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Paper: 12
Entered: April 3, 2019

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.

Case IPR2018-01710
Patent 8,586,045 B2

Before JENNIFER MEYER CHAGNON, JAMES A. WORTH, and RICHARD J. SMITH, *Administrative Patent Judges.*

SMITH, *Administrative Patent Judge*.

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

I. INTRODUCTION

Eli Lilly and Company ("Petitioner") filed a Petition to institute an *inter partes* review of claims 1, 3, 4, 8–17, 19, 20, and 24–31 of U.S. Patent 8,586,045 B2 (the "'045 patent"). Paper 1 ("Pet."). Teva Pharmaceuticals International GmbH ("Patent Owner") filed a Preliminary Response to the Petition. Paper 8 ("Prelim. Resp.").

In its Preliminary Response, Patent Owner argued that we should exercise our authority to deny the Petition based on 35 U.S.C. § 325(d) because the same or substantially the same prior art or arguments previously were presented to the Patent and Trademark Office. Prelim. Resp. 12–28. Petitioner thereafter requested permission to file a reply to the Preliminary Response to address that issue, which we granted, allowing Petitioner to file a reply and Patent Owner to file a sur-reply. Petitioner thereafter filed its reply (Paper 10, "Pet. Reply") and Patent Owner filed its sur-reply (Paper 11, "PO Surreply").

We have authority under 35 U.S.C. § 314 to determine whether to institute an *inter partes* review. To institute an *inter partes* review, we must determine that the information presented in the Petition shows "a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." 35 U.S.C. § 314(a). For the reasons set forth below, we conclude that Petitioner has established a reasonable likelihood that it would prevail in showing the unpatentability of at least one challenged claim of the '045 patent. Therefore, we institute an *inter partes* review for claims 1, 3, 4, 8–17, 19, 20, and 24–31 of the '045 patent.

A. Related Proceedings

Petitioner identifies a declaratory judgment action filed by Patent Owner on October 24, 2017, in the District Court for the District of

Massachusetts ("the first DJ action"). Pet. 66. According to Petitioner, the first DJ action seeks a declaration that Petitioner's investigational drug galcanezumab will infringe U.S. Patent Nos. 8,597,649; 9,266,951; 9,340,614; 9,346,881; and the '045 patent, and Patent Owner filed an amended complaint in the first DJ action on January 16, 2018. *Id.* Petitioner also identifies a declaratory judgment action filed by Patent Owner on February 6, 2018, seeking a declaration that Petitioner's product will infringe U.S. Patent Nos. 9,884,907 and 9,884,908 ("the second DJ action"). *Id.* Petitioner states that Patent Owner thereafter filed an amended complaint in the second DJ action to incorporate U.S. Patent Nos. 9,890,210 and 9,890,211. *Id.*

According to Petitioner, the court dismissed Patent Owner's amended complaints in the first DJ action and the second DJ action, and Patent Owner filed a third action for infringement of the same patents on September 27, 2018. *Id.* Those patents purport to claim priority to the same provisional application as the '045 patent, and two applications (15/883,218 and 15/956,580) based on the same provisional application are pending before the United States Patent and Trademark Office. *Id.* Petitioner also identifies six *inter partes* review proceedings that it filed naming Patent Owner, and that have been now been instituted. *Id.* at 67; *see* IPR2018-01422, IPR2018-01423, IPR2018-01424, IPR2018-01425, IPR2018-01426, and IPR2018-01427.

Patent Owner identifies the first DJ action and the second DJ action, as well as a litigation styled *Teva Pharmaceuticals International GmbH v. Eli Lilly & Co.*, Civ. No. 1-18-cv-12029 (D. Mass.). Paper 6. Patent Owner also identifies the above-referenced *inter partes* reviews identified by Petitioner, and further identifies petitions for *inter partes* review against U.S.

Patent No. 9,884,907 (IPR2018-01711) and U.S. Patent No. 9,884,908 (IPR2018-01712), styled *Eli Lilly & Co. v. Teva Pharmaceuticals International GmbH*. *Id.* Patent Owner also identifies U.S. Patent Nos. 9,365,648; 9,328,168; 9,115,194; 8,734,802; and 8,007,794, in addition to the patents and patent applications identified by Petitioner. *Id.*

B. The '045 Patent (Ex. 1001)

The '045 patent is titled "Methods of Using Anti-CGRP[1] Antagonist Antibodies" and "relates 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) and hot flushes." Ex. 1001, [54], 1:18–21.

According to the Specification, CGRP is a 37 amino acid neuropeptide, which belongs to a family of peptides that includes calcitonin, adrenomedullin and amylin. *Id.* at 1:25–27. In humans, two forms of CGRP with similar activities (α-CGRP and β-CGRP) exist and exhibit differential distribution. *Id.* at 1:27–30. At least two CGRP receptor subtypes may also account for differential activities. *Id.* at 1:30–31. CGRP 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. *Id.* at 1:31–35.

CGRP-mediated vasodilatation is also associated with neurogenic inflammation, as part of a cascade of events that results in extravasation of plasma and vasodilation of the microvasculature and is present in migraine. *Id.* at 1:35–38. CGRP has been noted for its possible connection to

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[1] Calcitonin Gene-Related Peptide is abbreviated throughout as CGRP. *See* Ex. 1001, 1:25.

vasomotor symptoms. *Id.* at 1:39–40. Vasomotor symptoms include hot flushes and night sweats. *Id.* at 1:42–43. CGRP is a potent vasodilator that has been implicated in the pathology of other vasomotor symptoms, such as all forms of vascular headache, including migraines (with or without aura) and cluster headache. *Id.* at 2:3–6.

According to the Specification, the precise pathophysiology of migraine is not yet well understood. *Id.* at 3:17–18. Dilation of blood vessels is associated with and exacerbates the pain symptoms of migraine. *Id.* at 3:23–24. The variety of pharmacologic interventions that have been used to treat migraine and the variability in responses among patients indicate that migraine is a diverse disorder. *Id.* at 2:57–59. Different classes of drugs have been used in treatment (and some patients, usually those with milder symptoms, are able to control their symptoms with non-prescription remedies). *See id.* at 2:60–3:8. Some patients respond well to sumatriptan, which is a 5HT1 receptor agonist, which also inhibits release of CGRP; others are relatively resistant to its effects. *See id.* at 2:14–16, 3:8–13, 4:4–6.

The ’045 patent is directed, *inter alia*, to methods of treating or preventing a vasomotor symptom, migraine headache, or cluster headache in an individual using an effective amount of an anti-CGRP antagonist antibody. *See id.* at 3:37–54. The ’045 patent is also directed to methods of ameliorating, controlling, reducing incidence of, or delaying the development or progression of a migraine headache or cluster headache, using an effective amount of an anti-CGRP antagonist antibody with or without additional agents. *See id.* at 3:55–4:36. In various embodiments, the antibody is a human antibody or humanized antibody, the antibody recognizes a human CGRP, or the antibody comprises modified regions. *See*

id. at 4:40–5:34, 7:64–66. Other embodiments are directed to a polypeptide, which may or may not be an antibody. *See id.* at 6:56–7:63. Other embodiments are directed to a polynucleotide encoding a fragment or region of the antibody or its variants, or to expression and cloning vectors and host cells comprising any of the disclosed polynucleotides. *See id.* at 8:9–38. Other embodiments are directed to methods of making the same. *See id*. at 8:49–64.

The ’045 patent includes a Table 4 showing amino acid sequences of different variants of human α-CGRP and related peptides. *Id.* at 50:55–58; cols. 52–53 (Table 4). Table 4 identifies CGRP 1–37 (WT) as SEQ ID NO:15 and CGRP human β (1–37) as SEQ ID NO:43. *See id.*

Figure 5 (not reproduced here) shows the amino acid sequence of the heavy chain variable region (SEQ ID NO:1) and light chain variable region (SEQ ID NO:2) of antibody G1. *Id.* at 10:4–6. Table 6 provides data on binding affinity for G1 variants. *See id.* at cols. 60–65. Another table (cols. 72–97) lists additional antibody sequences.

C. Illustrative Claims

Claims 1 and 17, the only independent claims, are illustrative:

> 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.

Ex. 1001, 99:2–7.

> 17. A method for reducing incidence of or treating headache in a human, comprising administering to the human 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.

Id. at 100:3–7.

Claims 3, 4, and 8–16 depend directly on claim 1, and claims 19, 20, and 24–31 depend directly on claim 17. *Id.* at 99:17–25; 99:38–100:2; 100:17–24, 37–59.

D. The Asserted Ground of Unpatentability

Petitioner contends that the challenged claims are unpatentable on the sole ground of obviousness under (pre-AIA) 35 U.S.C. § 103(a) based on the following combination of references:

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) ("Olesen"). Ex. 1025.

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) ("Tan"). Ex. 1022.

Queen et al., US 6,180,370 B1, issued Jan. 30, 2001 ("Queen"). Ex. 1023.

Petitioner also relies on the Declaration of Dr. Andrew C. Charles, M.D. (Ex. 1014, "Charles Declaration") and the Declaration of Dr. Alain P. Vasserot, Ph.D. (Ex. 1015, "Vasserot Declaration").

II. ANALYSIS

A. Person of Ordinary Skill in the Art

Petitioner asserts that "a POSA [person of ordinary skill in the art] with respect to the aspects of the '045 patent pertaining to using anti-CGRP antibodies would have generally possessed a Ph.D. in a relevant field (e.g., neurobiology, neurology, pharmacology) or an M.D. with a residency in a relevant field (e.g., neurology), with several years of experience studying CGRP or treating patients with migraine." Pet. 18–19 (citing Ex. 1014

¶¶ 76–78). Petitioner further asserts that "a POSA with respect to the aspects of the '045 patent pertaining to designing and optimizing anti-CGRP antibodies would have generally possessed a Ph.D. in immunology, molecular biology, or pharmacology with several years of post-doctoral research experience focused on antibody engineering and/or antibody pharmacology." *Id.* at 19 (citing Ex. 1015 ¶¶ 77–79).

Patent Owner contends that "[b]ecause the '045 patent relates to methods of treatment using anti-CGRP antagonist antibody therapeutics, a POSA would draw upon the knowledge and experience of related disciplines of a multi-disciplinary team that might lie outside the POSA's primary training." Prelim. Resp. 32. Thus, according to Patent Owner, a POSA relevant to the '045 patent would have the knowledge of, or be able to draw upon the knowledge of, (for example): "(1) a medical doctor with a specialty in neurology, specifically in treating headache and migraine, including approximately 5 years of experience in its research, diagnosis, and/or treatment," "(2) a scientist having a Ph.D. in pharmacology, pharmacy, or an equivalent discipline, with approximately 3-5 years of experience in preclinical and clinical pharmacokinetics and pharmacodynamics;" or "(3) a scientist having a Ph.D. in immunology, biochemistry, or an equivalent discipline, with approximately 3-5 years in antibody design and engineering." *Id.* at 32–33.

On this record and at this stage of the proceeding, we do not discern an appreciable difference in the parties' respective definitions of a person of ordinary skill in the art. Accordingly, for purposes of the present Decision, we find that a person of ordinary skill in the art would have (1) a Ph.D. in a relevant field, such as immunology, biochemistry, or pharmacology, with several years of post-doctoral experience in antibody engineering,

pharmacokinetics, and pharmacodynamics, or (2) an M.D. with a residency or specialty in neurology, and several years of experience studying CGRP or treating patients with migraine headaches.

We further note that the prior art itself demonstrates the level of skill in the art at the time of the invention. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (explaining that specific findings regarding ordinary skill level are not required "where the prior art itself reflects an appropriate level and a need for testimony is not shown") (quoting *Litton Indus. Prods., Inc. v. Solid State Sys. Corp*., 755 F.2d 158, 163 (Fed. Cir. 1985)).

B. Claim Construction

In this *inter partes* review, filed October 4, 2018,[2] the claims of the '045 patent, which has not expired, shall be given their broadest reasonable construction in light of the specification. 37 C.F.R. § 42.100(b) (2018); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2142 (2016) (affirming applicability of broadest reasonable construction standard to *inter partes* review proceedings). Under that standard, and absent any special definitions, we generally give claim terms their ordinary and customary meaning, as would be understood by one of ordinary skill in the art at the time of the invention. *See In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). Any special definitions for claim terms must be set forth

[2] The claim construction standard to be employed in *inter partes* reviews has changed for proceedings in which the petition was filed on or after November 13, 2018. *See* Changes to the Claim Construction Standard for Interpreting Claims in Trial Proceedings Before the Patent Trial and Appeal Board, 83 Fed. Reg. 51,340 (Oct. 11, 2018) (to be codified at 37 C.F.R. pt. 42).

with reasonable clarity, deliberateness, and precision. *See In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

Petitioner requests construction of the terms "reducing incidence of or treating," "effective amount," "anti-CGRP antagonist antibody," and "humanized monoclonal antibody." Pet. 19–24. Patent Owner disputes Petitioner's proposed constructions of "reducing incidence of or treating" and "effective amount," but does not (at this stage of the proceeding) dispute Petitioner's proposed constructions of "anti-CGRP antagonist antibody" or "humanized monoclonal antibody." Prelim. Resp. 29–32.

"reducing incidence of or treating"

Petitioner argues that "[t]he '045 patent expressly defines 'treatment' as 'an *approach* for obtaining a beneficial or desired result'—it does not require *achieving* any particular result." Pet. 20 (citing Ex. 1001, 17:37–38 (emphases by Petitioner)). Thus, according to Petitioner, "'treating' merely refers to an *approach* for a particular outcome without requiring a clinical response." *Id.* (citing Ex. 1014 ¶ 102 (emphasis by Petitioner)). Similarly, Petitioner contends that "the '045 patent expressly defines 'reducing incidence of' to encompass merely '*administering* the anti-CGRP antagonist antibody based on a reasonable expectation that such administration *may likely* cause such a reduction in incidence'—it does not require achieving any particular 'reduction.'" *Id.* at 21 (citing Ex. 1001, 17:61–65 (emphases by Petitioner)). Thus, according to Petitioner, "[t]he express definitions [of 'reducing incidence of' or 'treating'] do not require a clinical response." Pet. 20.

Patent Owner argues that Petitioner's proposed construction is "incomplete" and that the '045 patent clearly ties both "reducing incidence of" and "treating" to achieving an intended clinical effect. Prelim. Resp. 30–

31. Patent Owner further argues that "the explicit definition of treatment provided in the specification . . . requires administering the anti-CGRP antagonist antibody to achieve a clinical result." *Id.*

On this record and at this stage of the proceeding, we determine that "reducing incidence of or treating" is a statement of intended purpose that does not require achieving a result. 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." Ex. 1001, 17:60–65.

"effective amount"

Petitioner argues that "effective amount" should be construed as "(1) including, at least via the doctrine of claim differentiation, doses of an anti-CGRP antagonist antibody that are less than 3 μg/kg, and (2) not requiring a clinical response." Pet. 21 (citing Ex. 1014 ¶ 104). According to Petitioner, the '045 patent states that "the term 'effective amount' encompasses amounts that produce merely biochemical or histochemical effects, such as stimulation of cAMP," but should not be construed to require a clinical response. *Id.* at 22–23.

Patent Owner argues that Petitioner's proposed construction of "effective amount" is incorrect, and refers to the Specification of the '045 patent. Prelim. Resp. 31–32. According to Patent Owner, the term "effective amount" should be tied to a clinical result and "construed as 'an amount sufficient to effect beneficial or desired results.'" *Id.* at 31 (citing Ex. 1001, 18:38–40).

An "effective amount" is defined in the '045 patent as "an amount sufficient to effect beneficial or desired results." Ex. 1001, 18:38–40.

Therefore, an "effective amount" of an anti-CGRP antagonist antibody requires achievement of beneficial or desired results. Nevertheless, the Specification proceeds to define what the achieved "beneficial or desired results" are:

> For prophylactic use, beneficial or desired results include results such as eliminating or reducing the risk, lessening the severity, or delaying the outset of the disease, including biochemical, histological and/or behavioral symptoms of the disease, its complications and intermediate pathological phenotypes presenting during development of the disease. For therapeutic use, beneficial or desired results include clinical results such as reducing pain intensity, duration, or frequency of headache attack, and decreasing one or more symptoms resulting from headache (biochemical, histological and/or behavioral), including its complications and intermediate pathological phenotypes presenting during development of the disease, increasing the quality of life of those suffering from the disease, decreasing the dose of other medications required to treat the disease, enhancing effect of another medication, and/or delaying the progression of the disease of patients.

Id. at 18:41–57.

Although the Specification describes blocking or decreasing CGRP receptor activation as including cAMP activation, and measures cAMP to determine the extent of receptor activation blocked or decreased by anti-CGRP antibodies (*see id*. at 25:51–55, 31:31–36, 61–64, 34:21–25, 53:36–54:64, & Tables 2, 3), it is unclear on this record whether the referenced "biochemical" and "histological" symptoms include cAMP stimulation, as argued by Petitioner.

On this record and at this stage of the proceeding, we determine that an "effective amount" means "an amount sufficient to effect beneficial or desired results," including results of prophylactic or therapeutic use, as those terms are used in the '045 patent. *See, e.g.*, Ex. 1001, 18:41–57. We do not

take a position on this record, as requested by Petitioner, as to the specific dosages that produce such results. *See Curtiss-Wright Flow Control Corp. v. Velan, Inc.*, 438 F.3d 1374, 1381 (Fed. Cir. 2006) ("'[c]laim differentiation is a guide, not a rigid rule.'") (quoting *Laitram Corp. v. Rexnord, Inc.*, 939 F.2d 1533, 1538 (Fed. Cir. 1991)).

We also determine, for purposes of determining whether to institute an *inter partes* review in this case, that we need not expressly construe any undisputed terms. *See Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999) (only those terms which are in controversy need to be construed and only to the extent necessary to resolve the controversy); *see also Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) (applying *Vivid Techs.* in the context of an *inter partes* review).

C. Principles of Law

A patent claim is unpatentable under 35 U.S.C. § 103(a) if the differences between the claimed subject matter and the prior art are such that the subject matter, as a whole, would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. *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) objective evidence of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

An obviousness analysis "need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in

the art would employ." *KSR*, 550 U.S. at 418; *see Translogic*, 504 F.3d at 1262. "Often, it will be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue." *KSR*, 550 U.S. at 418.

We analyze the asserted ground of unpatentability in accordance with the above-stated principles.

D. Obviousness over Olesen, Tan, and Queen

Petitioner asserts that claims 1, 3, 4, 8–17, 19, 20, and 24–31 of the '045 patent are unpatentable as obvious over Olesen, Tan, and Queen. Pet. 24–55. Patent Owner opposes. Prelim. Resp. 28–54.

1. Olesen (Ex. 1025)

Olesen is an article published in the New England Journal of Medicine that describes a multicenter clinical trial of BIBN4096BS[3], a highly specific and potent nonpeptide CGRP-receptor antagonist, to test its efficacy in the treatment of migraine attacks. Ex. 1025, 1104. Using a group-sequential adaptive treatment-assignment procedure, 126 patients presenting with acute migraine received one of the following: placebo or 0.25, 0.5, 1, 2.5, 5, or 10 mg of BIBN4096BS intravenously over a period of 10 minutes. *Id.* at 1104, 1107. Patients receiving 2.5 mg had a 66%

[3] The article refers to BIBN4096BS throughout as "BIBN 4096 BS." *See generally* Ex. 1025.

response rate, with a pain-free rate of 44% after two hours, and a recurrence rate of 19%. *Id.* at 1107, 1109.

Olesen states that proof of concept was established and that the main end point, the rate of response to pain two hours after treatment, was significantly higher than placebo. *Id.* at 1108–1109. The adverse event rate was 25% for the 2.5 mg group and 20% overall for the treatment group, which Olesen considers to be a low overall rate of adverse events. *Id.* at 1108–09. Olesen characterized the adverse events as mild or moderate, with the most frequent adverse events (within 15 hours after infusion) being paresthesia, nausea, headache, dry mouth, and abnormal vision. *Id.* at 1109 & Table 3.

With respect to adverse events and potential clinical applications, Olesen concludes:

> Paresthesia was the only adverse event of note. BIBN 4096 BS does not seem to have vasoconstrictor properties, but our data base was too small for us to assess cardiovascular safety. If subsequent studies prove the drug to be without vasoconstrictor properties, this will represent an advantage over the triptans.
>
> Our results pose some important clinical and fundamental pathophysiological questions. Would patients who have no response to triptans benefit from treatment with a CGRP antagonist, or would the benefit be confined to those who have a response to triptans? How would a CGRP antagonist and a triptan compare if studied contemporaneously? Given that CGRP antagonists have no direct vasoconstrictor effects, would this class of compounds offer similar efficacy and be safer than triptans? Can CGRP antagonists establish the primacy of the nerve over the vessel during a migraine attack? Only future studies that use a more easily administered formulation of a CGRP antagonist can answer these questions, but our findings offer the prospect of both better treatment and a greater

> understanding of one of the most common clinical problems in medicine.

Id. at 1109 (internal footnote omitted).

2. Tan (Ex. 1022)

Tan states that "[i]mmunoblockade may be described as the blockade of the effects of a biological mediator by inhibition of its binding to specific receptors with antibodies directed against the mediator." Ex. 1022, 566. Tan describes a comparative study, wherein the results of using an anti-CGRP monoclonal antibody (MAb) IgG and its Fab' fragment for immunoblockade *in vivo* were compared to those obtained by receptor blockade with hαCGRP$_{8–37}$. *Id.*

Tan reports on an *in vivo* study with intravenous administration of rat CGRP and various anti-CGRP antibody preparations in male Sprague-Dawley rats. *See* Ex. 1022, 565–566. The effects of an anti-CGRP monoclonal antibody (MAb C4.19) and its Fab' fragment on CGRP changes in blood pressure were studied in anaesthetized rats. *Id.* at 565. Tan reports that MAb C4.19 IgG increased MAP [mean arterial pressure] slightly, but MAP was decreased by rαCGRP in a dose-dependent manner. *Id.* at 568. In experiments involving MAb C4.19 Fab' fragment, a control dose of 0.1 nmol/kg rαCGRP decreased MAP by 29.5 mm Hg. *Id.* at 569. The hypotensive response to rαCGRP was accompanied by a dose-dependent tachycardia in some experiments. *Id.* at 568. Tan states that "[t]his study has clearly demonstrated the ability of MAb C4.19 IgG and its Fab' fragment to block the hypotensive effects of exogenous rαCGRP." *Id.* at 570.

Tan reports that the skin blood flow response to antidromic stimulation of the saphenous nerve was effectively blocked 30 minutes after administration of MAb C4.19 Fab' fragment (2 mg/rat) but not 60 minutes

after administration of MAb C4.19 IgG (1 mg/rat). *See id.* at 565, 569–570. Nerve stimulation performed at 2 hours after 3 mg/rat MAb C4.19 IgG produced an AUC (area under the flux-time curve attributable to nerve stimulation) that was slightly smaller compared with baseline stimulation. *Id.* at 569. Tan states that the slow distribution of IgG to the site of immunoblockade could be overcome by chronic or repeated administration of IgG. *Id.* at 571. Tan further states that "MAb C4.19 does not cross-react with rat amylin *in vitro*" and that "the routine use of Fab' fragment should be advocated for acute immunoblockade experiments *in vivo*." *Id.* at 572.

3. Queen (Ex. 1023)

Queen is titled "Humanized Immunoglobulins and Methods of Making the Same," and "relates generally to the combination of recombinant DNA and monoclonal antibody technologies for developing novel therapeutic agents and, more particularly, to the[] production of non-immunogenic antibodies having strong affinity for a predetermined antigen." *See* Ex. 1023, [54], 1:19–23.

Queen describes problems with prior art monoclonal antibodies, i.e., most monoclonal antibodies were mouse derived and did not fix human complement well, lacked other functional characteristics when used in humans, and contained substantial stretches of amino acid sequences that would be immunogenic when injected into a human patient. *Id.* at 1:26–47. According to Queen, the production of so-called "chimeric antibodies" (e.g., mouse variable regions joined to human constant regions) proved somewhat successful but a significant immunogenicity problem remained. *Id.* at 1:58–61. Queen discloses that then-recent recombinant DNA technology had been used to produce immunoglobulins with reduced immunogenicity, called "reshaped" or "humanized" antibodies, which have human framework

regions with complementarity determining regions (CDRs) from a donor mouse. *Id.* at 1:65–2:11. However, Queen discloses that a major problem existed with humanized antibodies, i.e., a loss of affinity for the target antigen (by 10-fold or more) with poorer function and higher adverse effects (e.g., if a higher dose is consequently administered). *Id.* at 2:13–27.

Queen discloses a method of humanizing donor (e.g., mouse) antibodies by selecting a human framework sequence (i.e., containing a light chain or heavy chain) from a collection of sequences based on homology to the donor sequence such that the selected human framework sequence will have 65% to 70% homology or more to the donor framework sequence. *Id.* at 13:5–36. As further step(s), amino acids in the human acceptor sequence will be replaced by corresponding amino acids from the donor sequence if (1) the amino acid is in a CDR; (2) the amino acid in the human framework region is rare for that position and the corresponding amino acid in the donor sequence is common for that position in human sequences; (3) the amino acid is immediately adjacent to one of the CDRs; (4) the amino acid is predicted to be within about 3A of the CDRs in a three-dimensional model and capable of interacting with the antigen or CDRs of the donor or humanized immunoglobulin; and/or (5) the amino acid is rare for that position in a human sequence and the corresponding amino acid from the donor sequence is also rare, relative to other human sequences. *See id.* at 2:61–3:26.

4. Analysis

Petitioner sets forth its contentions as to why claims 1, 3, 4, 8–17, 19, 20, and 24–31 are obvious over the combination of Olesen, Tan, and Queen. Pet. 24–63. Patent Owner opposes. Prelim. Resp. 28–63. We address the parties' respective contentions below. We emphasize that the following

determinations regarding the sufficiency of the Petition are preliminary in nature at this stage of the proceeding.

Claim 17

Petitioner argues that "[e]ach and every element of claim 17 is disclosed or suggested by the prior art." Pet. 24. Petitioner points to Olesen's clinical study as demonstrating "that blocking the CGRP pathway effectively treats migraine in human patients," and as validating "the CGRP pathway as a therapeutic target for treating migraine." *Id.* at 24–25 (citing Ex. 1025, 1104, 1108–09; Ex. 1014 ¶¶ 31–36, 68–69, 109). Petitioner points to Tan as describing murine anti-CGRP antagonist antibodies that blocked the effects of CGRP *in vivo*. *Id.* at 24 (citing Ex. 1022, 567–71; Ex. 1014 ¶ 71). Petitioner cites to Queen as teaching humanized antibodies, and methods of making humanized antibodies, and that humanized antibodies minimize potential immunogenic responses, thereby rendering them suitable for administration to humans. *Id.* at 24–25 (citing Ex. 1023).

Petitioner argues that a POSA would have been motivated to treat migraine with a humanized monoclonal anti-CGRP antagonist antibody, and advances several contentions in support of that argument. *Id.* at 25–35.

First, Petitioner contends that a POSA would have been motivated to use a *CGRP antagonist* to treat migraine. *Id.* at 25–29. Petitioner refers to Olesen's reference to CGRP antagonists, and the report by the Olesen investigators/authors that their study establishes that "CGRP antagonism" is a novel principle in the treatment of migraine, and concludes that "a POSA reading Olesen would have extended its teachings to other CGRP antagonists." *Id.* at 25–26 (citing Ex. 1025, 1104, 1108–09; Ex. 1029, 119 (S26); Ex. 1014 ¶¶ 107–113). Petitioner also cites to Tan's teachings comparing immunoblockade with anti-CGRP antagonist antibodies to

blocking with CGRP receptor antagonists. *Id.* at 26–27 (citing Ex. 1022, 566, 571); *see* Ex. 1022, 571 ("Immunoblockade should be regarded as a technique that is complementary to the use of receptor antagonists."). Petitioner also cites to Tan and the Charles Declaration as support for the contention that "a POSA in 2005 would have known that targeting the ligand—CGRP—as opposed to one of its receptors, had several therapeutic advantages." Pet. 28–29 (citing Ex. 1022, 572; Ex. 1014 ¶¶ 113, 128–30; Ex. 1099, 235–237).

Second, Petitioner contends that a POSA would have been motivated to use an anti-CGRP antagonist *antibody* to treat migraine. *Id.* at 29–33. In support of that contention, Petitioner asserts that "[t]he prior art had already identified anti-CGRP antagonist antibodies as suitable options for treating migraine." *Id.* at 29 (citing Ex. 1096, 567, 569–70). Petitioner also cites to Tan (among other references) as support for the contentions that "[m]ultiple murine anti-CGRP antagonist monoclonal antibodies had already been developed and characterized, and were also available commercially," that "[t]hese antibodies had been shown to bind to and block the biological activity of CGRP in both *in vitro* and *in vivo* assays," and that "Tan demonstrated that anti-CGRP antagonist antibodies inhibited CGRP activity *in vivo* in the rat saphenous nerve model." *Id.* at 30 (citing Ex. 1022, 568–70; Ex. 1014 ¶¶ 86, 118; Ex. 1015 ¶¶ 88–91; Ex. 1033, 98–102; Ex. 1051, 350; Ex. 1055, 90–93).

Petitioner further supports its contention regarding motivation to use an anti-CGRP antagonist antibody to treat migraine by asserting that there were "several known advantages of antibodies compared to small molecule drugs like Olesen's BIBN4096BS compound," pointing to the longer half-life of antibodies (as compared to BIBN4096BS) that would be desirable for

treating chronic migraine conditions. *Id.* at 31–32 (citing Ex. 1014 ¶¶ 124–126; Ex. 1042, 652; Ex. 1070, 18; Ex. 1253, 938, 2955, 1338, 1359, 1966; Ex. 1031, 323). Petitioner also asserts that a "POSA also would have chosen antibodies to avoid the known side effects of existing small-molecule migraine drugs," pointing to the reduced risk of liver toxicity. *Id.* at 32 (citing Ex. 1014 ¶ 127; Ex. 1057, 1348; Ex. 1015 ¶ 55; Ex. 1250, 4, 22; Ex. 1247, 3969). Petitioner further asserts that antibodies would have been particularly appealing "for disrupting ligand-receptor interactions, such as inhibiting CGRP from binding with its receptors," pointing to FDA-approved antibodies and that "it was known that anti-migraine drugs did not need to cross the BBB [blood brain barrier] to effectively treat migraine." *Id*. at 32–33 (citing Ex. 1057, 1348–49; Ex. 1015 ¶ 55; Ex. 1014 ¶¶ 128–129, 151; Ex. 1056, 1075; Ex. 1022, 572, Ex. 1033, 102; Ex. 1090, 702–03; Ex. 1241, Abstract, 454–55; Ex. 1242, Abstract; Ex. 1243, 591–92; Ex. 1244, 286).

Third, Petitioner contends that a POSA would have been motivated to use a *humanized* monoclonal anti-CGRP antagonist antibody to treat migraine. *Id.* at 33–35. Petitioner relies on Queen as evidence that "the prior art had embraced *humanized* antibodies for treating human patients to reduce immunogenicity," and that because repeated administration of a therapeutic agent is required for treating migraine, but also associated with unwanted immunogenic responses, "a POSA would have been motivated to make a humanized anti-CGRP antagonist antibody to minimize the risk of immunogenicity." *Id.* at 33–34 (citing Ex. 1023, 1:19–21, 44–57; Ex. 1014 ¶¶ 120–122; Ex. 1015 ¶¶ 21, 30–33, 93–100). Thus, according to Petitioner, a POSA "would have been motivated to combine and follow the disclosures of Olesen, Tan, and Queen to obtain a humanized anti-CGRP antagonist

antibody for reducing incidence of or treating migraine in a human patient." *Id.* at 35 (citing Ex. 1014 ¶ 137).

Petitioner also argues that the prior art provided a reasonable expectation of success, and advances several contentions in support of that argument. Pet. 35–43. Petitioner reasserts its claim construction arguments, but also asserts that "[e]ven if the Board construes claim 17 to require a clinical response . . . a POSA would have reasonably expected a humanized anti-CGRP antagonist antibody to reduce incidence of or treat migraine in humans." *Id.* at 35–36. Petitioner points to Olesen as establishing that blocking the CGRP pathway had been clinically proven to treat migraine, and other prior art references associating CGRP antagonists with treating migraine. *Id.* at 37–38 (citing Ex. 1024, 420, 422; Ex. 1022, 569–70; Ex. 1052, 773–74; Ex. 1047, 60; Ex. 1025, Abstract, 1107–09; Ex. 1040, 182–183); *see also* Ex. 1014 ¶¶ 139–41. Petitioner also points to Tan as establishing that immunoblockade with anti-CGRP antagonist antibodies had been confirmed *in vivo*, and was a known alternative technique for blocking the CGRP pathway. Pet. 38–40 (citing Ex. 1022, 566, 568–572; Ex. 1014 ¶¶ 60, 86–87, 142, 144, 146). Thus, according to Petitioner, "a POSA would have reasonably expected that a humanized anti-CGRP antagonist antibody would successfully reduce incidence of or treat migraine, regardless of whether the Board determines that the claims require a clinical response." *Id.* at 39–40 (citing Ex. 1025, 1104, 1108; Ex. 1029, 119; Ex. 1014 ¶ 148).

Petitioner also contends that a POSA would have had a reasonable expectation of success in making a humanized anti-CGRP antagonist antibody for therapeutic use in humans. *Id.* at 40–43. Petitioner asserts that "a POSA would have reasonably expected to succeed in making a murine anti-CGRP antagonist antibody that bound *human* CGRP like those reported

in Tan . . . and elsewhere," and "would have had a reasonable expectation of success in humanizing that antibody," citing to the teachings of Queen. *Id.* at 40–41 (citing Ex. 1021, 704, 706; Ex. 1055, 88, 90, 93; Ex. 1023; Abstract, 2:28–34; Ex. 1014 ¶ 154; Ex. 1015 ¶¶ 41, 47, 103–109).

Claim 1

Petitioner argues that claim 1, the only other independent claim, is broader than claim 17 because it is directed to any vasomotor symptom and any individual (rather than just humans).[4] Pet. 49–50. Thus, according to Petitioner, claim 1 would have been obvious for the reasons discussed in connection with claim 17. *Id.* We agree with Petitioner that the scope of claim 1 is broader than claim 17.

Petitioner further argues that a POSA would have been motivated to use an anti-CGRP antagonist antibody, including a humanized antibody, to reduce incidence of or treat skin vasodilation (a vasomotor symptom), pointing to Tan as establishing that murine monoclonal anti-CGRP antagonist antibodies reduced incidence of skin vasodilation in rats. *Id.* at 50 (citing Ex. 1143, 10; Ex. 1245, 1:18–23; Ex. 1001, 19:51; Ex. 1022, 569). Petitioner also argues that a POSA would have reasonably expected to succeed, "at least because Tan previously disclosed reducing incidence of skin vasodilation in an individual with a monoclonal anti-CGRP antagonist antibody." *Id.* (citing Ex. 1014 ¶¶ 56–58).

Having considered the arguments and evidence, and at this stage of the proceeding, we are persuaded that Petitioner has sufficiently shown that

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[4] The '045 patent defines the term "individual" as "a mammal, more preferably a human. Mammals also include, but are not limited to, farm animals, sport animals, pets, primates, horses, dogs, cats, mice and rats." Ex. 1001, 19:4–7.

the combination of Olesen, Tan, and Queen teaches or suggests each limitation of claims 1 and 17. We are also persuaded that Petitioner has sufficiently shown that, as to claims 1 and 17, a person of ordinary skill in the art would have had a reason to combine the teachings of Olesen, Tan, and Queen with a reasonable expectation of success.[5]

Dependent claims

Petitioner provides further evidence and arguments regarding dependent claims 3, 4, 8–16, 19, 20, and 24–31. Pet. 50–61. For example, Petitioner argues that claims 3, 9, 19, and 24 specifically encompass reducing incidence of or treating migraine, and are obvious for the reasons set forth above. *Id.* at 51. Patent Owner does not advance any substantive arguments regarding dependent claims 3, 4, 8–16, 19, 20, and 24–31. *See generally* Prelim. Resp.

Patent Owner's Arguments

Patent Owner argues that the Petition is deficient in several ways.[6] Prelim. Resp. 29, 34–63.

Patent Owner argues that Petitioner has not sufficiently established that a POSA would have been motivated to "1) target CGRP, as opposed to small molecule CGRP receptor antagonist as Olesen did, to treat migraine, and 2) use anti-CGRP antagonist antibodies for this purpose." Prelim. Resp.

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[5] Petitioner also argues that its (and others) near-simultaneous development precludes a holding of nonobviousness. Pet. 53–55. We do not rely on that argument for purposes of our decision to institute *inter partes* review.

[6] Patent Owner also argues that Petitioner should be held to its Olesen, Tan, and Queen obviousness combination. Prelim. Resp. 33–34. We find on this record and at this stage of the proceeding that the Petition is sufficient to institute *inter partes* review.

29, 34–46. Patent Owner advances several contentions in support of that argument. *Id.* at 34–36.

First, Patent Owner contends that Petitioner's "argument that a POSA would have understood Olesen's results to extend beyond the small molecule CGRP-receptor antagonists is wrong in view of a plain reading of Olesen." *Id.* at 36–39. Patent Owner challenges Petitioner's extension of the meaning of the term "CGRP antagonists," as used in Olesen, as "allegedly teaching 'without limitation' agents that target both CGRP and CGRP receptors." *Id.* at 36 (citing Pet. 26). According to Patent Owner, "Olesen's use of the term 'CGRP antagonist,' when put in context, is clearly directed to CGRP receptor antagonists and cannot be extended to antagonists that target the CGRP ligand." *Id.* at 37.

Although we appreciate that the issue of what Olesen as a whole would have taught or suggested to a POSA may well be developed further during trial, we find on this record and at this stage of the proceeding that Petitioner's view of Olesen is sufficiently supported by the record. In addition to citing Olesen, Petitioner cites to statements in the Charles Declaration (Ex. 1014) that Olesen "demonstrated that blocking the CGRP pathway was a valid method for treating migraine" (*id.* ¶ 31), that "Olesen's study reinforced the already high level of optimism in the field extending broadly to CGRP antagonism generally as well as anti-CGRP antagonist antibodies specifically" (*id.* ¶ 36 (citing Ex. 1026, 7:5–20; Ex. 1096, 567)), and "Olesen thus conclusively demonstrates that blocking the CGRP biological pathway reduces incidence of or treats migraine in the clinic, thereby validating CGRP as a viable clinical target for migraine" (*id.* ¶ 69). *See* Pet. 25.

Petitioner also cites to a symposium report by the Olesen investigators/authors concluding that "BIBN4096BS is effective in the acute treatment of migraine and the present study, therefore, establishes a totally novel principle in the acute treatment of migraine: CGRP antagonism." *Id.* at 26 (citing Ex. 1029, 119 (S26)). Reference to CGRP antagonism as a "novel principle" suggests that the Olesen investigators/authors may have viewed their work as broader than simply the use of receptor antagonists. Petitioner further cites to Arulmozhi[7] for the statement that "inhibition of CGRP *or* antagonism of CGRP receptors" may be a viable therapeutic target for treating migraine. Pet. 38 (citing Ex. 1040, 182–83 (emphasis by Petitioner)). Arulmozhi thereafter states "[i]n line with this concept, an important breakthrough in the field of CGRP is the development of . . . BIBN4096BS," citing Olesen and other articles. Ex. 1040, 183. Again, this suggests a POSA may well have understood Olesen's teachings more broadly than simply the use of receptor antagonists.

In contrast, Patent Owner's contention regarding Olesen's use of the term "CGRP antagonist" relies on attorney argument (*see* Prelim. Resp. 36–37) and the allegation that Petitioner's "sole support . . . for its interpretation of Olesen is paragraph 109 of [the Charles Declaration], which simply parrots the Petition and should therefore be given little weight on this point" (*id*. at 37–39). In view of Petitioner's arguments and evidence at this stage of the proceeding, we are unpersuaded by Patent Owner's contention that

[7] D.K. Arulmozhi et al., *Migraine: Current Concepts and Emerging Therapies*, VASCULAR PHARMACOLOGY 43, 176–87 (2005) ("Arulmozhi"). Ex. 1040.

Petitioner's position regarding how a POSA would have understood Olesen is "wrong." *See id.* at 36.

Second, Patent Owner argues that Petitioner "fails to show a motivation to target CGRP instead of CGRP receptors for treating migraine." Prelim. Resp. 39–44. Patent Owner specifically contends that Petitioner "has not provided adequate support for its argument that targeting CGRP ligand, instead of CGRP receptors, to treat migraine 'had several therapeutic advantages.'" *See id.* at 39–42. Patent Owner further specifically contends that Petitioner "does not reconcile its alleged reasons to antagonize CGRP with the teachings in the art of 'potential dangers' associated with targeting CGRP," referring to Wimalawansa.[8] *Id.* at 42–43 (citing Ex. 1096, 540, 543, 568–69).

Patent Owner's "adequate support" contention regarding Petitioner's assertion that there were therapeutic advantages for targeting CGRP, as opposed to its receptors, is not persuasive. We note that Petitioner does provide support for its assertion of therapeutic advantages, including the Charles Declaration (*see* Pet. 28–29, 31–33), whereas Patent Owner relies principally on attorney argument (*see* Prelim. Resp. 39–42). Moreover, Patent Owner's primary contention is that Petitioner disregarded Olesen's findings regarding the efficacy of using BIBN4096BS to treat migraine. *See id*. We do not find that contention persuasive, at least because Petitioner relies on Olesen for its obviousness challenge. *See* Pet. 14–15; *see, e.g.*, *id.*

[8] S.J. Wimalawansa, *Calcitonin Gene-Related Peptide and its Receptors: Molecular Genetics, Physiology, Pathophysiology, and Therapeutic Potentials*, 17 ENDOCRINE REVIEWS 5, 533–85 (1996) ("Wimalawansa"). Ex. 1096.

at 15 ("Olesen concluded that BIBN4096BS was effective in treating migraine.").

Similarly, we are not persuaded by Patent Owner's contention that Petitioner does not reconcile its alleged reasons to antagonize CGRP with teachings in the art of "potential dangers" associated with targeting CGRP. Prelim. Resp. 42. Petitioner does acknowledge that "[w]hile, as of 1996, Wimalawansa appreciated the need for further studies before initiating human clinical trials," and also points to Wimalawansa's teaching that "[t]he role of CGRP antagonists and humanized monoclonal antibodies should be explored."[9] *See* Pet. 29.

Third, Patent Owner argues that Petitioner "fails to show motivation to treat migraine with anti-CGRP antibodies." Prelim. Resp. 44–46. Patent Owner points to Tan and other references to argue that Petitioner "does not show how existence of anti-CGRP antagonist antibodies before 2005 would have motivated a POSA to use such an antibody "in place of" Olesen's BIBN4096BS receptor antagonist for treating migraine." Prelim. Resp. 44–45. Patent Owner also contends that Petitioner provides no evidence that anti-CGRP antibodies would have decreased side effects and have a longer half-life as compared to BIBN4096BS. *Id.* at 45–46. Thus, according to Patent Owner, Petitioner has not demonstrated that a POSA would have been motivated to use anti-CGRP antibodies "in place of" Olesen's small molecule receptor antagonist to treat migraine. *Id.* at 46.

[9] The parties may choose to develop during trial the extent to which any concerns raised by Wimalawansa in 1996, regarding administration of an anti-CGRP antagonist antibody to humans, may have been addressed in the art before the filing of Patent Owner's first application in November 2005.

We are not persuaded by Patent Owner's argument on this record and at this stage of the proceeding. Patent Owner narrowly characterizes the reason to combine the teachings and suggestions of the prior art to treat migraine with anti-CGRP antibodies as simply whether a POSA would have been motivated to use anti-CGRP antibodies *in place of* Olesen's small molecule receptor antagonist. *See id.* at 44–46. But Olesen shows, at a minimum, that blocking the CGRP pathway by a specific receptor antagonist treated migraine in humans. Ex. 1025, Abstract. Olesen's results also show the selected dose of 2.5 mg resulted in a response rate of 66% and a rate of adverse events of 25%. *Id.* Tan teaches that anti-CGRP monoclonal antibodies were successful in blocking CGRP *in vivo*, and set forth the protocols for using a full length anti-CGRP monoclonal antibody at its site of action. Ex. 1022, 568–71. Thus, anti-CGRP antibodies were not only known, they were expressly taught by Tan as "complementary to the use of receptor antagonists." *Id.* at 571. Therefore, we find at this stage of the proceeding that Petitioner's evidence provides a sufficient reason to treat migraine with anti-CGRP antibodies, and that such reason need not necessarily be or include *replacing* Olesen's specific receptor antagonist. *See KSR*, 550 U.S. at 418.

Patent Owner argues that Petitioner does not demonstrate why a POSA would have had a reason to select and humanize Tan's full-length antibody to treat migraine, and advances several contentions in support of that argument. Prelim. Resp. 29, 46–57. Patent Owner contends that Petitioner failed to show that a POSA would have selected C4.19 for humanization, that Petitioner has not shown that the data in Tan demonstrates to a POSA that its full-length antibody (C4.19) would be useful *in vivo* as a therapeutic antibody, much less for treating migraine, and

that Petitioner failed to show that the resulting humanized antibody based on C4.19 would be reasonably expected to be therapeutically active for migraine. *Id.* at 29, 46–49. Moreover, according to Patent Owner, Tan did not establish that C4.19 antagonized endogenous CGRP at its site of action—an alleged failure that Patent Owner characterizes as "a critical prerequisite to [Petitioner's] argument that is missing for motivation"—and that Petitioner fails to address why a POSA would not expect Tan's "negative result" to apply to other full-length anti-CGRP antibodies. *Id.* at 49–56.

On this record, we are unpersuaded by Patent Owner's arguments. As an initial matter, Patent Owner's arguments focus on the specific modification of Tan's full-length MAb C4.19, and also ignores the teachings and suggestions of Olesen and Queen. *See id*. at 29, 46–49. But the ultimate burden on Petitioner is to show that a POSA had a reason to combine the elements of the claim in the manner claimed. *See KSR*, 550 U.S. at 418. Moreover, the test for obviousness is not that the claimed invention was "expressly suggested in any one or all of the references," but "what the combined teachings of the references would have suggested to those of ordinary skill in the art." *MCM Portfolio LLC v. Hewlett-Packard Co.*, 812 F.3d 1284, 1294 (Fed. Cir. 2015) (quoting *In re Keller*, 642 F.2d 413, 425 (CCPA 1981)).

On this record, we are unpersuaded by the contention that Petitioner's obviousness challenge must be based on specifically modifying C4.19, or that the "data" in Tan must demonstrate the C4.19 antibody to be useful to treat migraine, particularly in view of Olesen and the teachings and suggestions of Tan as a whole. Moreover, we find that Petitioner has sufficiently shown, based on the teachings and suggestions of Olesen, Tan,

and Queen, a reasonable expectation of success in combining those teachings and suggestions to meet the limitations of at least claims 1 and 17.

Patent Owner's argument that Tan did not establish that C4.19 antagonized endogenous CGRP at its site of action (the synaptic cleft), and that Petitioner failed to explain why a POSA would not expect a similar "negative result" for other full length anti-CGRP antibodies, is similarly unpersuasive at this stage of the proceeding.

Tan used a saphenous nerve assay to determine if the MAb C4.19 antibody and its Fab' fragment can access endogenously produced CGRP at its site of action. Ex. 1022, 569–70. Tan reports "that effective immunoblockade was achieved with MAb C4.19 Fab' fragment 30 min after administration, while the IgG was ineffective up to 2 h after the dose." *Id.* at 571. But based on Tan's own studies and the studies of others,[10] Tan was able to conclude that "[g]iven an adequate incubation period in a tissue bath, Mab C4.19 IgG *clearly diffuses into the synaptic cleft* since it was effective at blocking CGRP released from primary afferent nerves by capsaicin *in vitro*," and "[t]he slow distribution of whole IgG to the site of immunoblockade could be overcome by . . . *chronic administration of IgG*. . . . With *repeated administration* IgG should eventually distribute into interstitial space and achieve the sufficiently high concentrations required for immunoblockade." Pet. 45–46 (citing Ex. 1022, 571 (emphases added by Petitioner)).

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[10] For example, Tan cites Covell et al., *Pharmacokinetics of Monoclonal Immunoglobulin G_1, $F(ab')_2$, and Fab' in Mice*, CANCER RESEARCH 46, 3969–78 (1986), as support for its statement that "much larger doses and longer distribution times are required for successful immunoblockade with IgG." Ex. 1022, 571.

We understand Patent Owner to essentially argue that the particular experimental results reported by Tan would have discouraged or taught away from the use of a full length antibody generally, and specifically the C4.19 antibody. Prelim. Resp. 49–57. But a reference "does not teach away . . . if it merely expresses a general preference for an alternative invention but does not 'criticize, discredit, or otherwise discourage' investigation into the invention claimed." *See DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1327 (Fed. Cir. 2009) (citation omitted).

Rather than discouraging further investigation into the use of a full-length antibody such as C4.19, Tan actually *encourages* such investigation and use by explaining the protocols that would lead to successful results. Ex. 1022, 570–72. Moreover, to the extent that Tan may suggest that use of a Fab' fragment may generally be preferred over a full length antibody, that does not constitute a teaching away. *See Bayer Pharma AG v. Watson Labs., Inc.*, 874 F.3d 1316, 1327 (Fed. Cir. 2017).

Patent Owner further contends that "Tan makes no statement concerning, or suggestion toward, any role for CGRP antagonist antibodies in treating migraine," and that "[Tan's] data demonstrates a lack of ability to engage with CGRP at its active site, and thus provides no motivation to a POSA to humanize Tan's C4.19 for treating migraine." *See* Prelim. Resp. 49, 56–57. But those contentions ignore the teachings and suggestions of Olesen and Queen, and focus on Tan's "data" rather than what Tan as a whole would have taught or suggested to a POSA.

On this record and at this stage of the proceeding, we determine that Petitioner has sufficiently established that the combination of Olesen, Tan, and Queen teaches or suggests blocking the CGRP pathway for treating migraine in humans (Olesen), the use of an anti-CGRP antagonist antibody

to block the CGRP pathway, a technique complementary to the use of receptor antagonists (Tan), and the routine and desirable humanization of antibodies (Queen).

Patent Owner argues that the Petition fails to address motivation to humanize the Fab' fragment of Tan. Prelim. Resp. 58–61. We find that argument neither particularly compelling, nor a basis for denying institution. Claims 1 and 17 are directed to the step of administering "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." *See* Ex. 1001, 99:2–7, 100:3–7. Those claims are not limited to a Fab' fragment (Tan's or otherwise). Moreover, Petitioner's motivation arguments focus on use of an anti-CGRP antagonist antibody to treat migraine, and Petitioner uses the term "anti-CGRP [antagonist] antibodies" in discussing Tan's disclosure, presumably encompassing the Fab' fragment. *See, e.g.*, Pet. 26, 30. We thus determine, on this record and at this stage of the proceeding, that the Petition sufficiently establishes a reason to administer "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." *See* Ex. 1001, 99:2–7, 100:3–7.

Claim 1

Patent Owner contends that Petitioner's arguments for claim 1 rely on migraine treatment, but that claim 1 is not limited to migraine treatment. Prelim. Resp. 57. This is not persuasive, at least because migraine is "at least one vasomotor symptom" as recited in claim 1. *See* Ex. 1001, 19:48–51.

Patent Owner also argues against Petitioner's contention that "a POSA would have been motivated to use an anti-CGRP antagonist antibody 'to reduce incidence of or treat skin vasodilation.'" Prelim. Resp. 57. Patent Owner also relies on arguments advanced above to assert that Petitioner "has not demonstrated that a POSA would have humanized a full-length antibody for therapeutic use," or "explained why a POSA would have had a motivation to humanize Tan's full-length antibody to reduce incidence of or treat skin vasodilation in view of Tan's negative results with the antibody." *Id.* We find those arguments unpersuasive for the reasons set forth above.

Accordingly, on this record, we find that Petitioner has shown a reasonable likelihood that it would prevail in showing that at least one of claims 1, 3, 4, 8–17, 19, 20, and 24–31 of the '045 patent is unpatentable based on the combined teachings of Olesen, Tan, and Queen.

E. Patent Owner's Arguments Regarding 35 U.S.C. § 325(d)

Patent Owner argues that the Board should deny institution under 35 U.S.C. § 325(d) because the Petition is based on substantially the same prior art and arguments already considered by the Office, e.g., during prosecution of the '045 patent. Prelim. Resp. 12–28 (citing, e.g., *Becton, Dickinson & Co. v. B. Braun Melsungen AG*, Case IPR2017-01586, slip op. at 17–18 (PTAB Dec. 15, 2017) (Paper 8) (informative) ("*Becton Dickinson*")). As described in more detail below, Patent Owner argues that Olesen, Tan, and Queen are cumulative to information considered by the Examiner during prosecution or were already considered by the Examiner.

In advancing those arguments, Patent Owner relies on the prosecution of the parent application to the '045 patent, that issued as U.S. Patent No. 8,007,794 ("the '794 patent"), and the prosecution of a child application of the '045 patent that issued as U.S. Patent No. 8,597,649 ("the '649 patent").

Prelim. Resp. 19; *see* Ex. 2005; Ex. 2033. The '649 patent is part of the family tree that includes the '045 patent, and Patent Owner argues that the same Examiners examined the '649 patent and the '045 patent. *See* Prelim. Resp. 15. Patent Owner also argues that "any arguments or art considered in related applications is applicable to the '045 patent."[11] *Id.* at 15–16.

We address Patent Owner's contentions for each reference in turn, and then analyze the § 325(d) issue in view of the factors set forth in *Becton Dickinson*.

1. Arguments Based on Olesen

Patent Owner argues that Olesen is cumulative to the Specification's disclosure that there has been development and testing of CGRP antagonists including BIBN4096BS, and the Specification's disclosure in Example 6 of data showing testing. Prelim. Resp. 16–17 (citing Ex. 1001, 2:14–23, Example 6, Fig. 9). Patent Owner also asserts that the applicant referred to Example 6 during examination of the '045 patent. *Id.* (citing Ex. 2034, 497).

We agree with Patent Owner that the Examiner was aware of the development and testing of BIBN4096BS, which is a CGRP receptor antagonist. *See*, *e.g.*, Ex. 1001, 2:14–23. However, the portion of the Specification relied on merely refers to the existence of the compound and the fact that it is being tested. That portion of the Specification does not disclose testing in humans and Patent Owner at most is relying on data from studies in rats, e.g., in Example 6 and Figure 9. *See* Ex. 1001, 68:59–69:39. We determine that Olesen is not cumulative of the disclosure of testing in

[11] Although we consider the prosecutions of the '794 patent and '649 patent in this case, we take no position on whether or to what extent this statement by Patent Owner is necessarily applicable to any case before the Board involving 35 U.S.C. § 325(d).

rats because Olesen presents a clinical study that describes testing for efficacy and tolerability in human patients, and is published in a well-regarded medical journal (The New England Journal of Medicine). *See* Ex. 1025, 1104. Accordingly, we do not consider Olesen to be cumulative over the disclosures in the Specification, alone or as relied on in the examination of the '045 patent.

Patent Owner also argues that Olesen and Tan, discussed below, are cumulative over Frobert[12] and Pisegna[13] which the Examiner relied on for rejections during examination of the '794 patent and the '649 patent. *See* Prelim. Resp. 22–25 (citing Ex. 2033, 393, 429–430, 470; Ex. 2005, 162–164, 180–182). In particular, Patent Owner asserts that the Examiner stated that "Frobert teaches agonists/antagonists that compete with ligands to the CGRP receptors such as monoclonal antibodies to human CGRP I or CGRP alpha (Table 1)." *Id.* at 24 (citing Ex. 2033, 429 (citing Ex. 1032). However, we agree with Petitioner that neither Pisegna nor Frobert discloses treatment of migraines in humans. *See* Pet. Reply 3–4. Frobert discloses mouse monoclonal antibodies directed against rat CGRP (Ex. 1032, 275) and Pisegna discloses an example applying cloning techniques to a rat model (Ex. 1134 ¶¶ 228–239). Accordingly, Olesen's clinical data in humans is not cumulative to Frobert or Pisegna.

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[12] Yveline Frobert et al., *A Sensitive Sandwich Enzyme Immunoassay for Calcitonin Gene-related Peptide (CGRP): Characterization and Application*, 20 PEPTIDES 275–84 (1999) (Ex. 1032, "Frobert").
[13] U.S. Patent Application Pub. 2004/0110170 A1, pub. June 10, 2004 (Ex. 1134, "Pisegna").

2. Arguments Based on Tan

Patent Owner argues that the Examiner was aware of Tan because (a) an Information Disclosure Statement (IDS) initialed by the Examiner, in each application throughout the priority chain of the '045 patent, listed Tan as prior art (citing, e.g., Ex. 2034, 480); (b) the Specification of the '045 patent cites Tan multiple times, and in connection with the statement that "[a]nti-CGRP antagonist antibodies are known in the art" (citing Ex. 1001, 25:59–61); (c) the applicant brought Tan to the Examiner's attention in a Response to an Office Action during examination of the '649 patent, in arguing for patentability during examination (citing Ex. 2005, 182) and while the '045 patent was still pending; and (d) Petitioner's reliance on Tan's teaching of mouse monoclonal antibodies that block CGRP from binding to its receptor, which Patent Owner asserts is cumulative over Frobert, and that the Examiner considered during prosecution of the '794 patent and the '649 patent. Prelim. Resp. 17–20.

We agree with Patent Owner that the Examiner was already aware that anti-CGRP antibodies were known based on the Specification's citation of Tan (*see* Ex. 1001, 25:59–61). We agree with Patent Owner that the Examiner relied on Frobert in an Office Action for the teaching of monoclonal antibodies to CGRP (Ex. 2005, 162), and indeed, Frobert discloses mouse monoclonal antibodies directed against rat CGRP (Ex. 1032, 275). The antibodies used in Tan were also mouse monoclonal antibodies directed against rat CGRP. *See* Ex. 1021, 704 (*cited in* Ex. 1022, 572).

Accordingly, we agree with Patent Owner that Tan is cumulative over Frobert for purposes of teaching that anti-CGRP antagonist antibodies were known. *See* Ex. 1032, 275–276. Although we recognize that Tan may well

provide additional teachings not present in Frobert (*see* Pet. Reply 4), we acknowledge for purposes of this § 325(d) analysis that Petitioner's reliance on Tan is the same or substantially the same as the Examiner's reliance on Frobert for the purpose of showing that anti-CGRP antagonist antibodies were known.[14] Further, to the extent that Tan may provide additional teachings not found in Frobert, we recognize that the Examiner was aware of the Tan reference, e.g., based on the applicant's Response to an Office Action. *See* Ex. 2005, 182.

3. Arguments Based on Queen

Patent Owner argues, *inter alia*, that Petitioner's reliance on Queen for an explanation of how to humanize antibodies is redundant over Pisegna's disclosure that cites prior art to provide details on how to humanize antibodies. Prelim. Resp. 20–21 (citing Ex. 1134 ¶ 125). However, Queen itself recognizes that methods for humanizing antibodies were previously known and seeks to provide improved methods thereof to prevent loss in binding affinity of humanized antibodies. *See, e.g.*, Ex. 1023, 2:12–34, 10:60–63. It is, therefore, not clear on this record whether Queen would have been redundant over the prior art cited in Pisegna.

Nevertheless, Patent Owner also argues that the Specification of the '045 patent cites Queen and discusses humanization of antibodies. *See* Prelim. Resp. 20–21 (citing Ex. 1001, 27:41–47, 31:27–31, 32:7–8, 35:46–

[14] The applicant argued in the Response to an Office Action (and the IDS) that Tan teaches away from using a full-length antibody based on one of the experiments in Tan. Ex. 2005, 182. There, the applicant argued that the Fab' fragment and not the full-length antibody was effective for blockade of endogenous CGRP in the "hind paw" experiment. *Id.* However, Petitioner now brings additional evidence, and we determine that these issues may be best considered as part of a trial on the merits.

47, cols. 28–30). We agree with Patent Owner that the Specification of the '045 patent cites Queen, although it is unclear the extent to which the Examiner considered Queen during prosecution (e.g., as opposed to relying on Frobert and Pisegna as representative of the teachings of the prior art).

4. Analysis under Becton Dickinson factors

In evaluating whether to exercise our discretion under § 325(d), we weigh the following non-exclusive factors: (a) the similarities and material differences between the asserted art and the prior art involved during examination; (b) the cumulative nature of the asserted art and the prior art evaluated during examination; (c) the extent to which the asserted art was evaluated during examination, including whether the prior art was the basis for rejection; (d) the extent of the overlap between the arguments made during examination and the manner in which Petitioner relies on the prior art or Patent Owner distinguishes the prior art; (e) whether Petitioner has pointed out sufficiently how the Examiner erred in its evaluation of the asserted prior art; and (f) the extent to which additional evidence and facts presented in the Petition warrant reconsideration of prior art or arguments. *Becton Dickinson*, slip op. at 17–18.

In the preceding sections, we compared the asserted art (i.e., Olesen, Tan, and Queen), with the prior art involved during examination (e.g., Tan, Frobert, and Pisegna). Assuming for the purposes of this discussion that Tan was already considered during examination (or is cumulative over Frobert) for the teaching of (mouse) anti-CGRP antibodies, we have determined that other asserted prior art provides teachings not present during examination. Specifically, we have determined that Olesen is materially different than the disclosure in the Specification because Olesen provides a clinical study of BIBN4096BS conducted in humans.

Patent Owner argues there has been extensive prosecution before the examiner with overlapping and cumulative references cited in the Petition and the Information Disclosure Statement, and that the facts of this case are therefore comparable to those in the following matters where institution was denied: *Microsoft Corp. v. Koninklijke Philips N.V.*, Case IPR2018-00279, slip op. at 8–18 (PTAB June 8, 2018) (Paper 11); *Indivior Inc. v. Rhodes Pharmaceuticals, L.P.*, Case IPR2018-00795, slip op. at 9 (PTAB Oct. 4, 2018) (Paper 23). *See* PO Surreply 5. However, on the facts of this case, we conclude that there is new, noncumulative evidence asserted in the Petition, e.g., at least Olesen. We determine that the clinical data in human trials presented in Olesen was not considered during examination. For at least this reason, we determine not to exercise our discretion under § 325(d) to deny the Petition.

III. CONCLUSION

For the foregoing reasons, we conclude that Petitioner has established a reasonable likelihood of prevailing on its assertion that one or more of claims 1, 3, 4, 8–17, 19, 20, and 24–31 of the ’045 patent are unpatentable.

IV. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that, pursuant to 35 U.S.C. § 314(a), an *inter partes* review of claims 1, 3, 4, 8–17, 19, 20, and 24–31 of U.S. Patent No. 8,586,045 B2 is instituted with respect to all grounds set forth in the Petition; and

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

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