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Paper 11
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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

ELI LILLY AND COMPANY,
Petitioner,

v.

TEVA PHARMACEUTICALS INTERNATIONAL GMBH,
Patent Owner.

Case IPR2018-01712
Patent 9,884,908 B2

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

WORTH, *Administrative Patent Judge*.

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

I. INTRODUCTION

On October 1, 2018, Eli Lilly and Co. ("Petitioner") filed a Petition (Paper 1, "Pet.") requesting an *inter partes* review of claims 1–18 (the "challenged claims") of U.S. Patent No. 9,884,908 B2 (Ex. 1001, "the '908 patent"). On January 4, 2019, Teva Pharmaceuticals International GmbH ("Patent Owner") filed a Preliminary Response (Paper 8, "Prelim. Resp.").

On January 28, 2019, with authorization, Petitioner filed a Reply to Patent Owner's Preliminary Response (Paper 9, "Reply"). On February 6, 2019, with authorization, Patent Owner filed a Surreply thereto (Paper 10, "Surreply").

Institution of an *inter partes* review is authorized by statute when "the information presented in the petition filed under [35 U.S.C. §] 311 and any response filed under [35 U.S.C. §] 313 shows that there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." 35 U.S.C. § 314(a). For the reasons set forth below, we determine that Petitioner has demonstrated that there is a reasonable likelihood that one or more of claims 1–18 are unpatentable, and we institute an *inter partes* review of claims 1–18 based on the ground set forth in the Petition.

A. Related Matters

The parties note as related the following district court proceedings: *Teva Pharmaceuticals International GmbH v. Eli Lilly & Co.*, No. 1-17-cv-12087 (D. Mass. filed Feb. 6, 2018); *Teva Pharmaceuticals International GmbH v. Eli Lilly & Co.*, No. 1-18-cv-10242 (D. Mass. filed Oct. 24, 2017); *Teva Pharmaceuticals International GmbH v. Eli Lilly & Co.*, No. 1-18-cv-12029 (D. Mass. filed Sept. 27, 2018). *See* Pet. 66; Paper 5, 1. The parties note as related the following Board proceedings: IPR2018-01422, -1423, -1424, -1425, -1426, -1427, -1710, -1711. *See* Pet. 67; Paper 5, 1–2. The parties note as related the following patents: U.S. Patent Nos. 9,890,211; 9,890,210; 9,884,907; 9,365,648; 9,346,881; 9,340,614; 8,597,649; 9,328,168; 9,266,951; 9,115,194; 8,734,802; 8,586,045; and 8,007,794. Pet. 66; Paper 5, 2–3. The parties note as related the following patent

applications, which were pending at the time of the parties' notices: U.S. Patent Application Nos. 15/883,218 and 15/956,580. Pet. 66; Paper 5, 3.

B. The '908 Patent (Ex. 1001)

The '908 patent is titled "Methods for Treating Headache Using Antagonist Antibodies Directed Against Calcitonin Gene-Related Peptide[1]" 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], 1:34–37.

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 1:41–43. In humans, two forms of CGRP with similar activities (α-CGRP and β-CGRP) exist and exhibit differential distribution. *Id.* at 1:43–46. At least two CGRP receptor subtypes may also account for differential activities. *Id.* at 1:46–47. 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 1:47–51.

CGRP-mediated vasodilatation is 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 1:51–54. CGRP has been noted for its possible connection to vasomotor symptoms. *Id.* at 1:50–52. Vasomotor symptoms include hot

[1] Calcitonin Gene-Related Peptide is abbreviated throughout as CGRP. *See* Ex. 1001, 1:41.

flushes and night sweats. *Id.* at 1:58–60. 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 2:20–23.

According to the Specification, the precise pathophysiology of migraine is not yet well understood. *Id.* at 3:33–36. Dilation of blood vessels is associated with and exacerbates the pain symptoms of migraine. *Id.* at 3:41–44. 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 3:8–10. Different classes of drugs have been used in treatment. *See id.* at 3:11–30. 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 2:32–34, 3:27–30, 4:22–28.

The ’908 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 3:55–4:5. The ’908 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 4:6–4:54. 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 4:58–5:55, 8:20–22. Other embodiments are directed to a polypeptide, which may or may not be an antibody. *See id.* at 7:10–8:19. 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 8:32–9:4. Other embodiments are directed to methods of making the same. *See id*. at 9:5–9:21.

The Specification describes an experiment involving antibody G1 Fab fragment, and states that "human amylin . . . did not compete with binding of G1 Fab to human α-CGRP," and that "[t]hese data demonstrate that G1 targets a C-terminal epitope of CGRP and that both the identity of the most terminal residue (F37) and its amidation is important for binding." *Id.* at 67:52–58.

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 10:26–28. Table 4 provides sequences of human α-CGRP fragments (SEQ ID NOS: 15–40) and related peptides (SEQ ID NOS: 41–47). *Id.* at cols. 53–54. Table 6 provides data on binding affinity for G1 variants. *See id.* at cols. 61–67. Another table (*id.* at cols. 72–100) lists additional antibody sequences.

C. Illustrative Claim

Claim 1, reproduced below, is the sole independent claim and is illustrative of the subject matter:

> 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.

Ex. 1001, 99:55–100:58.

D. The Prior Art

Petitioner relies on the following prior art:

> 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 CLIN. SCI. 565–573 (Dec. 1995) (Ex. 1022, "Tan");
>
> U.S. Patent No. 6,180,370 B1, iss. Jan. 30, 2001 (Ex. 1023, "Queen");
>
> Jes Olesen, *Calcitonin Gene-Related Peptide Receptor Antagonist BIBN 4096 BS for the Acute Treatment of Migraine*, 350 NEW ENGL J OF MED 1104–1110 (2004) (Ex. 1025, "Olesen").

E. The Alleged Ground of Unpatentability

Petitioner challenges claims 1–18 of the '908 patent as unpatentable under (pre-AIA) 35 U.S.C. § 103(a) over the combination of Olesen, Tan, and Queen.

II. ANALYSIS

A. Person of Ordinary Skill in the Art

Petitioner asserts that a person of ordinary skill in the art "with respect to the aspects of the '908 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. 20–21 (citing Ex. 1018 ¶¶ 84–86). Petitioner further asserts that a person of ordinary skill "with respect to the aspects of the '908 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 21 (citing Ex. 1236 ¶¶ 84–86).

Patent Owner contends that "[b]ecause the '908 patent relates to methods of treatment using anti-CGRP antagonist antibody therapeutics, a [person of ordinary skill in the art] would draw upon the knowledge and experience of related disciplines of a multi-disciplinary team that might lie outside the [person's] primary training." Prelim. Resp. 31. Thus, according to Patent Owner, a person of ordinary skill "relevant to the '908 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 31–32.

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 1, 2018,[2] the claims of the '908 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 (2018) (affirming

[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).

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

Petitioner requests construction of the terms "treating," "effective amount," and "specific binding." Pet. 21–24. Patent Owner argues that Petitioner's proposed constructions of these terms are incorrect or incomplete. Prelim. Resp. 28–31. We construe these terms as follows. We emphasize that the foregoing constructions are preliminary at this stage of the proceeding.

1. "treating"

According to Petitioner, the '908 patent "expressly defines 'treatment' as 'an *approach* for obtaining a beneficial or desired clinical result'—it does not require *achieving* any particular result." Pet. 20 (citing, e.g., Ex. 1001, 18:4–5 (emphasis by Petitioner)). Petitioner thus asserts that "'treating' merely refers to an *approach* for a particular outcome without requiring a clinical response." *Id.* (citing Ex. 1018 ¶ 110).

Patent Owner argues that Petitioner's construction of "treating" is incomplete, and that the '908 patent "clearly ties 'treating' to achieving an intended clinical effect." Prelim. Resp. 28. According to Patent Owner, the '908 patent "expressly defines 'treatment' as 'an approach for obtaining beneficial or desired clinical results,' and lists the beneficial or desired

clinical results, e.g., 'lessening severity, alleviation of pain intensity . . . reducing frequency of recurrence . . . decreasing dose of other medications required to treat the headache . . . .'" *Id.* at 28–29 (citing Ex. 1001, 18:5–13). Patent Owner thus asserts that "[t]hat definition is controlling . . . and requires administering the anti-CGRP antagonist antibody to achieve a clinical result." *Id.* at 29.

The parties appear to be in agreement, and we agree, that there is a definition of "treatment" in the Specification marked by the word "is," i.e., "an approach for obtaining beneficial or desired clinical results." *See* Ex. 1001, 18:4–5. Treatment is thus defined as "an approach" and the only disagreement is whether there must be "beneficial or desired clinical results" obtained.[3]

We determine, on this record and at this stage of the proceeding, that the term "treating" refers to a statement of intended purpose, i.e. to achieve a clinical result, without requiring achievement of any clinical result. In our view, the definition uses the term "approach" to reflect an intent to benefit without guaranteeing a benefit. Indeed, even if the language "for obtaining beneficial or desired clinical results" were limiting, such results could be either beneficial or desired. In other words, the term "desired" reflects a statement of intent. Further, although Patent Owner argues that the Specification immediately thereafter lists beneficial or desired results, the

[3] According to the Specification, "[a]n 'individual' or a 'subject' is 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, 19:36–39.

list is preceded by the terms "include" and "are not limited to," which indicates that what follows is exemplary and not limiting. *See id.* at 18:5–8.

2. "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. 22–23 (citing Ex. 1018 ¶¶ 111–112). According to Petitioner, the '908 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 23–24 (citing Ex. 1001, 19:3–35, 32:34–41; Ex. 1018 ¶ 112).

Patent Owner argues that Petitioner's proposed construction of "effective amount" is incorrect, and refers to the Specification of the '908 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 30 (citing Ex. 1001, 19:3–5).

An "effective amount" is defined in the '908 patent as "an amount sufficient to effect beneficial or desired results." *Id.* Therefore, although "treatment" does not necessarily involve achieving beneficial or desired results, an "effective amount" of a humanized monoclonal anti-Calcitonin Gene-Related Peptide (CGRP) antagonist antibody does require 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 19:6–22

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 26:20–25, 32:11–13, 32:39–40, 35:1–3, 54:43–60 & 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 '908 patent. *See, e.g., id.* at 19:3–22. 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 (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)).

3. "specific binding"

According to Petitioner, the term "specific binding" includes antibodies that may bind to more than one isoform of CGRP, and does not preclude binding to another peptide. Pet. 23–24 (citing Ex. 1018 ¶ 114; Ex. 1236 ¶ 89–90). Petitioner further asserts that pursuant to the '908 patent, a binding preference for a first target or a second target is not required, and that "specific binding" is not limited to "exclusive binding." *Id.* at 24–25 (citing Ex. 1018 ¶ 114; Ex. 1236 ¶¶ 89–90; Ex. 1001, 16:34–37).

Patent Owner does not agree with Petitioner's proposed construction of the claim term "specific binding." Prelim. Resp. 30–31. According to Patent Owner, Petitioner's construction is "impermissibly broad" because it does not require specific binding to any target and does not account for the language of claim 1. *Id.*

We agree with Patent Owner that claim 1 uses the term "specific binding" in the phrase stating "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." Ex. 1001, 99:66–100:54. However, we do not view Petitioner's statement that "under the '908 patent's definition, a binding preference for a first target or a second target is not required" (Pet. 24–25) to be inconsistent with the recitation in claim 1 that "the CDRs impart to the antibody specific binding to a CGRP consisting of . . . ." Rather, we view Petitioner's statement to be an attempt to capture the Specification's statement that "an antibody . . . that specifically or

preferentially binds to a first target may or may not specifically or preferentially bind to a second target. . . . . '[S]pecific binding' or 'preferential binding' does not necessarily require (although it can include) exclusive binding." Ex. 1001, 16:32–37. Thus, in view of the arguments at this time and the apparent lack of inconsistency in the positions of the parties, we determine that it is not necessary to construe the term "specific binding" on this record and at this stage of the proceeding.

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. Obviousness of Claims 1–18 over Olesen (Ex. 1025), Tan (Ex. 1022), and Queen (Ex. 1023)

Petitioner contends that claims 1–18 are unpatentable as obvious over Olesen, Tan, and Queen. Pet. 25–60. Petitioner relies on the declarations of Andrew C. Charles, M.D. (Ex. 1018, "Charles Decl.") and Alain P. Vasserot, Ph.D. (Ex. 1236, "Vasserot Decl.") in support. Patent Owner opposes. Prelim. Resp. 32–62.

1. 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 also reports on an *in vivo* study with intravenous administration of rat CGRP and various anti-CGRP antibody preparations in male Sprague-Dawley rats. *See id.* at 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.

2. Olesen (Ex. 1025)

Olesen is an article published in the New England Journal of Medicine that describes a multicenter clinical trial of BIBN4096BS[4], 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% response rate, with a pain-free rate of 44% after two hours, and a recurrence rate of 19%. *Id.* at 1107, 1109. Olesen stated 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 considered to be a low overall rate of adverse events. *Id.* at 1108–1109. 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 concluded:

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

> 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).

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], 1:19–24.

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

In its Petition, Petitioner sets forth its contentions as to how the limitations of claims 1–18 are disclosed in, or obvious over, the combination of Olesen, Tan, and Queen. Pet. 26–60. Patent Owner opposes. Prelim. Resp. 27–63. We address these contentions below. We emphasize that the following determinations regarding the sufficiency of the Petition are preliminary in nature at this stage of the proceeding.

a. Claim 1

i. preamble; "administering to the individual an effective amount of a humanized monoclonal anti-Calcitonin Gene-Related Peptide (CGRP) antagonist antibody"

Petitioner contends that a person of ordinary skill would have been motivated to treat migraine with the humanized monoclonal anti-CGRP antagonist antibody. Pet. 25–35. Petitioner argues that Olesen tested a small molecule CGRP-receptor inhibitor, and that Olesen's successful results would have provided a concrete impetus to pursue CGRP antagonism broadly. *See id.* at 26–27. Petitioner asserts that Olesen identifies CGRP antagonists, without limitation, as agents to treat migraine. *Id.* at 26 (citing Ex. 1025, 1105, 1109; Ex. 1018 ¶ 117). Petitioner asserts that Olesen confirmed the reasonable expectation that a CGRP antagonist could be

successfully used to treat migraine. *Id.* at 39 (citing Ex. 1025, 1108–1109; Ex. 1040[5], 182–183; Ex. 1018 ¶¶ 153–154).

On this record, we are persuaded by Petitioner that Olesen demonstrates that a CGRP antagonist can be used to treat migraines in human patients. In particular, Olesen reports that patients receiving 2.5 mg of BIBN4096BS had a significantly higher rate of response to pain two hours after treatment as compared to patients receiving placebo. Ex. 1025, 1108–1109. Olesen reported a 25% incidence of adverse events for this treatment group, which it considered to be a low rate of adverse events, and it characterized the adverse events as mild to moderate. *Id.*

Patent Owner asserts that Petitioner acknowledges that "at least two CGRP receptors may exist" and that the art "had not yet identified which one was implicated in migraine." Prelim. Resp. 45–46 (citing Pet. 28). Patent Owner argues that Petitioner does not explain how and why the knowledge of which receptor is involved in migraine would influence a person of skill's choice for migraine treatment, i.e., to fully block the CGRP pathway as opposed to one or both receptors. *Id.* at 46.

Patent Owner argues that Petitioner does not demonstrate why a person of ordinary skill would have been motivated to treat migraine with anti-CGRP antibodies. Prelim. Resp. 40–52. Patent Owner asserts that Olesen does not expressly mention any CGRP antagonists other than receptor antagonists, and argues that Petitioner's extension of the meaning of antagonists to include agents that target both CGRP and CGRP receptors is

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

unsupported. *Id.* at 41–42. Patent Owner contends that Dr. Charles's declaration provides only conclusory support for Petitioner's argument. *See* Prelim. Resp. 43–45 & n.6 (citing *Edmund Optics, Inc., v. Semrock, Inc.*, Case IPR2014-00583, slip op. at 9 (PTAB Sept. 9, 2015) (Paper 50); *InfoBionic, Inc. v. Braemer Mfg., LLC*, Case IPR2015-01704, slip op. at 6 (PTAB Feb. 6, 2016) (Paper 11)).

Although Olesen reports success with BIBN4096BS specifically, we are persuaded at this stage of the proceeding that a person of ordinary skill reading Olesen would have been encouraged to make and test other CGRP antagonists for therapeutic use. *See* Ex. 1018 ¶¶ 32, 34, 36–40, 64; *see also* Ex. 1040, 183. On this record, we agree with Petitioner that Arulmozhi states that "inhibition of CGRP or antagonism of CGRP receptors" could be a viable therapeutic target for treating migraine. Ex. 1040, 182–183; *see* Pet. 48. Petitioner relies on other references, discussed below, in support of the use of antibody antagonists for treatment of migraines.

Petitioner relies on several references to support the use of anti-CGRP antibodies to treat migraine. For example, Petitioner asserts that Sveinsson[6] discloses using anti-CGRP antagonist antibodies to treat migraine in human patients. Pet. 29 (citing Ex. 1026, 7:5–12, 7:19–24, 10:25–30; Ex. 1018 ¶ 123). Petitioner asserts that Wimalawansa[7] specifically identified humanized anti-CGRP antagonist antibodies for use in treating several diseases, including migraine and neurogenic inflammation and suggested

[6] WO 2004/014351 A2, pub. Feb. 19, 2004 (Ex. 1026, "Sveinsson").

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

exploring their use. *See id.* at 30 (citing Ex. 1096, 567–568, 570). Patent Owner argues that Petitioner fails to demonstrate that anti-CGRP antibodies, as generically recited in Sveinsson, could engage with CGRP at its site of action so that they can be useful to treat migraine and that Wimalawansa cautions against indiscriminately antagonizing CGRP. Prelim. Resp. 49–50 (citing Ex. 1026; Ex. 1096, 568). On this record, we find that Petitioner has made an adequate showing that a person of ordinary skill would have sought to develop antibodies capable of binding and antagonizing human CGRP, and would have sought to humanize antibodies, such as those taught by Tan. In particular, Wimalawansa expressly calls for study of CGRP antagonists and monoclonal antibodies as part of a discussion of the therapeutic potential for treating pain, inflammation, and intractable hypotension, such as septic shock syndrome. *See, e.g.*, Ex. 1096, 570. Sveinsson also suggests the use of CGRP antagonist antibodies to treat migraine. *See* Ex. 1026, 7:5–8.

Patent Owner argues 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. 3–4, 9–10, 47–48. Petitioner acknowledges that "as of 1996, Wimalawansa appreciated the need for further studies before initiating human clinical trials," and points to Wimalawansa's teaching that "[t]he role of CGRP antagonists and humanized monoclonal antibodies *should be explored*" but asserts that sufficient clinical work had occurred by 2005. *See* Pet. 28, 30.[8]

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

Petitioner asserts that Tan, among others, referred to the effectiveness of CGRP antagonist antibodies as an alternative strategy to blocking CGRP with CGRP receptor antagonists. *Id.* at 27–29 (citing Ex. 1022, 566, 571; Ex. 1033, 95; Ex. 1040, 182; Ex. 1001, 2:27–31; Ex. 1082, 1; Ex. 1240, 923; Ex. 1026, 7:5–24, 10:25–30; Ex. 1027 ¶¶ 2–3, 39, claim 8; Ex. 1028, Abstract, 1:16–21, 2:7–10, 2:66–67, 3:21–22, Example 2, granted claim 2; Ex. 1096, 567, 570; Ex. 1018 ¶¶ 63, 121, 123–125, 141–143). Petitioner asserts that a person of ordinary skill would have recognized that an antibody might have therapeutic advantages, particularly for treatment of a chronic condition, i.e., specificity, being long acting, fewer side effects, less toxicity. *Id.* at 28, 31–32, 34 (citing, e.g., Ex. 1018 ¶¶ 133, 137–139, 140–143).

Patent Owner argues (1) a person of ordinary skill would not have selected Tan's full-length C4.19 antibody in the first instance based on Tan's results, and (2) Olesen and Queen provide insufficient reason to humanize Tan's full-length C4.19 antibody. Prelim. Resp. 53–62. We explore these arguments as follows.

Patent Owner argues that Petitioner does not demonstrate why a person of ordinary skill would have had a reason to select and humanize Tan's full-length antibody. *Id.* at 52–62. Patent Owner asserts that Petitioner has not shown that the data in Tan demonstrates that C4.19 would be useful *in vivo* as a therapeutic antibody. *Id.* at 50–58. Patent Owner also argues that Tan did not establish that C4.19 antagonized endogenous CGRP at its site of action and that a person of ordinary skill would have expected this "negative result" to other full-length anti-CGRP antibodies. *Id.* at 54–62.

With respect to Tan's saphenous nerve assay, Tan reports "that effective immunoblockade was achieved with MAb C4.19 Fab' fragment 30 min after administration, while the IgG was ineffective up to 2h after the dose." Ex. 1022, 571. Nevertheless, based on Tan's own studies and the studies of others, Tan also concluded 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*," "[t]he slow distribution of whole IgG to the site of immunoblockade could be overcome by . . . chronic administration of IgG," and "[w]ith repeated administration, IgG should eventually distribute into interstitial space and achieve the sufficiently high concentrations required for immunoblockade." *Id.*; *see also* Pet. 46–47 (citing Ex. 1136, 4; Ex. 1018 ¶¶ 59, 146–149; Ex. 1236 ¶¶ 114–115; Ex. 1022, 569, 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. *See* Prelim. Resp. 24–25, 52–59. 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); *see also Bayer Pharma AG v. Watson Labs., Inc.*, 874 F.3d 1316, 1327 (Fed. Cir. 2017). 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. 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 on the record at this stage of the proceeding. *See Bayer*, 874 F.3d 1327. Indeed, Tan's teachings must be considered together with other evidence of record, such as Wimalawansa, which suggests therapeutic uses for anti-CGRP antibodies. *See* Ex. 1096, 567–570.

Petitioner asserts that Queen (and others) taught humanization of antibodies (citing, e.g., Ex. 1023, 2:61–3:32) and that a person of ordinary skill would have been motivated to humanize anti-CGRP antibodies in order to minimize unwanted immunogenic responses (citing Ex. 1023, Abstract, 1:19–23, 1:44–57; Ex. 1236 ¶¶ 105–108). Pet. 14, 19, 34.

On this record, we find that Petitioner has made an adequate showing that a person of ordinary skill would have sought to develop antibodies capable of binding and antagonizing human CGRP, and would have sought to humanize antibodies, such as those taught by Tan. In particular, Wimalawansa expressly calls for study of CGRP antagonists and monoclonal antibodies as part of a discussion of the therapeutic potential for treating pain, inflammation, and intractable hypotension, such as septic shock syndrome. *See, e.g.*, Ex. 1096, 570. Mouse anti-CGRP antibodies were already known (as taught by Tan), as were methods to humanize mouse antibodies without a significant loss in affinity in order to reduce immunogenicity (as taught by Queen). Ex. 1022, 565; Ex. 1023, 1:19–23, 2:41–3:26.

ii and iii. "two human IgG heavy chains, each heavy chain comprising three complementarity determining regions (CDRs) and four framework regions";"two light chains, each light chain comprising three CDRs and four framework regions"

Petitioner asserts that a person of ordinary skill following Queen's teachings would have readily been able to graft CDRs from a donor murine anti-CGRP antagonist antibody onto a human IgG scaffold. Pet. 43. Petitioner asserts that humanized antibodies made with a human IgG scaffold contain the following features and humanized anti-CGRP antagonist IgG antibodies would have them: two human IgG heavy chains where each heavy chain comprising three CDRs and four framework regions and portions of the two heavy chains together forming an Fc region; two light chains where each light chain comprising three CDRs and four framework regions. *Id.* (citing Ex. 1058, 95, 100–101; Ex. 1018 ¶ 172; Ex. 1236 ¶¶ 130–131). On this record, we are persuaded that a person of ordinary skill would have understood Queen to disclose the heavy chain and light chain limitations. 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. Ex. 1023, 13:5–36. Queen discloses CDR regions in the heavy and light chains, and, on this record, a person of ordinary skill would have understood that there are three CDR regions flanked by four framework regions, for the heavy and light chains. *See* Ex. 1058, 100–101; Ex. 1023, 3:62–66, 47:12–13.

iv. "wherein the CDRs impart to the antibody specific binding to a CGRP consisting of amino acid residues 1 to 37 of SEQ ID N0:15 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"

According to Petitioner, the recited Sequence IDs 15 and 43 correspond to human αCGRP and βCGRP, respectively. Pet. 6 (citing Ex. 1018 ¶ 91; Ex. 1001, cols. 53–54 (Table 4)). We agree. *See* 1018 ¶ 91. Accordingly, the claim recites antibodies that bind human CGRP, exclusively or nonexclusively. *See supra* § II.B.3. (Claim Construction).

Tan 1994[9] (cited in Tan) reported that MAb C4.19, raised against rat CGRP, bound to rat αCGRP and βCGRP with affinities of 1.9 nM and 2.5 nM, respectively. Pet. 25 (citing, e.g., Ex. 1021, 707; Ex. 1018 ¶ 79) (*cited in* Ex. 1022, 566). Relying on the testimony of Dr. Vasserot, among other evidence, Petitioner asserts that a person of ordinary skill would have reasonably expected to succeed in obtaining an anti-CGRP antagonist antibody with a binding affinity of 10 nM or less as measured by surface plasmon resonance [SPR] at 37°C because conventional techniques (e.g., Queen) preserved or even improved the binding affinity of the humanized antibody (citing Ex. 1023, 2:28–34; Ex. 1018 ¶ 170; Ex. 1236 ¶¶ 127–129). Pet. 42–44.

Patent Owner makes three arguments as to why this limitation is not obvious. We address each in turn.

[9] K.K.C. Tan et al., *Demonstration of the Neurotransmitter Role of Calcitonin Gene-Related Peptides (CGRP) by Immunoblockade with Anti-CGRP Monoclonal Antibodies*, 111 BR. J. PHARMACOL. 703–10 (1994) (Ex. 1021, "Tan 1994").

First, Patent Owner argues that Petitioner has not explained how measurement of binding affinity by radioimmunoassay (RIA) compares to measurement by SPR. Prelim. Resp. 35; *see also* Pet. vii. (RIA is abbreviation for Radioimmunossay). However, Petitioner has adduced evidence that values measured by RIA and SPR are in close agreement. Pet. 45 (citing Ex. 1086[10], 117; Ex. 1236 ¶¶ 67, 124; Ex. 1083, Abstract; Ex. 1021, 705, 707). Tan's monoclonal anti-CGRP antibody MAb C4.19 had a binding affinity (K_D) of 1.9 nM to rat α-CGRP and an affinity of 2.5 nM to β-CGRP as measured by RIA. Ex. 1021, 706–07; Ex. 1236 ¶ 102. On this record, Petitioner has made an adequate showing that affinity measured by SPR would be in close agreement with affinity measured by RIA. Ex. 1086, 117; Ex. 1236 ¶ 67.

Second, Patent Owner argues that Petitioner has not explained how measurement of binding affinity at 4°C compares to measurement at 37°C. Prelim. Resp. 34–35. However, Petitioner's declarant avers that temperature differences typically have only a small effect on affinity measurements for stronger-binding antibodies. Ex. 1236 ¶¶ 68, 135. Although we agree with Patent Owner that Tan does not disclose the recited conditions, the issue is whether the prior art indicates a reasonable expectation of success based on the record evidence. Petitioner asserts that a person of ordinary skill would have had a reasonable expectation of success in obtaining antibodies with the claimed affinity. Pet. 35 (citing Ex. 1018 ¶¶ 127–131; Ex. 1236 ¶¶ 102–104). Based on the record at this stage of the proceeding, and in particular

[10] Robert F. Kelley, *Thermodynamics of Protein-Protein Interaction Studied by Using BIAcore and Single-Site Mutagenesis*, 6 METHODS: A COMPANION TO METHODS IN ENZYMOLOGY 111–20 (1994) (Ex. 1086).

on the testimony of Dr. Vasserot (discussed in more detail below), we determine that Petitioner has made an adequate showing that it was within a person of ordinary skill's capacity to make antibodies against a desired antigen, and that a person of ordinary skill would have had a reasonable expectation of doing so with the desired affinity. *See* Ex. 1236 ¶¶ 102–104.

Petitioner asserts that by November 2005, nearly all FDA-approved antibodies were reported to have binding affinities of 10 nM or less as measured by SPR at 37°C. Pet. 2, 31–32, 35 (citing Ex. 1018 ¶ 128; Ex. 1236 ¶¶ 69–70; Ex. 1253, 938, 1338, 1359, 1966, 2955; Ex. 1056, 1075; Ex. 1022, 572; Ex. 1033, 102). Petitioner asserts that a person of ordinary skill would have conducted SPR at human body temperature (i.e., 37°C) because the art recognized that binding affinities obtained at physiological temperatures more accurately reflect the binding affinity of the antibody in the human body. *Id.* at 36 (citing Ex. 1018 ¶ 130; Ex. 1236 ¶¶ 68, 109; Ex. 1087, Abstract, 333.). We are persuaded by Petitioner that a person of ordinary skill would have sought to obtain antibodies with the recited affinities and would have tested them at 37°C in order to test them at temperatures that reflect the human body, and in order to match the affinities of other antibodies that had been developed for therapeutic use. *See* Ex. 1018 ¶ 130; Ex. 1236 ¶¶ 68, 109. On this record, we are persuaded that it would have been routine to obtain antibodies with the claimed affinity at the recited temperature.

Third, Patent Owner argues that there is simply a lack of correlation between the measured binding affinity of Tan's antibodies to rat CGRP and the claimed binding affinity of an antibody to human CGRP. Prelim. Resp.

35–39 (citing, e.g., Ex. 1001, cols. 53–54 & Tables 4, 7).[11] [12] However, even if Tan's monoclonal anti-CGRP antibody MAb C4.19 binds human CGRP with less affinity than rat CGRP, Petitioner argues that antibody affinity could have been improved. Pet. 42 (citing Ex. 1023, 2:28–34; Ex. 1018 ¶ 170; Ex. 1236 ¶¶ 127–129). At this stage of the proceeding, based in part on the testimony of Dr. Vasserot, we determine that Petitioner has made an adequate showing that a person of ordinary skill would have had a reasonable expectation of improving the binding affinity of Tan's MAb C4.19. *See* Ex. 1236 ¶¶ 55, 127–129.

Further, Petitioner is not necessarily arguing that a person of ordinary skill would have started with Tan's antibodies (MAb C4.19) and simply humanized them. Rather, Petitioner appears to be arguing that, just as Tan immunized a mouse against rat CGRP to create MAb C4.19, it was known to

[11] In other words, Patent Owner argues that in addition to "humanizing" Tan's antibody framework from mouse to human, a person of ordinary skill in the art would have had to take into account that Tan's antibodies would have had a different affinity for rat and human CGRP targets. Prelim. Resp. 35–39. Tan's mouse antibodies bound both rat and human CGRP, but, according to Dr. Vasserot, the binding affinity for rat CGRP is reported on this record. *See* Ex. 1021, 707; Ex. 1236 ¶ 97.

[12] Dr. Vasserot states that Tan's affinity to rat αCGRP and rat βCGRP is 1.9 nM and 2.5 nM. Ex. 1236 ¶ 97. We observe that Tan 1994 describes its methodology as estimating binding affinity by fitting experimental data to a mathematical model, where the displacement of ligand 2-[^{125}]-iodohistidyl^{10}-human αCGRP was investigated in the presence of displacer rat CGRP, and where K_d is the dissociation constant of ligand. *See* Ex. 1021, 705. Thus, human CGRP was used as a labeled ligand in these displacement experiments, in the presence of rat CGRP. The parties are invited to develop this aspect of the record further at trial.

a person of ordinary skill (e.g., based on Andrew[13]) to immunize a mouse against human protein in the first instance to create an antibody with affinity for human CGRP. *See* Pet. 12, 42 (citing Ex. 1055, 89, 92; Ex. 1018 ¶ 168; Ex. 1236 ¶ 123), 52. Petitioner's declarant, Dr. Vasserot, avers that a person of ordinary skill would have readily known such antibody generation techniques. *See* Ex. 1236 ¶ 104. Dr. Vasserot relies, *inter alia*, on Andrew's disclosure of antibodies against human CGRP with binding affinities in the range of 40 nM to 4 nM. *Id.* (citing Ex. 1055, 88, 90, 92); *see* Pet. 42, 58. Andrew reports affinities within the range of 2.5 x 107–108 M^{-1}. Ex. 1055, 92. On this record, we are persuaded by Petitioner that a person of ordinary skill would have had a reasonable expectation of success in generating anti-human antibodies with the recited affinity.[14]

In view of the evidence provided by Petitioner, we find on this record and at this stage of the proceeding that Petitioner has established a reasonable likelihood of prevailing on its contentions as to claim 1.[15]

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[13] D.P. Andrew, et al., *Monoclonal Antibodies Distinguishing a and /3 Forms of Calcitonin Gene-Related Peptide*, 154 JOURNAL OF IMMUNOLOGICAL METHODS, 87–94 (1990) (Ex. 1055).

[14] Patent Owner also argues that Petitioner should be held to its Olesen, Tan, and Queen obviousness combination. Prelim. Resp. 32. We find on this record and at this stage of the proceeding that the Petition is sufficient to institute *inter partes* review.

[15] Patent Owner does not make any arguments for "secondary considerations" of nonobviousness at this time, and we do not consider "secondary considerations" on this record. Petitioner argues that "near-simultaneous development of humanized anti-CGRP antibodies to treat migraine by others serves as objective evidence of *obviousness*." Pet. 63. We do not reach Petitioner's argument at this time.

b. Claims 2–18

Based on our review of the evidence at this stage of the proceeding, we determine that Petitioner has established a reasonable likelihood of prevailing on its contentions as to claims dependent claims 2–18, for similar reasons as for independent claim 1. See Pet. 53–61. Patent Owner does not raise separate arguments as to any of claims 2–18.

We note that claim 2, which recites "a pharmaceutically acceptable carrier, excipient, or stabilizer," and claims 3 and 4, which recite certain routes of administration, might present additional considerations regarding tolerability and safety that might not be required for claim 1, which recite antibodies themselves. *See* Ex. 1001, 100:59–67. However, Patent Owner does not argue claims 2–4 separately in its Preliminary Response.

D. 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 '908 patent. Prelim. Resp. 15–27 (citing, e.g., *Becton, Dickinson & Co. v. B. Braun Melsungen AG*, Case IPR2017-01586, slip op. 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 were cumulative to information considered by the Examiner during prosecution or were already considered by the Examiner. 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*.

i. 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. 15–16 (citing Ex. 1001, 2:32–36, Example 6, Fig. 9). Patent Owner also asserts that the applicant referred to Example 6 during examination of related U.S. Patent 8,586,045 ("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, 2:32–36. 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, 69:64–65. We determine that Olesen is not cumulative of the disclosure of testing in 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, 3. 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 related '045 patent.

Patent Owner also argues that Olesen and Tan, discussed below, are cumulative over Frobert[16] and Pisegna[17] which the Examiner relied on for rejections during examination of related U.S. Patent No. 8,597,649 ("the '649 patent") and U.S. Patent No. 8,007,794 ("the '794 patent"). *See* Prelim. Resp. 21–23 (citing Ex. 2033, 393, 429–430, 470; Ex. 2005, 162–164, 180–182). In particular, Patent Owner asserts that the Examiner stated during the rejections 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)." Prelim. Resp. 23 (citing Ex. 2033, 429 (citing Ex. 1032); Ex. 2005, 162). However, we agree with Petitioner that neither Pisegna nor Frobert discloses treatment of migraines in humans. *See* 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.

ii. 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, listed Tan as prior art (citing, e.g., Ex. 2005, 295); (b) the Specification of the '908 patent cites Tan multiple times, and in connection with the statement that "[a]nti-CGRP

[16] 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").

[17] U.S. Patent Application Pub. 2004/0110170 A1, pub. June 10, 2004 (Ex. 1134, "Pisegna").

antagonist antibodies are known in the art" (citing Ex. 1001, 26:28–30, 56:20–24); (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 (d) Tan's teaching that anti-CGRP antibodies exist is cumulative over Frobert, which the Examiner relied on for a teaching of anti-CGRP antibodies in an Office Action during examination (citing Ex. 2005, 162). Prelim. Resp. 16–18.

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, 26:28–30). We agree with Patent Owner that the Examiner relied on Frobert in an Office Action during examination of the related '649 patent 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 also cumulative over Frobert for purposes of this teaching (*see* Ex. 1032, 275–276), i.e., that anti-CGRP antagonist antibodies were known. Although we recognize that Tan may well provide additional teachings not present in Frobert (*see* 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.[18] 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 during examination of the related '649 patent. *See* Ex. 2005, 182.

iii. 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. 19 (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 '908 patent cites Queen and discusses humanization of antibodies. *See* Prelim. Resp. 19–20 (citing Ex. 1001, 28:10–16, 32:4–8, 32:51–52, 36:24–25, cols. 28–30). We agree with Patent Owner that the Specification of the

[18] 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 on the issues of motivation and reasonable expectation of success, and we determine that these issues may be best considered as part of a trial on the merits.

’908 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).

iv. 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 (Ex. 2005) 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 Pharms, L.P.*, Case IPR2018-00795, slip op. at 9 (PTAB Oct. 4, 2018) (Paper 23). *See* 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

We conclude that Petitioner has demonstrated a reasonable likelihood of prevailing on its assertion that claims 1–18 of the '908 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 1–18 of the '908 patent is instituted with respect to all grounds set forth in the Petition (*see* Section I.E., *supra*);

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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