United States Court of Appeals for the Federal Circuit

ELI LILLY AND COMPANY,
Appellant

v.

TEVA PHARMACEUTICALS INTERNATIONAL GMBH,
Appellee

2020-1876, 2020-1877, 2020-1878

Appeals from the United States Patent and Trademark Office, Patent Trial and Appeal Board in Nos. IPR2018-01710, IPR2018-01711, IPR2018-01712.

Decided: August 16, 2021

WILLIAM BARRETT RAICH, Finnegan, Henderson, Farabow, Garrett & Dunner, LLP, Washington, DC, argued for appellant. Also represented by PIER DEROO, ERIN SOMMERS, YIEYIE YANG; SANJAY M. JIVRAJ, MARK STEWART, Eli Lilly and Company, Indianapolis, IN.

WILLIAM M. JAY, Goodwin Procter LLP, Washington, DC, argued for appellee. Also represented by ELAINE BLAIS, EDWINA CLARKE, ALEXANDRA LU, Boston, MA; NATASHA ELISE DAUGHTREY, Los Angeles, CA; WILLIAM

MILLIKEN, DEBORAH STERLING, Sterne Kessler Goldstein & Fox, PLLC, Washington, DC.

Before LOURIE, BRYSON, and O'MALLEY, *Circuit Judges*.

LOURIE, *Circuit Judge*.

Eli Lilly and Company ("Lilly") appeals from a combined final written decision of the U.S. Patent and Trademark Office ("PTO") Patent Trial and Appeal Board ("Board") holding that the claims of U.S. Patents 8,586,045 ("'045 patent"), 9,884,907 ("'907 patent"), and 9,884,908 ("'908 patent") are not unpatentable as obvious. *Eli Lilly & Co. v. Teva Pharms. Int'l GmbH*, Nos. IPR2018-01710, IPR2018-01711, IPR2018-01712, 2020 WL 1540364 (P.T.A.B. Mar. 31, 2020) ("*Board Decision*"). For the reasons provided below, we affirm.

BACKGROUND

I. Patents

Teva Pharmaceuticals International GmbH ("Teva") owns the '045, '907, and '908 patents (collectively, the "challenged patents") directed to methods of using humanized antagonist antibodies that target calcitonin gene-related peptide ("CGRP"). CGRP is a 37-amino acid peptide that is "a neurotransmitter in the central nervous system, and has been shown to be a potent vasodilator in the periphery, where CGRP-containing neurons are closely associated with blood vessels." '045 patent, col. 1 ll. 31–35.

The challenged patents explain that "CGRP has been noted for its possible connection to vasomotor symptoms," *id.* at col. 1 ll. 39–40, such as "all forms of vascular headache, including migraines," *id.* at col 2 ll. 3–6. Although at the time of the challenged patents the pathophysiology of migraine was not well understood, dilation of blood vessels was associated with and thought to exacerbate the pain symptoms of migraine. *Id.* at col. 3 ll. 14–26. Thus, even

before the challenged patents, the possible connection between CGRP as a vasodilator and the pathology of migraine informed the development of treatments for migraine that sought to restrict the activity of CGRP in the body. For example:

> Possible CGRP involvement in migraine has been the basis for the development and testing of a number of compounds that inhibit release of CGRP (e.g., sumatriptan), antagonize at the CGRP receptor (e.g., dipeptide derivative BIBN4096BS (Boe[]hringer Ingelheim); CGRP (8-37)), or interact with one or more of receptor-associated proteins, such as, receptor activity membrane protein (RAMP) or receptor component protein (RCP), both of which affect binding of CGRP to its receptors.

Id. at col. 2 ll. 14–22.

The challenged patents are directed to methods of treatment using humanized antibodies that antagonize CGRP and thus inhibit its activity in the body by targeting and binding to the CGRP ligand (as opposed to CGRP receptors). The challenged patents' written description describes "anti-CGRP antagonist antibodies and methods of using anti-CGRP antagonist antibodies for treating or preventing vasomotor symptoms, such as headaches, such as migraine." *Id.* at col. 3 ll. 37–45. The claims at issue are directed to methods of treatment comprising the step of administering a humanized anti-CGRP antagonist antibody.[1] Claim 1 in each patent is representative:

---

[1] In contrast with the claims at issue in this case, which are directed to methods of using anti-CGRP antibodies in treatment, Teva also owns related patents with claims directed to the antibodies themselves. Those claims are at issue in Appeal Nos. 2020-1747, 2020-1748, 2020-1749, 2020-1750, 2020-1751, and 2020-1752.

> 1. A method for reducing incidence of or treating at least one vasomotor symptom in an individual, comprising administering to the individual an effective amount of an anti-CGRP antagonist antibody, wherein said anti-CGRP antagonist antibody is a human monoclonal antibody or a humanized monoclonal antibody.

'045 patent, col. 99 ll. 2–7.

> 1. A method for treating headache in an individual, comprising:
>
> administering to the individual an effective amount of a humanized monoclonal anti-Calcitonin Gene-Related Peptide (CGRP) antagonist antibody, comprising:
>
> two human IgG heavy chains, each heavy chain comprising three complementarity determining regions (CDRs) and four framework regions, wherein portions of the two heavy chains together form an Fc region; and
>
> two light chains, each light chain comprising three CDRs and four framework regions;
>
> wherein the CDRs impart to the antibody specific binding to a CGRP consisting of amino acid residues 1 to 37 of SEQ ID NO:15 or SEQ ID NO:43.

'907 patent, col. 103 ll. 21–35.

> 1. A method for treating headache in an individual, comprising:
>
> administering to the individual an effective amount of a humanized monoclonal anti-

> Calcitonin Gene-Related Peptide (CGRP) antagonist antibody, comprising:
>
> two human IgG heavy chains, each heavy chain comprising three complementarity determining regions (CDRs) and four framework regions, wherein portions of the two heavy chains together form an Fc region; and
>
> two light chains, each light chain comprising three CDRs and four framework regions;
>
> wherein the CDRs impart to the antibody specific binding to a CGRP consisting of amino acid residues 1 to 37 of SEQ ID NO:15 or SEQ ID NO: 43, and wherein the antibody binds to the CGRP with a binding affinity (K_D) of about 10 nM or less as measured by surface plasmon resonance at 37° C.

'908 patent, col. 99 l. 55–col. 100 l. 57. The differences between these claims have not been argued as significant to these appeals.

II. IPR Petitions and Prior Art

Lilly filed petitions for *inter partes* review of claims 1, 3, 4, 8–17, 19, 20, and 24–31 of the '045 patent, claims 1–18 of the '907 patent, and claims 1–18 of the '908 patent. Lilly asserted that each of the challenged claims would

have been obvious over a combination of prior art references that includes Olesen,[2] Tan,[3] and Queen.[4]

Olesen describes a clinical trial proving the efficacy of BIBN4096BS ("BIBN"), a nonpeptide CGRP-receptor antagonist, in the treatment of migraine. In Olesen's study, patients receiving 2.5 mg of BIBN intravenously over a period of 10 minutes had a 66% response rate, with a pain-free rate of 44% after two hours and a recurrence rate of 19%. *See Board Decision*, 2020 WL 1540364, at *11 (citing Olesen). In short, Olesen teaches that BIBN was effective and safe in treating acute attacks of migraine. Olesen also discusses past studies and discloses that CGRP may have a role in initiating and mediating migraine attacks. J.A. 3741.

Tan is a publication describing an *in vivo* study in rats using an anti-CGRP monoclonal antibody for immunoblockade.[5] The study investigated the anti-CGRP activity of a full-length monoclonal antibody called "MAb C4.19" as well as its Fab' fragment.[6] *See* J.A. 3708–18. Tan describes the results of one experiment demonstrating that both the

---

[2] J. Olesen et al., *Calcitonin Gene-Related Peptide Receptor Antagonist BIBN 4096 BS for the Acute Treatment of Migraine*, N. ENG. J. MED. 350, 1104–10 (2004).

[3] K.K.C. Tan et al., *Calcitonin gene-related peptide as an endogenous vasodilator: immunoblockade studies in vivo with an anti-calcitonin gene-related peptide monoclonal antibody and its Fab' fragment*, 89 CLINICAL SCI. 6, 565–73 (1995).

[4] U.S. Patent 6,180,370.

[5] Tan defines "immunoblockade" as "the blockade of the effects of a biological mediator by inhibition of its binding to specific receptors with antibodies directed against the mediator." J.A. 3711.

[6] A "Fab' fragment" is the portion of an antibody that binds to the target antigen.

full-length antibody and the Fab' fragment successfully achieved immunoblockade by inhibiting the effects of exogenously administered CGRP. *See* J.A. 3711–12. Tan also describes the results of a second experiment analyzing whether the antibody and its Fab' fragment inhibit endogenous CGRP-induced blood flow after a prescribed incubation period. J.A. 3714. The results demonstrated that the Fab' fragment effectively blocked skin blood flow after a 30-minute incubation period. *Id.* The full-length antibody did not block skin blood flow after a 60-minute incubation, but a 2-hour incubation period and higher dose resulted in a 16% block in skin blood flow. *Id.* Tan posited that "much larger doses and longer distribution times are required for successful immunoblockade" with the full-length antibody. J.A. 3716.

Queen "relates generally to the combination of recombinant DNA and monoclonal antibody technologies for developing novel therapeutic agents." J.A. 27230 at col. 1 ll. 19–21. Specifically, Queen discloses a method of humanizing antibodies to address traditional problems associated with injecting monoclonal antibodies from donors (*e.g.*, mice) into humans.

III. Board Decision

After a combined oral hearing, the Board issued a combined final written decision in the three IPRs. The Board first construed the claims, including the preambles and the term "effective amount." The Board then analyzed the asserted prior art and concluded that Lilly failed to prove that the challenged claims in the three patents would have been obvious over the stated references.

For the constructions of the claim preambles, the Board noted that "[t]he parties do not dispute that the preamble claim language is a statement of intended purpose." *Board Decision*, 2020 WL 1540364, at *7. The Board thus determined that the preambles are "limiting to the extent that they require that the recited method must be performed

with the intentional purpose of 'reducing incidence of or treating' at least one vasomotor symptom . . . or headache." *Id.* The Board also discussed how the claim construction affected Lilly's burden to demonstrate that a skilled artisan would have had a reasonable expectation of success in combining the teachings of the prior art to achieve the claimed invention:

> [W]e determine here that to prove a reasonable expectation of success with respect to a limitation that recites achieving a particular result as the intended purpose for which a recited method must be performed, what is required is not proof that the recited method would *actually* bring about the recited result, but rather proof that a person of ordinary skill in the art would have had a reasonable expectation that performing the recited method would bring about the recited result.

Id. at *8.

For the term "effective amount," the Board determined that the written descriptions defined the term to mean "an amount sufficient to effect beneficial or desired results." *Id.* at *10. The Board specifically addressed the relationship between an "effective amount" under the claims, and potential clinical results demonstrating efficacy:

> Although the term "effective amount" may *encompass* a clinical result, we do not interpret the term "effective amount" as *requiring* a clinical result because, as defined in the Specification, the term "effective amount" refers only to "beneficial or desired results" without the qualifier "clinical." That is, the term "effective amount" requires a beneficial or desired result, but it need not be a "clinical" result.

Id. at *9.

After construing the claims, the Board considered the evidence pertaining to obviousness. The Board first found that Lilly had shown by a preponderance of the evidence that the asserted prior art discloses or suggests each and every element of the challenged claims. *Id.* at *18. Next, the Board found that a skilled artisan would have been motivated to combine the teachings of the prior art:

> [T]here are clearly reasons that a person of ordinary skill in the art would have been motivated to combine the teachings of Olesen, Tan, and Queen to pursue a method to reduce incidence of or treat a vasomotor symptom, such as a migraine headache, by administering a human or humanized monoclonal anti-CGRP antagonist antibody.

Id. at *43. Moreover, the Board found that "any alleged safety concerns would not have deterred, discouraged, or taught away from pursuing" the patented methods of treatment. *Id.*

After finding a motivation to combine the teachings of the prior art, the Board next considered whether a skilled artisan would have had a reasonable expectation of success. The Board first addressed Lilly's arguments based on the asserted prior art references, namely, Olesen and Tan. Regarding Olesen, the Board found that "the data provided by Olesen only relate[] to a small molecule (BIBN) and to blocking a CGRP receptor" and "Olesen does not provide a reasonable expectation of success of administering an anti-CGRP antibody (a different compound) that binds to the CGRP ligand rather than the CGRP receptor (a different site upstream of the receptor) to treat migraine." *Id.* at *44. Regarding Tan, the Board found that "Tan did not provide data showing that a full length anti-CGRP antibody could reach the synaptic cleft, the site of action for immunoblockade, to thereby achieve inhibition of endogenous CGRP *in vivo*" and "Tan provides no information or data regarding the use of a full-length anti-CGRP antibody to reduce

incidence of or treat a vasomotor symptom such as migraine headache." *Id.* at *45–46.

Having found no reasonable expectation of success based on the asserted prior art references, the Board next addressed the evidence relied on by each party and its experts pertaining to "whether migraine drugs would have been required to cross the blood brain barrier (BBB)." *Id.* at *47–59. The Board noted that the blood-brain barrier "raised uncertainty, unpredictability, and skepticism in using full-length anti-CGRP antibodies to reduce incidence of or treat headache such as migraine." *Id.* at *57. The Board determined that "in 2005, a [skilled artisan] would have been aware of the differences of opinion among key opinion leaders as to the pathogenesis of migraine and that it was largely unresolved." *Id.* at *58. Thus, the Board found that:

> [I]t was unknown as of November 14, 2005, whether anti-CGRP antibodies needed to cross the blood-brain barrier to reduce incidence of or treat headache such as migraine. Although absolute predictability in the art is not required to establish a reasonable expectation of success, the uncertainty and unpredictability about this basic knowledge and the pathogenesis of migraine headache, as well as the skepticism around whether full-length anti-CGRP antibodies would be effective, counsel against finding a reasonable expectation of success.
>
> *Id.*

The Board also relied on precedent from this court to support its finding that a skilled artisan would not have had a reasonable expectation of success. For example, the Board cited *Honeywell International Inc. v. Mexichem Amanco Holdings S.A. DE C.V.*, 865 F.3d 1348, 1356 (Fed. Cir. 2017), for the proposition that "when there is a high enough quantum of unpredictability, . . . a proponent of

unpatentability may not have met its burden of showing a reasonable expectation of success." *Board Decision*, 2020 WL 1540364, at *59. Based on *Honeywell*, the Board stated:

> [Lilly] is arguing that a person of ordinary skill would have taken the leap from a small molecule antagonist such as BIBN to a large molecule anti-CGRP antagonist antibody. We determine that [Lilly] has not demonstrated that a person of ordinary skill in the art would have had a reasonable expectation of success in using an antibody treatment in view of the level of unpredictability in whether the blood brain barrier would have been an obstacle, i.e., the uncertainty in whether anti-CGRP antibodies needed to cross the blood-brain barrier to reduce incidence of or treat headache such as migraine.

Id.

The Board also found that the facts in this case resembled the fact pattern in *Novartis Pharmaceuticals Corp. v. West-Ward Pharmaceuticals International Ltd.*, 923 F.3d 1051 (Fed. Cir. 2019), where this court held that the asserted art would not have given a skilled artisan a reasonable expectation of success. *See Board Decision*, 2020 WL 1540364, at *60. The Board found:

> Similar to *West-Ward* where clinical results had been obtained with temsirolimus but not with everolimus, clinical results had been obtained with BIBN (e.g., Olesen []) but not with anti-CGRP antagonist antibodies. Indeed, the anti-CGRP antibodies are pharmacologically different from BIBN because anti-CGRP antibodies have different half-lives and different sizes than BIBN. . . . Further, as above, the mechanisms of migraine and its treatment were still uncertain in 2005.

Id. Thus, the Board concluded that "*West-Ward* illustrates how a jump from one molecule to another may result in a lack of a reasonable expectation of success in an area with uncertainty." *Id.* at *61.

In summary, the Board found that Lilly failed to prove by a preponderance of the evidence that a skilled artisan would have had a reasonable expectation of success as to any of the challenged claims. *Id.* at *62–64. Accordingly, the Board concluded that Lilly failed to satisfy its burden of demonstrating that the challenged claims would have been obvious over the combination of Olesen, Tan, and Queen. *Id.* at *64.

Lilly appealed from the Board's combined final written decision with respect to each of the three challenged patents, and we consolidated the appeals. We have jurisdiction under 28 U.S.C. § 1295(a)(4)(A).

DISCUSSION

We review the Board's legal determinations de novo, *In re Elsner*, 381 F.3d 1125, 1127 (Fed. Cir. 2004), but we review the Board's factual findings underlying those determinations for substantial evidence, *In re Gartside*, 203 F.3d 1305, 1316 (Fed. Cir. 2000). A finding is supported by substantial evidence if a reasonable mind might accept the evidence as adequate to support the finding. *Consol. Edison Co. v. NLRB*, 305 U.S. 197, 229 (1938).

While Lilly makes a number of interrelated arguments in its briefing, Lilly's appeal can be broadly broken down into two primary challenges. In its first challenge, Lilly contends that the Board erred by reading a result into the constructions of the preambles and the term "effective amount," which led the Board to erroneously require Lilly to prove that a skilled artisan would have expected to achieve results that are unclaimed. In its second challenge, Lilly contends that even if the preambles are limiting and the claims thus require administration of an

antibody with an expectation of results, the Board erred by applying too high a standard when weighing the evidence to determine whether a skilled artisan would have had a reasonable expectation of success. We address each challenge in turn.

I

We first consider Lilly's challenge that the Board improperly required proof that a skilled artisan would have had a reasonable expectation of achieving a result that was not claimed. In considering this challenge, we think it is helpful to break down the challenge into two parts. In the first part, we discuss the aspects of the challenge that sound in claim construction. In the second part, we discuss the aspects of the challenge that relate more directly to the impact of the Board's constructions on its analysis of the reasonable expectation of success.

A

Claim construction is a matter of law that we review de novo. *See Poly-America, L.P. v. API Indus., Inc.*, 839 F.3d 1131, 1135–36 (Fed. Cir. 2016). Because the challenged patents are unexpired and the IPR petitions in this case were filed before November 13, 2018, the claims are to be given their broadest reasonable interpretation. *See* 37 C.F.R. § 42.100(b) (2018); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2142 (2016).

Lilly challenges the Board's construction of the claim preambles as limiting to the extent that they require that the recited methods be performed with an intentional purpose. According to Lilly, a preamble that contains only a statement of purpose cannot as a matter of law be a claim limitation. Lilly argues that a proper construction would attribute no weight to the claim preambles, and thus render them irrelevant to the obviousness analysis. And Lilly argues that the Board erred in its construction of the term

"effective amount," which compounded the Board's errors in imposing required results from the preambles.

Teva responds that Lilly's argument is based on a false dichotomy between limiting preambles as contrasted with preambles that are merely statements of intended purpose. Teva further argues that the preambles here are limiting because they are central to the invention, they provide antecedent basis for later claim limitations, and they give meaning to the substantive claim requirement of administering an "effective amount," which, Teva argues, the Board construed correctly.

First, we agree with Teva that our case law does not support Lilly's proposed binary distinction between statements of mere intended purpose on the one hand and limiting preambles on the other. On the contrary, we have stressed that there is no "litmus test" for determining whether a preamble is limiting. *See Bicon, Inc. v. Straumann Co.*, 441 F.3d 945, 952 (Fed. Cir. 2006) (citing *Catalina Mktg. Int'l, Inc. v. Coolsavings.com, Inc.*, 289 F.3d 801, 808 (Fed. Cir. 2002)). Rather, "[w]hether to treat a preamble as a claim limitation is determined on the facts of each case in light of the claim as a whole and the invention described in the patent." *Storage Tech. Corp. v. Cisco Sys., Inc.*, 329 F.3d 823, 831 (Fed. Cir. 2003).

The claims in this case are directed to methods, and more specifically to methods of using a composition for a specific purpose. Each claim is directed to a method for treating or reducing the incidence of vasomotor symptoms, and the method comprises a single step of administering an effective amount of a composition, namely, a humanized anti-CGRP antagonist antibody. This claim format is particularly relevant in our consideration of the claim as a whole because, while there is no bright-line rule for determining whether a preamble is limiting, we have generally construed statements of intended purpose in such method claims as limiting.

To illustrate the significance of methods of using apparatuses and compositions for specific purposes, we start by contrasting them with more general claims directed to apparatuses or compositions of matter, which are governed by the well-established principle that "[a]pparatus claims cover what a device *is*, not what a device *does*." *Hewlett-Packard Co. v. Bausch & Lomb Inc.*, 909 F.2d 1464, 1468 (Fed. Cir 1990). With regard to claims directed to apparatuses or compositions, we have often relied on the proposition that "[p]reamble language that merely states the purpose or intended use of an invention is generally not treated as limiting the scope of the claim." *Bicon*, 441 F.3d at 952. For example, in *Cochlear Bone Anchored Solutions AB v. Oticon Med. AB*, we held that a statement of intended purpose in the preamble—"for rehabilitation of unilateral hearing loss"—was not limiting because the claimed apparatus was fully structurally claimed in the body of the claim, and its structure would allow it to function identically whether or not used for its stated intended purpose. *See* 958 F.3d 1348, 1355 (Fed. Cir. 2020).

Even with respect to apparatus or composition claims, however, we have, when warranted by the facts, found statements of intended purpose to be limiting. For example, in *Bicon*, we considered a claim in which the preamble recited an apparatus and its intended use: "[a]n emergence cuff member for use in preserving the interdental papilla during the procedure of placing an abutment on a root member implanted in the alveolar bone of a patient." 441 F.3d at 948. We held that the preamble's statement of intended use was limiting because it "recites essential elements of the invention pertaining to the structure of the abutment that is used with the claimed emergence cuff." *Id.* at 952. We further noted that the body of the claim "refers back to the features of the abutment described in the preamble"—*i.e.*, the preamble provided antecedent basis for the structural terms in the body of the claim. *Id.* at 952–53. Similarly, in *Pacing Technologies, LLC v. Garmin*

International, Inc., we held that a statement of intended use—"[a] repetitive motion pacing system for pacing a user"—was limiting because the term "user" in the preamble provided antecedent basis for that term later in the body of the claim. 778 F.3d 1021, 1023–24 (Fed. Cir. 2015).

In contrast to apparatus and composition claims, claims to methods of using such apparatuses or compositions are not directed to what the method "is," but rather they typically rely entirely on what the method "does." And what a method does is usually recited in its preamble. Accordingly, our claim construction analysis of statements of intended purpose in methods of using apparatuses or compositions has tended to result in a conclusion that such preamble language is limiting. *See, e.g.*, *Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corp.*, 320 F.3d 1339, 1345 (Fed. Cir. 2003); *Jansen v. Rexall Sundown, Inc.*, 342 F.3d 1329, 1333 (Fed. Cir. 2003); *but cf. Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc.*, 246 F.3d 1368, 1375–76 (Fed. Cir. 2001) (holding preamble language non-limiting in method of treatment claims containing two steps, the second of which was administering a compound).

For example, in *Boehringer Ingelheim Vetmedica*, we considered a claim directed to "[a] method of growing and isolating swine infertility and respiratory syndrome virus, ATCC-VR2332." 320 F.3d at 1344. In holding the preamble language limiting, we explained that:

> [P]reamble language will limit the claim if it recites not merely a context in which the invention may be used, but the essence of the invention without which performance of the recited steps is nothing but an academic exercise. . . . This principle holds true here, *as it frequently does for method claims*: "growing" and "isolating" are not merely circumstances in which the method may be useful, but instead are the *raison d'etre* of the claimed method itself.

Id. at 1345 (emphasis added). Similarly, in *Jansen*, we held that the preamble of a method "for treating or preventing macrocytic-megaloblastic anemia" was limiting because it "set[] forth the objective of the method, and the body of the claim directs that the method be performed on someone 'in need.'" 342 F.3d at 1332–33. We elaborated that the preamble "is therefore not merely a statement of effect that may or may not be desired or appreciated. Rather, it is a statement of the intentional purpose for which the method must be performed." *Id.* Again, while there is no bright-line rule, it is instructive that this court has not hesitated to hold preambles limiting when they state an intended purpose for methods of using a compound.

Here, like in *Boehringer Ingelheim* and *Jansen*, the preambles are not merely statements of effect but rather statements of the intentional purpose for which the methods must be performed. First and foremost, the treatment of vasomotor symptoms such as migraine is central to the inventions of the challenged patents. That reality is reflected in the extensive discussions of such treatment in every section of the patents' written description. For example, the Abstract states that the invention "features methods for preventing or treating CGRP associated disorders such as vasomotor symptoms, including headaches." '045 patent at Abstract. The "Field of the Invention" describes the invention as relating to "the use of anti-CGRP antagonist antibodies for the prevention, amelioration, or treatment of vasomotor symptoms, such as CGRP related headaches (e.g., migraine)." *Id.* at col. 1 ll. 15–21. The "Background of the Invention" section is largely devoted to discussions of the connection between CGRP and vasomotor symptoms. *See id.* at col. 1 l. 39–col. 3 l. 29. The "Brief Summary of the Invention" describes a number of aspects of the invention, all of which are directed to "methods of using anti-CGRP antagonist antibodies for treating or preventing vasomotor symptoms, such as headaches, such as migraine." *Id.* at col. 3 ll. 38–40; *see also id.* at col. 3 l. 46–

col. 4 l. 3. And the "Detailed Description of the Invention" begins by stating that "[t]he invention disclosed herein provides methods for treating and/or preventing vasomotor symptoms such as headache (e.g., migraine, cluster headache, chronic headache, and tension headache)." *Id.* at col. 11 ll. 36–39.

After this heavy emphasis on the treatment of vasomotor symptoms throughout the written description, the claims also reference such treatment, but only in the preambles. Thus, the preambles are the portions of the claims that embody the essence of the claimed invention—methods for treating vasomotor symptoms. Under these circumstances, we reject Lilly's suggestion that the preambles merely state an intended purpose that need not be performed to practice the claims. The preambles limit the scope of the claims because these claims would not read on, for example, the performance of the same method step to treat other conditions.

Building on this idea, the claim language provides further support for the limiting nature of the preambles by including in each independent claim a step of administering an "effective amount" of an anti-CGRP antibody. The preambles provide the only metric by which one practicing the claim could determine whether the amount administered is an "effective amount." For this reason, Lilly is incorrect when it argues that the methods would be "performed 'in the same way' regardless of the preamble," *see* Lilly Br. at 32–33, because an "amount" of anti-CGRP antagonist antibodies that is "effective" for treatment of vasomotor symptoms may not be—and likely is not—the same amount that would be effective for treatment of other conditions. This case is, therefore, not like cases in which the administration of a specified amount is the same regardless of the purpose. *See, e.g.*, *Bristol-Myers Squibb*, 246 F.3d at 1375 (noting that the method step of administering "135–175 mg/m2 taxol over about three hours"

would be performed in the same way regardless of the intended purpose).

Lilly takes issue with the Board's construction of the term "effective amount" and argues that "effective amount" cannot support treating the preambles as limiting because that term must encompass administering clinically ineffective doses as low as "3 μg/kg" claimed in the dependent claims. But the Board derived the construction of "effective amount" directly from the definition provided by the patents' written description: "an amount sufficient to effect beneficial or desired results." *Board Decision*, 2020 WL 1540364, at *9 (citing '045 patent, col. 18 ll. 38–40). The Board further noted that the written description provides examples of beneficial or desired results in the context of prophylactic or therapeutic uses. *Id.* (citing '045 patent, col. 18 ll. 41–57). And the Board found that while the claims encompass a clinical result, they do not *require* such a result. *Id.* Thus, Lilly's argument about whether the 3 μg/kg in the dependent claims would achieve a "clinical" result is irrelevant, and it does not dissuade us from our conclusion that the preambles give life and meaning to the "effective amount" recited in the lone method step of each challenged claim.

In addition to giving life and meaning to the method step of each claim, the preambles also provide antecedent basis for at least one later claim term in the independent claims, namely, the term "administering to *the individual*," which refers back to the preamble term "treating . . . in *an individual*." *See, e.g.*, '045 patent, col. 99 ll. 2–4 (emphases added). Lilly cites *Cochlear Bone* for the proposition that a statement of intended purpose in a preamble can be nonlimiting even if a different term in the preamble provides antecedent basis for later claim terms. *See* 958 F.3d at 1355 ("A conclusion that some preamble language is limiting does not imply that other preamble language, or the entire preamble, is limiting."). But *Cochlear* involved an apparatus claim in which the statement of intended

purpose in the preamble provided no structure to the fully claimed structural apparatus described in the body of the claim. *Id.* In *Cochlear*, although the preamble term "patient" provided antecedent basis for the later claim terms that specifically referenced "the patient's" skull bone, the claimed apparatus would function identically whether or not it was used for the stated intended purpose—"for rehabilitation of unilateral hearing loss." *See id.* Here, in contrast, the preamble notes that the claim is a method for treating symptoms "in an individual"—*i.e.*, an individual who is suffering from those symptoms—by administering "to the individual" an "effective amount" to treat those symptoms. Axiomatically, without an individual experiencing vasomotor symptoms, there would be no effective amount that could be used to treat the nonexistent symptoms. Thus, the "individual" is part of the statement of intended purpose—for "treating at least one vasomotor symptom in an individual"—the entirety of which provides antecedent basis for the later claim term "administering to the individual."

In view of our case law regarding statements of intended purpose in claims directed to methods of using compositions, and in view of the intrinsic evidence, including the claim language and the written description of the challenged patents, we find no error in the Board's conclusion that the preambles are limiting.

B

Having found no error in the Board's claim constructions, we turn to Lilly's related argument regarding the impact of those constructions on the burden to prove a reasonable expectation of success. Before addressing Lilly's specific arguments, however, we must first emphasize the clear distinction in our case law between a patent challenger's burden to prove that a skilled artisan would have been motivated to combine prior art references and the additional requirement that the patent challenger also

prove that the skilled artisan would have had a reasonable expectation of successfully achieving the claimed invention from the combination. *See, e.g.*, *Procter & Gamble Co. v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009) ("A party seeking to invalidate a patent based on obviousness must demonstrate 'by clear and convincing evidence that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so.'" (quoting *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1361 (Fed. Cir. 2007))). A finding by the Board that a patent challenger has demonstrated a motivation to combine references does not necessarily imply that the challenger has also met its burden of showing a reasonable expectation of success in achieving a claimed method of treatment. *See, e.g.*, *West-Ward*, 923 F.3d at 1062.

Our analysis in *West-Ward* is particularly instructive here. In *West-Ward*, the claims at issue were directed to a method of treatment with a single step:

> A method for inhibiting growth of solid excretory system tumors in a subject, said method consisting of administering to said subject a therapeutically effective amount of a compound of formula I.

Id. at 1054. Regarding the motivation to combine requirement, we held that the appellant-defendant had met its burden of showing that a skilled artisan "would have been motivated to pursue everolimus as one of several potential treatment options for advanced solid tumors." *Id.* at 1060. We then considered the reasonable expectation of success requirement, noting that the appellant-defendant "argue[d] that the district court erred by imposing 'a heightened standard under which it found no reasonable expectation of success simply because there was not yet clinical proof that everolimus would successfully treat

advanced RCC.'" *Id.* (quoting the appellant-defendant's brief). But we rejected that argument and concluded that the district court had not erred when, based on its review of the evidence, the court "determined that the molecular biology of advanced RCC was not fully understood, recognized the limitations in the temsirolimus phase I data, and found that such data did not provide a person of ordinary skill with a reasonable expectation of success." *Id.* at 1062. Said differently, we held that it was not enough for the appellant-defendant to have shown that a skilled artisan would have pursued the claimed method as a treatment option, but the appellant-defendant also had to show that the skilled artisan would have reasonably expected to achieve success in the treatment.

The claims in this case, which are written in a "method for treating" format and comprise a single step of administering an effective amount of a compound, are analogous to the claims at issue in *West-Ward*. Like the appellant-defendant in *West-Ward*, Lilly must not only prove that a skilled artisan would be motivated to combine Olesen, Tan, and Queen, but also that the skilled artisan would have reasonably expected success in administering a humanized anti-CGRP antagonist antibody for "treating at least one vasomotor symptom."

Because we reject Lilly's claim construction argument that the preambles are non-limiting, we find Lilly's reliance on case law regarding unclaimed limitations to be misplaced. For example, Lilly cites *Intelligent Bio-Systems, Inc. v. Illumina Cambridge, Ltd.*, where we clarified that the reasonable expectation of success requirement "refers to the likelihood of success in combining references to meet the limitations of the claimed invention." 821 F.3d 1359, 1367 (Fed. Cir. 2016). In that case, we rejected the Board's approach of looking to "whether one would reasonably expect the prior art references to operate as those references intended once combined." *Id.* We determined that, although one prior art reference contained a "quantitative

deblocking" requirement that was not met by a different reference in the asserted obviousness combination, that fact was irrelevant to the reasonable expectation of success analysis because the challenged claim itself did not contain that requirement. *Id.* Here, in contrast, the claims do contain limitations related to their intended purpose for treating vasomotor symptoms, and thus those limitations are undoubtedly relevant to the reasonable expectation of success.

We are also unpersuaded by Lilly's argument that the patents' definitions of "treatment" and "reducing incidence" conflict with the notion that a skilled artisan must reasonably expect success from the claimed methods. On the contrary, we find that those definitions further support our conclusion as to what is required by the claims. As defined by the patents' written description, a "'treatment' is an approach for obtaining beneficial or desired clinical results" and "'[r]educing incidence of headache means any of reducing severity . . . , duration, and/or frequency." *See* '045 patent, col. 17 ll. 37–38, 52–58. But, included in those definitions, the patents also expressly recognize that:

> As is understood by those skilled in the art, individuals may vary in terms of their response to treatment, and, as such, for example, a "method of reducing incidence of headache in an individual" reflects administering the anti-CGRP antagonist antibody based on a reasonable expectation that such administration may likely cause such a reduction in incidence in that particular individual.

Id. at col. 17 ll. 58–65. This language from the written description is consistent with our conclusion that, in order to prove that the claims would have been obvious, Lilly was required to show that a skilled artisan would have had a "reasonable expectation" of success in treating vasomotor symptoms, even if such success was not guaranteed in all cases.

At bottom, the Board's conclusion on this issue was summed up as follows:

> [W]hat is required is not proof that the recited method would *actually* bring about the recited result, but rather proof that a person of ordinary skill in the art would have had a reasonable expectation that performing the recited method would bring about the recited result.

See Board Decision, 2020 WL 1540364, at *8. In view of our determination that the claim preambles are limiting in this case, and in view of our case law regarding the requirement that a patent challenger prove only a reasonable expectation of success, we find no error in this conclusion by the Board.

II

We next turn to Lilly's challenge that the Board imposed a heightened standard regarding the reasonable expectation of success. In this challenge, Lilly first contends that the Board erred by requiring that the prior art references include anticipatory data rather than the type of guidance in prior art references that is generally accepted for a showing of a reasonable expectation of success. And Lilly also contends that the Board erred by requiring a showing of certainty regarding the blood-brain barrier. We address each argument below.

A

Lilly contends that the Board applied the wrong standard to evaluate whether the asserted prior art references, specifically Tan and Olesen, would have given a skilled artisan a reasonable expectation of success. According to Lilly, the Board erroneously focused on the fact that Olesen and Tan lacked clinical data regarding the efficacy of using anti-CGRP antibodies to treat vasomotor symptoms. Lilly argues that this error was particularly problematic because the challenged patents themselves do not provide the

kind of data that the Board demanded from the prior art references. Had the Board not required efficacy data, Lilly argues, the Board would have credited the express guidance and instructions in Tan and Olesen that would have led to a reasonable expectation of success.

Teva responds that the Board did not purport to require efficacy data, clinical or otherwise. Rather, Teva argues, the Board observed that both Olesen and Tan lacked efficacy data, which the Board then considered as part of the overall obviousness analysis. And Teva contends that substantial evidence supports the Board's findings that neither Tan nor Olesen would have given a skilled artisan a reasonable expectation of success in treating vasomotor symptoms with an anti-CGRP antibody.

We agree with Teva that Lilly's argument misreads the Board's decision. To be sure, our case law makes clear that a showing of a reasonable expectation of success in a method of treatment claim need not rely on clinical data (which might, in fact, lead to a finding of anticipation), nor must it include a demonstration of certainty that the treatment would be successful in every instance. Indeed, in *OSI Pharmaceuticals, LLC v. Apotex Inc.*, we expressly stated that "we d[id] not hold . . . that efficacy data is always required for a reasonable expectation of success," and that the law does not require "absolute predictability of success." 939 F.3d 1375, 1385 (Fed. Cir. 2019). But in this case, the Board followed our case law and did not demand that the prior art include efficacy data.

Lilly directs its argument at isolated, out-of-context statements plucked from dozens of pages of the Board's factual findings regarding the reasonable expectation of success. Moreover, even those statements are not as limited to "data" as Lilly would have us believe. For example, as a summation of five paragraphs of analysis regarding Olesen, the Board stated:

> We find that Olesen provides no data *or direction* regarding the administration of a humanized monoclonal anti-CGRP antagonist antibody in an amount effective to achieve a beneficial or desired result in reducing the incidence of or treating migraine or any other vasomotor symptom, *or otherwise specifically suggest such use*.

Board Decision, 2020 WL 1540364, at *44 (emphases added). Similarly, after eight paragraphs of analysis of Tan's disclosures—including analysis of Tan's reported 16% experimental result, analysis of the differences between the full-length antibody and the Fab' fragment, and analysis of whether an antibody could reach the synaptic cleft—the Board included the following statement about Tan:

> We *also* find that Tan provides no *information or* data regarding the use of a full-length anti-CGRP antibody to reduce incidence of or treat a vasomotor symptom such as migraine headache (or any other disease).

Id. at *46 (emphases added).

Far from demands for data, these statements reflect the Board's recognition that if the prior art had included efficacy data regarding use of an anti-CGRP antibody to treat vasomotor symptoms, that fact would have been important in the obviousness analysis, *but no such data were disclosed*. The statements also demonstrate that the Board considered whether the references included any other "information," "direction," or "specific[] suggest[ion]" that would have led to a reasonable expectation of success. In *Sanofi v. Watson Labs. Inc.*, we rejected the appellants' argument that the district court had "by necessary implication demand[ed] known certainty" simply because it had used phrases like "not a 'concrete' factual assertion" and "in less than certain terms" to describe statements in the prior art. 875 F.3d 636, 647 (Fed. Cir. 2017). Similarly here, we

decline to infer a demand for data from the Board's observation that references did not include those data.

Beyond its argument about the Board's supposed demand for data, Lilly argues that the Board "omitt[ed]" from its analysis "express statements of expected success" in the prior art. Lilly Br. at 59. Lilly focuses on Tan's statement that higher doses, longer distribution times, and repeated administration would achieve positive results. Lilly also emphasizes Olesen's clinical trial demonstrating success in treating migraine with a CGRP-receptor antagonist. But the Board's opinion includes an extensive section on the reasonable expectation of success, with subsections specifically dedicated to findings about Tan and Olesen. As a factual matter, the Board found that neither of those references contained disclosures sufficient to create a reasonable expectation of success in treating vasomotor symptoms with a humanized anti-CGRP antibody. For Olesen, that finding was based on the undisputed differences between Olesen's small molecule CGRP-receptor antagonist as compared to the large ligand-targeting antibodies of the challenged claims. *See Board Decision*, 2020 WL 1540364, at *44. For Tan, the Board's finding was based on the competing expert interpretations of Tan's results, the unresolved dispute about whether the antibody could reach the synaptic cleft, and the fact that Tan studied skin vasodilation in rats rather than any condition in humans. *Id.* at *45–46.

Lilly's disagreement with the Board's interpretations of Tan and Olesen does not amount to a demonstration that the Board somehow failed to use the proper analysis. Ultimately, what a piece of prior art teaches presents a question of fact that is reviewed for substantial evidence. *See, e.g.*, *In re Warsaw Orthopedic, Inc.*, 832 F.3d 1327, 1332 (Fed. Cir. 2016) ("An examination of the scope and content of the prior art produces factual findings reviewed for substantial evidence."). When it comes to competing interpretations of the teachings of prior art references, we must

uphold the principle that "if two 'inconsistent conclusions may reasonably be drawn from the evidence in record, the PTAB's decision to favor one conclusion over the other is the epitome of a decision that must be sustained upon review for substantial evidence.'" *Elbit Sys. of Am., LLC v. Thales Visionix, Inc.*, 881 F.3d 1354, 1356 (Fed. Cir. 2018) (quoting *In re Cree, Inc.*, 818 F.3d 694, 701 (Fed. Cir. 2016) (internal brackets omitted)). Under this deferential standard of review, we cannot replace the Board's reasonable interpretation of references with a different interpretation that Lilly would prefer.

For the foregoing reasons, we are not persuaded that the Board imposed a heightened standard, or otherwise erred, in its analysis of whether the prior art references would have given a skilled artisan a reasonable expectation of success.

B

We finally consider Lilly's argument that the Board erred in its analysis of the blood-brain barrier. For background, large compounds like the anti-CGRP antibodies of the challenged claims have difficulty crossing the blood-brain barrier, as compared with, for example, small molecule receptor antagonists. *See Board Decision*, 2020 WL 1540364, at *57–58. Thus, the issue before the Board pertained to whether migraine treatment must cross the blood-brain barrier to be effective. *Id.* If migraine treatment does have to cross the blood-brain barrier, that fact would have detracted from an expectation of successfully treating migraine with a large anti-CGRP antibody. *Id.* Conversely, if migraine treatment does not have to cross the blood-brain barrier, then the large size of the anti-CGRP antibodies of the challenged claims would have been less relevant to whether a skilled artisan would have had a reasonable expectation of success.

Lilly contends that the Board incorrectly credited generalized assertions of uncertainty about the blood-brain

barrier and omitted the latest clinical prior art, "Petersen 2005."[7] Lilly argues that Petersen 2005 conclusively demonstrated that anti-CGRP drugs prevent headache without crossing the blood-brain barrier. Teva responds that substantial evidence supports the Board's findings with respect to the blood-brain barrier. Fundamentally, Teva argues, the Board's decision was based on the uncertainty about whether migraine treatment must cross the blood-brain barrier, and Lilly's identification of one reference among many is not sufficient to overturn the Board's analysis.

We again agree with Teva. In analyzing the blood-brain barrier issue, the Board first considered the evidence relied on by Teva and its expert as well as the evidence relied on by Lilly and its expert (including Petersen 2005). *See Board Decision*, 2020 WL 1540364, at *47–57. Based on all of the evidence, the Board determined that "in 2005, a [skilled artisan] would have been aware of the differences of opinion among key opinion leaders as to the pathogenesis of migraine and that it was largely unresolved." *Id.* at *58. In view of those different opinions, the Board stated its finding regarding the blood-brain barrier:

> We determine that it was unknown as of November 14, 2005, whether anti-CGRP antibodies needed to cross the blood-brain barrier to reduce incidence of or treat headache such as migraine. Although absolute predictability in the art is not required to establish a reasonable expectation of success, the uncertainty and unpredictability about this basic knowledge and the pathogenesis of migraine headache, as well as the skepticism

---

[7] K. A. Petersen et al., *BIBN4096BS antagonizes human α-calcitonin gene related peptide-induced headache and extracerebral artery dilatation*, 77 CLIN. PHARMACOL. THER. 202–13 (2005).

> around whether full-length anti-CGRP antibodies would be effective, counsel against finding a reasonable expectation of success.

Id.

As discussed above, the law does not require certainty; it requires a reasonable expectation of success. *See OSI*, 939 F.3d at 1385 ("Nor are we requiring 'absolute predictability of success.'"). But, in considering what constitutes a reasonable expectation of success, we must also consider that the law places the burden of proof on the petitioner to prove a proposition of unpatentability by a preponderance of the evidence. 35 U.S.C. § 316(e). Thus, in this case, it was, at all times, Lilly's burden to show that the claims would have been obvious, including that a skilled artisan would have had a reasonable expectation of success in achieving the claimed invention. *See Sinskey v. Pharmacia Ophthalmics, Inc.*, 982 F.2d 494, 498 (Fed. Cir. 1992) ("The statutory presumption of validity under 35 U.S.C. § 282 puts the burden of proving invalidity on the party asserting it and the burden never shifts to the patentee."); *see also Honeywell*, 865 F.3d at 1355 ("In an *inter partes* reexamination involving obviousness, the standard is not whether the patent owner can persuasively show that one of ordinary skill would have expected *failure*. Rather, the burden is on the Examiner to show that one of ordinary skill would have had a motivation to combine the references with a *reasonable expectation of success*.").

To the extent that the blood-brain barrier dispute was relevant to the expectation of success in this case, which neither party appears to dispute, it was Lilly's burden to demonstrate that despite any unpredictability in the literature, a skilled artisan nevertheless would have had a reasonable expectation of success. Both sides presented numerous pieces of evidence on the blood-brain barrier issue, including prior art references and expert testimony. The Board weighed the evidence supporting each side of

the factual dispute and found that sufficient uncertainty and unpredictability remained—*i.e.*, that Lilly's evidence failed to demonstrate *enough* certainty that migraine treatment does not have to cross the blood-brain barrier to give a skilled artisan a reasonable expectation of success. That finding is consistent with our past holdings that "[u]npredictability of results equates more with nonobviousness rather than obviousness." *Honeywell*, 865 F.3d at 1356.

Unsurprisingly, Lilly would have preferred that the Board accept its expert's opinion that Petersen 2005 settled the question regarding the blood-brain barrier. But in view of the Board's extensive analysis of the evidence, it is impossible for us to conclude that the Board's finding on the blood-brain barrier issue is unsupported by substantial evidence. We are therefore not persuaded that the Board erred in analyzing the blood-brain barrier issue and its impact on whether a skilled artisan would have had a reasonable expectation of success in combining the prior art teachings to achieve the claimed invention.

CONCLUSION

We have considered Lilly's remaining arguments but we find them unpersuasive. Accordingly, we affirm the Board's final written decision upholding the patentability of the claims of the challenged patents.

AFFIRMED