible priority date of the '434 patent specifically targeted it. For instance, anticonvulsants (such as topiramate and valproic acid) were thought to act on migraine by regulating glutamate activity and gamma-aminobutyric acid (GABA). EX1019 (DeMaagd 2008 II), 3. Tricyclic antidepressants are "thought to involve the inhibition of central cortical depression and sympathetic activity associated with migraine pathophysiology." EX1019 (DeMaagd 2008 II), 2. And, although not entirely understood, beta-blockers were believed to function via "modulation of the adrenergic nervous system and an influence on cranial blood vessels." EX1019 (DeMaagd 2008 II), 1.

Ex. 1109 ¶ 177.

Consistent with this testimony, Dr. Hays testifies, and we agree, that the POSA would have understood that "unlike traditional preventatives, anti-CGRP pathway mAbs 'targeted' CGRP in the sense that they specifically bind CGRP or the CGRP receptor." Ex. 1239 ¶ 40; *see also* Tr. 69 (counsel for Patent Owner, explaining that "those molecules that were in the prior art were known to affect the CGRP pathway, even if they weren't doing it by directly binding to the ligand or by directly binding to the receptor"). For the reasons discussed at length in her declaration (Ex. 1239 ¶¶ 43–62), we agree with Dr. Hays that the evidence cited by Patent Owner and Dr. Grosberg does not show that prior art non-mAb treatments "work against migraine in a manner analogous or equivalent to the anti-CGRP pathway mAbs" (*id.* ¶ 42).

We also agree with Dr. Hays that the "mechanistic distinction between anti-CGRP pathway mAbs and traditional migraine preventatives was recognized throughout the literature." *Id.* ¶ 41 (citing evidence). Dr. Hays's testimony is consistent with prior art that discusses anti-CGRP monoclonal antibody treatments as having a distinct mechanism of action. Ex. 1230, 2 ("mAbs against CGRP or its receptor [CGRP mAbs] represent the unique disease-specific and mechanism-based migraine prevention treatment"); Ex. 1042, 1 ("Monoclonal antibodies antagonizing the CGRP pathway represent a novel approach to prevention: a mechanism-specific migraine-targeted therapy."); Ex. 1224, 7 (discussing the mAb, fremanezumab, as an "add-on therapy to other migraine prophylactics" and explaining that the idea is "plausible" because "all other migraine prophylactic medications act through non-CGRP mechanisms"); Ex. 1023 (opining that mAbs against CGRP "deserve to be called a breakthrough" in part because they "were developed based on the pathophysiologic concept

that the trigeminovascular system and CGRP have a key role in the development of migraine pain").

Perhaps in view of the mechanistic distinction between mAbs and other available treatments, the prior art discussed mAb treatments as novel and different from other types of migraine treatments. *See e.g.,* 1027, 1 (discussing "the evolution from older traditional treatments to the innovative CGRP target drugs that are revolutionizing the way to approach this debilitating neurological disease"); Ex. 1049, 1–2 ("CGRP antagonists showed efficacy in several clinical trials, but their severe side effects and adverse events with long-term administration discouraged further research. . . . The recently developed monoclonal antibodies against CGRP or its receptor (anti-CGRP mAbs) have triggered much interest in the headache community."); Ex. 1025, 2 ("Although the small molecule agents that target the CGRP receptor are still under investigation, the recent development of humanized antibodies to CGRP and its receptor appear more promising for three important reasons: they are unlikely to cause liver toxicity or other serious AEs; they are biological products with extreme specificity for their target and very long half-lives, compared to oral medications; and they may have considerably better tolerability and safety profiles."); Ex. 1053, 13 ("More-effective and better-tolerated acute and preventive treatments are needed for migraine and cluster headache patients in episodic, chronic and medically refractory subgroups. mAbs targeting CGRP or its receptor hold the most promise for preventive treatment in all of these subgroups"); Ex. 1028, 8 ("mAbs targeting the CGRP pathway are a promising new drug class that may provide a valuable new option for clinicians aiming to relieve the burden of individuals with episodic or chronic migraine").

Based on their different mechanism of action, Dr. Evers concludes that "a POSA would have reasonably expected that patients that had failed these other treatments could nonetheless be treated with compounds targeting CGRP directly, such as fremanezumab." Ex. 1109 ¶ 178. Dr. Evers's testimony is consistent with the multiple articles discussed *supra* § III.F.2.c.i suggesting that anti-CGRP mAbs have the potential to treat refractory patients. *See e.g.,* Ex. 1037, 1; Ex. 1072, 73; Ex. 1040, 14–15; Ex. 1040, 329; Ex. 1041, 2; Ex. 1023, 7; *see also* Ex. 1053, 13. At least one of these reference attributes this potential to their distinct mechanism of action. Ex. 1023, 7 (explaining that anti-CGRP mAbs "are effective for relatively refractory headaches" and that this "was not a serendipitous discovery" because there "were developed based on the pathophysiologic concept that the trigeminovascular system and CGRP have a key role in the development of migraine pain").

Dr. Evers also testifies, with citation to consistent supporting evidence, that combination therapy with "then-available prophylactics had shown little to no success," but that fremanezumab "demonstrated an effect in patients allowed to remain on preventative treatments." Ex. 1109 ¶¶ 166–168 (citing Ex. 1038). This suggests that fremanezumab works by a different mechanism of action than the drugs with which it was combined. Ex. 2037 ¶ 122 (Dr. Grosberg's testimony regarding the "common knowledge in the prior art suggesting using medications having different mechanisms of action in combination therapy"); PO Resp. 31 (arguing that "a POSA would have expected combination therapy to . . . combine drugs from different classes with different mechanisms of action."). We agree with Dr. Evers that this helps support the expectation that targeting CGRP with a mAb would treat the claimed patient population. *Id.* ¶ 165.

To summarize, the evidence of record supports: 1) that anti-CGRP pathway mAbs are unlike traditional treatments in the sense that they block the CGRP pathway by specifically binding CGRP or the CGRP receptor, 2) that this difference in mechanism of action was recognized in the art, 3) that anti-CGRP mAbs were treated as novel and different than prior treatments, and 4) that the POSA would have expected that patients that had failed these other treatments could nonetheless be treated with compounds targeting CGRP directly, such as fremanezumab. Patent Owner's assertion that non-mAb prior art treatments also affect the CGRP pathway does not persuade us that the failure of such treatments materially detracts from the expectation that fremanezumab and erenumab would have similar efficacy or otherwise negatively impacts a POSA's motivation to substitute one for the other. To the contrary, the unique mechanism of action of anti-CGRP mAbs helps to support a reasonable expectation that treating the claimed patients with fremanezumab would be successful.

d) Clinical trials that did not exclude refractory 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's 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.

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

e) Additional evidence relating to contraindicated patients

Petitioner argues that in addition to the reasons already discussed as to why the POSA would reasonably have expected fremanezumab to treat the claimed patients, the POSA would expect success in contraindicated patients because "in terms of migraine treatment, they were physiologically indistinguishable from the broader migraine population." Pet. 43.[28] 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.

[28] We do not separately address motivation to combine for contraindicated patients because Petitioner relies only on the evidence already discussed. Pet. 43 ("A POSA would have been motivated to use fremanezumab to treat these 'contraindicated' patients taught by Sun for at least the same reasons described above for the other 'inadequate response' patients.").

Id. at 44 (citing Ex. 1109 ¶¶ 194–196). Petitioner continues, "rather than expecting comorbidities to impact the efficacy of non-contraindicated medications, POSAs typically relied upon efficacy as evaluated in the general migraine population as opposed to the specific comorbid subpopulation." *Id.* at 44 (citing Ex. 1109 ¶¶ 197–198; Ex. 1016, 5; Ex. 1005, 13, Ex. 1087, Table e-1).

Patent Owner disputes that contraindicated patients are indistinguishable from the general migraine population, citing the testimony of Dr. Grosberg that "patients with one or more comorbidities often had greater risk for more frequent or more intense headaches and possibly even more resistance to treatment." Ex. 2037 ¶ 280; PO Resp. 53. Patent Owner also argues that none of the references relied upon by Petitioner and Dr. Evers support that POSAs project efficacy in contraindicated patients based on efficacy as assessed in the general migraine population. *Id.* at 54. Patent Owner explains: "In each case, the references discuss[] considering a patient's comorbidities when selecting a drug, and says nothing about expectations of any clinical benefit." *Id.*

We agree with Patent Owner that the references Petitioner and Dr. Evers rely upon do not discuss expectations for efficacy with respect to any particular contraindication or with respect to contraindications in general. Absent such evidence, we are left with dueling experts, with Dr. Grosberg testifying that "a POSA would have expected that . . . patients *with* comorbidities may have a poorer response, or no response at all, to fremanezumab compared to patients *without* comorbidities" and Dr. Evers testifying that "the expectation of success for using fremanezumab to treat these 'contraindicated' patients was even higher because a POSA would have reasonably expected that contraindications to some migraine preventive

medications due to comorbidities would not adversely affect the safety and efficacy of fremanezumab." Ex. 2037 ¶ 280; Ex. 1109 ¶ 194. Accordingly, we weigh this evidence as neutral in our analysis, neither supporting nor detracting from whether a POSA would have had a reasonable expectation of success with respect to contraindicated patients.

f) Conclusion regarding reasonable expectation of success

We find that Petitioner has established, by a preponderance of the evidence that a POSA would reasonably have expected fremanezumab to be successful when used in place of erenumab in Sun's methods, which, as discussed *supra* § II.F.1, include treating the claimed patients. This finding is supported by Phase II clinical studies teaching that fremanezumab is effective in treating the general migraine population as well as by the statement in the Teva Press Release that fremanezumab provided a "very fast onset of preventive response" and an "impressive decrease in migraine days" in "highly refractory patients." *See supra* § II.F.3.a. Evidence supporting the efficacy of erenumab in patients who had failed prior treatments, particularly Tepper, also supports this finding. *See supra* §§ II.F.3.b.i–iii. So too does evidence supporting that galcanezumab showed "statistically significantly greater treatment effect" in patients with a "history of failure to preventive treatments." *See supra* § II.F.3.b.iv. Finally, our conclusion that the POSA would reasonably have expected success using fremanezumab in Sun's methods finds support in anti-CGRP mAb's distinct mechanism of action. *See supra* § II.F.3.c.

4. Does using fremanezuab in Sun's methods meet the limitations of claim 1 for all three patient groups?

Having determined that Sun discloses or suggests treating the claimed patient groups (*see supra* § II.F.1), and that the evidence of record supports using fremanezumab in Sun's methods with a reasonable expectation of success (*see supra* §§ II.F.2–3), we now consider whether using fremanezumab in Sun's methods meets each of the limitations of claim 1.

a) Preamble

The preamble of claim 1 recites "[a] method of treating or preventing migraine in a subject." Patent Owner contends that the preamble limits the claims. PO Resp. 10. We need not determine whether the preamble limits the claims because we find that the prior art discloses it. For the reasons discussed *supra* § II.F.1, Sun discloses or suggests treating each of Group I, Group II, and Group III patients respectively under our construction of the term "inadequate response." Using fremanezumab to treat these patients, as proposed by Petitioner, meets the language of the preamble. According, we find that Petitioner has established, by a preponderance of the evidence, that the cited art teaches or suggests the language recited in the preamble.

b) The "selecting" limitation

Claim 1 next recites "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."

As discussed *supra* § II.F.1.a–c, Sun discloses treating each of Group I, Group II, and Group III patients respectively under our construction of the term "inadequate response. Sun provides a list of prior treatments and

classes of treatments that its patients may have failed or been intolerant to. Ex. 1006 ¶¶ 67–68. Many of the treatments on Sun's list overlap with those called listed in claim 1. *Compare* Ex. 1006 ¶¶ 67–68, *with* Ex. 1045, 173:4–10. In addition, Sun identifies examples of patients that failed classes of the claimed preventive treatments. *See, e.g.,* Ex. 1006 ¶ 68 ("In one embodiment, the patient may have failed or is intolerant to treatment with an antiepileptic (e.g. topiramate) and a beta-blocker (e.g. propranolol)"). Petitioner contends that Sun's direction to treat such patients teaches selecting and treating the claimed patients. Pet. 20, 42. We agree.

c) The "administering" limitation

The final limitation of claim 1 recites "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."

As an initial matter, there does not appear to be any dispute, and thus we find, that 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 correspond to fremanezumab. Ex. 1109 ¶ 50. For the reasons discussed *supra* § II.F.2, the POSA would have been motivated to use fremanezumab in Sun's method of treating the claimed Group I, Group II, and Group III patients, respectively. For the reasons discussed *supra* §§ II.F.3, the POSA would reasonably have expected success in doing so. Accordingly, we find that Petitioner has established, by a preponderance of

the evidence, that the cited art teaches or suggests the language recited in the "administering" limitation.

G. Ground 1, claims 2–13

Claims 2–13 depend from and further limit claim 1 by reciting additional requirements: that the subject be human (claim 2), that the mAb be administered at a particular dose (claims 3, 9, 10, 11, and 13), that the mAb be administered using one of several listed devices (claim 4), that the mAb be administered as a formulation at a particular concentration (claim 5) in a particular volume (claim 6), that the mAb be administered in combination with an acute headache medication (claim 7) where the use of the acute headache medication monthly use is decreased by at least 50% (claim 8), and that the mAb is administered subcutaneously (claim 12).

Petitioner contends that the limitations recited in claims 2–13 are disclosed in Sun and the Teva Press Release. Pet. 45–51. Petitioner provides documentary and testimonial evidence to back its assertions. *Id.*; *see also* Ex. 1109 ¶¶ 200–244.

Patent Owner does not challenge Petitioner's showing with respect to dependent claims 2–13 other than to assert, as to all 12 claims, that "Petitioner focuses solely on claim elements purportedly disclosed in the art, without *any* meaningful discussion of why a POSA would have allegedly modified the references or had a reasonable expectation of success in practicing any of the methods of the dependent claims." PO Resp. 60. This argument lacks merit. For example, for claims 2, which requires administration to humans, Petitioner cites the testimony of Dr. Evers, who explains that "Sun expressly motivated administration to humans, disclosing a successful Phase 2 study evaluating the safety and efficacy of erenumab conducted in human patients" and that the "expectation of success for

administering anti-CGRP mAbs to human subjects was reinforced by the art as a whole, which expressly taught successful administration of fremanezumab to humans." Ex. 1109 ¶¶ 202–203. Contrary, to Patent Owner's assertion, Petitioner does not focus solely on where claim elements are recited in the prior art; Petitioner clearly explains both why the POSA would have been motivated to treat the patients recited in claim 2 why the POSA would reasonably have expected success in doing so.

Similarly, for claim 3, which requires that the mAb be administered at a dose of "about 225 mg followed by subsequent doses of about 225 at one month intervals," Petitioner asserts:

> Teva Press Release rendered this claim obvious, disclosing a successful Phase II study in which "individuals given 225mg and 675mg" of fremanezumab "once monthly for the preventive treatment of high frequency episodic migraine." EX1041, 1-2; EX1109, ¶¶204-206. The motivation and expectation of success were reinforced by numerous prior art references teaching success of fremanezumab with this dosing regimen (EX1102, [0419]; EX1039, 2; EX1072, 77) and the POSA's understanding that monthly administration could improve patient convenience and adherence (EX1028, 5; EX1036, 7; EX1074, 7). EX1109, ¶¶207-208.

Pet. 45–46. As with claim 2, discussed above, Petitioner does not rest solely on the identification of where claim elements can be found in the prior art. Petitioner provides articulated reasoning with rational underpinning to support it proposed finding of obviousness. The same holds true for the remainder of the challenged dependent claims. Accordingly, we are not persuaded by Patent Owner's argument that the Petition lacks "*any* meaningful articulation of why a POSA would have allegedly modified the references or had a reasonable expectation of success in practicing any of the methods of the dependent claims." PO Resp. 60.

We have reviewed Petitioner's contentions and determine that Petitioner has shown, by a preponderance of the evidence, that claims 2–13 would have been obvious over the combination of Sun and the Teva Press Release. *See In re NuVasive, Inc*., 841 F.3d 966, 974 (Fed. Cir. 2016) ("The Board, having found the only disputed limitations together in one reference, was not required to address undisputed matters."); *see also* Paper 12 at 8 (emphasizing that "any arguments not raised in the response may be deemed waived").

H. Ground 2

Petitioner argues claims 1–13 of the '434 patent would have been obvious over Bigal. We have already determined claims 1–13 are unpatentable based on Petitioner's Ground 1. *See supra* § II.F. and II.G. Therefore, we need not, and to conserve the Board's resources, we do not, reach Ground 2. *See SAS Inst. Inc. v. Iancu*, 138 S. Ct. 1348, 1359 (2018) (holding that a petitioner "is entitled to a final written decision addressing all of the claims it has challenged"); *Bos. Sci. Scimed, Inc. v. Cook Grp. Inc*., 809 F. App'x 984, 990 (Fed. Cir. 2020) (non-precedential) (recognizing that the "Board need not address issues that are not necessary to the resolution of the proceeding" and, thus, agreeing that the Board has "discretion to decline to decide additional instituted grounds once the petitioner has prevailed on all its challenged claims").

III. PATENT OWNER'S MOTION TO EXCLUDE

Patent Owner filed a Motion to Exclude seeking to exclude Exhibits 1040, 1041, 1065, 1073, 1075, 1088, 1089, 1208, 1209, 1210, 1220, and 1221 as inadmissible hearsay under FRE 801 and 802. Paper 37, 2 ("Motion" or "Mot."). Patent Owner also sought to exclude the portions of

Dr. Evers's declaration that rely on the allegedly inadmissible exhibits. *Id.* Petitioner filed an Opposition (Paper 38, "Opposition" or "Opp.") and Patent Owner filed a Reply (Paper 39, "Mot. Reply"). We deny Patent Owner's motion in part and dismiss Patent Owner's motion in part as moot.

A. Exhibits 1065, 1073, 1088, 1089, 1220, and 1221

We do not rely on Exhibits 1065, 1073, 1088, 1089, 1220, and 1221 in our Final Written Decision. Accordingly, we dismiss Patent Owner's Motion as it relates to these exhibits.

B. Exhibit 1040

Exhibit 1040 ("Goadsby") is prior art describing the results of Sun's proposed Phase III trial. Ex. 1040, 15–16. In relevant part, it states:

> Robust treatment effects were observed for both 70 mg and 140 mg erenumab in subjects who had previously failed preventative migraine treatments. For 140 mg, effects were numerically greater in this sub-population than in the overall trial population, and as in the overall population, erenumab 140 mg showed numerically greater efficacy than erenumab 70 mg. These results suggest that erenumab may have particular utility in this subgroup of patients.

Id.

Patent Owner argues that Petitioner relies on Goadsby to show that erenumab had "shown success in patients with a history of treatment [] failure" as well as to show that it achieved "robust treatment effects . . . in subjects who had previously failed preventive migraine treatments' and suggested 'particular utility in this subgroup of patients.'" Mot. 3 (emphasis omitted). We disagree. Petitioner relies on Goadsby, not for the truth of its assertions. Rather, Petitioner relies on Goadsby for the non-hearsay purpose of showing its effect on the hypothetical person of ordinary skill in the art. *See* Opp. 5–6 (describing Petitioner's use of Goadsby). We rely on it in the

same manner. *See supra* § II.F.3.b.iii (discussing whether Goadsby supports that the POSA would have expected success in using galcanezumab in Sun's methods). Accordingly, we deny Patent Owner's Motion as it relates to Exhibit 1040.

C. Exhibit 1041

Exhibit 1041 ("the Teva Press Release") is prior art characterizing the results of two clinical studies of fremanezumab. In relevant part, it states:

> "The 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," stated Marcelo E. Bigal, Teva's Head of Global Clinical Development for Migraine and Headaches [and a named inventor on the '434 patent]. "The 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."

Ex. 1041, 2 (emphasis added).

Patent Owner argues that Petitioner improperly relies on Exhibit 1041 to prove several assertions about fremanezumab, including that it "show[ed] success in patients with a history of treatment failure." Mot. 4–5. We disagree. As with Goadsby, Petitioner relies on the Teva Press Release not for the truth of the matter asserted in the reference at issue, but for the non-hearsay purpose of showing the effect of the reference on the hypothetical person of ordinary skill in the art. *See* Opp. 6–7 (describing Petitioner's use of the Teva Press Release). We rely on it in the same manner. *See supra* §§ II.F.2.c and II.F.3.a (discussing whether the Teva Press Release supports that the POSA would have been motivated to use fremanzumab in Sun's

methods and whether the POSA would have expected success in doing so). Accordingly, we deny Patent Owner's Motion as it relates to Exhibit 1041.[29]

D. Exhibits 1208, 1209, and 1210

Exhibits 1208 and 1209 are FDA guidance documents and Exhibit 1210 is guidance from the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). All three of these Exhibits provide definitions of the term "adverse event." Patent Owner argues that "Petitioner . . . uses these references to prove that the definitions asserted therein are the true definitions that should be used to interpret the claims." Mot. 8. We disagree. As with Goadsby and the Teva Press Release, Petitioner relies on Exhibits 1208–1210 not for the truth of the matter asserted, but to show how the POSA would have understood the term "adverse event." *See* Opp. 11–12 (describing Petitioner's use of Exhibits 1208, 1209, 1210). We rely on them in the same manner. *See supra* § II.F.1.b. Accordingly, we deny Patent Owner's Motion as it relates to Exhibits 1208–1210

E. Dr. Evers's Declaration

Patent Owner argues that we should exclude ¶¶ 35, 41, 121, 155, 163, and 167 of Dr. Evers's Declaration because they "rely on Exhibits 1040 and 1041 for an improper hearsay purpose." Mot. 9–11. We deny Patent Owner's Motion as it relates to Dr. Evers's declaration. For the reasons discussed in Petitioner's Opposition (Opp. 13–14) we agree that the challenged testimony relies upon Exhibits 1040 and 1041 for non-hearsay purposes. Moreover, even if the cited exhibits were hearsay, FRE 703

[29] The Teva Press Release is also a statement authorized and made by Patent Owner and, therefore, not hearsay under Fed. R. Evid. 801(d)(2).

permits an expert to rely on the kinds of facts and data an expert in a field would reasonably rely on, regardless of whether those facts or data are themselves admissible. FRE 703 ("If experts in the particular field would reasonably rely on those kinds of facts or data in forming an opinion on the subject, they need not be admissible for the opinion to be admitted"); *i4i Ltd. P'ship v. Microsoft Corp*., 598 F.3d 831, 852, (Fed. Cir. 2010).

F. Conclusion

We deny Patent Owner's motion as to Exhibits 1040, 1041, 2008–2010, and Dr. Evers's testimony. We dismiss as moot, Patent Owner's motion as it relates to Exhibits 1065, 1073, 1088, 1089, 1220, and 1221.

IV. CONCLUSION

Based on the evidence presented with the Petition, the evidence introduced during the trial, and the parties' respective arguments, Petitioner has established by a preponderance of the evidence that claims 1–13 are unpatentable as obvious over the combination of Sun and the Teva Press Release.[30] We decline to reach the merits of Petitioner's Ground 2, which asserts that claims 1–13 of the '434 patent would have been obvious over Bigal, because we have already determined that claims 1–13 are

[30] Should Patent Owner wish to pursue amendment of the challenged claims in a reissue or reexamination proceeding after the issuance of this Final Written Decision, we draw Patent Owner's attention to the April 2019 Notice Regarding Options for Amendments by Patent Owner Through Reissue or Reexamination During a Pending AIA Trial Proceeding. *See* 84 Fed. Reg. 16,654 (Apr. 22, 2019). If Patent Owner chooses to file a reissue application or a request for reexamination of the challenged patent, we remind Patent Owner of its continuing obligation to notify the Board of any such related matters in updated mandatory notices. *See* 37 C.F.R. §§ 42.8(a)(3), (b)(2).

unpatentable based on Petitioner's Ground 1. We deny Patent Owner's Motion to Exclude as it relates to Exhibits 1040, 1041, 2008–2010, and Dr. Evers's testimony. We dismiss as moot, Patent Owner's Motion to Exclude as it relates to Exhibits 1065, 1073, 1088, 1089, 1220, and 1221.

In summary:

Claims	**35 U.S.C. §**	**Reference(s)/ Basis**	**Claims Shown Unpatentable**	**Claims Not Shown Unpatentable**
1–13	103(a)	Sun, Teva Press Release	1–13	
1–13	103(a)	Bigal[31]		
Overall Outcome			1–13	

[31] We do not reach this ground for the reasons discussed *supra* § II.H.

V. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that claims 1–13 in the ’434 patent are determined to be unpatentable;

FURTHER ORDERED that Patent Owner’s Motion to Exclude is denied as it relates to Exhibits 1040, 1041, 2008–2010, and paragraphs 35, 41, 121, 155, 163, and 167 of Dr. Evers’s Declaration (Ex. 1109);

FURTHER ORDERED that Patent Owner’s Motion to Exclude is dismissed as moot as it relates to Exhibits 1065, 1073, 1088, 1089, 1220, and 1221; and

FURTHER ORDERED that because this is a final written decision, parties to the proceeding seeking judicial review of the decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

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