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Paper 69
Date: March 31, 2020

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.

IPR2018-01710 (Patent 8,586,045 B2)
IPR2018-01711 (Patent 9,884,907 B2)
IPR2018-01712 (Patent 9,884,908 B2)[1]

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

Per Curiam

JUDGMENT
Final Written Decision
Determining No Challenged Claims Unpatentable
35 U.S.C. § 318(a)

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[1] The proceedings have not been consolidated. The parties are not authorized to use a combined caption unless an identical paper is being entered into each proceeding and the paper contains a footnote indicating the same.

I. INTRODUCTION

This is a Final Written Decision addressing three *inter partes* reviews challenging claims 1, 3, 4, 8–17, 19, 20, and 24–31 of U.S. Patent No. 8,586,045 B2 ("the '045 patent") (IPR2018-01710), claims 1–18 of U.S. Patent No. 9,884,907 B2 ("the '907 patent") (IPR2018-01711), and claims 1–18 of U.S. Patent No. 9,884,908 B2 ("the '908 patent") (IPR2018-01712).[2] We have jurisdiction under 35 U.S.C. § 6(b). This Final Written Decision is issued pursuant to 35 U.S.C. § 318(a). Having reviewed the arguments of the parties and the supporting evidence, we find that Petitioner has failed to demonstrate by a preponderance of the evidence that any of the challenged claims are unpatentable.

A. Procedural History

Eli Lilly and Company ("Petitioner" or "Lilly") filed three Petitions (Paper 1,[3] "Pet.") requesting an *inter partes* review of the respective challenged claims of the '045 patent, the '907 patent, and the '908 patent. Teva Pharmaceuticals International GmbH ("Patent Owner" or "Teva") filed a Preliminary Response to each of the Petitions. Paper 8 ("Prelim. Resp.").

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[2] All of the respective challenged claims are referred to collectively as the "challenged claims," and the '045 patent, the '907 patent, and the '908 patent are referred to collectively as the "challenged patents." IPR2018-01710 ("1710 IPR"), IPR2018-01711 ("1711 IPR"), and IPR2018-01712 ("1712 IPR") are referred to herein as "the three *inter partes* reviews."

[3] Unless this Decision otherwise indicates, all citations are to the Papers and Exhibits in IPR2018-01710. Similar Papers and Exhibits were filed in each of the three *inter partes* reviews.

We entered our three Decisions on Institution (Paper 12, "Inst. Dec." or "Institution Decision"),[4] instituting *inter partes* review of all challenged claims under the only ground asserted in each of the three petitions. In each of the three *inter partes* reviews, Patent Owner filed a substantially similar Response (Paper 21, "PO Resp."), Petitioner filed a substantially similar Reply (Paper 32, "Reply"), and Patent Owner filed a substantially similar Sur-reply (Paper 43, "Sur-reply").

In each of the three *inter partes* reviews, Patent Owner filed a substantially similar Motion to Strike (Paper 38, "Mot. Strike") and Petitioner filed a substantially similar Opposition to the Motion to Strike (Paper 40, "Opp. Strike"). In each of the three *inter partes* reviews, Patent Owner also filed a substantially similar Motion to Exclude (Paper 51, "Mot. Excl."), Petitioner filed a substantially similar Opposition to the Motion to Exclude (Paper 52, "Opp. Excl."), and Patent Owner filed a substantially similar Reply to Petitioner's Opposition to the Motion to Exclude (Paper 57).

On November 21, 2019, Patent Owner filed the following documents, in each of the three *inter partes* reviews, regarding our denial of its request to file a motion to stay based on the Federal Circuit decision in *Arthrex, Inc. v. Smith & Nephew, Inc.*, 941 F.3d 1320 (Fed. Cir. 2019) ("Arthrex"):

> Patent Owner's Request for Rehearing Pursuant to 37 C.F.R. § 42.71(d) on Denial of Authorization to File a Motion to Stay and Supplemental Brief Addressing Arthrex (Paper 49);[5]

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[4] The three *inter partes* reviews were instituted on April 3, 2019. *See also* 1711 IPR Paper 12; 1712 IPR Paper 11.

[5] Patent Owner also requested Precedential Opinion Panel (POP) review of the requests for rehearing. *See* Ex. 3002 (e-mail dated November 21, 2019). That request was denied on February 13, 2020. Paper 65.

Patent Owner's Petition to Expedite Under 37 C.F.R. § 1.182 (Paper 48); and

Patent Owner's Petition Under 37 C.F.R. § 1.181(a)(3) Invoking the Supervisory Authority of the Director (Paper 47).

Patent Owner's Petition invoking the supervisory authority of the Director (Paper 47) was denied on February 18, 2020. Paper 66. Patent Owner's request for rehearing (Paper 49) also was denied on February 18, 2020. Paper 67.

We held a combined[6] oral hearing on January 8, 2020, and the transcript of that hearing has been entered into the record. Paper 68 ("Tr.").

On December 18, 2019, the U.S. Court of Appeals for the Federal Circuit issued an opinion in *Fox Factory, Inc. v. SRAM, LLC*, 944 F.3d 1366 (Fed. Cir. 2019). In *Fox Factory*, the court "address[ed] the Board's application of the presumption of nexus" to certain claims at issue. *Id.* at 1374. Because Patent Owner argued a presumption of nexus with respect to its proffered evidence of objective indicia of nonobviousness,[7] we authorized both of the parties to file, in each of the three *inter partes* reviews, a supplemental brief, and a brief responsive to the other party's supplemental brief, addressing the application, if any, of *Fox Factory* to the three *inter partes* reviews. Paper 60. Petitioner filed a substantially similar supplemental brief and responsive brief (Paper 62, Paper 63), and Patent

[6] The hearing included the three *inter partes* reviews addressed in this Decision.

[7] Because we determine that Petitioner has failed to establish by a preponderance of the evidence that a person of ordinary skill in the art would have had a reasonable expectation of success in achieving the invention of the independent claims of the challenged patents (*see infra* Section II.D.4.b)), we need not rely on Patent Owner's evidence of objective indicia of nonobviousness for purposes of this Final Written Decision.

Owner filed a substantially similar supplemental brief and responsive brief (Paper 61, Paper 64) in each of the three *inter partes* reviews.

B. Real Parties-in-Interest

Petitioner identifies Eli Lilly and Company as the real party-in-interest. Pet. 66.

Patent Owner identifies Teva Pharmaceuticals International GmbH and Teva Pharmaceuticals USA, Inc. as the real parties-in-interest. Paper 6, 2.

C. Related Matters

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 the '907 patent and '908 patent ("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.* Petitioner asserts that those patents purport to claim priority to the

same provisional application as the '045 patent, and that 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.*

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 U.S. Patent Nos. 9,365,648; 9,328,168; 9,115,194; 8,734,802; and 8,007,794, as related to the challenged patents, in addition to the patents and patent applications identified by Petitioner. *Id.*

The parties also identify six related *inter partes* review proceedings. Pet. 67; Paper 6; *see* IPR2018-01422, IPR2018-01423, IPR2018-01424, IPR2018-01425, IPR2018-01426, and IPR2018-01427. Final Written Decisions issued in these six related *inter partes* review proceedings on February 18, 2020.[8] *See, e.g.*, *Eli Lilly & Co. v. Teva Pharms. Int'l GmbH*, IPR2018-01422, Paper 80 (PTAB Feb. 18, 2020); *Eli Lilly & Co. v. Teva Pharms. Int'l GmbH*, IPR2018-01424, Paper 78 (PTAB Feb. 18, 2020).

D. The Challenged Patents[9]

The '045 patent is titled "Methods of Using Anti-CGRP[10] Antagonist Antibodies" and "relates to the use of anti-CGRP antagonist antibodies for

[8] In those decisions, claims directed to human or humanized monoclonal anti-CGRP antagonist antibodies were held unpatentable as obvious.
[9] The challenged patents are direct or indirect continuations of U.S. Patent Application No. 12/093,638 (now U.S. Patent No. 8,007,794) and share a common specification. Ex. 1001, code (60); 1711 IPR Ex. 1001, code (60); 1712 IPR Ex. 1001, code (60). We refer to the '045 patent in this Decision unless otherwise indicated.
[10] Calcitonin Gene-Related Peptide is abbreviated throughout as CGRP. *See* Ex. 1001, 1:25.

the prevention, amelioration, or treatment of vasomotor symptoms, such as CGRP related headaches (e.g., migraine) and hot flushes." Ex. 1001, code (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 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 sumatriptan's effects. *See id.* at 2:14–16, 3:8–13, 4:4–6.

Embodiments described in the '045 patent are 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. Other embodiments of the '045 patent are 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.

E. Illustrative Claims

Claims 1 and 17, the only independent claims of the '045 patent, are reproduced below:

> 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 of the '045 patent depend directly from claim 1, and claims 19, 20, and 24–31 of the '045 patent depend directly from claim 17. *Id.* at 99:17–25; 99:38–100:2; 100:17–24, 37–59.

Claim 1, the only independent claim of the '907 patent, is reproduced below:

> 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.

1711 IPR Ex. 1001, 103:21–35.

Claims 2–18 of the '907 patent depend directly or indirectly from claim 1. *Id.* at 103:36–104:49.

Claim 1, the only independent claim of the '908 patent, is reproduced below:

> 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.

1712 IPR Ex. 1001, 99:55–100:58.

Claims 2–18 of the '908 patent depend directly or indirectly from claim 1. *Id.* at 100:59–102:18.

F. The Asserted Prior Art and Declaration Evidence

Petitioner's asserted grounds of unpatentability rely on the following 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 relies on the Declaration of Dr. Andrew C. Charles, M.D. dated September 27, 2018 (Ex. 1014, "First Charles Declaration"[11]), the Declaration of Dr. Alain P. Vasserot, Ph.D. (Ex. 1015, "Vasserot Declaration"[12]), the Declaration of Dr. Andrew C. Charles, M.D. dated

[11] The First Charles Declaration is Ex. 1016 in the 1711 IPR, and Ex. 1018 in the 1712 IPR.

[12] The Vasserot Declaration is Ex. 1017 in the 1711 IPR, and Ex. 1236 in the 1712 IPR.

September 30, 2019 (Ex. 1338, "Second Charles Declaration"[13]), and the Declaration of Dr. Joseph P. Balthasar, Ph.D. (Ex. 1337, "Balthasar Declaration"[14]).

Patent Owner relies on the Declaration of Dr. Michael Ferrari, M.D., Ph.D. (Ex. 2268, "Ferrari Declaration"[15]), the Declaration of Dr. Ian M. Tomlinson, M.A., Ph.D. (Ex. 2271, "Tomlinson Declaration"[16]), the Declaration of Steven M. Foord, Ph.D. (Ex. 2265, "Foord Declaration"[17]), the Declaration of Alan M. Rapoport, M.D. (Ex. 2262, "Rapoport Declaration"[18]), the Declaration of Robert D. Stoner, Ph.D. (Ex. 2274, "Stoner Declaration"[19]), and the Declaration of Jaume Pons, Ph.D. (Ex. 2331, "Pons Declaration"[20]).

[13] The Second Charles Declaration is Ex. 1340 in the 1711 IPR, and Ex. 1342 in the 1712 IPR.
[14] The Balthasar Declaration is Ex. 1339 in the 1711 IPR, and Ex. 1341 in the 1712 IPR.
[15] The Ferrari Declaration is Ex. 2269 in the 1711 IPR, and Ex. 2270 in the 1712 IPR.
[16] The Tomlinson Declaration is Ex. 2272 in the 1711 IPR, and Ex. 2273 in the 1712 IPR.
[17] The Foord Declaration is Ex. 2266 in the 1711 IPR, and Ex. 2267 in the 1712 IPR.
[18] The Rapoport Declaration is Ex. 2263 in the 1711 IPR, and Ex. 2264 in the 1712 IPR.
[19] The Stoner Declaration is Ex. 2275 in the 1711 IPR, and Ex. 2276 in the 1712 IPR.
[20] The Pons Declaration is Ex. 2332 in the 1711 IPR, and Ex. 2333 in the 1712 IPR.

G. The Asserted Grounds of Unpatentability

Petitioner asserts that the challenged claims would have been unpatentable on the following grounds:

Claim(s) Challenged	35 U.S.C. §	Reference(s)/Basis
IPR2018-01710 1, 3, 4, 8–17, 19, 20, 24–31	103(a)	Olesen, Tan, Queen
IPR2018-01711 1–18	103(a)	Olesen, Tan, Queen
IPR2018-01712 1–18	103(a)	Olesen, Tan, Queen

II. DISCUSSION

A. Level of Ordinary Skill in the Art

In determining the level of skill in the art, we consider the type of problems encountered in the art, the prior art solutions to those problems, the rapidity with which innovations are made, the sophistication of the technology, and the educational level of active workers in the field. *Custom Accessories, Inc. v. Jeffrey-Allan Indus., Inc.*, 807 F.2d 955, 962 (Fed. Cir. 1986); *Orthopedic Equip. Co. v. United States*, 702 F.2d 1005, 1011 (Fed. Cir. 1983).

Petitioner advanced a proposed definition of a person of ordinary skill in the art ("POSA") in its Petition. Pet. 18–19 (citing Ex. 1014 ¶¶ 76–78; Ex. 1015 ¶¶ 77–79). Patent Owner advanced its own proposed definition of a person of skill in the art in its Preliminary Response. Prelim. Resp. 32–33.

We found in our Institution Decision that we did not discern an appreciable difference in the parties' respective definitions of a person of ordinary skill in the art. Inst. Dec. 8. Accordingly, we determined for purposes of our Institution Decision that a person of ordinary skill in the art

would have had (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 a CGRP-related disease, such as migraine headaches. *See id*. at 8–9.

The parties do not contest this definition of a person of ordinary skill in the art. *See generally* Reply; PO Resp. 2 n.3. Accordingly, for purposes of this Final Written Decision, we maintain the definition of a person of ordinary skill in the art as set forth in our Institution Decision, and restated above. *See* Inst. Dec. 8–9. We also find on this record that Dr. Charles, Dr. Vasserot, Dr. Balthasar, Dr. Foord, Dr. Ferrari, Dr. Rapoport, and Dr. Tomlinson are persons of at least ordinary skill in the art under this standard. *See curriculum vitaes* at Ex. 1014, Appendix A; Ex. 1015, Appendix A; Ex. 1337, Appendix A; Ex. 2055; Ex. 2138; Ex. 2142; and Ex. 2160.

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 an *inter partes* review filed before November 13, 2018, a claim in an unexpired patent is given its broadest reasonable construction in light of the specification of the patent in which it appears.[21] 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). The broadest reasonable construction standard applies to the three *inter partes* reviews because the Petitions were filed prior to November 13, 2018.[22] Under that standard, and absent any special definitions, we generally give claim terms their ordinary and customary meaning, as would have been 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 (1) the terms "reducing incidence of or treating," "anti-CGRP antagonist antibody," and "humanized monoclonal antibody" in the 1710 IPR, (2) the term "effective amount" in all

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[21] 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, 51,343 (amending 37 C.F.R. § 42.100(b) effective November 13, 2018) (now codified at 37 C.F.R. § 42.100(b) (2019)).

[22] The Petition in the 1710 IPR was accorded a filing date of October 4, 2018. Paper 4. The Petitions in the 1711 IPR and the 1712 IPR were each accorded a filing date of October 1, 2018. 1711 IPR Paper 5; 1712 IPR Paper 4.

three *inter partes* reviews, and (3) the terms "treating" and "specific binding" in the 1711 IPR and the 1712 IPR. *See* Pet. 19–24; 1711 IPR Pet. 20–23; 1712 IPR Pet. 21–25. Patent Owner does not advance constructions for any claim terms other than those advanced by Petitioner. *See generally* PO Resp.; Sur-reply. We address the parties' claim construction arguments with respect to the identified claim terms in the following sections.

1. Claim Preambles: "reducing incidence of or treating" and "treating"

Certain of the claim terms for which Petitioner requests construction are found in the preambles of the challenged claims. These terms include: "reducing incidence of or treating" (in claims 1 and 17 of the '045 patent) and "treating" (in claim 1 of the '907 patent and claim 1 of the '908 patent). Ex. 1001, 99:2, 100:3; 1711 IPR Ex. 1001, 103:21; 1712 IPR Ex. 1001, 99:55.

We determined in our Institution Decision in the 1710 IPR that "'reducing incidence of or treating' is a statement of intended purpose that does not require achieving a result." Inst. Dec. 11. Similarly, we determined in our Institution Decisions in the 1711 IPR and the 1712 IPR 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." 1711 IPR Inst. Dec. 11; *see also* 1712 IPR Inst. Dec. 10 (same). The parties do not dispute that the preamble claim language is a statement of intended purpose. *See* Reply 2; 1711 IPR Reply 2; 1712 IPR Reply 2; *generally* PO Resp.; 1711 IPR PO Resp.; 1712 IPR PO Resp.

The preambles of the challenged claims are thus limiting to the extent that they require that the recited method must be performed with the intentional purpose of "reducing incidence of or treating" at least one

vasomotor symptom (claim 1, '045 patent) or headache (claim 17, '045 patent); or the with the intentional purpose of "treating" headache (claim 1, '907 patent; claim 1, '908 patent). *See Sanofi Mature IP v. Mylan Labs. Ltd.*, 757 F. App'x 988, 993–94 (Fed. Cir. 2019) (instructing the Board on remand to treat the preamble "as an additional limitation of" the claim that "require[s] 'increasing survival'" as the "intentional purpose . . . for which the [recited] method must be performed" (quoting *Jansen v. Rexall Sundown, Inc.*, 342 F.3d 1329, 1333 (Fed. Cir. 2003))); *Jansen*, 342 F.3d at 1333 (in claimed method "for treating or preventing" particular anemia, to be performed on "human in need thereof," the preamble is a "statement of intentional purpose for which the method must be performed"); *Rapoport v. Dement*, 254 F.3d 1053, 1058–61 (Fed. Cir. 2001) (in claimed method "for treatment of sleep apneas," comprising administration "to a patient in need of such treatment," the preamble requires that the method (administering a certain compound) must be practiced to achieve the purpose stated in the preamble). This is consistent with our construction from the Institution Decisions that the preambles are a "statement of intended purpose" of the recited methods, and we maintain the constructions from the Institution Decisions for purposes of this Final Written Decision.

In discussing claim construction, Patent Owner further contends that the claimed method for "reducing incidence of or treating," as recited in the challenged claims of the '045 patent, "requires a reasonable expectation that the method will be therapeutically effective." PO Resp. 10. Regarding the "treating" claim language, Patent Owner also contends that the challenged claims of the '907 and '908 patents "require at least a reasonable expectation that treatment with anti-CGRP antibodies would have a beneficial clinical

result in an individual." *See* 1711 IPR Sur-reply 3 (citing 1711 IPR PO Resp. 10–11 (citing Ex. 2266 ¶ 53; Ex. 2269 ¶¶ 19–20; Ex. 2272 ¶ 18; 1711 IPR Ex. 1001, 18:4–18); Ex. 2336, 41:19–42:2). Petitioner reiterates that the claims do not require actually achieving a clinical result/response. *See* Reply 2–3; 1711 IPR Reply 2. In other words, the parties dispute what is required for a showing of a reasonable expectation of success with respect to the recited intended purpose of the claimed methods.

As relevant to the parties' arguments set forth in the claim construction discussion, we determine here that to prove a reasonable expectation of success with respect to a limitation that recites achieving a particular result as the intended purpose for which a recited method must be performed, what is required is not proof that the recited method would *actually* bring about the recited result, but rather proof that a person of ordinary skill in the art would have had a reasonable expectation that performing the recited method would bring about the recited result. *See Sanofi v. Watson Labs. Inc.*, 875 F.3d 636, 647 (Fed. Cir. 2017); *see also Mylan Labs. Ltd. v. Aventis Pharma S.A.*, IPR2016-00712, Paper 112 at 12–14 (PTAB Oct. 22, 2019) (discussing requirements to prove reasonable expectation of success of similar claim language). The parties' specific arguments regarding whether Petitioner has shown a reasonable expectation of success are addressed below. *See infra* Section II.D.4.b).

2. "effective amount"

The term "effective amount" is recited in all of the independent challenged claims, and thus is recited in all of the challenged claims. We determined in our Institution Decisions 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 challenged patents. *See, e.g.*, Ex. 1001, 18:41–57; Inst. Dec. 11–13.

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.

In our Institution Decision, we found that it was "unclear on this record whether the referenced 'biochemical' and 'histological' symptoms [referenced in the Specification in connection with 'effective amount'] include cAMP stimulation, as argued by Petitioner." Inst. Dec. 12. In its Reply, Petitioner argued that "[t]he Board invited testimony on whether such symptoms include stimulated cAMP formulation, but Teva provided none. . . . As Dr. Charles explains, cAMP stimulation was recognized as a direct biochemical response to elevated CGRP levels, which are characteristic of migraine." Reply 2–3 (citing Inst. Dec. 11–12; Ex. 1338 ¶¶ 5–10; Ex. 1014 ¶¶ 26–38; Ex. 1001, 25:51–59; Ex. 1303, 61:15–62:12; Ex. 1343, 28:18–29:18). Thus, according to Petitioner, "an 'effective amount' includes amounts sufficient to reduce biochemical or histological symptoms (such as cAMP stimulation) without requiring any clinical result." *Id.* at 3 (citing Ex. 1343, 33:17–34:6).

Patent Owner agrees with our construction of the term "effective amount" as set forth in our Institution Decision "because the patent provides

a clear definition of that term." PO Resp. 10–11 (citing Inst. Dec. 11–12; Ex. 1001, 18:38–19:3; Ex. 2268 ¶ 21; Ex. 2265 ¶ 54). However, Patent Owner further contends that "[t]he claims . . . require clinical results," and that Petitioner misreads "effective amount" to not require a clinical result because "the specification unambiguously ties biochemical or histological symptoms to clinical results." Sur-reply 3–4 (citing Ex. 1001, 18:41–44). Patent Owner supports this contention by arguing that "Dr. Charles agreed that a physician treating migraine would want 'to administer an effective amount that will help you achieve that clinical response,'" and that "[t]his admission undercuts Dr. Charles' testimony that 'biochemical or histological changes' merely requires 'inhibiting cAMP activation,' which admittedly 'can change ***without any effect*** on symptoms of a disease.'" *Id.* at 4 (citing Ex. 1338 ¶¶ 7–8; Ex. 2336, 66:1–5, 57:13–15 ("Q. Are you aware if cAMP levels can change without any effect on symptoms of a disease? A. Yes.")) (emphasis by Patent Owner).

An "effective amount" of a drug, compound, or pharmaceutical composition is defined in the '045 patent as "an amount sufficient to effect beneficial or desired results." Ex. 1001, 18:38–40. The Specification provides examples of such beneficial or desired results in the context of prophylactic or therapeutic use of a drug, compound, or pharmaceutical composition:

> 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 (emphases added).

Although the term "effective amount" may *encompass* a clinical result, we do not interpret the term "effective amount" as *requiring* a clinical result because, as defined in the Specification, the term "effective amount" refers only to "beneficial or desired results" without the qualifier "clinical." That is, the term "effective amount" requires a beneficial or desired result, but it need not be a "clinical" result. Although the Specification refers to "clinical results" in the context of therapeutic use, it also refers to prophylactic use without using the words "clinical results." Moreover, based on the use of the words "include" and "such as" in discussing prophylactic and therapeutic uses, we interpret the Specification as providing exemplary "beneficial or desired results" from prophylactic or therapeutic uses, and not a requirement of any particular beneficial or desired result. Likewise, we do not find the testimony of Dr. Charles to alter or modify the Specification's definition of "effective amount" or the proper construction thereof.

In our Institution Decision, we indicated that it was unclear whether "biochemical" and "histological" symptoms, as referenced in the examples of beneficial or desired results, include cAMP stimulation, as argued by Petitioner. After considering the parties' arguments and the Specification, we decline to adopt Petitioner's proposed interpretation because the

Specification refers to biochemical or histological "symptoms of the disease" or "symptoms resulting from headache." Ex. 1001, 18:44–51. Petitioner has not sufficiently shown how cAMP stimulation is a biochemical or histological *symptom* of the disease (e.g., headache).

Petitioner also argued that the term "effective amount" should be construed as including at least doses of an anti-CGRP antagonist antibody that are less than 3 μg/kg (as recited, e.g., in dependent claim 16 of the '045 patent). Pet. 21–23; *see* Ex. 1001, 100:1–2. In the Institution Decision, we did not take a position on the record at that time as to the specific dosages that produce "beneficial or desired results" as stated in the construction we determined for the term "effective amount." Inst. Dec. 12–13. Petitioner did not further pursue this argument. *See generally* Reply. The definition of "effective result" provided in the Specification does not include any express dosage limitations, and we decline to incorporate into that definition the inclusion of "doses of an anti-CGRP antagonist antibody that are less than 3 μg/kg" as requested by Petitioner. The definition of "effective amount" is "an amount sufficient to effect beneficial or desired results," i.e., whatever that dosage or amount may be.

For the foregoing reasons, we maintain the construction of the term "effective amount" as set forth in our Institution Decision; namely, "'an amount sufficient to effect beneficial or desired results,' including results of prophylactic or therapeutic use, as those terms are used in [the challenged patents]." Inst. Dec. 12.

3. "specific binding"

The term "specific binding" is recited in independent claim 1 of both the '907 patent and the '908 patent, and thus is recited in the corresponding

dependent claims of those patents. We determined in our Institution Decisions that, in view of the arguments at that time and the apparent lack of inconsistency in the positions of the parties, it was not necessary to construe the term "specific binding" at that stage of the proceeding. 1711 IPR Inst. Dec. 14; 1712 IPR Inst. Dec. 14. Neither party further pursued a construction of the term "specific binding" during trial. *See generally, e.g.*, 1711 IPR PO Resp.; 1711 IPR Reply; 1711 IPR Sur-reply. In the absence of any apparent controversy over the construction of the term "specific binding," we decline to expressly construe that term. *See Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc*., 200 F.3d 795, 803 (Fed. Cir. 1999) (only those terms need be construed that are in controversy, and only to the extent necessary to resolve the controversy).

4. "anti-CGRP antagonist antibody" and "humanized monoclonal antibody"

Petitioner's request for construction of these terms refers to the definitions thereof in the Specification. Pet. 23–24. Patent Owner does not challenge those proposed constructions, PO Resp. 10–11; *see also generally* PO Resp., Sur-reply, and in the absence of controversy with respect thereto, we decline to enter an express construction of these terms. *See Vivid Techs.*, 200 F.3d at 803.

5. Conclusion as to Claim Construction

We apply the foregoing constructions for purposes of this Final Written Decision. We determine that no other term requires express construction. *See Vivid Techs.*, 200 F.3d at 803.

C. General Principles of Law

To prevail in its challenges to the patentability of the claims, Petitioner must demonstrate by a preponderance of the evidence that the

challenged claims are unpatentable. 35 U.S.C. § 316(e); 37 C.F.R. § 42.1(d). "In an [*inter partes* review], the petitioner has the burden from the onset to show with particularity why the patent it challenges is unpatentable." *Harmonic Inc. v. Avid Tech., Inc.*, 815 F.3d 1356, 1363 (Fed. Cir. 2016) (citing 35 U.S.C. § 312(a)(3) (requiring *inter partes* review petitions to identify "with particularity . . . the evidence that supports the grounds for the challenge to each claim")). This burden of persuasion never shifts to Patent Owner. *See Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015) (discussing the burden of proof in *inter partes* review).

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 grounds of unpatentability in accordance with the above-stated principles.

D. Discussion of the Asserted Obviousness Grounds

Petitioner asserts that the challenged claims would have been obvious over Olesen, Tan, and Queen as set forth above (*see supra* Section I.G). Pet. 24–61; Reply 1–27; 1711 IPR Pet. 23–57; 1711 IPR Reply 1–27; 1712 IPR Pet. 25–60; 1712 IPR Reply 1–27. Patent Owner opposes. PO Resp. 11–66; Sur-reply 1–29; 1711 IPR 11–59; 1711 IPR Sur-reply 1–29; 1712 IPR PO Resp. 12–65; 1712 IPR Sur-reply 1–29. The thrust of Patent Owner's opposition is that (1) a person of ordinary skill in the art would not have combined the asserted references, including because of potential safety concerns, to arrive at the claimed invention, (2) a person of ordinary skill in the art would not have had a reasonable expectation of success, and (3) the objective indicia compel a finding of nonobviousness. *See* PO Resp. 29–45, 55–64; Sur-reply 6–24, 27–29; 1711 IPR PO Resp. 20–46, 48–59; 1711 IPR Sur-reply 6–24, 26–29; 1712 IPR PO Resp. 21–46, 53–63; 1712 IPR Sur-reply 6–24, 27–29.

1. The Asserted Prior Art

a) Olesen (Ex. 1025)

Olesen is an article published in the New England Journal of Medicine that describes a multicenter clinical trial of BIBN4096BS[23] ("BIBN"), a highly specific and potent nonpeptide CGRP-receptor antagonist, to test its efficacy in the treatment of migraine attacks. Ex. 1025, 1104.[24] 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 BIBN 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 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 1108–09. 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.* 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.

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

[24] Throughout this Decision, we refer to the original pagination of a reference, as opposed to the page numbers added to the exhibit.

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).

In short, Olesen discloses that BIBN was effective in treating acute attacks of migraine. *Id.* at 1104. Olesen, which is a clinical study, discusses some past studies and discloses that CGRP may have a role both in initiating and mediating migraine attacks, and observes that sumatriptan, which is a serotonin agonist has also been observed to normalize elevated CGRP levels as it terminates a migraine attack. *Id.* at 1108. Olesen reported that BIBN does not seem to have vasoconstrictor properties but stated that "our data base was too small for us to assess cardiovascular safety" and suggested further studies, including comparing BIBN to triptans. *Id.* at 1109.

b) 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 566–567. 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 567. Tan reports that MAb C4.19 IgG increased mean arterial pressure ("MAP") 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 min 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.

c) 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, code (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 2:12–27.

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), the human sequence will be replaced by corresponding amino acids from the donor sequence if they are (1) in a CDR, and/or (2) if the amino acid is rare for that position and that 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, (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 2:41–3:26.

d) Other Prior Art Reflective of the State of the Art as of the Filing Date

Petitioner relies on other prior art references as evidence of what would have been in the knowledge of one of ordinary skill in the art, in assessing the combination of Olesen, Tan, and Queen. We discuss those other references here.

The Olesen Abstract[25] reports that BIBN was effective in the acute treatment of migraine. Ex. 1029, 119.

The Arndt Abstract[26] discloses that BIBN had an overall responder rate of 60% in a randomized clinical trial for the treatment of migraine pain with no serious side effects reported. Ex. 1030, 129.

Arulmozhi[27] is a literature review, which discloses a concentration dependent relaxation of the middle cerebral artery when CGRP was applied abluminally, and states that "inhibition of CGRP or antagonism of CGRP receptors could be a viable therapeutic target for the pharmacological treatment of migraine." Ex. 1040, 182.

Sveinsson[28] is a published patent application, which lists some antagonists of CGRP including antibodies against CGRP. Ex. 1026, 7:5–19. Sveinsson discloses that small molecular non-peptide compounds, peptides, and antibodies have been found to selectively inhibit the CGRP receptor and that such active CGRP antagonists are expected to be useful to treat a variety diseases mediated by CGRP, including migraines, NIDDM, neurogenic inflammation, cardiovascular disorders, chronic inflammation, pain, endotoxic shock, arthritis, allergic rhinitis, allergic contact dermatitis,

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[25] J. Olesen et al., *S26 CGRP antagonism as a new therapeutic principle in acute migraine*, Abstracts, 38 NEUROPEPTIDES 110–31 (2004) (Ex. 1029, "the Olesen Abstract").

[26] K. Arndt et al., *P25 CGRP antagonism — a valid new concept for the treatment of migraine pain*, Abstracts, 38 NEUROPEPTIDES 110–31 (2004) (Ex. 1030, "the Arndt Abstract").

[27] D.K. Arulmozhi et al., *Migraine: Current concepts and emerging therapies*, 43 VASCULAR PHARMACOLOGY 176–87 (2005) (Ex. 1040, "Arulmozhi").

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

inflammatory skin conditions, and asthma. *Id.* at 7:5–12. Sveinsson also suggests CGRP antagonists for the treatment of psoriasis. *See id.* at 7:1–3. Sveinsson also discloses the use of CGRP antagonists in therapeutic/cosmetic compositions for treating diseases of the skin, including lichens, prurigos, prurignous toxidermas, severe pruritus, skin redness, rosacea, and discrete erythema. *Id.* at 7:21–24.

Sveinsson states "[a]ntibodies against CGRP have also been described," as well as "inactive derivatives of CGRP, e.g., CGRP8–37 which differs from normal CGRP in that it lacks 8 N-terminal amino acids." *Id.* at 7:19–20. Sveinsson lists the following CGRP antagonists: 4-sulfinyl benzamide compounds, 3,4-dinitrobenzamide compounds, benzamidazolinyl piperadine compounds, CGRP derivatives including $CGRP_{8–37}$, *anti-CGRP antibodies*, BIBN (a non-peptide molecule), tryptase, tryptase active polypeptide, and compounds stabilizing tryptase, including heparin, and a group of modified amino acids. *Id.* at 7:15–18, 10:25–32, claims 2, 7 (emphasis added). Thus, Sveinsson suggests the use of anti-CGRP antibodies as one of several types of CGRP antagonists.

Salmon[29] is a published patent application, which states that its invention relates to methods and compositions for modulation of neurogenic inflammatory pain and the inhibition of αCGRP. *See* Ex. 1027 ¶¶ 2–3. Salmon defines modulation of neurogenic inflammatory pain or physical opiate withdrawal as increase or decrease of neurogenic pain and/or physical opiate withdrawal. *Id.* ¶ 27. Salmon discloses that pharmaceutical compounds can be used for amelioration of neurogenic inflammatory pain or opiate withdrawal including αCGRP antagonists such as small peptides,

[29] Salmon, US 2002/0162125 A1, pub. Oct. 31, 2002 (Ex. 1027, "Salmon").

small organic molecules, antisense, triple helix molecules, and polyclonal or monoclonal antibodies. *Id.* ¶¶ 13, 39. Salmon concludes that mice lacking αCGRP display an attenuated response to capsaicin, formalin, carrageenan, and acetic acid, and a decreased physical opiate withdrawal precipitated by naloxone. *Id.* ¶ 87. Salmon discloses that homozygous mutant mice from all generations were healthy, fertile, and do not present obvious abnormalities with no differences in body weight or temperature. *See id.* ¶ 69. Claim 1 recites a method of screening for a compound that is an antagonist of CGRP. *Id.* at claim 1. Claim 8, which depends ultimately from claim 1, recites that the compound is a monoclonal antibody. *Id.* at claim 8.

The '438 patent[30] discloses the use of at least one CGRP antagonist, advantageously in combination with an antagonist of another neuropeptide such as substance P. Ex. 1028, Abstract, 2:7–10, 2:66–67, 6:18–20 (claim 2). Example 2 of the '438 patent is an ointment containing anti-CGRP antibody. *Id.* at 5:37–49. The '438 patent states that $CGRP_{8-37}$ and anti-CGRP antibodies are suitable antagonists according to the invention thereof. *See id.* at 3:21–22. The '438 patent states in the introduction to this section that the CGRP antagonist or antagonists are preferably administered via topical injection and may also be ingested or injected (for systemic administration). *Id.* at 2:64–67.

Lassen[31] is a study which reports that administered CGRP caused headache in migraine sufferers. Ex. 1047, 55, 59. Lassen suggests that a

[30] De Lacharriere, US 6,344,438 B1, iss. Feb. 5, 2002 (Ex. 1028, "the '438 patent").
[31] LH Lassen et al., *CGRP may play a causative role in migraine*, 22 CEPHALALGIA 54–61 (2002) (Ex. 1047, "Lassen").

CGRP antagonist may be effective in the treatment of migraine attacks and reported that drugs that antagonize CGRP development were known to be in pre-clinical or clinical trials. *Id.* at 60.

Vater[32] is a research article that discloses that it developed a method to identify aptamers (oligonucleotide ligands) and identified a mirror image aptamer that inhibits the action of the migraine-associated target α-CGRP in cell culture. Ex. 1082, Abstract. Vater carried out an *in vitro* selection approach against the optical antipode of rat α-CGRP. *Id.* at 2. Vater suggested future studies to address target and species specificity of the rat α-CGRP binding spiegelmer[33] in cell culture. *Id.* at 7.

Messlinger[34] is a poster presentation abstract that reports that a CGRP-binding spiegelmer applied topically to exposed rat cranial dura mater caused a significant and dose-dependent inhibition of the evoked meningeal blood flow responses evoked by periodic local electrical stimulation to about 50% of the control, with unchanged basal blood flow and systemic arterial pressure. Ex. 1240, 923.

Wong[35] is a research article, which reports that the authors produced anti-rat CGRP antibodies in mice and administered it to rats. Ex. 1033,

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[32] Axel Vater et al., *Short bioactive Spiegelmers to migraine-associated calcitonin gene-related peptide rapidly identified by a novel approach: Tailored-SELEX*, 31 NUCLEIC ACIDS RESEARCH 21e130, 1–7 (2003) (Ex. 1082, "Vater").

[33] A spiegelmer is a "mirror-image aptamer." Ex. 1082, Abstract.

[34] Karl Messlinger et al., *F022 Inhibition of neurogenic blood flow increases in the rat cranial dura mater by a CGRP-binding Spiegelmer*, Poster Presentations F022, 25 CEPHALALGIA 923 (2005) (Ex. 1240, "Messlinger").

[35] Wong et al., *Monoclonal Antibody to Rat* α*-CGRP: Production, Characterization, and In Vivo Immunoneutralization Activity*, 12(1) HYBRIDOMA 93 (1993) (Ex. 1033, "Wong").

Abstract. Wong reports that the antibodies prevented the fall in mean arterial blood pressure and the increased heart rate caused by intravenous injection of rat α-CGRP. *Id.*

Andrew[36] is a research article that reports that the authors raised monoclonal antibodies to human CGRP in rats and mice. Ex. 1055, Abstract, 88, 89, Table 2, Fig. 1. Andrew reports that "[a]lthough the immunised rats had high levels of circulating antibodies to rat CGRP, they did not show any signs of physical or behavioural abnormality." *Id.* at 93.

Lu[37] is a research article. *See* Ex. 1288. The abstract reports that "[m]ice lacking αCGRP expression demonstrate no obvious phenotypic differences from their wild-type litter-mates. Detailed analysis of systemic cardiovascular function revealed no differences between control and mutant mice regarding heart rate and blood pressure under basal or exercise-induced conditions and subsequent to pharmacological manipulation." *Id.* at Abstract. The abstract further reports that "[t]hese results suggest that αCGRP is not required for the systemic regulation of cardiovascular hemodynamics or development of the neuromuscular junction." *Id.*

Frobert[38] is a study that raised and analyzed thirty mouse monoclonal antibodies against rat αCGRP. *See* Ex. 1032, Abstract.

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[36] D.P. Andrew et al., *Monoclonal antibodies distinguishing α and β forms of calcitonin gene-related peptide*, 154 J. OF IMMUNOLOGICAL METHODS 87–94 (1990) (Ex. 1055, "Andrew").

[37] Lu et al., *Mice Lacking* α*-Calcitonin Gene-Regulated Peptide Exhibit Normal Cardiovascular Regulation and Neuromuscular Development*, 14 MOLECULAR AND CELLULAR NEUROSCIENCE 99–120 (1999) (Ex. 1288, "Lu").

[38] 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").

Tan 1994[39] is a study, prior to Tan, which raised and characterized mouse antibodies directed to rat αCGRP, including Mab C4.19. Ex. 1021, 703, 706. This was the same antibody later used in Tan. *See* Ex. 1022, 566 & n.11.

Wimalawansa[40] is a review article that describes the molecular biology, distribution, activity, and "therapeutic potentials" of CGRP. *See* Ex. 1096, 533–70. According to Wimalawansa, CGRP is a 37-amino acid neuropeptide resulting from alternative splicing of the primary RNA transcript of the CT [calcitonin]/CGRP gene. *Id.* at 534. There are two genes responsible for α and β subforms of the peptide. *See id.*

Wimalawansa teaches that CGRP and CGRP receptors are widely distributed in the mammalian nervous system (e.g., discrete brain areas and the peripheral nervous system), in the cardiovascular system (e.g., arteries, veins, and the heart), the gastrointestinal tract, and several endocrine organs (e.g., the thyroid gland and pancreatic islet cells), often co-located with other neurotransmitters and neuropeptides. *See id.* at 539–540. Wimalawansa suggests that CGRP has potent vasodilatory activity, may play a major role in regulating peripheral vascular tone, and has an ability to change coronary blood flow. *Id.* at 540. Wimalawansa also suggests an association between a decrease in CGRP and strokes and heart attacks in older populations, e.g.,

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[39] 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").

[40] 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").

during parts of the circadian cycle. *See id.* at 543. CGRP has various direct and indirect mechanisms for its vasodilatory effects, including causing vasorelaxation through specific receptors in vascular smooth muscle (e.g., in coronary vasculature). *Id.* at 553, 556 & Fig. 18 (not reproduced here).

Wimalawansa discloses that α- and β-CGRP are agonists for all receptor subtypes, but a synthetically-derived fragment of CGRP (e.g., $CGRP_{8-37}$) instead acts as a competitive antagonist at certain receptor subtypes, e.g., CGRP-type 1 receptors. *Id.* at 543, 547. Receptors that do not respond to the antagonist $CGRP_{8-37}$ are generally grouped as CGRP-type 2 receptors, but other receptor types have been postulated. *Id.* at 548. Wimalawansa states: "The fact that different vascular beds respond differently to CGRP and $CGRP_{8-37}$ may indicate receptor heterogeneity." *Id.*

In a section titled "Therapeutic potentials of CGRP antagonists," Wimalawansa states "[c]learly, more data from carefully designed studies are necessary before any definitive conclusions can be reached and before CGRP antagonist, humanized anti-CGRP monoclonal antibodies, or both, can be evaluated as therapeutic agents in humans." *Id.* at 567. In a subsection on "Migraine headache and premenstrual syndrome," Wimalawansa states:

> CRGP agonists designed specifically for cerebral vascular bed, when available, can be used during the early phase (i.e. vasoconstructive phase) of migraine headaches, and CGRP antagonist can be used in the late phase (prolonged vasodilatory phase). However, the antagonist must be extremely specific to the CGRP receptors located in cerebral arteries to avoid potential deleterious side effects caused by blocking other vascular and nonvascular CGRP receptors. Ideally, this compound should be a peptide mimetic of simple structure specific to cardiovascular

> CGRP receptors, so that the drug can be given orally, buccally, or sublingually.

Id. at 568.

Wimalawansa concludes:

> CGRP is a potent neuropeptide involved in human physiopathology but, in spite of 14 yr of intense research, its role is still not fully understood.
>
> . . .
>
> The role of CGRP antagonists and humanized monoclonal antibodies should be explored with respect to control of pain and inflammation, type II diabetes, and in conditions with intractable hypotension, such as septic shock syndrome.

Id. at 569–570.

Doods[41] states that CGRP is one of the most potent endogenous vasodilators known, and "is increased during migraine attacks and has been implicated in the pathogenesis of migraine headache." Ex. 1024, Abstract. Doods describes *in vitro* and *in vivo* testing of BIBN, a small-molecule CGRP receptor antagonist. *Id.*

The *in vitro* testing involved a radioligand binding assay using two different cell types. In the first assay, rat spleen homogenates were prepared and incubated with ^{125}I-hCGRP (the radioligand) and BIBN, and a gamma counter was used to measure the inhibition of ^{125}I-hCGRP to CGRP receptors. *Id.* at 420. Doods reports that in this assay, BIBN inhibited the binding of ^{125}I-hCGRP to rat CGRP receptors. *Id.* at 422.

[41] Doods et al., *Pharmacological Profile of BIBN4096BS, the first selective small molecule CGRP antagonist*, 129 BR. J. PHARMACOL. 420–23 (2000) (Ex. 1024, "Doods").

SK-N-MC[42] cells were used in the second assay, and the results showed that BIBN inhibited the binding of ^{125}I-hCGRP to human CGRP receptors in SK-N-MC cells. *Id.* at 420–22. Doods also used SK-N-MC cells to measure BIBN's antagonistic effects on inhibiting cAMP activation. *Id.* at 420–21. Doods confirmed that BIBN antagonizes CGRP because it inhibited CGRP-induced cAMP activation. *Id.* at 422.

The *in vivo* testing reported by Doods measured the inhibition of CGRP's effects on facial blood flow in marmosets, and Doods reports that BIBN inhibits blood flow. *Id.* at 421–22. Doods concludes by stating that "[s]ince several lines of evidence indicate that CGRP might be a key factor in the initiation of migraine headache, we expect that CGRP antagonists will be effective anti-migraine drugs." *Id.* at 422.

2. Petitioner's Arguments

a) Disclosure or suggestion of each and every element of the challenged independent claims

(1) Claim 17 of the '045 patent and claim 1 of the '907 patent

Petitioner argues that "[e]ach and every element of claim 17 [of the '045 patent] 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). According to Petitioner, "[a]nti-CGRP antagonist antibodies had already been proven to block the CGRP pathway and were proposed to treat

[42] SK-N-MC, as used by Doods, stands for "neuroblastoma cell line of human origin." Ex. 1024, Abstract (Abbreviations).

migraine, and thus were an obvious choice after Olesen's study due to their specificity, affinity, and demonstrated *in vivo* activity." *Id.* at 24 (citing Ex. 1096, 567–70; Ex. 1022, 572; Ex. 1014 ¶ 71). Petitioner points to Tan as describing murine anti-CGRP antagonist antibodies that blocked the effects of CGRP *in vivo*. *Id.* (citing Ex. 1022, 567–71; Ex. 1014 ¶ 71). Petitioner points to Queen as teaching humanized antibodies, 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 advances the same arguments with respect to claim 1 of the '907 patent. *See* 1711 IPR Pet. 23–24. In addition, Petitioner argues with respect to claim 1 of the '907 patent that Tan's disclosure includes a full length antibody, that the recited SEQ ID NOs 15 and 43 correspond to human αCGRP and βCGRP, respectively, and that "[t]he recited 'heavy chain' and 'light chain' limitations are *generic* to IgG antibodies and do not provide meaningful structure that correlates with specific binding to CGRP for treating headache." *Id.* at 5–6, 23 (citing Ex. 1022, 567–71; 1711 IPR Ex. 1016 ¶¶ 79, 91; 1711 IPR Ex. 1001, cols. 53–54 (Table 4)).

(2) Claim 1 of the '045 patent

Petitioner refers to its arguments regarding claim 17 of the '045 patent and further argues that claim 1 of the '045 patent is broader than claim 17 of the '045 patent, that claim 1 is directed to any vasomotor symptom and any individual (rather than just humans),[43] and that Patent Owner defined

[43] The Specification 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.

vasomotor symptoms to include migraine. Pet. 49 (citing Ex. 1001, 19:51, 99:2–7, 100:3–7; Ex. 1014 ¶¶ 83, 156). Petitioner further argues that Tan "established that murine monoclonal anti-CGRP antagonist antibodies reduced incidence of skin vasodilation in rats." *Id.* at 50 (citing Ex. 1022, 569).

(3) Claim 1 of the '908 patent

Petitioner advances the same arguments as advanced in connection with claim 1 of the '907 patent. 1712 IPR Pet. 25–26. In addition, Petitioner argues that Tan "had binding affinities of 1.9 nM and 2.5nM to αCGRP and βCGRP, respectively," and that "Dr. Vasserot confirms [that] SPR [(surface plasmon resonance)] was a routine assay for measuring binding affinity." *Id.* (citing Ex. 1022, 567–71; Ex. 1021, 707; Ex. 1018 ¶ 79; Ex. 1236 ¶¶ 66–67; Ex. 1084, Abstract).

Petitioner asserts that, by 2005, SPR was a technique known to measure an antibody's binding affinity and was described as "the standard method for measuring the affinity of antigen-antibody interactions." *Id.* at 15 (quoting Ex. 1084[44], Abstract; citing 1712 IPR Ex. 1236 ¶¶ 62–67; Ex. 1084, Abstract, 141, 148–49; Ex. 1086, 117).

(4) Summary

Patent Owner's arguments focus on Petitioner's alleged failure to establish a reason to combine the asserted references and a reasonable expectation of success in doing so, rather than whether each claim element was independently known in the art. Accordingly, based on the totality of

[44] M.H.V. Van Regenmortel, *Improving the Quality of BIACORE-Based Affinity Measurements*, 112 IMMUNOGENICITY OF THERAPEUTIC BIOLOGICAL PRODUCTS 141–151 (2003) (Ex. 1084).

the evidence, we find that Petitioner has shown by a preponderance of the evidence that the asserted prior art discloses or suggests each and every element of claims 1 and 17 of the '045 patent, claim 1 of the '907 patent, and claim 1 of the '908 patent. *See* Ex. 1025; Ex. 1022; Ex. 1023.

b) Suggestions or reasons to combine the asserted references

Petitioner argues that a person of ordinary skill in the art would have been motivated to treat migraine with a humanized monoclonal anti-CGRP antagonist antibody, and advances several contentions in support of that argument. Pet. 25–35.

(1) The prior art would have motivated a POSA to use a CGRP antagonist to treat migraine

Petitioner argues that "Olesen's published clinical trial validated the CGRP pathway as a therapeutic target for treating migraine, and established that blocking the CGRP pathway reduced the incidence of migraine." Pet. 25 (citing Ex. 1025, 1104, 1108–09; Ex. 1014 ¶¶ 31–36, 68, 69, 109). Petitioner argues further that Olesen identifies CGRP antagonists, without limitation, thus extending its results beyond BIBN to CGRP antagonists generally. *Id.* at 26 (citing Ex. 1025, 1105, 1109; Ex. 1014 ¶ 109). Petitioner also argues that "[t]he Olesen investigators also broadly reported that 'CGRP antagonism [w]as a new therapeutic principle' for treating migraine." *Id.* (quoting Ex. 1029, 119 (S26); citing Ex. 1024, 422; Ex. 1014 ¶ 109). Thus, according to Petitioner, "a POSA reading Olesen would have extended its teachings to other CGRP antagonists." *Id.* (citing Ex. 1014 ¶¶ 107–113).

Petitioner argues that other prior art supports Olesen's broad teachings, citing Tan's reference to immunoblockade with anti-CGRP antagonist antibodies as "an alternate" strategy to blocking CGRP with

CGRP receptor antagonists, such as BIBN. Pet. 26–27 (citing Ex. 1022, 566, 571; Ex. 1019, Examples 3 and 5); *see* Ex. 1022, 571 ("Immunoblockade should be regarded as a technique that is complementary to the use of receptor antagonists."). Petitioner also cites to Wong for the statement that antagonism of CGRP can be achieved "either at the receptor level using specific CGRP antagonists, or by neutralizing endogenous [CGRP] peptide with a specific antibody." Pet. 27 (citing Ex. 1033, 95) (alteration in original). Petitioner cites to Arulmozhi for the statement that "inhibition of CGRP *or* antagonism of CGRP receptors could be a viable therapeutic target for the pharmacological treatment of migraine." *Id.* (citing Ex. 1040, 182) (emphasis by Petitioner). According to Petitioner, the '045 patent also reflects this prior art understanding by stating that CGRP "has a causative role in migraine." *Id.* (citing Ex. 1001, 2:3–31 (citing Lassen (Ex. 1047))).

Petitioner also argues that multiple prior art publications "focused on inhibiting CGRP rather than the receptor," citing the studies of aptamers ("compounds . . . that bound to CGRP and interrupted receptor binding") by Vater and Messlinger. Pet. 27 (citing Ex. 1082, 1; Ex. 1240, 923; Ex. 1014 ¶ 62). Petitioner also cites to Sveinsson, Salmon, and the '438 patent as patent publications that "specifically referenced anti-CGRP antagonist antibodies for treating migraine and neurogenic pain." *Id.* (citing 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. 1014 ¶¶ 115–117.)

Petitioner also cites to Wimalawansa as identifying humanized anti-CGRP antagonist antibodies for treating migraine, and its statement that

"[t]he role of CGRP antagonists and humanized monoclonal antibodies should be explored." *Id.* at 27–28 (citing Ex. 1096, 567, 570).

Petitioner argues that a POSA in 2005 would have known that targeting CGRP (the ligand), rather than one of its receptors, had several therapeutic advantages. Pet. 28 (citing Ex. 1014 ¶¶ 128–130). According to Petitioner, "a POSA would have known that small molecule receptor antagonists are often not sufficiently specific for a given receptor target, which leads to off-target effects from non-specific binding." *Id.* (citing Ex. 1014 ¶ 128; Ex. 1022, 572 (monoclonal antibodies have the "inherent advantage[] of defined specificity")). Petitioner further argues that "by 2005, the art recognized that at least two CGRP receptors may exist but had not yet identified which one was implicated in migraine," thereby motivating a POSA to "target CGRP to fully block the pathway by preventing CGRP from binding to its receptors." *Id.* (citing Ex. 1099, 235–37). Petitioner also argues that "blocking receptors has consequences beyond simply blocking the targeted biological process," such as the body upregulating receptor concentrations (i.e., producing more receptors) that can result in tolerance to the administered drug. *Id.* (citing Ex. 1014 ¶ 130).

Thus, according to Petitioner, "a POSA would have been motivated to target CGRP for treating and reducing incidence of migraine" because "the prior art explicitly identified CGRP itself as a therapeutic target for treating various conditions including migraine, and Olesen confirmed that blocking the CGRP pathway would work in the clinic." *Id.* at 28–29 (citing Ex. 1014 ¶ 113).

(2) A POSA would have been motivated to use an anti-CGRP antagonist antibody to treat migraine

Petitioner contends that a POSA would have been motivated to use an anti-CGRP antagonist *antibody* to treat migraine. Pet. 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 cites to Sveinsson, Wimalawansa, and Salmon as examples to support its contention. *Id.* at 29–30.

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 30–31 (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 [BIBN] compound," pointing to the longer half-life of antibodies (as compared to BIBN) 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 alleging 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, 454s–55s; Ex. 1242, Abstract; Ex. 1243, 591–92; Ex. 1244, 286).

(3) A POSA would have been motivated to use a humanized monoclonal anti-CGRP antagonist antibody for treating migraine

Petitioner contends that a POSA would have been motivated to use a *humanized* monoclonal anti-CGRP antagonist antibody to treat migraine. Pet. 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).

(4) Additional Claim Limitations

(a) Claim 1 of the '045 patent

Petitioner argues that claim 1 "is broader than claim 17" and would have been obvious for all the reasons discussed in connection with claim 17. Pet. 49–50. Petitioner also provides a cursory paragraph of "additional" reasons claim 1 would have been obvious.

As to reasons to combine, Petitioner argues that "a POSA would have been motivated to use an anti-CGRP antagonist antibody, including humanized antibody, to reduce incidence of or treat skin vasodilation, which [Patent Owner] admitted was a vasomotor symptom, and is an underlying cause of hot flush." *Id.* at 50 (citing Ex. 1143, 10; Ex. 1245, 1:18–23; Ex. 1001, 19:5). Petitioner also argues that "Tan established that murine monoclonal anti-CGRP antagonist antibodies reduced incidence of skin vasodilation in rats," and that "[o]thers had demonstrated similar effects using an anti-CGRP antagonist in a marmoset model of hot flush." *Id.* (citing Ex. 1022, 569; Ex. 1245, 1:18–23, 9:32–66).[45] According to Petitioner, "[a] POSA thus would have been motivated to make and use a humanized anti-CGRP antagonist antibody to reduce skin vasodilation and hot flush." *Id.*

(b) Claim 1 of the '907 patent

Petitioner argues that "Queen teaches humanization techniques that maintain an antibody's binding specificity after CDR grafting, [and] a POSA would have reasonably expected that the CDRs grafted from a donor

[45] Exhibit 1245 does not describe administration of an anti-CGRP antibody.

antibody to a human IgG antibody scaffold would impart the same or similar binding affinity and specificity as the donor murine antibody." 1711 IPR Pet. 24, 40–41 (citing Ex. 1022, 567–71; 1711 IPR Ex. 1016 ¶ 79; Ex. 1023, 2:61–3:32, 3:33–41; 1711 IPR Ex. 1017 ¶ 107).

(c) Claim 1 of the '908 patent

Petitioner advances the same arguments as advanced in connection with claim 1 of the '907 patent. 1712 IPR Pet. 43–44. In addition, Petitioner argues that a person of ordinary skill in the art "would have been motivated to prepare a humanized anti-CGRP antagonist antibody that binds to human CGRP with sufficient affinity (i.e., a relatively low K_D) to effectively block its interaction with receptors." *Id.* at 35 (citing 1712 IPR Ex. 1018 ¶¶ 127–131; 1712 IPR Ex. 1236 ¶¶ 102–104). According to Petitioner, "antibodies with such affinities were known [by 2005] to be associated with increased biological potency." *Id.* (citing, e.g., Ex. 1088, 350; 1712 IPR Ex. 1018 ¶ 128; 1712 IPR Ex. 1236 ¶ 102). Petitioner also argues that "the prior art demonstrated a clear preference for antibodies with strong binding affinities," asserting that "most of the antibodies approved by [the] FDA before 2005 had binding affinities of less than 10 nM." *Id.* (citing 1712 IPR Ex. 1018 ¶ 128; 1712 IPR Ex. 1236 ¶¶ 69, 70, 102; Ex. 1088, 350).

Petitioner supports its arguments with reference to Tan's studies, and asserts that a person of ordinary skill in the art would have understood from Tan's studies that a lower K_D would lead to predictive blocking effects *in vivo* and would have been motivated to obtain an anti-CGRP antibody that possessed at least similar (if not stronger) binding affinity to their human counterparts. *Id.* at 35–36 (citing 1712 IPR Ex. 1018 ¶ 129; 1712 IPR

Ex. 1236 ¶¶ 102–103; Ex. 1021, 706, 707; Ex. 1022, 569–71). According to Petitioner, "Tan's studies would have reinforced a POSA's motivation to obtain a humanized anti-CGRP antagonist antibody with an affinity to human CGRP of less than 10 nM since antibodies within that range had already been shown to have anti-CGRP antagonist activity both *in vitro* and *in vivo*." *Id.* at 35 (citing 1712 IPR Ex. 1018 ¶ 129; 1712 IPR Ex. 1236 ¶ 102). Petitioner specifically argues that "MAb C4.19, which bound both human and rat CGRP, had a binding affinity (K_D) of 1.9 nM and 2.5 nM to rat α and βCGRP, respectively," and "possessed desirable characteristics, such as inhibiting CGRP from binding to its receptors." *Id.* at 35–36 (citing Ex. 1021, 706, 707; 1712 IPR Ex. 1018 ¶ 129; 1712 IPR Ex. 1236 ¶ 102).

Petitioner also argues that a person of ordinary skill in the art "would have screened for such antibodies using SPR," asserting that "SPR was the preferred screening method because it was easy to use, commercially available, and reliable." *Id.* at 36 (citing 1712 IPR Ex. 1236 ¶¶ 67, 109; Ex. 1084, Abstract). Petitioner further argues that a person of ordinary skill in the art "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.* (citing Ex. 1712 IPR 1018 ¶ 130; 1712 IPR Ex. 1236 ¶¶ 68, 109; Ex. 1087, Abstract, 333).

c) Reasonable Expectation of Success

Petitioner argues that the prior art provided a reasonable expectation of success because (1) a POSA would have reasonably expected that a humanized anti-CGRP antagonist antibody would successfully reduce incidence of or treat migraine, and (2) a POSA would have had a reasonable

expectation of success in making a humanized anti-CGRP antagonist antibody for therapeutic use in humans. Pet. 35–43. Petitioner advances several contentions in support of those arguments, focusing on claim 17 of the '045 patent. *Id.*

(1) Claim 17 of the '045 patent

Petitioner reasserts its claim construction arguments, particularly that claim 17 is directed to an "approach" without requiring a clinical response, and that the term "effective amount" does not require a clinical response and encompasses "exceedingly low doses." Pet. 35 (citing Ex. 1014 ¶¶ 104, 105). Petitioner 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 36. Petitioner points to Olesen as establishing that blocking the CGRP pathway had been clinically proven to treat migraine, and argues that other prior art references, such as Doods and Lassen, broadly recognized that CGRP antagonism was a therapeutic principle for migraine treatment. *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 asserts that blocking the CGRP pathway had been clinically proven to treat migraine. Pet. 37–38. Petitioner argues that "[b]efore 2005, researchers understood that anti-CGRP drugs would treat migraine based on the strong evidence that CGRP plays a causative role in migraine." *Id.* at 37 (citing Ex. 1014 ¶ 139). According to Petitioner, researchers in the early 2000s recognized the implication of CGRP in the pathogenesis of migraine, and thus a POSA would have expected that inhibition of CGRP-induced

vasodilation would attenuate migraine symptoms. *Id.* (citing Ex. 1024, 42, 422; Ex. 1022, 569–70; Ex. 1052, 773–74). Petitioner also cites to the statement in Doods that, because of "several lines of evidence indicat[ing] that CGRP might be a key factor in the initiation of migraine headache, *we expect* that CGRP antagonists *will be effective* anti-migraine drugs." *Id.* (citing Ex. 1024, 422) (emphasis by Petitioner). Petitioner further argues that "after demonstrating that CGRP causes migraine, researchers in 2002 emphasized that '[t]his finding greatly increases the likelihood that a CGRP antagonist may be effective in the treatment of migraine attacks.'" *Id.* (citing Ex. 1047, 60; Ex. 1014 ¶ 139).

Petitioner also argues that Olesen's Phase II study "provided clinical proof-of-concept that blocking the CGRP pathway treats migraine, further validating the reasonable expectation of success in the art." Pet. 37 (citing Ex. 1025, 1108–09; Ex. 1014 ¶ 140). Petitioner points to Olesen's reporting that 66% of patients exhibited a response after treatment with BIBN, as compared to only 27% of patients on placebo, and that BIBN also met all secondary endpoints. *Id.* at 37–38 (citing Ex. 1025, 1107–08). Thus, according to Petitioner, CGRP antagonism was broadly recognized as a "therapeutic principle" in migraine treatment, and "Olesen's clinical study confirmed the reasonable expectation that a CGRP antagonist could be successfully used to reduce incidence of or treat migraine." *Id.* at 38 (citing Ex. 1025, Abstract, 1108–09; Ex. 1040, 182–83; Ex. 1014 ¶¶ 140, 141). Petitioner further supports the alleged significance of Olesen by citing Arulmozhi as "characterizing Olesen's study as an 'important breakthrough' and reporting that 'inhibition of CGRP or antagonism of CGRP receptors'

may be 'a viable therapeutic target for treating migraine.'" *Id.* (citing Ex. 1040, 182–83).

Petitioner also argues 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). Petitioner points to Tan to argue that "[a] POSA would have reasonably expected to reduce incidence of or treat migraine with an anti-CGRP antagonist antibody." *Id.* at 38 (citing Ex. 1022).

Petitioner argues that "Tan successfully demonstrated the effectiveness of its anti-CGRP antibody at blocking the CGRP pathway *in vivo*." Pet. 39 (citing Ex. 1014 ¶ 142). Petitioner describes a first *in vivo* experiment in which "Tan confirmed that both MAb C4.19 and its Fab' fragment blocked the biological activity of CGRP in a blood pressure assay in rats." *Id.* (citing Ex. 1022, 568–69, 571; Ex. 1014 ¶ 142). Petitioner also describes a second *in vivo* experiment in which "Tan reported that MAb4.19 and its Fab' fragment inhibited the biological activity of CGRP in the rat saphenous nerve model—i.e., an animal model of neurogenic inflammation that had been linked to migraine pain, and the same model used in Examples 3 and 5 of the '045 patent." *Id.* (citing Ex. 1022, 569–72; Ex. 1014 ¶¶ 86, 87, 144). Petitioner argues that "[u]nder the conditions tested, Tan's anti-CGRP antagonist Fab' fragment demonstrated similar activity to a known CGRP-receptor antagonist, $CGRP_{8-37}$" and that "[t]hese results established that an anti-CGRP antagonist antibody or a receptor inhibitor produces similar *in vivo* effects." *Id.* (citing Ex. 1022, 569–70; Ex. 1014 ¶¶ 60, 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."[46] *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).

(2) Additional Claim Limitations

(a) Claim 1 of the '045 patent

As discussed above, Petitioner relies on its discussion of claim 17, and provides a cursory discussion of additional reasons claim 1 would have been obvious. *See* Pet. 50; *supra* Section II.D.2.b)(4)(a). Petitioner 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).

[46] Petitioner also argues that "a POSA also would have known that an anti-migraine drug did not need to cross the BBB to treat migraine." Pet. 40 n.2 (citing Ex. 1014 ¶¶ 149–152; Ex. 1090, 702–03 ("The present study strongly suggests that the clinically effective migraine drug [BIBN] (Olesen *et al.*, 2004) does not cross the BBB.")).

(b) Claim 1 of the '907 patent

Petitioner's arguments for a reasonable expectation of success in combining Olesen, Tan, and Queen to arrive at a method of treatment using a humanized antibody, as claimed in claim 1 of the '907 patent are similar to those presented for claim 17 of the '045 patent. 1711 IPR Pet. 35–41. In addition, Petitioner argues that humanized antibodies made with a human IgG scaffold contain the heavy chain and light chain features recited in claim 1. *Id.* at 40 (citing Ex. 1058, 95–96, 100–101; 1711 IPR Ex. 1016 ¶ 163; 1711 IPR Ex. 1017 ¶¶ 106, 107). Petitioner further argues that "[b]ecause Queen teaches humanization techniques that maintain an antibody's binding specificity after CDR grafting, a POSA would have reasonably expected that the CDRs grafted from a donor antibody to a human IgG antibody scaffold would impart the same or similar binding affinity and specificity as the donor murine antibody." *Id.* at 40–41 (citing Ex. 1023, 2:61–3:32, 3:33–41; 1711 IPR Ex. 1017 ¶ 107). Thus, according to Petitioner, "a POSA would have expected the CDRs of the resulting humanized antibody to impart specific binding to human CGRP (i.e., SEQ ID NO: 15 and/or SEQ ID NO: 43), just like the monoclonal anti-CGRP antagonist antibodies of the prior art." *Id.* at 41 (citing 1711 IPR Ex. 1017 ¶ 107; Ex. 1021, 707, 709; Ex. 1022, 572; Ex. 1033, 97, 102; Ex. 1055, 90).

(c) Claim 1 of the '908 patent

Petitioner's arguments for a reasonable expectation of success in combining Olesen, Tan, and Queen to arrive at a method of treatment using a humanized antibody, as claimed in claim 1 of the '908 patent, are similar to those presented for claim 1 of the '907 patent. *See* 1712 IPR Pet. 37–51. In addition, Petitioner also argues that a person of ordinary skill in the art

"would have screened for such antibodies using SPR," asserting that "SPR was the preferred screening method because it was easy to use, commercially available, and reliable." *Id.* at 35–36 (citing 1712 IPR Ex. 1236 ¶ 109). Petitioner further argues that a person of ordinary skill in the art "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. 1712 IPR Ex. 1018 ¶ 130; 1712 IPR Ex. 1236 ¶¶ 68, 109; Ex. 1087, Abstract, 333).

Petitioner cites to Andrew and Wong, as well as Tan 1994, to argue that a person of ordinary skill in the art "would have been motivated to make, and readily expected to obtain, antibodies against human CGRP with affinities lower than 10 nM." 1712 IPR Reply 19–20 (citing Ex. 1021, 707 (1.9 nM rat CGRP); Ex. 1055, 92; Ex. 1033, 102 (reporting "high affinity" antibody 4901); 1712 IPR Ex. 1341 ¶¶ 80–87; 1712 IPR Pet. 35–37). Petitioner further replies that "[t]he parties' experts agree . . . that single-digit nM affinities are typically obtained as a 'general rule,' and that further affinity maturation[47] was routine." *Id.* (citing Ex. 1068, 351; 1712 IPR Ex. 1341 ¶¶ 80–81, 87; 1712 IPR Ex. 1236 ¶¶ 121–126; Ex. 1301, 211:22–214:25[48]).

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[47] Affinity maturation is a process by which antibody engineers can further improve the affinity of an antibody. Ex. 1301, 212:24–213:3.

[48] During his deposition, in response to counsel's reading from Exhibit 1068, 351 that "[a]s a general rule, antibodies generated either by animal immunization or by repertoire library screening exhibit antigen affinities (K_D) in the 10^{-6} to 10^{-9} M range," Dr. Tomlinson answered: "As a general rule, I think that's about right." Ex. 1301, 213:9–16. A binding affinity of 10^{-9} is 1 nanomolar (1 nM). *See id.* at 213:17–20.

d) Simultaneous Invention – Objective Indicia of Obviousness

Petitioner argues that there are objective indicia of *obviousness* by virtue of near-simultaneous development of humanized monoclonal antibodies by Lilly and by Stanford University (in partnership with other groups). Pet. 63–65 (citing Ex. 1127[49], 13 (Example 5); Ex. 1128[50] ¶¶ 21, 108; *Ecolochem, Inc. v. S. Cal. Edison Co.*, 227 F.3d 1361, 1376, 1379 (Fed. Cir. 2000); *Geo. M. Martin Co. v. Alliance Mach. Sys. Int'l LLC*, 618 F.3d 1294, 1305 (Fed. Cir. 2010)). Patent Owner disagrees, arguing that the Stanford provisional application does not disclose humanized antibodies; that Lilly's antibodies were invented after Teva's; and that interference practice suggests that near simultaneous invention does not necessarily mean that the first invention is obvious. PO Resp. 64–65 (citing 35 U.S.C. § 135; *E.I. Du Pont de Nemours & Co. v. Berkley & Co.*, 620 F.2d 1247, 1265 (8th Cir. 1980); *Lindemann Maschinenfabrik GMBH v. Am. Hoist & Derrick Co.*, 730 F.2d 1452, 1460–61 (Fed. Cir. 1984)). Patent Owner also argues that this is not a situation where a "considerable number of persons who were not inventors" developed a similar technology. *Id.* at 65 (citing *Detroit Motor Appliance Co. v. Taylor*, 66 F.2d 319, 321 (7th Cir. 1933)).

Taking Petitioner's arguments regarding the Lilly and Stanford provisional applications as evidence of objective indicia, we are not persuaded that they indicate obviousness. We find that the Lilly provisional application discloses humanized anti-CGRP antibodies. *See* Ex. 1127, 13, 18. We find that although the Stanford provisional application does not

[49] Benschop, US Provisional Application 60/753,044 (filed Dec. 22, 2005) (Ex. 1127, "the Lilly provisional application").
[50] Yeomans, US Provisional Application 60/711,950 (filed Aug. 26, 2005) (Ex. 1128, "the Stanford provisional application").

explicitly disclose humanized antibodies, it suggests treatment of an individual for trigeminal-associated pain. *See* Ex. 1128 ¶ 21. We understand treatment of an individual to include treatment of humans. However, we agree with Patent Owner that the Lilly and Stanford provisional applications do not of themselves establish that the work was so routine as to be merely the work of an ordinary artisan, i.e., without resort to the other art of record. *Cf. Ecolochem*, 227 F.3d at 1379 ("[T]he possibility of near simultaneous invention by two or more equally talented inventors working independently, . . . may or may not be an indication of obviousness when considered in light of all the circumstances.") (quoting *Lindemann*, 730 F.2d at 1460 (alterations in original)).

In sum, we conclude that the proffered evidence of near-simultaneous invention should be accorded little or no weight based on the discussion above.

3. Patent Owner's Arguments, Petitioner's Reply, and Patent Owner's Sur-reply

Patent Owner's arguments related to Petitioner's alleged reasons to combine and reasonable expectation of success focus on the contention that "the prior art completely discredits Lilly's alleged expectations and motivations to use an anti-CGRP antibody to treat migraine." PO Resp. 11. We discuss those arguments, Petitioner's Reply, and Patent Owner's Sur-reply below.

a) Petitioner mischaracterizes the disclosures of the prior art

Patent Owner argues that Petitioner mischaracterizes what the prior art discloses, and particularly that "Lilly vastly overstates what a POSA would have understood about treating migraine with anti-CGRP antibodies from Olesen and Tan." PO Resp. 11–17. According to Patent Owner,

neither Olesen nor Tan provided a POSA a reason to treat migraine with an anti-CGRP antagonist antibody. *Id.* at 12 (citing Ex. 2265 ¶¶ 14–23, 46–111; Ex. 2271 ¶¶ 85–106; Ex. 2286 ¶¶ 96–102, 137–141, 148–153). Patent Owner specifically contests Petitioner's reading of Olesen, as well as arguing that Tan does not provide guidance regarding the use of anti-CGRP antibodies to treat diseases. *Id.* at 11–17.

(1) Olesen

Patent Owner disputes Petitioner's argument that "a POSA reading Olesen would have extended its teachings to other CGRP antagonists" (Pet. 26), because Olesen investigated only BIBN, a small molecule receptor antagonist, and it distinguishes triptans from CGRP antagonists as selective agonists of serotonin. PO Resp. 12 (citing Ex. 2265 ¶¶ 60–63; Ex. 1026, Abstract; Ex. 1025, 1105). Patent Owner points to Dr. Foord's testimony as confirming that "Olesen does not suggest that 'CGRP antagonists' extends to any antagonist beyond small-molecule receptor antagonists." *Id.* (citing Ex. 2265 ¶¶ 60–63).

Patent Owner argues that other evidence also fails to support a broad reading of "CGRP antagonists," referring specifically to Olesen 2004 as relating only to BIBN and to Arulmozhi as citing Edvinsson that refers only to CGRP receptor antagonists and triptans. PO Resp. 12–13 (citing Ex. 1029, Abstract; Ex. 1040; Ex. 2268 ¶ 98; Ex. 2009, 617–618).[51]

Petitioner responds that Patent Owner "attempts to limit Olesen's teachings to small-molecule receptor antagonists," and that Patent Owner's

[51] Patent Owner also criticizes the testimony of Dr. Charles, arguing that "his opinion as to what a POSA would have understood from Olesen deserves no weight." PO Resp. 13–14. In view of our determination that the challenged claims are not unpatentable, we deem this argument moot.

arguments are inconsistent with Dr. Ferrari's statement that Olesen's CGRP antagonists (BIBN) "seem [to be] promising, new antimigraine drugs," and Dr. Rapoport's statement, based on Olesen, that "antagonizing the effect of CGRP may provide acute relief of migraine headache. Preventative drugs might be developed on the same principle." Reply 5 (citing Ex. 1290, 657; Ex. 1297, S119 (footnote omitted)). Petitioner also cites to Tan as "expressly disclos[ing] that targeting the CGRP ligand with antibodies and targeting CGRP receptors . . . were 'alternative' approaches for antagonizing the CGRP pathway." *Id.* (citing Ex. 1022, 566, 571; Ex. 1040, 182 ("inhibition of CGRP or antagonism of CGRP receptors could be a viable therapeutic target for the pharmacological treatment of migraine"); Ex. 1033, 95). Petitioner also refers to disclosures of treating migraine with a ligand antagonist, citing Wimalawansa, Vater, and Messlinger. *Id.* at 5–6 (citing Pet. 27–30; Ex. 1096, 567, 570; Ex. 1082, Abstract; Ex. 1240, 923).

Patent Owner replies that Exhibit 1332, Exhibit 1290, and Exhibit 1297, relied on by Petitioner, "undeniably discuss only [BIBN] as a 'CGRP antagonist,'" and "nothing in the record supports Lilly's extension of 'CGRP antagonists' beyond [BIBN]." Sur-reply 6 (citing Ex. 1332, 443; Ex. 1290, 567; Ex. 1297, S119).

(2) Tan

Patent Owner argues that Tan is a basic science paper that draws no therapeutic or clinical conclusions, and "nothing in Tan has anything to do with humans, treatments, migraine or dosing." PO Resp. 14–15 (citing Ex. 2265 ¶¶ 82–84; Ex. 2268 ¶¶ 137–141; Ex. 2271 ¶¶ 90–91; Ex. 1022, Abstract). Patent Owner points to Dr. Vasserot's testimony that Tan does not "provide any clinical evidence regarding efficacy of administering an

anti-CGRP antagonist antibody to humans to treat a disease." *Id.* at 15 (citing Ex. 2191, 122:16–123:13). Thus, according to Patent Owner, "[t]he evidence simply does not support [Petitioner's] assertion that Tan provides 'guidance' on how to use anti-CGRP antibodies to treat migraine." *Id.*

Petitioner responds that "Tan's antibody specifically bound and antagonized CGRP *in vitro* and *in vivo*," and that "[a]lthough Teva argues Tan is a basic research paper having 'nothing to do with humans or treatment,' . . . Dr. Tan contemporaneously wrote that there is 'no reason' why humanized anti-CGRP antagonist antibodies should not be developed and used for treating migraine." Reply 6 (citing Ex. 1021; Ex. 1022; Pet 16–17; PO Resp. 4; Ex. 1287, 247; Ex. 1096, 567, 570).

Patent Owner challenges Petitioner's reliance on the Tan Thesis (Ex. 1287[52]), arguing that none of Petitioner's experts cite it, that Petitioner has not established that Exhibit 1287 was publicly available or that it qualifies as prior art,[53] and that Petitioner "failed to establish that a POSA would ignore the weight of the prior art and lack of suitability of a full length anti-CGRP antibody for human therapeutic use." Sur-reply 9 n.3.

b) Uncertainty in the field regarding CGRP as a biomarker for migraine

Petitioner asserts that by the early 2000s, it was understood that: (1) levels of CGRP—but not other neuropeptides—are significantly elevated in migraine patients compared to those without migraine; (2) plasma CGRP

[52] K.K.C. Tan, *Application of Monoclonal Antibodies to the Investigation of the Role of Calcitonin Gene-Related Peptide as a Vasodilatory Neurotransmitter*, Dissertation Submitted to the University of Cambridge (1994) (Ex. 1287, "Tan Thesis").
[53] We address this issue in Section III.A.1. *infra*.

concentrations and migraine headache strongly correlate; (3) baseline CGRP levels are considerably higher during migraine; and (4) the changes in plasma CGRP levels during migraine attacks significantly correlate with headache intensity. Pet. 11 (citing Ex. 1043, 185; Ex. 1044, 48; Ex. 1045, 467; Ex. 1040, 182–83; Ex. 1014 ¶¶ 28, 35).

Patent Owner argues, on the other hand, that there was uncertainty in the field as to whether CGRP was a biomarker for migraine. PO Resp. 17. According to Patent Owner, Petitioner relies heavily on the supposedly "understood" fact that "levels of CGRP . . . are significantly elevated in migraine patients compared to those without migraine," based on articles from Goadsby[54] from the early 1990's. *Id.* at 17–18 (citing Pet. 11; Ex. 2014 [sic, 1014] ¶ 28; Ex. 1043, 185; Ex. 1044, 48, 52) (alteration by Patent Owner). Patent Owner contends, however, that Petitioner did not consider a 2005 article from Tvedskov[55] and Olesen that challenged the validity of Goadsby's findings. *Id.* at 18 (citing Ex. 2277, 23:11–17). Patent Owner argues that Tvedskov recognized that Goadsby's findings had not been confirmed or convincingly reproduced, that Tvedskov's data showed no difference between CGRP in external jugular blood and peripheral blood during an attack, and that Dr. Ferrari opined that a person of ordinary skill in 2005 would have had doubts about CGRP's status as a biomarker in view of Tvedskov's data. *Id.* (citing Ex. 2309, Abstract, 564–567, Table 3, Figs. 2,

[54] Goadsby et al., *Vasoactive Peptide Release in the Extracerebral Circulation of Humans During Migraine Headache*, 28(2) ANNALS OF NEUROLOGY 183–87 (1990) (Ex. 1043).
[55] J. F. Tvedskov et al., *No Increase of Calcitonin Gene–Related Peptide in Jugular Blood during Migraine*, 58(4) ANNALS OF NEUROLOGY 561 (Oct. 2005) (Ex. 2309).

3; Ex. 2268 ¶¶ 57, 60). Patent Owner argues that Dr. Charles relied on Goadsby and Edvinsson because he "trust[ed]" them but ignored the work of Olesen who he also considered reputable. *Id.* at 19 (citing Ex. 2277, 18:13–14, 81:17–22). Patent Owner argues that, when considering these uncertainties, prevention and treatment of migraine would have been much more unpredictable than alleged by Petitioner. *Id.* at 20.

In view of the conflicting studies by Goadsby and Tvedskov, we find that there was a debate in the literature as to whether CGRP could be measured in the external jugular blood and peripheral blood as a biomarker during a migraine attack for diagnostic purposes. *See* Ex. 1014 ¶ 28 (citing Ex. 1043, 185; Ex. 1044, 48, 52–53); Ex. 2268 ¶ 57 (citing Ex. 2309, 567). In the context of the prior art, we determine that the issue of whether CGRP could be used for diagnostic purposes is not dispositive of whether CGRP causes migraine or whether an anti-CGRP drug would treat migraine. For example, Wimalawansa and others proposed exploration of anti-CGRP antagonists to treat migraine (Ex. 1096, 569–570) and Olesen found that BIBN, a CGRP receptor antagonist, can be used to treat migraine (Ex. 1025, 1104, 1108). We, therefore, consider, as more relevant to the issue of obviousness of the challenged claims, the questions of whether an anti-CGRP drug would be required to pass beyond the BBB and whether an anti-CGRP drug would reach the synaptic cleft. *See infra* Section II.D.3.c)(3) & (4).

c) Petitioner incorrectly extrapolates Olesen's small-molecule receptor antagonist results to any CGRP antagonist, and in particular, to an anti-CGRP antibody

(1) Olesen's "proof of concept" study would not have given a POSA a reasonable expectation that an anti-CGRP antibody would be effective in treating migraine

Patent Owner argues that Petitioner has not demonstrated that Olesen's BIBN can serve as a proxy for an antibody against the CGRP ligand for treating migraine. PO Resp. 20–23. Patent Owner specifically argues that there are pharmacological differences between antagonizing a receptor versus a ligand, and material differences between antagonizing the CGRP ligand with an antibody versus antagonizing the CGRP receptor with a small molecule. *Id.* at 20 (citing Ex. 2265 ¶¶ 64–76). Patent Owner argues that Olesen dealt with blocking the CGRP receptor with a small molecule "which is far too attenuated from" how Teva's claimed antibody works "for the POSA to have given it value in drawing any conclusions about the safety and efficacy of Teva's claimed methods." *Id.* (citing Ex. 2265 ¶¶ 60–64). Patent Owner advances three contentions in support of those arguments.

First, Patent Owner relies on the Foord Declaration to assert that "antagonizing a CGRP receptor would be expected to affect only the downstream CGRP pathway—primarily, vasodilation," but "antagonizing CGRP itself would evoke multiple other physiological responses, because CGRP was known to cross-react with the receptors for calcitonin, amylin, and adrenomedullin" (i.e., "cross-binding"). PO Resp. 21 (citing Ex. 2265 ¶¶ 25–40, 66–68; Ex. 1099, 240; Ex. 2140, 239; Ex. 2197, 2886–2889; Ex. 2198, 1056; Ex. 2059, 63; Ex. 2060, 1655). Thus, according to Patent Owner, "activation of each different receptor by CGRP would elicit different

physiological responses," and "a POSA would have understood that antagonizing CGRP would potentially alter any or all of the physiological responses regulated by these other receptors, whereas antagonizing the CGRP receptor would be expected to alter only the vasodilatory response it evokes." *Id.* (citing Ex. 2265 ¶¶ 25–31, 66–68; Ex. 2059, 63; Ex. 2003, 903–906).

In response, Petitioner argues that "Dr. Foord's own table illustrates that CGRP is a secondary or worse binding ligand to ancillary, non-CGRP receptors." Reply 19 (citing Ex. 2265 ¶ 37 ("by 2005 it was unclear what physiological activities were mediated by CGRP binding at these receptors")). According to Petitioner "[m]ere speculation about theoretical physiological effects from CGRP's poor binding to other receptors would not have undermined a reasonable expectation of success." *Id.* (citing Ex. 1338 ¶¶ 119–124). Patent Owner replies that Petitioner failed to adequately address cross-reactivity, including with the Second Charles Declaration, and reasserts that "one cannot equate receptor and ligand antagonism without considering the differences." Sur-reply 7–8 (citing Reply 19; PO Resp. 21; Ex. 1338 ¶ 120; Ex. 2265 ¶ 68).

Second, Patent Owner argues that the "spare receptor" theory would have further diminished any correlation a POSA would have drawn between receptor and ligand antagonism.[56] PO Resp. 22–23 (citing Ex. 2265 ¶¶ 41–45, 69–76; Ex. 2062, 74; Ex. 2063, 15; Ex. 2064, 537). That theory posits that "a significantly higher percentage of ligands than receptors need[]

[56] Patent Owner notes that "[a] POSA would have understood that the CGRP receptor has a high receptor reserve in the microvasculature." PO Resp. 22 n.8 (citing Ex. 2265 ¶¶ 69–73; Ex. 1024, 422; Ex. 2065, 1071; Ex. 2219, 57).

to be antagonized to elicit the same pharmacological response; suggesting a higher concentration of ligand antagonist would be necessary to obtain the same effect as a receptor antagonist." *Id.* at 22 (citing Ex. 2265 ¶¶ 44, 45, 73–75). Thus, according to the Foord Declaration, "Olesen's receptor antagonism study would not have allowed a POSA to draw conclusions regarding therapeutic efficacy of an anti-CGRP antibody." *Id.* at 23 (citing Ex. 2265 ¶¶ 67, 130).

Petitioner argues that the spare receptor theory does not apply, and particularly that "a POSA would have understood that a *large* percentage of CGRP receptors—not 1%—would need to be bound to elicit a full biological response," contrary to Patent Owner's theory that "less than 1% of [CGRP] receptors need to be bound by ligand to elicit a full response." Reply 18–19 (citing PO Resp. 22; Ex. 1337 ¶¶ 45–52). Petitioner further argues that "[s]uccessful migraine treatment also did not require functionally depleting all CGRP or antagonizing 99.999% of CGRP ligands, as Teva contends." *Id.* at 19 (citing PO Resp. 22). Rather, according to Petitioner, "normalizing *elevated* or *inappropriate* levels of CGRP was accompanied by subsidence of migraine headache." *Id.* (citing Ex. 1044, Abstract; Ex. 1096, 567; Pet. 11; Ex. 1338 ¶¶ 114–118). Patent Owner replies that "Dr. Foord's testimony that CGRP receptor and ligand antagonism are not 'alternative' because of CGRP receptor reserve remains sound and effectively unrebutted." Sur-reply 7 (citing Ex. 2265 ¶ 75; Ex. 1300, 69:18–22; Ex. 2339, 112:21–114:9).

Third, Patent Owner points to two examples that it asserts show that receptor antagonism is not a proxy for ligand antagonism. PO Resp. 23. Patent Owner points to the Avastin® (bevacizumab) antibody that inhibits

the ligand VEGF-A, and asserts that subsequent attempts to target VEGF-A's receptor with an antibody failed. *Id.* (citing Ex. 2271 ¶¶ 46–51, 84; Ex. 2111, 448; Ex. 2128, 11). Patent Owner also points to the Erbitux® (cetuximab) antibody antagonist to the EGFR receptor, and further asserts that "no antibodies targeting any of [the EGFR receptor's] various ligands have ever been approved for human therapy, despite various attempts." *Id.* (citing Ex. 2271 ¶ 84; Ex. 2129, 4880). Patent Owner also refers to the Tomlinson Declaration to argue that "there were no antibody therapies validated for humans where targeting the receptor and the ligand had resulted in the same outcome as of November 2005." *Id.* (citing Ex. 2271 ¶ 84).

(2) There would not have been an expectation of any therapeutic advantages for using an anti-CGRP antibody to treat migraine

(a) A POSA would have expected an anti-CGRP antibody to have unacceptable cardiovascular and cerebrovascular side-effects in migraine patients

Patent Owner argues that Petitioner "fails to fully consider safety factors in its 'motivation' analysis," and that Petitioner "touts the alleged importance of making the antibodies 'safe' for human administration" but says "nothing about the art's real and genuine safety concerns as potential reasons a POSA would not have been motivated to pursue humanized anti-CGRP antibodies." PO Resp. 24 (citing Pet. 33–35). Patent Owner specifically argues that anti-CGRP antibodies presented safety concerns for migraineurs and that Olesen does not overcome the known safety concerns. *Id.* at 6, 24–31. Patent Owner argues that the various safety concerns provide reasons not to combine the asserted prior art. *Id.* at 31–33 (citing *Arctic Cat Inc. v. Bombardier Recreational Prods. Inc.*, 876 F.3d 1350, 1363

(Fed. Cir. 2017)). According to Patent Owner, "the lack of any evidence of efficacy in using an anti-CGRP antibody, coupled with the extensive safety concerns based on the available information as of November 2005 to a POSA, are all strong 'reasons not to combine' that defeat Lilly's obviousness case." *Id.* at 32.

Patent Owner argues that anti-CGRP antibodies presented safety concerns for migraineurs because of CGRP's known and important vasoprotective role. PO Resp. 24–28. Patent Owner specifically argues that CGRP was known "to be involved in long-term regulation of resting blood pressure, protecting against development of hypertension," and was known to "have a protective effect against exacerbation of pulmonary hypertension." *Id.* at 24–25 (citing Ex. 2268 ¶¶ 113, 114, 125–131; Ex. 2265 ¶¶ 57, 117–120, 124, 125; Ex. 2061, 4–6; Ex. 2084, Abstract, H687).

Patent Owner cites to Dr. Ferrari as explaining that "by 2005, CGRP was known to serve a myocardial protective function, with studies confirming that CGRP helps safeguard against myocardial ischemia, leading to 'a cardiac protective effect.'" PO Resp. 25 (citing Ex. 2003, 915, 919; Ex. 2268 ¶¶ 119–124; Ex. 2058, 1477). Furthermore, according to Patent Owner, "in 2005 a POSA would have known that inadequate CGRP during an ischemic attack heightened the risk for transient mild ischemic events turning into full-blown infarctions." *Id.* (citing Ex. 2268 ¶¶ 105, 119–124).

Patent Owner also argues that a "POSA would have known that there is 'a complex bidirectional relation between migraine and stroke, including migraine as a cause of stroke, migraine as a risk factor for or as a consequence of cerebral ischaemia, and migraine and cerebral ischaemia

sharing a common cause,'" and that "CGRP was known to protect against this risk." PO Resp. 25 (citing Ex. 2157, 533 (endnotes omitted); Ex. 2268 ¶¶ 115–136; Ex. 2003, 919; Ex. 2009, 614–15). But, according to Patent Owner, "Lilly has no explanation for how disrupting the CGRP-mediated emergency response mechanism to ischemic events in patients susceptible to stroke would have affected a POSA's alleged motivation for developing anti-CGRP antagonist antibodies for treatment of migraines." *Id.* at 25–26. Patent Owner supports this argument with the deposition testimony of Dr. Charles, who stated that he believed a person of ordinary skill in the art would have been concerned over administering anti-CGRP antibodies to a patient who had a history of stroke. *Id.* at 26 (citing Ex. 2192, 117:3–6 ("Q. Would a POSA prior to November 2005 be concerned over administering anti-CGRP antibodies to a patient who has a history of stroke? A. Yes, I believe so.")).

Patent Owner also argues that "Wimalawansa recognizes that reduced levels of circulating CGRP causes systemic vasoconstriction and potential deleterious consequences to the cerebrovascular and cardiovascular system." PO Resp. 26 (citing Ex. 2268 ¶¶ 149, 153). Patent Owner cites to several statements in Wimalawansa, such as "a relative deficiency of circulatory CGRP . . . may correlate with the increased incidence of . . . cardiovascular episodes (e.g. cerebrovascular accidents and myocardial infarctions)." *Id.* (citing Ex. 1096, 543; Ex. 2268 ¶¶ 149, 153). Patent Owner concludes that "a POSA would have understood from Wimalawansa that functionally-depleting CGRP, as would be expected with anti-CGRP antagonists, presented substantial risk of adverse events." *Id.* (citing Ex. 2268 ¶¶ 148, 149).

Patent Owner also argues that Tan "demonstrates that anti-CGRP antibodies increase baseline mean arterial pressure (MAP)—the precise response with which Wimalawansa, and the field were concerned." *Id.* (citing Ex. 2268 ¶ 128; Ex. 2265 ¶¶ 122, 123). According to Patent Owner, Dr. Foord and Dr. Vasserot agree that the rise in MAP in Tan was a direct effect of antibody administration. *Id.* (citing Ex. 2191, 110:13–15; Ex. 2265 ¶ 123). But, according to Patent Owner, "Lilly entirely ignores how MAb C4.19's raising MAP would have influenced a POSA's motivation." *Id.* at 27. According to Patent Owner, "[i]t is uncontested that 1 mg/rat of MAb C4.19 in Tan's saphenous nerve assay did not achieve immunoblockade," but "that same dose had a 'significant[]' effect on MAP." *Id.* (citing Ex. 1022, 568–69, Abstract; Ex. 2265 ¶¶ 84, 112; Ex. 2268 ¶¶ 128, 137). Patent Owner also argues that "at 3 mg/rat, MAb C4.19 raised MAP nearly 13-fold, while having minimal, if any, effect in the saphenous nerve assay." *Id.* (citing Ex. 1022, 568, Figure 2, 569; Ex. 2265 ¶¶ 85, 122; Ex. 2268 ¶ 137).

Patent Owner argues further that "[a] POSA would have understood these results to mean that an anti-CGRP antibody would have a ***systemic*** vascular effect, potentially leading to serious adverse consequences, well before it might have any ***local*** anti-CGRP effect (as in the saphenous nerve assay) in treating migraine." PO Resp. 27–28 (citing Ex. 2265 ¶ 123; Ex. 2268 ¶ 139). Patent Owner also argues that Tan's suggestion for "chronic administration . . . to achieve the sufficiently high concentrations required for immunoblockade" would have "given a POSA pause over concerns that repeated dosing of anti-CGRP antibodies would further exacerbate the expected vascular side-effects." *Id.* at 28 (citing Ex. 2268

¶¶ 137–141; Ex. 2265 ¶¶ 86–88). Patent Owner further argues that "the repeated dosing would have been expected to result in a build-up of antibody in a human patient." *Id.* (citing Ex. 2271 ¶ 55).

Patent Owner also argues that it was known by 2005 that migraine sufferers had a higher rate of hypertension, and that a POSA "would have been concerned that antagonizing CGRP would diminish its vasoprotective efforts to prevent adverse outcomes from hypertension." PO Resp. 26–27 (citing Ex. 2268 ¶¶ 125–131; Ex. 2193, 222; Ex. 2185, 259). According to Patent Owner, "Dr. Charles agreed." *Id.* (citing Ex. 2192, 115:9–118:3).

Patent Owner further argues that Olesen does not overcome the known safety concerns associated with anti-CGRP antibodies in 2005. PO Resp. 28–31. According to Patent Owner, "even assuming *arguendo* that Olesen suggests effectiveness of blocking CGRP receptors with a small molecule, Olesen still would not have assuaged the safety concerns associated with using an anti-CGRP antibody in migraineurs." *Id.* at 28–29. Patent Owner specifically argues that Olesen did not establish cardiovascular safety because Olesen's "data base was too small for [Olesen] to assess cardiovascular safety," and that Olesen says nothing about cerebrovascular safety. *Id.* at 29 (citing Ex. 1025, 1109; Ex. 2268 ¶ 50). Patent Owner thus argues that "a POSA could not draw any conclusion from Olesen regarding cerebrovascular or cardiovascular safety of CGRP antagonism in humans." *Id.* (citing Ex. 2268 ¶ 50).

Patent Owner also argues that there are differences between BIBN and full-length antibodies. PO Resp. 29–30. Patent Owner asserts that BIBN is not an antibody and does not antagonize the CGRP ligand, and its molecular weight (867 g/mol) is much smaller than an antibody's typical molecular

weight (~ 150,000 g/mol). *Id.* at 29 (citing Ex. 2265 ¶ 65; Ex. 1024, 420–21; Ex. 2268 ¶ 50; Ex. 2068, 32; Ex. 2271 ¶¶ 25, 54, 58; Ex. 2090, 9; Ex. 1059, 143). Patent Owner also argues that BIBN's half-life is about 2.5 hours, due in part to its small molecular weight, and any associated side effects would are cleared from the body in less than 24 hours. *Id.* (citing Ex. 2230 ¶ 84; Ex. 1024, 420, 421; Ex. 2068, 32; Ex. 2224 ¶¶ 21, 50, 54; Ex. 2090, 9; Ex. 1059, 143; Ex. 2212 ¶ 22; Ex. 1042, 645). According to Patent Owner, this clearance from the body "is especially true given the fact that Olesen infused [BIBN] for only 10 minutes—too short a time to have any lasting effects." *Id.* (citing Ex. 2265 ¶ 65; Ex. 1025, 1106).

Patent Owner further argues that, in contrast, it was known that full length antibodies have a much longer half-life (several weeks to months), and "any serious side-effects produced by the antibody will persist much longer than any produced by" BIBN. PO Resp. 29–30 (citing Ex. 2271 ¶¶ 54–59, 76–80; Pet. 31–32; Ex. 1059, 143, Fig. 4.16; Ex. 2265 ¶¶ 65, 120). Thus, according to Patent Owner, "Olesen would not have been helpful to a POSA in assessing these risks," such as myocardial infarction or stroke. *Id.* at 30 (citing Ex. 2271 ¶¶ 76–80; Ex. 2268 ¶¶ 12, 50, 104, 105, 144–147; Ex. 2265 ¶¶ 65, 120).

Patent Owner also argues that the same considerations regarding pharmacological differences associated with antagonizing a receptor (i.e., BIBN) versus a ligand also apply to safety profiles of BIBN and an anti-CGRP antibody. PO Resp. 30 (citing Ex. 2268 ¶¶ 144–147). Patent Owner supports this argument by asserting that "the anti-CGRP receptor antibody Aimovig® can cause constipation in patients, but the same

side-effect is not observed with the anti-CGRP antibody Ajovy®." *Id.* at 30–31 (citing Ex. 2271 ¶ 84; Ex. 2238, 1; Ex. 2262 ¶¶ 63–64).

Thus, according to Patent Owner, substantial safety concerns of anti-CGRP antibodies would have made a POSA skeptical of their use in treating migraine, and Petitioner's "failure to balance the well-known association between migraine and cerebrovascular and cardiovascular diseases defeats motivation." PO Resp. 27.

(i) Petitioner's Reply

Petitioner responds to Patent Owner's safety arguments by arguing that "Olesen confirmed that antagonizing the CGRP pathway in human patients produced *no serious side effects and no cardiovascular events*." Reply 12 (citing Ex. 1025, 1109; Ex. 1338 ¶¶ 82, 83; Pet. 25–26; Ex. 1303, 84:13–22, 73:8–18). Petitioner also contradicts Patent Owner's argument that "Olesen says nothing about cerebrovascular safety" (PO Resp. 29) by pointing to Olesen's statement that BIBN "had no constrictor effect on the middle cerebral, radial, or superficial temporal artery or on regional cerebral blood flow, blood pressure, or heart rate." Reply 12 (citing Ex. 1025, 1108).

Petitioner supports its arguments regarding BIBN by citing studies other than Olesen demonstrating "a very favorable safety profile" for BIBN in human volunteers. Reply 12 (citing Ex. 1042, Abstract (reporting no "clinically relevant, drug-induced changes" in blood pressure, pulse rate, blood flow, or vital signs); Ex. 2019, Abstract; Ex. 1338 ¶¶ 84–87; Ex. 1303, 84:23–85:7, 87:1–11, 90:22–92:20). Petitioner further argues that, in view of these studies, both of Patent Owner's clinician experts independently praised "CGRP antagonists" in 2005 as "promising, safe antimigraine drugs 'without vascular side effects.'" *Id.* (citing Ex. 1290, 657; Ex. 1297, S119).

Petitioner argues that "Olesen's safety results were also consistent with—and even improved upon—sumatriptan." Reply 13 (citing Ex. 1338 ¶¶ 19, 93; Ex. 1025, 1108; Ex. 1031, 326; Ex. 2010, 2561). Petitioner further argues that sumatriptan was considered "very safe" when prescribed to appropriate patients notwithstanding "transient" blood pressure increases. *Id.* (citing Ex. 1282, 1521; Ex. 1308, 1673; Ex. 1338 ¶ 93; Ex. 1303, 211:2–9). Petitioner also cites to studies and corresponding papers co-authored by Patent Owner's expert, Dr. Rapoport, that Petitioner asserts "advocated *daily*, long-term triptan administration for migraine prevention." *Id.* (citing Ex. 1294, Abstract, 487 ("[T]his may be the first article to suggest that naratriptan may be used in the long-term preventative treatment of [chronic migraine]."); Ex. 1295, Abstract, 1405; Ex. 1338 ¶ 19).

Petitioner argues that, contrary to Patent Owner's arguments (PO Resp. 29–30), "safety lessons from antagonizing the CGRP pathway with [BIBN] were pertinent for therapeutics that directly targeted CGRP, as the prior art recognized that targeting CGRP and its receptor were known, alternative techniques." Reply 13 (citing Ex. 1022, 566, 571; Ex. 1014 ¶¶ 145–148; Ex. 1040, 182; Ex. 1338 ¶¶ 22–24, 86; Ex. 1337 ¶¶ 40–44, 53–58). Petitioner also argues that researchers, citing Wimalawansa, "had developed prior art aptamers that bound CGRP for treating migraine." *Id.* at 9 (citing Ex. 1082, Abstract, 2 (ref. 19)).[57] Petitioner argues that anti-CGRP aptamers demonstrated efficacy in a cranial model similar to Patent Owner's Specification examples, as well as vascular safety: "[b]asal blood flow and

[57] Exhibit 1082 cites to Wimalawansa and three other references for the statement that "α-CGRP has been recognized as a potent vasodilator and has recently attracted attention as a novel target in acute migraine treatment." Ex. 1082, 2.

systemic arterial pressure were unchanged." *Id.* (citing Ex. 1240, 923; Ex. 1338 ¶ 80; Ex. 1337 ¶¶ 43, 56–58, 60; Ex. 1001, 68:60–69:67). Petitioner also asserts that "[t]he prior art explained that 'aptamers can be thought of as . . . *analogs to antibodies*,' recognizing their relatively longer half-life." *Id.* (citing Ex. 1309, Abstract (emphasis added by Petitioner)[58]; Ex. 1240, 923; Ex. 1082, Abstract, 7; Ex. 1338 ¶ 24; Ex. 1337 ¶¶ 57, 60).

Petitioner responds to Patent Owner's argument that the blood pressure increase in Tan would have raised safety concerns that could be exacerbated by the long half-lives of anti-CGRP antibodies, by arguing that "a POSA would have viewed anti-CGRP drugs with longer half-lives as desirable for preventative migraine treatments, without posing safety concerns." Reply 14 (citing Ex. 1338 ¶¶ 11–24, 90–100; Ex. 1337 ¶¶ 33, 53–76; Pet. 30–31). Petitioner relies on the testimony of Dr. Balthasar to argue that "a POSA would have understood that the minor blood-pressure increase in Tan's anesthetized rats normalized within 10 to 15 minutes of administering MAb C4.19, and 'had no relationship to the half-life' of the antibody." *Id.* (citing Ex. 1337 ¶¶ 62–66; Ex. 1022, 568). Petitioner also argues that "a POSA would not have viewed minor, transient blood-pressure increases as a safety concern, as similar increases observed with sumatriptan and other CGRP-pathway antagonists did not deter their development or

[58] "[A]ptamers composed of modified nucleotides have a long in vivo half-life (hours to days), are nontoxic and nonimmunogenic, and are easily produced . . . These properties make aptamers ideal for . . . a new class of therapeutics. . . . [A]ptamers bridge the gap between small molecules and biologics. Like biologics, biologically active aptamers are rapidly discovered, have no class-specific toxicity, and are adept at disrupting protein-protein interaction." Ex. 1309, Abstract.

FDA approval." *Id.* (citing Ex. 1338 ¶¶ 90–94; Ex. 1337 ¶¶ 65, 72–76; Ex. 1303, 25:11–17).

Petitioner also cites to other prior art publications that it contends "further confirm that anti-CGRP antagonist antibodies did not have any chronic blood-pressure or vascular effects." Reply 15 (citing Ex. 1337 ¶¶ 67–71; Ex. 1338 ¶¶ 92–102). Petitioner cites to Wong's "blood pressure testing on the same antibody (#4901) evaluated in Teva's patent and concluded that it 'had *no significant effect* on [mean arterial pressure] and heart rate.'" *Id.* (citing Ex. 1033, 101; Ex. 1001, 51:27) (emphasis by Petitioner). Petitioner also cites to Andrew's evaluation that "immunized animals with 'high levels of circulating antibodies to rat CGRP . . . did not show any signs of physical or behavioral abnormality' after 10-15 weeks." *Id.* (citing Ex. 1055, 88, 93). Petitioner further cites to Salmon and other researchers for disabling "αCGRP production entirely in knockout mice, and rather than experiencing any safety concerns, they *claimed* therapeutic uses of anti-CGRP antagonist antibodies for treating neurogenic inflammatory pain." *Id.* (citing Ex. 1027 ¶ 69, claims 8, 9; Ex. 1026, claim 2; Ex. 1288, Abstract). Petitioner also argues that the Tan Thesis states "that there was 'no reason' why *humanized* anti-CGRP monoclonal antibodies should not be developed and used as 'therapeutic agents' for migraine and other diseases." *Id.* (citing Ex. 1287, 247 ("There seems to be no reason why anti-peptide MAbs or their fragments should not be investigated as therapeutic agents," referencing "inflammation and migraine" as therapeutic targets.)).

Petitioner also argues that Patent Owner relies on "early studies reporting the effects of administering *exogenous* CGRP (Exs. 2058, 2079, 2139), which *increases* CGRP levels instead of antagonizing CGRP." Reply

16 (citing Ex. 1338 ¶ 70). According to Petitioner, Patent Owner also "relies on early studies attempting to discern CGRP's biological effects without the benefit of a specific antagonist, making it impossible to separate the effects of CGRP from other vasopeptides." *Id.* (citing Exs. 2150, 2151, 2154, 2070, 2089, 2209; Ex. 1338 ¶¶ 71, 72). Petitioner also argues that "[i]n the one study that used $CGRP_{8-37}$ (a receptor antagonist) under physiological conditions, *no* vascular changes were observed." *Id.* (citing Ex. 2152, 165; Ex. 1338 ¶ 73; Ex. 1303, 111:23–119:13).

Petitioner argues that Patent Owner ignored prior-art studies "demonstrating that blocking the effects of endogenous CGRP with specific antagonists does *not* worsen ischemic events." Reply 16–17 (citing Ex. 1338 ¶¶ 75–81; Ex. 1238, 498 ("locally released CGRP does *not* function as a cardioprotective agent") (emphasis by Petitioner); Ex. 1284, Abstract (CGRP-antagonism had *no effect* on infarct size); Ex. 1303, 134:23–136:17, 140:5–7, 142:2–7) (emphasis by Petitioner)). Petitioner also argues that two 2003 publications "similarly concluded that endogenous CGRP played *no* major role in cardiovascular regulation, including in late-stage heart failure." *Id.* (citing Ex. 1318, 76; Ex. 1285, Abstract; Ex. 1303, 142:24–143:22).

Petitioner further cites to a 2004 publication from Dr. Ferrari's Ph.D. advisor, Dr. Saxena, "studying global and regional cardio- and cerebro-vascular effects of antagonizing the CGRP pathway" with BIBN. Reply 17 (citing Ex. 1263, Abstract; Ex. 1303, 97:10–98:2). Petitioner argues that Dr. Saxena's study demonstrated that "[n]o undesired effects were observed, even at high doses, leading the investigators to conclude that 'endogenous CGRP does *not* play an important role in regulating systemic and regional

haemodynamics.'" *Id.* (quoting Ex. 1263, 296 (emphasis added by Petitioner); citing Ex. 1303, 102:9–106:19). Petitioner further argues that Dr. Saxena summarized the data by advocating the use of CGRP antagonists "'in patients with coronary artery disease.'" *Id.* (quoting Ex. 1031, 326; citing Ex. 1338 ¶¶ 88, 89).

Petitioner contends that Patent Owner's arguments directed to the risk of stroke in sub-populations of migraine patients are irrelevant. Reply 17 (citing *Bayer Healthcare Pharm., Inc. v. Watson Pharm., Inc.*, 713 F.3d 1369, 1376 (Fed. Cir. 2013) (rejecting patient sub-population arguments where the "claims at issue do not distinguish between target patient populations")). According to Petitioner, "*[n]o correlation* existed between migraine and stroke for two-thirds of migraine patients." *Id.* at 17–18 (citing Ex. 2157, 536; Ex. 1040, 177; Ex. 1303, 193:3–10; Ex. 1338 ¶ 108). Petitioner also argues that "the absolute risk of stroke and myocardial ischemia in young women with migraine was very low." *Id.* at 18 (citing Ex. 2157, 535; Ex. 1303, 190:3–194:23; Ex. 1315, Abstract; Ex. 1338 ¶¶ 106–111). According to Petitioner, "anti-migraine treatments could be contraindicated in patients with particular risk factors, as had been done with sumatriptan[59] and ergots,[60]" and that "such concerns did not discourage researchers from pursuing anti-CGRP therapies in the prior art (*e.g.*, aptamers, antibodies, and [BIBN]." *Id.* (citing Ex. 1282, 1520; Ex. 1290,

[59] The contraindications for the sumatriptan IMITREX state that "IMITREX injection should not be given to patients with history, symptoms, or signs of ischemic cardiac, cerebrovascular, or peripheral vascular syndromes." Ex. 1282, 1520.

[60] The term "ergots" refers to ergotamine and its derivatives, which have reportedly been used to treat acute migraine since 1926. Ex. 1316, 1.

564–65; Ex. 1338 ¶¶ 11–24, 112, 113; Ex. 1337 ¶¶ 77–79; Ex. 1026; Ex. 1027).

(ii) Patent Owner's Sur-reply

Patent Owner argues that Dr. Balthasar "undermined any broad assertion that antibodies are necessarily safer than small-molecule drugs," and that Petitioner ignored teachings showing CGRP's vasoprotective role. Sur-reply 8–9 (citing Ex. 2337, 52:8–19; Ex. 1057, 1348). According to Patent Owner, by 2005, "the art recognized CGRP's 'pivotal role' in the 'physiology and pathophysiology of cardiovascular regulation,' including protecting tissues during ischemia." *Id.* at 9 (citing Ex. 2003, 923; Ex. 2268 ¶ 113; PO Resp. 24–25; Ex. 2338, 25:8–26:17, 29:16–30:25, 35:1–36:21; Ex. 2340, 53–54; Ex. 2341, 246).

Patent Owner argues that Petitioner wrongly discounts the findings that anti-CGRP antibodies increase blood pressure because, according to Dr. Ferrari, "even 'mild' or 'transient' increases in BP can have a significant effect: 'mortality from a myocardial infarction (MI) or cerebrovascular accidents doubles for each 20-mm Hg increase in systolic blood pressure (BP) above 115 mm Hg.'" Sur-reply 10 (citing Ex. 2127, S383; Ex. 2268 ¶ 131). Patent Owner also replies that "none of Lilly's antibody-related references determine the consequences of obliterating CGRP-mediated vasodilation ***during an ischemic attack***—the real concern in the field in 2005." *Id.* (citing Ex. 2268 ¶¶ 132–136, 159; PO Resp. 25).

Patent Owner replies to Petitioner's contention that more recent art shows that no safety concern existed, arguing the Petitioner's "small molecules, receptor antagonists, and aptamer art does not inform about safety of anti-CGRP antibodies." Sur-reply 10–11 (citing Reply 13–14;

Ex. 1283, Abstract; Ex. 2152, 165; Ex. 1284, Abstract; Ex. 1285, Abstract; Ex. 1318, Abstract; Ex. 1263, Abstract).

Patent Owner argues that BIBN has a shorter half-life than an IgG; that any adverse effects from BIBN would have been cleared within 24 hours after administration; that each BIBN study was short-term, and would not have informed a person of ordinary skill in the art of long-term risks; and that all BIBN studies were done in healthy volunteers which would not assess whether BIBN would block rescue mechanisms in the times of ischemia. Sur-reply 13 (citing PO Resp. 7–8, 24–25, 29–30; Ex. 2271 ¶¶ 54–56, 83; Ex. 2268 ¶¶ 50, 113–144; Ex. 2265 ¶¶ 65, 120, 131; Ex. 2338, 83:22–88:12; Ex. 1042, 645; Pet. 31; Ex. 1059, 143, Fig. 4.16; Ex. 1025, 1104, 1108; Ex. 1042, 647; Ex. 2019, Abstract; Ex. 1290, 657; Ex. 1297, S119; Ex. 1303, 87:5–17, 89:21–90:3; Ex. 2193, 222; Ex. 2157, 533.) Patent Owner also argues that Dr. Balthasar confirmed that Olesen's statement that "our database was too small for us to assess cardiovascular safety" is consistent with what he would have expected from a clinical investigation because one "'can't make extrapolations off of—beyond the sample size that's present.'" *Id.* at 13–14 (quoting Ex. 2339, 119:5–120:4).

Patent Owner argues that triptans have a considerably shorter half-life than IgGs, and that any adverse effects of triptans are thus eliminated from the body within hours. Sur-reply 14 (citing Ex. 1282, 7; Ex. 2338, 99:1–4; Ex. 1338 ¶ 19; Ex. 2271 ¶¶ 54–59; Pet. 31–32; Ex. 1059, 143, Figure 4.16; Ex. 2265 ¶¶ 65, 120; PO Resp. 29). Patent Owner also argues that triptans agonize 5-HT receptors and thus operate by a different mechanism of action than anti-CGRP antibodies. *Id.* (citing Ex. 1040, 180–181; Ex. 2268 ¶ 49; Ex. 2338, 99:20–100:1; Ex. 1303, 23:22–24:18).

Patent Owner argues that aptamers have a short half-life of hours to days, would not have been informative about safety of long-acting antibodies, and have characteristics similar to *small molecules* and are not antibody "analogs." Sur-reply 14–15 (citing Ex. 1309, Abstract; Ex. 2338, 114:6–115:5; Reply 13). Patent Owner also argues that "the record lacks evidence that aptamers would have been safe in humans." *Id.* at 15 (citing Ex. 1240, Abstract F022; Ex. 2338, 115:19–117:7, 118:9–120:24).

Patent Owner argues that Petitioner minimizes CGRP's importance with respect to stroke and myocardial ischemia in young women, and that "a patient need not have a stroke or myocardial infarction for the concern over CGRP antagonism to be pertinent." Sur-reply 15–16 (citing Reply 18; Ex. 1338 ¶¶ 107–109). According to Patent Owner, a "POSA would have been concerned with 'common' ischemic episodes, such as transient ischemic attacks (TIAs) and angina, expecting that long-term loss of CGRP's protective effect would lead to the development of more serious events." *Id.* at 16 (citing Ex. 2268 ¶¶ 108–110, 114, 119–124) (footnote omitted). Patent Owner also argues that TIAs are a known stroke precursor in about 5,000–12,500 patients annually. *Id.* (citing Ex. 2144, 1665; Ex. 2268 ¶ 108; Ex. 2338, 65:12–68:6; Ex. 2342, 2901). Patent Owner further argues that Dr. Charles "offered no rebuttal to Dr. Ferrari's testimony that CGRP inhibition would worsen common ischemic episodes in migraineurs." *Id.*

(b) Petitioner provides no credible evidence that an anti-CGRP antibody would have had additional therapeutic advantages over a small molecule

Patent Owner argues that Petitioner has not persuasively shown that its alleged therapeutic advantages of an anti-CGRP antibody over a small

molecule would have given a POSA reason to use the antibody, rather than the small molecule, to treat migraine. PO Resp. 33–35. Patent Owner asserts that Petitioner's argument that small-molecule receptor antagonists are often not sufficiently specific to a given receptor target (Pet. 28), justifying use of anti-CGRP antibodies instead, is at odds with Wimalawansa's recommendation that "the antagonist must be extremely specific to the CGRP receptors." PO Resp. 33 (citing Pet. 28, 32–33; Ex. 1014 ¶¶ 119–132; Ex. 1096, 568). According to Patent Owner, Olesen's BIBN was a highly and extremely specific CGRP receptor antagonist. *Id.* (citing Ex. 1025, Abstract, 1105). Patent Owner also argues that the inherent advantages of anti-CGRP antibodies that Dr. Charles and Petitioner claim are shown in Tan have nothing to do with small molecules because "Tan compared advantages of monoclonal C4.19 antibody to polyclonal antibodies—not small-molecule receptor antagonists." *Id.* at 34 (citing Ex. 1022, 572; Ex. 2265 ¶¶ 92–94).

(3) Tan's data negates any reasonable expectation that a full-length antibody would safely treat migraine

Patent Owner argues that "Tan's results from the saphenous nerve assay with MAb C4.19 would have negated any reasonable expectation that a humanized full-length anti-CGRP antibody could successfully treat migraine." PO Resp. 35 (citing Ex. 2265 ¶ 134; Ex. 2271 ¶¶ 75, 95; Ex. 2268 ¶¶ 137, 138).

Patent Owner argues that, according to Tan, MAb C.19 failed to engage CGRP at the synaptic cleft,[61] and that Tan reported that engagement

[61] Patent Owner explains that the term "synaptic cleft" is used by Tan to refer to the site of action. PO Resp. 3 n.4. According to Patent Owner, in the context of the rat saphenous nerve assay, the term refers to a

of CGRP at the synaptic cleft is "a prerequisite for immunoblockade." PO Resp. 35 (citing Ex. 2265 ¶ 134; Ex. 1022, 571, 565–566, Abstract). Moreover, according to Patent Owner, Tan's statement that "[w]ith repeated administration, IgG should eventually . . . achieve the sufficiently high concentrations required for immunoblockade" does not trump the actual data and conclusion in Tan that MAb C4.19 did not work in the saphenous nerve assay. *Id.* at 36 (citing Ex. 2265 ¶ 134; Ex. 1022, 571–572; Ex. 2271 ¶¶ 75, 95; Ex. 2268 ¶¶ 137, 138).

Patent Owner further argues that Covell[62] (cited by Tan) would not have provided an expectation that "much larger doses and longer distribution times" (what Tan states is suggested by Covell) would cure the pharmacokinetic problem in Tan "because Covell does nothing to show that an anti-CGRP antibody would distribute into the synaptic cleft, even with larger doses or longer time." PO Resp. 36. According to Patent Owner, Covell reported distribution of a full-length antibody "between the capillary, interstitial, and cell-associated compartments" in mice. *Id.* (citing Ex. 1247, 3973, Table 5; Ex. 2265 ¶¶ 88–91) (footnote omitted). Patent Owner asserts that, for all organs except the carcass, Covell found that "the capillary plasma compartment had the greatest fraction of the total organ's residence time for whole IgG," which, according to Dr. Foord, means that a full-length antibody is present for longer periods of time and at higher concentrations in the systemic circulation after administration (i.e., the place where it can

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communicating cell to cell junction (a neuromuscular junction) allowing signals to pass from a nerve cell to a muscle cell. *Id.*

[62] Covell et al., *Pharmacokinetics of Monoclonal Immunoglobulin G_1, $F(ab')_2$, and Fab' in Mice*, CANCER RES. 46, 3969–78 (1986) (Ex. 1247, "Covell").

exert a negative effect on CGRP's vasodilation properties). *Id.* at 36–37 (citing Ex. 1247, 3973, Table 5; Ex. 2265 ¶ 89).

Patent Owner further argues that "even if the antibody reaches the interstitial spaces, that does not translate into an ability to reach the synaptic cleft—the site of action for immunoblockade." PO Resp. 37. That is, according to Patent Owner, because "the interstitial space incorporates the synaptic cleft [but] the synaptic cleft represents a different biological compartment than the interstitial spaces." *Id.* (citing Ex. 2265 ¶ 90; Ex. 1022, 566).

Petitioner argues in response that Tan expressly disclosed that MAb C4.19 "clearly diffuses into the synaptic cleft," which is consistent with multiple experiments with anti-CGRP polyclonal antibodies establishing *in vivo* effectiveness. Reply 10 (citing Ex. 1022, 571 (citing Ex. 1021); Ex. 1048[63]; Ex. 1049[64]; Ex. 1050[65]; Pet. 45–46; Ex. 1337 ¶¶ 15–39). Petitioner also argues that "Tan 1994 showed that 'the concentration of the [full-length] antibody had reached equilibrium *in the synaptic cleft* after 45 min.'" *Id.* (citing Ex. 1021, 709; Ex. 1337 ¶ 21) (alteration and emphasis by Petitioner). Petitioner further argues that a POSA would have expected that longer distribution times and/or higher doses would improve distribution of

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[63] Louis et al., *Antibodies to Calcitonin-Gene Related Peptide Reduce Inflammation Induced by Topical Mustard Oil But Not that Due to Carrageenin in the Rat*, NEUROSCIENCE LETTERS 102, 257–60 (1989) (Ex. 1048, "Louis 1989").

[64] Dockray et al., *Immunoneutralization Studies with Calcitonin Gene-Related Peptide*, ANNALS OF N.Y. ACAD. SCIS., 258–67 (1992) (Ex. 1049, "Dockray").

[65] Louis et al., *The Role of Substance P and Calcitonin Gene-Related Peptide in Neurogenic Plasma Extravasation and Vasodilation in the Rat*, NEUROSCIENCE 32(3), 581–86 (1989) (Ex. 1050).

full-length antibodies to the synaptic cleft, thereby enhancing response, "consistent with well-understood principles of antibody pharmacokinetics and the *express guidance* of Tan." *Id.* (citing Ex. 1337 ¶¶ 24–34; Ex. 1022, 571; Ex. 1247, 3972).[66] In support, Petitioner argues that "Tan observed a more pronounced 16% response when a higher antibody dose and a longer, two-hour incubation time were employed." *Id.* at 11 (citing Ex. 1022, 569; Pet. 16–17, 46–47; Ex. 1337 ¶¶ 24–26).

Petitioner also argues that Dr. Foord's argument that antibodies were too large to access the synaptic cleft was flawed because "he referenced IgE antibodies rather than IgG antibodies (which are smaller); failed to evaluate the size of relevant synapses (which are larger); and ignored the mobile, three-dimensional nature of antibodies." Reply 11 (citing Ex. 2265 ¶ 90; Ex. 1343, 66:9–68:10, 70:4–9; Ex. 1337 ¶¶ 35–39).[67]

Patent Owner replies that "[n]othing in the record demonstrates that IgGs would distribute into the synaptic cleft—the relevant site of action," and that "Tan's C4.19 failed to engage in the synaptic cleft in the *in vivo* assay." Sur-reply 18 (citing Reply 10; Ex. 2265 ¶ 134; Ex. 1022, 571, 565, Abstract; PO Resp. 35–36). Patent Owner asserts that "Tan 1994 does not

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[66] Petitioner cites to the Balthasar Declaration, Tan, and Covell for the stated proposition but does not otherwise address or rebut Patent Owner's arguments regarding Covell. *See* PO Resp. 36–37.

[67] Petitioner also argues that Teva followed Tan's instructions in examples disclosed in the patent Specification. Reply 11. We agree with Patent Owner that such an argument is irrelevant to the obviousness inquiry. Sur-reply 21; *see Standard Oil. Co. v. American Cyanamid Co.*, 774 F.2d 448, 454 (Fed. Cir. 1985) ("one should not go about determining obviousness under [Section 103] by inquiring into what *patentees* (i.e. inventors) would have known or would likely have done, faced with the revelations of references).

demonstrate IgG access to the synaptic cleft *in vivo*," because Tan 1994's "tissue bath" is not an "equivalent" to an *in vivo* study and, citing Dr. Balthasar, "does not represent an antibody's ability to penetrate multiple biological compartments in a complex system." *Id.* (citing Ex. 1021, 705; Ex. 2339, 77:20–78:3 ("as the in vitro system, it's not exactly equivalent to an in vivo system"); Ex. 1343, 61:17–62:4) (emphasis omitted).

Patent Owner also argues that Petitioner "belatedly" relies on Dr. Balthasar's assertion that Covell's "carcass" experiments "show that 'full-length antibodies were expected to distribute from general circulation into the interstitial space, so long as they are given sufficient time,'" but that "Covell does not support this conclusion." Sur-reply 19–20 (citing Reply 10–11; Ex. 1337 ¶¶ 24–29; Ex. 1247, 3972). According to Patent Owner, "Covell presents no data relating to an antibody's penetration of, or binding CGRP in, the synaptic cleft," and "the art shows that in a carcass, 'assignment of a site, or sites, of antibody localization was not possible.'" *Id.* at 20 (citing Ex. 2339, 92:14–16; 93:19–95:6; 95:10–12; Ex. 1022, 566; Ex. 2265 ¶¶ 89, 90; PO Resp. 37; Ex. 2279, 3045). Patent Owner cites to Dr. Balthasar's testimony to argue that "movement of antibodies is a 'random process,' and one needs to 'consider a number of factors' in determining the amount of time required to achieve 'concentration [] of interest' in the site of action," and that Petitioner "considered none of these factors." *Id.* (citing Ex. 2337, 64:10–65:5 ("so there's many factors to consider to answer your question about how much time would be required to achieve concentrations . . . of interest at a site of interest.")).

Patent Owner replies to Petitioner's challenge to Dr. Foord's testimony (Reply 11) by arguing that "even if an antibody could enter the

synaptic cleft based purely on the dimensions of each—which Teva does not concede—Lilly has not proven that the antibody would even ***reach*** the cleft in the first place." Sur-reply 20–21.

(4) A POSA would not have expected a full-length antibody to be efficacious because the field in 2005 was moving toward a central site of action for anti-migraine drugs

Petitioner asserts that it was known that anti-migraine drugs did not need to cross the BBB to effectively treat migraine. Pet. 32, 40 n.2 (citing Ex. 1014 ¶¶ 149–152; Ex. 1090, 702–703). Petitioner points to Olesen, and asserts that BIBN did not cross the BBB. *Id.* (citing Ex. 1090, 702–703). Petitioner also asserts that other migraine drugs were known to be effective despite poor penetration of the BBB. *Id.* at 32–33 (citing Ex. 1241, Abstract, 454s–55s; Ex. 1242, Abstract; Ex. 1243, 591–92; Ex. 1244, 286; Ex. 1014 ¶ 151).

Patent Owner responds that, contrary to Petitioner's assertions, the field in 2005 was starting to believe that anti-migraine drugs did need to cross the blood brain barrier (BBB). PO Resp. 38. Patent Owner argues that by 2005, the field had shifted toward a belief that the site of action of anti-migraine drugs was central rather than peripheral, citing, *inter alia*, Levy[68] and Fischer[69]. *Id.* at 39 (citing Ex. 2268 ¶¶ 71–90; Ex. 2298, 704; Ex. 2310, 5881).

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[68] Dan Levy et al., *Calcitonin Gene–Related Peptide Does Not Excite or Sensitize Meningeal Nociceptors: Implications for the Pathophysiology of Migraine*, 58 ANN. NEUROL. 698–705 (online publication Oct. 24, 2005) (Ex. 2298, "Levy").

[69] M.J.M. Fischer et al., *The Nonpeptide Calcitonin Gene–Related Peptide Receptor Antagonist BIBN4096BS Lowers the Activity of Neurons with Meningeal Input in the Rat Spinal Trigeminal Nucleus*, 22 THE J. OF NEUROSCIENCE (25)5877–5883 (June 22, 2005) (Ex. 2310, "Fischer").

Patent Owner asserts that Petitioner's arguments require that a person of ordinary skill would therefore have to have reasonably expected that a humanized antibody, "which admittedly 'may not cross' the BBB," would successfully reduce the incidence of or treat migraine. *Id.* (citing Pet. 32, 39–40); Ex. 1014 ¶ 132. Patent Owner argues that "[t]his is a remarkable and unsupported leap, given the state of the art in 2005." *Id.* at 38–39. Patent Owner also asserts that, as of 2005, it was not clear whether the antimigraine activity of the triptans involves an action only in the periphery or in the central nervous system (CNS) as well, but the field was moving toward a central site of action. *Id.* at 39–40 (citing Ex. 2291, Abstract; Ex. 2268 ¶¶ 71–84; Ex. 2308, 741; Ex. 2323, 70; Ex. 2326, Abstract; Ex. 2325, Abstract). Patent Owner asserts that Kaube[70] found that it is most likely that the disruption of the BBB is pivotal in facilitating the inhibitory effect of sumatriptan. *Id.* at 40 (citing Ex. 2306, 789).

Patent Owner argues that Petitioner's argument that Olesen's BIBN did not cross the BBB is based on Petersen 2004's[71] finding the BIBN affected the pial arteries, but that it was unsettled whether pial arteries possessed a BBB. PO Resp. 40 (citing Ex. 1090, 701–703, Figs. 2B–2C; Ex. 2268 ¶¶ 63–67; Ex. 2329, Abstract). Patent Owner also argues that rats might have a difference in their BBB as compared to humans and also that there was a hypothesis that the BBB was more permeable during a migraine

[70] Kaube et al., *Inhibition by sumatriptan of central trigeminal neurones only after blood-brain barrier disruption*, BR. J. PHARMACOL. 109, 788–92 (1993) (Ex. 2306, "Kaube").

[71] Petersen et al., *Inhibitory Effect of BIBN4096BS on Cephalic Vasoconstriction Induced by CGRP or Transcranial Electrical Stimulation in the Rat*, B. J. PHARM. 143, 697–704 (2004)(Ex. 1090, "Petersen 2004").

attack. *Id.* at 40–41 (citing Ex. 1090, 703; Ex. 2268 ¶ 69; Ex. 2277, 101:15–102:1).

Petitioner argues that Petersen 2004 used the same animal model as the subject patent to show that Olesen's BIBN blocked CGRP in the periphery (without a BBB), not in central pial arteries. Reply 7 (citing Ex. 1090, Abstract, 703; Ex. 1001, 60:60–69:67; Ex. 1345, 52:6–54:7; Ex. 2215, 75; Ex. 1031, 326; Ex. 1338 ¶¶ 36–42). Petitioner argues that Patent Owner's expert admitted it was "unlikely" BIBN crossed the BBB. *Id.* at 8 (citing Ex. 1343, 76:12–77:8). Petitioner also argues that the prior art recognized that pial arteries have a BBB. *Id.* at 7 (citing Ex. 2068, 39). Petitioner also argues that differences between humans and rats are immaterial because Petersen 2005[72] confirmed that BIBN in humans prevented CGRP headache with no effect on central vasodilation. *Id.* at 8 (citing, e.g., Ex. 1333, 211; Ex. 1338 ¶¶ 43–47).

Petitioner argues that Storer[73], Fischer, and Levy did not change the prior art understanding that peripheral antagonism of CGRP treats migraine, *inter alia*, because they used non-physiologic conditions and because Storer and Fischer observed that central and peripheral BIBN administration suppressed activity of the trigeminocervical complex. *Id.* at 8–9 (citing Ex. 2298, 699; Ex. 2310, 5878; Ex. 2307, 1172; Ex. 1345, 48:8-49:11; Ex. 1338 ¶¶ 48–50; Ex. 2307, 1175-1176; Ex. 2310, Abstract).

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[72] Kenneth A. Petersen et al., *BIBN4096BS antagonizes human a- calcitonin gene related peptide- induced headache and extracerebral artery dilatation*, 77 CLIN PHARMACOL THER 202–13 (2005) (Ex. 1333, "Petersen 2005").
[73] R. Storer et al., *Calcitonin gene-related peptide (CGRP) modulates nociceptive trigeminovascular transmission in the cat*, 142 B. J. OF PHARMACOLOGY 1171–81 (2004) (Ex. 2307, "Storer").

Petitioner argues that sumatriptan poorly penetrates the BBB, other triptans with better BBB penetration showed no additional clinical benefits over sumatriptan, aptamers showed no propensity to cross the BBB, and other treatments (ergotamine and atenolol) also acted peripherally. Reply 9 (citing, e.g., Ex. 1338 ¶¶ 18–21, 24, 57–66; Ex. 1281, S73; Ex. 1303, 23:22–24:22; Ex. 2291, Abstract, 2; PO Resp. 13, 39 n.11; Ex. 1334, 329; Ex. 1241, Abstract; Ex. 1310, 2244; Ex. 1082; Ex. 1240).

Patent Owner argues that a person of ordinary skill would not have used a full-length antibody to treat migraine because it would not have been expected to cross the BBB. PO Resp. 41 (citing Ex. 2265 ¶¶ 96–103; Ex. 2268 ¶¶ 84, 91–93; Ex. 2271 ¶¶ 63–68; Ex. 2284, 12). Patent Owner argues that transient changes in the BBB's permeability might occur during migraine that would account for BIBN to be an effective anti-migraine drug. *Id.* at 42 (citing Ex. 2268 ¶¶ 75, 88–89; Ex. 2310, 5881; Ex. 2222, Abstract; Ex. 2223, 2; Ex. 2306, 789). Patent Owner argues, however, that Petitioner "provided no evidence that would prove that a full-length anti-CGRP antibody would also be expected to cross the BBB, even during those transient changes." *Id.* Patent Owner argues that transient breaks in the BBB might allow for a small molecule (<1 kDa) like BIBN to cross the BBB because of its small size but not a sufficiently effective amount of a much larger full-length antibody (about 150 kDa). *Id.* (citing Ex. 2268 ¶ 55; Ex. 2265 ¶¶ 99–100).

Patent Owner argues that it is undisputed that IgGs are unlikely to cross the BBB. Sur-reply 21 (citing, e.g., Ex. 2268 ¶ 41; Ex. 2271 ¶ 68; PO Resp. 38). PO argues that the uncertainty in the art as to the peripheral versus central site of action of anti-migraine drugs persists even today. *Id.* at

22. Patent Owner asserts that in 2014, Professors Dodick and Goadsby, well-respected in the migraine field, still believed that "the site and mechanism of action of CGRP monoclonal antibodies is unclear." *Id.* (citing Ex. 2161, 6; Ex. 2336, 80:19–81:7). Patent Owner asserts that in 2019, Dr. Charles himself was "still debating over central versus peripheral site of action of anti-CGRP antibodies." *Id.* (citing Ex. 2336, 34:12–16; Ex. 2335, 1). Patent Owner asserts that Dr. Charles opined in his declaration that transient changes in BBB were speculative as of 2005, but admitted during cross-examination that in 2005 it was known that in some migraine patients, "there is clear disruption of the blood-brain barrier." *Id.* (citing Ex. 2336, 98:14–99:17). Patent Owner argues that such transient changes could account for the ability of small molecules (BIBN, triptans, ergots, aptamers) to have a physiological effect during migraine. *Id.* at 22–23 (citing Ex. 2268 ¶¶ 75, 88–89; Ex. 2310, 5881; Ex. 2222, Abstract; Ex. 2223, 2; Ex. 2306, 789; PO Resp. 42).

Patent Owner argues that "[a]dditional skepticism surrounded whether an anti-CGRP antagonist antibody could treat migraine when it is unable to cross the BBB into the CNS." PO Resp. 61–62 (citing Ex. 2331 ¶¶ 4–5, 14; Ex. 2226, 1). Moreover, a named inventor (Dr. Pons) listed on the challenged patents testified that "[a]t the time we were developing fremanezumab, the scientific community believed that migraine was a disorder of the central nervous system ('CNS') (EX2226), such that an effective migraine treatment must cross the blood-brain barrier." Ex. 2331 ¶ 5. Dr. Pons further testified that "since the early days of our research on [fremanezumab], artisans in the field were skeptical of the capacity of a full length antibody like [fremanezumab] to treat migraine." *Id.* ¶ 14. Although

Petitioner argues that the testimony of Dr. Pons should be given no weight because of his compensation for testifying, Petitioner does not substantively challenge Dr. Pons regarding the above testimony. *See* Reply 26.

(5) None of the additional art Petitioner cites provides a reasonable expectation that an anti-CGRP antibody can be safely used for treating migraine in humans

Patent Owner argues that "Lilly relies on Queen for a reasonable expectation of success only of humanizing a murine anti-CGRP antibody, and not of therapeutic efficacy or safety," and that "none of the additional references that Lilly cites provides any data to assuage safety concerns." PO Resp. 43 & n.12 (citing Pet. 41; Ex. 2271 ¶¶ 97–104; Ex. 2265 ¶¶ 127–131; Ex. 2268 ¶¶ 142, 143, 148–153). Patent Owner argues that Sveinsson "only very generally mentions that CGRP **receptor** antagonists might be useful for treating various conditions, including perhaps migraine." *Id.* at 43 (citing Ex. 1026, 7:5–12; Ex. 2265 ¶¶ 108, 128).

Patent Owner also argues that Wimalawansa "does not assess efficacy or safety of humanized antibodies in humans" and cites to Wimalawansa's statement that "[c]learly, more data from carefully designed studies are necessary before . . . humanized anti-CGRP monoclonal antibodies . . . can be evaluated as therapeutic agents." PO Resp. 44 (citing Ex. 2265 ¶¶ 104–107; Ex. 2268 ¶¶ 54, 149; Ex. 1096, 543, Figure 8C, 567). Patent Owner further argues that Salmon "provides no data for anti-CGRP antibodies in humans," and that none of Wong, Andrew, Louis 1989, or Dockray suggest or exemplify using anti-CGRP antibodies to treat migraine. *Id.* (citing Ex. 2265 ¶¶ 108, 109, 125, 129; Ex. 2268 ¶¶ 128, 151; Ex. 2277, 32:15–19; 35:4–7; 37:6–10; 40:7–16; 42:16–19; 72:4–8; Ex. 1033; Ex. 1055; Ex. 1048; Ex. 1050; Ex. 1049). Patent Owner additionally argues that Vater and

Messlinger deal with aptamers (called "spiegelmers"), not antibodies, that aptamers have lower molecular weights and shorter half-lives than full-length antibodies, and that since both molecular weight and half-life "influence how safe and effective a molecule will be in treating migraine—for example, whether it will access its site of action, cross the BBB, and linger in a patient's systemic circulation for too long—a POSA would not have been able to draw any conclusions as to a reasonable expectation of success based on spiegelmers." *Id.* at 44–45 (citing Ex. 1014 ¶ 62; Ex. 2265 ¶¶ 110, 111; Ex. 2277, 48:15–17, 49:2–11). Thus, according to Patent Owner, "none of Lilly's cited references would have given a POSA a reasonable expectation of successfully treating migraine with humanized anti-CGRP antagonist antibodies." *Id.* at 45.

Petitioner's reply regarding alleged safety concerns is addressed above in Section II.D.3.c)(2)(a)(i).

d) Petitioner failed to address motivation to humanize Tan's Fab' fragment

In connection with the '045 patent, Patent Owner argues that Petitioner fails to address a motivation to humanize a Fab' fragment, arguing further that Petitioner's motivation rationales regarding a full-length antibody are not applicable to a Fab' fragment. PO Resp. 47–50.

According to Patent Owner, there were no advantages to using a Fab' fragment compared to a small molecule, because the art taught that "[s]mall antibody fragments show rapid clearance from the circulation, and as a result the fraction of the injected dose that reaches its target is at present too low for a therapeutic benefit, even for bivalent fragments." *Id.* at 48–49 (citing Ex. 1077, 60; Ex. 2271 ¶¶ 57–61; Ex. 2113, 780–781; Ex. 2107, 434; Ex. 2131, 286, 272). Patent Owner thus argues that "[t]his rapid clearance

mitigates concern regarding immunogenic response." *Id.* at 49 (citing Ex. 1072, 45; Ex. 2271 ¶¶ 110–113; Ex. 2107, 434; Ex. 2131, 286, 272; Ex. 1062, 43). According to Patent Owner, Petitioner has thus failed to meet its burden to provide an evidentiary reason to humanize a Fab' fragment. *Id.* at 49–50.

Petitioner does not dispute Patent Owner's argument. *See generally* Reply. In fact, Petitioner argues that "[t]he prior art expressly recognized the downside of treating migraine patients with CGRP inhibitors having a short half-life," citing to a report that $CGRP_{8-37}$ (a peptide fragment of CGRP) "'proved ineffective in migraine treatment' due to 'its low potency and *short half-life*.'" Pet. 31 (citing Ex. 1031, 323; Ex. 1014 ¶ 124) (emphasis by Petitioner). Accordingly, we find that Petitioner has not sufficiently established that a POSA would have been motivated to humanize an anti-CGRP antibody fragment.

e) Patent Owner's arguments that Petitioner failed to prove that a POSA would have arrived at the claimed less than 10nM affinity (K_D) to CGRP

In connection with the '908 patent, Patent Owner argues that Petitioner "fails to prove that a POSA would have been motivated to arrive at an antibody having the claimed 10 nM K_D with a reasonable expectation of success." 1712 IPR PO Resp. 49. Patent Owner specifically challenges Petitioner's reliance on Tan 1994's binding assay demonstrating a K_D of 1.9 nM to rat αCGRP and 2.5 nM to βCGRP for MAb C4.19, and Petitioner's argument that these K_D values lead to predictive blocking effects *in vivo*. *Id.* at 42–43, 51 (citing 1712 IPR Pet. 36). According to Patent Owner, "Tan 1994's radioimmunoassay (RIA) was not designed in a manner to draw conclusions regarding affinity" because "RIA allows for estimating

the K_D of the antibody to the ligand only when the radiolabelled and unlabeled ligands are the same." *Id.* at 7 (citing1712 IPR Ex. 2273 ¶¶ 112–117); *id.* at 49–50 (citing Ex. 1021, 704–705; Ex. 2135, 278; Ex. 2136, 40, Fig. 5).

Patent Owner argues, however, that rather than using the same ligands, Tan "attempted to displace radiolabelled ***human*** αCGRP with unlabeled ***rat*** αCGRP, and did so at 4 °C, not 37 °C as claimed." *Id.* (citing Ex. 1021, 704–05). Patent Owner also argues that, based on the testimony of Dr. Tomlinson, "temperature has a considerable effect on antibody kinetics which are different for each antibody," and that "Tan 1994's K_Ds measured at 4°C are also not instructive as to K_D values at 37°C." *Id.* at 52 (citing Ex. 1087, 331; 1712 IPR Ex. 2273 ¶ 116). Patent Owner further argues that Dr. Charles admits that human and rat αCGRP are not the same, and that Dr. Vasserot confirms that differences in amino acids and temperature matter. *Id.* at 7, 50 (citing 1712 IPR Ex. 1018 ¶ 18; Ex. 2191, 154:21–156:12, 165:19–157:10 [sic]).

Patent Owner also argues that "Tan 1994's measurements with murine antibodies would not be applicable to the claimed humanized antibodies" because binding affinities decrease with humanization, as acknowledged by Queen. 1712 IPR PO Resp. 53 (citing 1712 IPR Ex. 2273 ¶¶ 121–122; Ex. 1023, 2:12–16, 58:11–25). According to Patent Owner, "to achieve high binding affinity with a humanized antibody, the starting affinity of a murine antibody must be high enough," and that "a POSA would not have known the starting affinities of Tan's murine antibodies." *Id.* (citing 1712 IPR Ex. 2273 ¶¶ 121–122). Thus, according to Patent Owner, a person of ordinary skill in the art would not have concluded that Tan 1994's

anti-CGRP antibodies had K_Ds of 10 nM or less (*id.* at 49), and "one cannot arrive at the claimed affinity absent hindsight" (*id.* at 53).

Patent Owner also challenges Petitioner's reliance on the existence of "other, unrelated FDA-approved therapeutic antibodies having affinities of less than 10 nM," arguing that those other antibodies provide no motivation to make an anti-CGRP antibody with a similar affinity because "the affinity required for any given antibody to have biological or therapeutic effects is specific for the particular antigen." *Id.* at 51 (citing 1712 IPR Ex. 2273 ¶¶ 119–120). Patent Owner further argues that, as demonstrated by Tan 1994 and its antibodies MAb R1.50 and MAb R2.73, higher affinity does not necessarily translate into better biological activity, as argued by Petitioner. *Id.* at 51 (citing Ex. 1021, 707; 1712 IPR Ex. 2273 ¶ 119).

4. Analysis

a) Reasons to combine

"Motivation to combine may be found in many different places and forms." *Allergan, Inc. v. Sandoz*, Inc., 726 F.3d 1286, 1292 (Fed. Cir. 2013); *see also Alza Corp. v. Mylan Labs., Inc.*, 464 F.3d 1286, 1294 (Fed. Cir. 2006) (the motivation to combine does not have to be explicitly stated in the prior art, and can be supported by testimony of an expert witness regarding knowledge of a person of skill in the art at the time of invention).

As discussed in detail above, Petitioner argues that a person of ordinary skill in the art would have been motivated to treat migraine with a humanized monoclonal anti-CGRP antibody based on Olesen, Tan, Queen, and other exhibits reflective of the art as of November 2005. Pet. 25–35, Reply 12–18. Patent Owner opposes by challenging Petitioner's interpretation of Olesen and Tan, and asserting safety concerns that Patent

Owner contends would have discouraged or deterred a POSA from combining the asserted references to arrive at the claimed invention. PO Resp. 24–35, 47–50; Sur-reply 8–15.

(1) Olesen

Petitioner essentially argues that Olesen's clinical data validated the CGRP pathway as a therapeutic target for treating migraine; that a person of ordinary skill in the art reading Olesen would have extended its teachings to other CGRP antagonists beyond BIBN, based on Olesen's use of the term "CGRP antagonists" and other prior art, such as Wong and Arulmozhi that distinguished between CGRP receptor and ligand antagonists; and that there were therapeutic advantages to targeting CGRP rather than one of its receptors. Pet. 25–29; *see supra* Section II.D.2.b)(1) & (2). Petitioner argues further that a POSA would have been motivated to use a humanized monoclonal anti-CGRP antagonist antibody to minimize the risk of immunogenicity in humans. Pet. 33–35; *see supra* Section II.D.2.b)(3).

Patent Owner essentially argues that Olesen investigated only BIBN, a small molecule receptor antagonist, and does not suggest that "CGRP antagonists" extends beyond small-molecule receptor antagonists. PO Resp. 6, 12–13; *see supra* Section II.D.3.a)(1).

We find that Olesen teaches that blocking the CGRP receptor with a small-molecule is effective in treating migraine. Ex. 1025. We find that a POSA would have understood that, in order to inhibit the binding of a CGRP ligand to a CGRP receptor, alternative approaches would have been to block the ligand or the receptor, and that Olesen demonstrates the efficacy of the latter approach. *Id.* This finding is supported by the prior art, such as Wong and Arulmozhi, that suggested blocking either the receptor or the ligand to

treat migraine. Ex. 1033; Ex. 1040. We further find no basis to conclude that Petitioner mischaracterized the disclosure of Olesen.

(2) Tan

Petitioner essentially argues that Tan (among other references) demonstrates that murine anti-CGRP antagonist antibodies were developed, characterized, and commercially available prior to November 2005, and that Tan demonstrated that anti-CGRP antagonist antibodies inhibited CGRP activity *in vivo*. Pet. 29–31; *see supra* Section II.D.2.b)(1) & (2). Patent Owner argues that Tan is a basic science paper that draws no therapeutic or clinical conclusions and has nothing to do with humans, treatments, migraine, or dosing. PO Resp. 14–15; *see supra* Section II.D.3.c)(2). Petitioner responds by asserting that Dr. Tan "contemporaneously wrote that there is 'no reason' why *humanized* anti-CGRP antagonist antibodies should not be developed and used for treating migraine." Reply 6 (citing Ex. 1287, 247; Ex. 1096, 567, 570).

We find that Tan expressed optimism that higher concentrations or longer incubation times of a full-length anti-CGRP antibody should achieve immunoblockade (blocking the effects of CGRP) by a full length anti-CGRP antibody. Ex. 1022, 571 ("With repeated administration, IgG should eventually distribute into interstitial space and achieve the sufficiently high concentrations required for immunoblockade"). We find that, in combination with Olesen's results, a POSA would have had a reason to investigate or explore the use (administration) of an anti-CGRP antibody to treat migraine.

(3) Queen

Patent Owner does not contest Petitioner's argument that "the prior art had embraced *humanized* antibodies for treating human patients to reduce immunogenicity" (Pet. 33–34). *See generally* PO Resp.; Sur-reply. We find that, based on Queen, a POSA would have had a reason (immunogenicity) to humanize an anti-CGRP monoclonal antibody for administration to humans.

(4) Therapeutic benefits over small molecules

Patent Owner argues that "[t]here is no support in the record for Lilly's argument that antibodies would have been expected to have 'lower toxicity and fewer off-target side effects than small molecules.'" PO Resp. 5, 24 (citing Ex. 1014 ¶ 127; Pet. 32). We disagree. Petitioner cites, for example, to Exhibit 1057 which states that "[a]re protein-based drugs less prone to toxicity than small molecule drugs? The short answer here is probably yes." Ex. 1057, 1348 (cited at Pet. 32). We thus find support in the record that would have provided an additional reason (lower toxicity) to use antibodies rather than small molecules in treating migraine.

(5) Safety concerns

We find that, as of 2005, CGRP was known to have an important vasoprotective role in humans. Ex. 1096, 540, 557–59; Ex. 2003, 904–05; Ex. 1033, 95. Patent Owner argues that "a POSA would have expected anti-CGRP antibodies to eliminate CGRP's vasoprotective role, *potentially* leading to significant cardiovascular and cerebrovascular consequences." PO Resp. 5 (citing Ex. 2268 ¶¶ 12, 103–143; Ex. 2265 ¶¶ 112–113) (emphasis added). Patent Owner also argues "the art's real and genuine safety concerns as *potential* reasons a POSA would not have been motivated to pursue humanized anti-CGRP antibodies." *Id.* at 24 (emphasis added).

Patent Owner's reliance on the "potential" side effects of administering anti-CGRP antibodies is reflected in the testimony of Patent Owner's experts. *See, e.g.*, Ex. 2271 (emphases added): "the antibody *may* cause catastrophic effects" (*id.* ¶ 49); "hitting a target that has many different functions or where that target has a complex role relating to multiple pathways or multiple tissues is *likely* to be associated with a large range of *potential* side effects. As noted by the European Medicines Agency, there is a *potential* for 'serious adverse reactions.'" (*id.*); "long half-life of antibodies . . . *can* amplify side effects" (*id.* ¶ 52); "[a]nother factor a POSA would have weighed in considering a potential therapeutic is how long *potential* side effects would persist in the patient." (*id.* ¶ 76); "a POSA also would have considered all *potential* side effects in analyzing CGRP as a therapeutic antibody target" (*id.* ¶ 81); *see also* Ex. 2268 (emphases added): "sequestering CGRP for long periods of time had the *potential* to cause deleterious side effects on the vascular system" (*id.* ¶ 114); "*potential* negative consequences" (*id.* ¶ 153).

In contrast, Petitioner focuses on evidence of actual studies of inhibiting CGRP or blocking the CGRP pathway that show few (if any) adverse events or side effects, including in long term use of CGRP inhibitors and blocking CGRP in humans. Reply 12–18. These include, in addition to Olesen and BIBN, the anti-CGRP antibody studies of Wong ("[t]he monoclonal antibody had no significant effect on [mean arterial pressure] and heart rate") and Andrew ("high levels of circulating antibodies to rat CGRP . . . [rats] did not show any signs of physical or behavioral abnormality" after 10–15 weeks). Ex. 1033, 101; Ex. 1055. Petitioner also cites to the FDA-approved drug, and CGRP inhibitor, sumatriptan as "very

safe" when prescribed to appropriate migraine patients, despite inducing transient blood pressure increases. Reply 13 (citing Ex. 1338 ¶ 93; Ex. 1282, 1521; Ex. 1308, 1673; Ex. 1303, 211:2–9).

Although some of the studies relied on by Petitioner did not involve anti-CGRP antibodies, they were actual studies or data available to a POSA regarding blockage or inhibition of the CGRP pathway, including the inhibition or blocking of the CGRP pathway in humans. *See, e.g.*, Ex. 1033; Ex. 1055. Moreover, although the data from those studies was limited and may not have risen to the level of Phase I clinical trial data, it need not have done so. *Persion Pharms. LLC v. Alvogen Malta Operations Ltd.*, 945 F.3d 1184, 1192 (Fed. Cir. 2019) (citing and accepting the district court's explanation that "[t]he standard to find a motivation to combine is far below what is sufficient to prove safety and efficacy to the FDA."). We address specific arguments below.

(a) Ischemic Events and Stroke

We find that Patent Owner's concern over inadequate CGRP during an ischemic attack is rebutted by actual studies showing that a POSA in November 2005 would have had a reasonable basis to believe that blocking the CGRP pathway with a CGRP antagonist does not worsen ischemic events. *See* Ex. 1238, 498; Ex. 1284, Abstract; Ex. 1318, 76; Ex. 1285, Abstract; Ex. 1031, 326. We also find that a POSA would have understood the relationship between migraine and stroke to be relatively isolated and could be addressed by appropriate contraindications. *See* Ex. 2157, 535–536; Ex. 1040, 177; Ex. 1315, Abstract; Ex. 1282, 1520; Ex. 1290, 564–65; Ex. 1026; Ex. 1027.

(b) Tan

We find that, although Tan reports an increase in the baseline arterial pressure and refers to "chronic administration" as a strategy to overcome slow distribution of whole IgG to the site of immunoblockade, a person of ordinary skill in the art would not have understood Tan as raising safety concerns due to the lack of deterrence of those in the art from developing anti-CGRP antagonists after Tan. Ex. 1025, 1109; Ex. 1033, 101; Ex. 1055, 88, 93; Ex. 1027 ¶ 69, claims 8, 9; Ex. 1026, claim 2; Ex. 1288, Abstract; Ex. 1294, Abstract, 487; Ex. 1295, Abstract, 1405.

(c) Olesen

We find that the safety information provided in Olesen and the additional studies cited by Petitioner, including articles by Patent Owner's experts, on balance, demonstrate that blocking the CGRP pathway in humans was considered sufficiently safe as of November 2005, and would not have discouraged a person of ordinary skill in the art from administering a humanized anti-CGRP antagonist antibody to treat a vasomotor symptom such as migraine headache. Ex. 1025; Ex. 1042, Abstract; Ex. 2019, Abstract; Ex. 1290, 657.

(d) Differences between BIBN and full-length antibodies

We find that BIBN's half-life is about 2.5 hours and that full-length antibodies, such as a full-length anti-CGRP antibody, generally have a longer half-life than BIBN. Ex. 1042, 645; Ex. 1059, 143 (Fig. 4.16). We also find that the prior art demonstrated that blocking the CGRP pathway for longer periods of time than BIBN (i.e. a longer half-life) resulted in few (if any) side effects. Ex. 1055, 93; Ex. 1082, Abstract; Ex. 1240, 923. Based on these actual studies, we find that the long half-life of an antibody would

not have discouraged a person of ordinary skill in the art from humanizing an anti-CGRP antagonist antibody. *See* Ex. 1056, 1075. Stated differently, we find that the advantages of the longer half-life of an anti-CGRP antibody for preventative treatments outweighed any potential disadvantages of the longer half-life of the antibody. *See Medichem, S.A v. Rolabo, S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006) ("a given course of action often has simultaneous advantages and disadvantages, and this does not necessarily obviate motivation to combine").

(6) Binding Affinity

We determine that a person of ordinary skill in the art would have been motivated to make a human or humanized anti-CGRP antibody having a binding affinity (K_D) of about 10 nM or less using SPR at human body temperature (i.e., 37° C). That is because (1) it was preferred for therapeutic antibodies prior to 2005 to have binding affinities less than 10 nM or 1 nM (*see* 1712 IPR Ex. 1236 ¶ 69); (2) the parties' experts testified that single digit nM affinities are obtained as a "general rule" (*see* 1712 IPR Ex. 1341 ¶ 81; Ex. 1301, 213:4–20); and (3) Dr. Tomlinson testified that "an ideal drug would have very high affinity and exquisite specificity for its target" (Ex. 1301, 214:6–12).

(7) Summary of Reasons to Combine

As of November 2005, the prior art suggested reasons that the administration of full-length anti-CGRP antagonist antibodies to treat migraine should be explored or investigated. Queen likewise provided a reason to humanize full-length anti-CGRP antagonist antibodies for immunogenicity purposes. Thus, for the reasons stated above, we find that there are clearly reasons that a person of ordinary skill in the art would have

been motivated to combine the teachings of Olesen, Tan, and Queen to pursue a method to reduce incidence of or treat a vasomotor symptom, such as a migraine headache, by administering a human or humanized monoclonal anti-CGRP antagonist antibody. *See supra* Section II.D.2.b)(1)–(3).

In *Sanofi-Aventis U.S. LLC v. Immunex Corp.*, IPR2017-01884, Paper 96 at 20 (PTAB Feb. 14, 2019), the PTAB was not persuaded that "the *potential* risk of side effects would have deterred a person of ordinary skill in the art" from developing a way to block both IL-4 and IL-13 signaling, notwithstanding Patent Owner's arguments that IL-4 and IL-13 were known to have protective effects. *Id.* (emphasis added). In the present case, Patent Owner relies on potential safety concerns based on the role of CGRP in the body and general characteristics of antibodies *in vivo*. However, we find that the evidence of alleged potential safety risks is outweighed by actual studies of CGRP antagonists, including antibodies. In this regard, we credit the testimony of Dr. Balthasar because his testimony addresses actual studies of blocking or inhibiting CGRP. *See* Ex. 1337 ¶¶ 67–76.

Accordingly, we find that any alleged safety concerns would not have deterred, discouraged, or taught away from pursuing a method for reducing incidence of or treating a vasomotor symptom, such as migraine headache, by administration of a human or humanized monoclonal anti-CGRP antagonist antibody, as recited in claims 1 and 17 of the '045 patent, and further including a full length antibody that specifically binds to the recited amino acid residues of CGRP, as recited in claim 1 of the '907 patent and the '908 patent, with the recited binding affinity recited in claim 1 of the '908 patent.

b) Reasonable Expectation of Success

The reasonable expectation of success requirement "refers to the likelihood of success in combining references to meet the limitations of the claimed invention." *Intelligent Bio-Systems, Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1367 (Fed. Cir. 2016); *see also Allergan*, 726 F.3d at 1292 ("[T]he person of ordinary skill need only have a reasonable expectation of success of developing the claimed invention."). Moreover, a reasonable expectation of success does not require "an absolute certainty for success." *Par Pharm., Inc. v. TWi Pharms., Inc*., 773 F.3d 1186, 1198 (Fed. Cir. 2014). "[O]bviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007). A reasonable expectation of success is to be assessed from the perspective of one of ordinary skill in the art at the time the invention was made (the critical date). *Life Techs., Inc. v. Clontech Labs., Inc.*, 224 F.3d 1320, 1326 (Fed. Cir. 2000).

Each of the challenged independent claims (i.e., claims 1 and 17 of the '045 patent, claim 1 of the '907 patent, and claim 1 of the '908 patent), requires administering a human or humanized monoclonal anti-CGRP antagonist antibody in an "effective amount" sufficient to effect beneficial or desired results in treating (or reducing incidence of) a vasomotor symptom such as headache or a migraine headache. Moreover, the method must be performed with the intentional purpose of "reducing incidence of or treating" or "treating" a vasomotor symptom, headache, or migraine. *See supra* Section II.B.1. Claim 1 of both the '907 patent and the '908 patent also require that the antibody be a full-length antibody. Petitioner relies on

Olesen, Tan, and Queen as support for establishing a reasonable expectation of success. Pet. 3.

(1) Olesen

Petitioner asserts that Olesen's clinical study confirmed the reasonable expectation that a CGRP antagonist could be successfully used to reduce incidence of or treat migraine. Pet. 38 (citing Ex. 1025, Abstract, 1108–09; Ex. 1040, 182–83; Ex. 1014 ¶¶ 140, 141). According to Petitioner, Olesen established that blocking the "CGRP pathway" had been clinically proven to treat migraine, and that various references, in addition to Olesen, broadly recognized CGRP antagonism as a "therapeutic principle" for treating migraine. *Id.* at 36 (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* Ex. 1014 ¶¶ 139–41.

We find that Olesen reported that BIBN (a small-molecule, CGRP receptor antagonist) was effective in treating migraine. Ex. 1025, 1104, 1108–1109. It is undisputed that BIBN is not an anti-CGRP antibody, and that an anti-CGRP antibody is larger than BIBN. Moreover, it is undisputed that BIBN binds to the CGRP receptor, and that an anti-CGRP antibody is a different type of molecule than BIBN and is intended to bind to the CGRP ligand rather than to the CGRP receptor. Accordingly, we adopt these undisputed facts as findings of fact.

We find that the data provided by Olesen only relates to a small molecule (BIBN) and to blocking a CGRP receptor. We also find that Olesen does not provide a reasonable expectation of success of administering an anti-CGRP antibody (a different compound) that binds to

the CGRP ligand rather than the CGRP receptor (a different site upstream of the receptor) to treat migraine, as further discussed below.

Although one may consider CGRP receptor antagonists and CGRP ligand antagonists as "alternatives" because both are intended to block the binding of a CGRP ligand to a CGRP receptor, the evidence of record reflects material differences between them. For example, although Petitioner dismisses cross-reactivity (an issue related only to ligand antagonism) as "mere speculation about theoretical physiological effects" (Reply 19), Petitioner does not contend that antagonizing the ligand rather than the receptor would not impede *any* binding to non-CGRP receptors. *Id.* ("CGRP is a secondary or worse binding ligand to ancillary, non-CGRP receptors"). In addition, the use of a small molecule such as BIBN would not have given rise to the same uncertainty and skepticism regarding the blood brain barrier (BBB) as would have existed in November 2005 with respect to use of a significantly larger compound, such as an antibody. *See infra* Section II.D.4.b)(4).

We find that Olesen provides no data or direction regarding the administration of a humanized monoclonal anti-CGRP antagonist antibody in an amount effective to achieve a beneficial or desired result in reducing the incidence of or treating migraine or any other vasomotor symptom, or otherwise specifically suggest such use. *See OSI Pharms., LLC v. Apotex Inc.*, 939 F.3d 1375, 1384 (Fed. Cir. 2019) (determining that "the asserted

references do not disclose any information about erlotinib's[74] efficacy in treating NSCLC in a mammal.").[75]

(2) Tan

Petitioner argues that Tan confirmed immunoblockade with anti-CGRP antagonist antibodies and that, based on Tan, "[a] POSA would have reasonably expected to reduce incidence of or treat migraine with an anti-CGRP antagonist antibody." Pet. 38–40 (citing Ex. 1022, 566, 568–572; Ex. 1014 ¶¶ 60, 86–87, 142, 144, 146). We disagree for the following reasons.

Petitioner refers to a blood pressure assay in Tan involving administration of exogenous CGRP and argues that "Tan confirmed that both MAb C4.19 and its Fab' fragment blocked the biological activity of CGRP in a blood pressure assay in rats." Pet. 39 (citing Ex. 1022, 568–69, 571; Ex. 1014 ¶ 142). There appears to be no dispute between the parties regarding the interpretation of this assay and we adopt it as a finding of fact. Petitioner also refers to another *in vivo* study in which, according to Petitioner, "Tan reported that MAb C4.19 and its Fab' fragment inhibited the biological activity of CGRP in the rat saphenous nerve model—i.e., an animal model of neurogenic inflammation that had been linked to migraine pain," that "[u]nder the conditions tested, Tan's anti-CGRP antagonist Fab' fragment demonstrated similar activity to a known CGRP-receptor

[74] OSI's 10-K stated that "[Erlotinib] is a potent, selective and orally active inhibitor of the epidermal growth factor receptor, a key oncogene in these cancers." *OSI Pharms.*, 939 F.3d at 1380.

[75] The court also stated that "we do not hold today that efficacy data is always required for a reasonable expectation of success." *OSI Pharms.*, 939 F.3d at 1385.

antagonist, $CGRP_{8-37}$," and that "[t]hese results established that an anti-CGRP antagonist antibody or a receptor inhibitor produces similar *in vivo* effects." *Id.* (citing Ex. 1022, 569–72; Ex. 1014 ¶¶ 60, 86, 87, 144, 146).

Petitioner's statement that "Tan reported that MAb C4.19 and its Fab' fragment inhibited the biological activity of CGRP in the rat saphenous nerve model" (Pet. 39) is not correct. Rather, Tan states that skin blood flow response to antidromic nerve stimulation was effectively blocked by the Fab' fragment "[i]n contrast to experiments with whole IgG," and further states the following with respect to MAb C4.19:

> MAb C4.19 IgG at 1 mg/rat given 60 min before nerve stimulation did not block the skin blood flow response to antidromic nerve stimulation *(n* = 2; Fig. 5a). Increasing the dose to 3 mg/rat did not produce a significant difference in F_{max} or AUC (P = 0.83; *n* = 4) after 60 min (Fig. 5*a).* Further nerve stimulation performed at 2h after 3 mg/rat MAb produced an AUC which was slightly smaller compared with baseline stimulation, but not by more than 16% *(n* = 2).

Ex. 1022, 569.

The dispute with respect to Tan focuses on the "16%" experimental result reported for the MAb C4.19 and the argument that Tan provided "guidance" on how to use anti-CGRP antibodies to treat migraine. Tan states that MAb C4.19 did "not . . . block[] the increased skin blood flow response to antidromic stimulation of the saphenous nerve." *Id.* at Abstract. Moreover, Patent Owner cites to Dr. Vasserot's testimony that Tan's "not more than 16% (n=2)" was a result that "cannot be statistically evaluated" and "something that I would take with caution and would need to repeat." PO Resp. 3–4, 16 (citing Ex. 2191, 118:18–119:1).

We find that, although Tan shows that its full length antibody has some anti-CGRP activity, as reflected in the blood pressure assay and blood pressure increase in the saphenous nerve assay, Tan (by its own admission) did not establish blockade of CGRP with its MAb C4.19. *See* Ex. 1022, Abstract. Moreover, Dr. Vasserot's testimony that he would need to repeat Tan's "16%" test supports a finding that Tan's data by itself is not such that it could be relied on by a POSA. We thus find that Tan did not provide data showing that a full length anti-CGRP antibody could reach the synaptic cleft, the site of action for immunoblockade, to thereby achieve inhibition of endogenous CGRP *in vivo*. *See OSI Pharms.*, 939 F.3d at 1384.

Petitioner argues that "consistent with well-understood principles of antibody pharmacokinetics and the *express guidance* of Tan, a POSA would have expected that longer distribution times and/or higher doses would improve distribution of full length antibodies to the synaptic cleft, enhancing response." Reply 10 (citing Ex. 1337 ¶¶ 24–34; Ex. 1022, 571; Ex. 1247, 3972). Indeed, Tan expressed optimism that higher concentrations or longer incubation times would achieve the desired results for anti-CGRP activity. Ex. 1022, 571 ("With repeated administration, IgG should eventually distribute into interstitial space and achieve the sufficiently high concentrations required for immunoblockade"). Tan supports this position by reference to Covell. *Id.*

Patent Owner argues that "Covell does nothing to show that an anti-CGRP antibody would distribute into the synaptic cleft, even with larger doses or longer time." PO Resp. 36. Specifically, Patent Owner argues that "[w]hile the interstitial space incorporates the synaptic cleft, the synaptic cleft represents a different biological compartment than the interstitial

spaces," and "Covell presents no data relating to an antibody's penetration of the synaptic cleft, or an antibody's ability to bind CGRP in the synaptic cleft." *Id.* at 37 (citing Ex. 2265 ¶ 90; Ex. 1022, 566). Moreover, Dr. Balthasar testified that there are "many factors to consider to answer your question about how much time would be required to achieve concentrations . . . of interest at a site of interest." Ex. 2337, 65:2–5. We find no evidence of record addressing those "many factors" in the context of an anti-CGRP antibody reaching the synaptic cleft.

As discussed above, Petitioner does not address or rebut Patent Owner's argument that Covell does not provide any data addressing the distribution of an anti-CGRP antibody into the synaptic cleft. *See* Reply 10; *supra* Section II.D.3.c)(3). Petitioner's reliance on the tissue bath experiment in Tan 1994 (Reply 10) as showing that the full-length antibody had reached equilibrium in the synaptic cleft is of limited value because, as Dr. Balthasar testified, the *in vitro* tissue bath experiment is "not exactly equivalent to an in vivo system." Ex. 1021, 705; Ex. 2339, 77:20–78:3. Thus, although Tan posited a broad approach to overcome the absence of blockade in the rat saphenous nerve assay with MAb C4.19 based on Covell, we find that neither Tan nor Covell provide a discussion of the "many factors" that would have needed to be addressed in order for a full-length anti-CGRP antibody to even reach the synaptic cleft ("site of action") *in vivo*.

We also find that Tan provides no information or data regarding the use of a full-length anti-CGRP antibody to reduce incidence of or treat a vasomotor symptom such as migraine headache (or any other disease). *See* Ex. 1022. As Tan states, "[t]he aim of the present study was to investigate

immunoblockade as an alternative strategy for probing the role of CGRP as a vasodilator *in vivo*." *Id.* at 566. Moreover, Dr. Vasserot testified that Tan does not "provide any clinical evidence regarding efficacy of administering an anti-CGRP antagonist antibody to humans to treat a disease," and that "I don't believe [Tan mentions] specific human diseases. He mentions some conditions like skin vasodilation and things like that." Ex. 2191, 122:16–123:15. But the "skin vasodilation" in Tan was simply measured (by laser Doppler fluxmetry) for the purpose of "probing the role of CGRP as an endogenous vasodilator." Ex. 1022, Abstract. Moreover, Tan found that only the Fab' fragment was effective in mediating skin vasodilation,[76] and, given Tan's lack of successful blockade with the full-length MAb C4.19, Petitioner does not satisfy its burden of showing that a person of ordinary skill in the art would have had a reasonable expectation that performing the recited method would bring about the recited result. *See supra* Section II.B.1.; *see also Intelligent Bio-Systems*, 821 F.3d at 1367 (question of reasonable expectation of success is based on the scope of the claims).

(3) Queen

Petitioner argues, based on Queen, that a person of ordinary skill in the art would have had a reasonable expectation of success in making a *humanized* anti-CGRP antagonist antibody. *See* Pet. 40–43. Patent Owner does not dispute this argument. *See generally* PO Resp., Sur-reply; *see, e.g.,* PO Resp. 43 n.12. Accordingly, we find that a person of ordinary skill in the

[76] Petitioner argues that Tan's anti-CGRP Fab' fragment was shown to have similar activity to the CGRP-receptor antagonist $CGRP_{8-37}$. Pet. 39. However, that data is different than what Tan describes for the full-length antibody. *See* Ex. 1022, Abstract.

art would have had a reasonable expectation of success in making a *humanized* anti-CGRP antagonist antibody.

(4) Blood-Brain Barrier

In this section, we make (a) factual findings as to the evidence presented and then (b) provide an analysis of the arguments and evidence as they relate to the issue of obviousness, and particularly to the question of a reasonable expectation of success.

In their written submissions, the parties rely on various documentary and testimonial evidence pertaining to whether migraine drugs would have been required to cross the blood brain barrier (BBB), and the parties highlighted several journal articles in their oral presentations to the Board. *See, e.g.*, Pet. 32, 39–40; PO Resp. 32–42; Reply 7–10; Sur-reply 21–23; Tr. 12:9–17:13, 37:3–4, 44:25–48:22, 57:13–59:24. We review the evidence and make factual findings as to the evidence presented.

(a) Evidence relied on by Patent Owner

Patent Owner relies, *inter alia*, on Levy, Fischer, Ahn,[77] Kaube, and Araki,[78] for which we make factual findings as follows:

Levy is a research article that studied administration of CGRP in rats. Levy stated: "A current hypothesis suggests that peripheral CGRP and its related meningeal vasodilatation results in activation and sensitization, leading to the generation of migraine headache. However, direct evidence supporting this idea is lacking." Ex. 2298, 698. Levy concluded: "Both topical and systemic administration of CGRP caused a significant increase in

[77] Andrew H. Ahn et al., *Where do triptans act in the treatment of migraine?*, 115 PAIN 1–4 (2005) (Ex. 2291, "Ahn").
[78] Nobuo Araki, *Migraine*, 47(3) JMAJ 124–129 (2004) (Ex. 2282, "Araki").

dural blood flow; however, neither method of CGRP administration resulted in activation or sensitization of meningeal nociceptors. The results of this study suggest that CGRP effects in the meninges, including meningeal vasodilatation, are not sufficient to activate or sensitize meningeal nociceptors." *Id.* Levy sought to "address the possibility that CGRP-induced vasodilatation may excite meningeal nociceptors by examining the vasodilatory effect of CGRP, while simultaneously recording changes in ongoing neuronal discharges of mechanosensitive Aδ and C nociceptive neurons with receptive fields located on dural blood vessels." *Id.* at 699. Levy also "examined whether CGRP can promote nociceptor sensitization by studying its effect on the mechanical responsiveness of meningeal nociceptors." *Id.* Levy observed that CGRP increases dural blood flow but does not activate meningeal nociceptors. *Id.* at 700. According to Levy, "systemic CGRP had no affect [sic] on the ongoing discharge rate of the Aδ," similar to the lack of effect of topically administered CGRP. *Id.* Further, "[t]opical administration of CGRP was also not effective in producing mechanical sensitization" as "[n]one of the Aδ or C-units increased their neuronal responses using threshold stimuli." *Id.* at 701. "Intravenous CGRP also did not produce mechanical sensitization of the meningeal nociceptors tested." *Id.* at 702.

In discussing other research, Levy stated: "The in vitro studies cited earlier did not describe any effect on discharge, and, in fact, no effect on discharge has been reported for CGRP, in vivo or in vitro, in any population of primary afferent nociceptors." *Id.* at 703. "Taken together, these data suggest that CGRP is unlikely to act directly on the peripheral terminals of nociceptors to produce increased firing or sensitization." *Id.* Discussing

another team that had obtained facilitation of responses in response to systemic infusion of CGRP, Levy stated: "our results are consistent with a growing body of evidence suggesting that the facilitatory effect of CGRP on discharge of central trigeminovascular neurons results from a central, rather than a peripheral, site of action." *Id.* at 703–704. Discussing Fischer's finding that BIBN reduced the activity of brainstem trigeminovascular neurons after central but not peripheral administration, Levy stated "[t]hese findings, together with our present results, support a central site of action for the role of CGRP in promoting migraine, as well as the antimigraine effect of CGRP antagonism by [BIBN]." *Id.* at 704.

Fischer is a research article studying topical and intravenous BIBN in rats. Ex. 2310, 5878. According to Fischer, "[l]ocal application of [BIBN] onto dural receptive fields did not change the activity of neurons in the spinal trigeminal neurons. Therefore, CGRP released from meningeal afferents is not likely to contribute to the spontaneous activity of central trigeminal neurons." *Id.* at 5881. Regarding intravenous administration of BIBN, Fischer states that "[b]ecause the neurons in our sample received convergent input from meningeal and facial areas, extracranial afferents also could have been targeted by intravenous administration of [BIBN] to bring about a reduction of the activity of central trigeminal neurons." *Id.* "In contrast to topical application, intravenous injection of [BIBN] was effective in lowering the activity of spinal trigeminal neurons. Consequently, we cannot exclude a central site of action of the CGRP receptor antagonist." *Id.* Fischer thus had two hypotheses regarding the effectiveness of intravenous BIBN, i.e., either that there was convergent input from facial areas, or there

was a central site of action. *See id.* Fischer then discusses the possibility of a central site of action as follows:

> An argument against a central effect of [BIBN] is its limited ability to penetrate the blood–brain barrier. However, it cannot be excluded that the blood–brain barrier is disrupted in the experimental situation. Even a small percentage of the intravenously applied [BIBN] crossing the intact blood–brain barrier may be sufficient to produce the changes seen in our experiments.

Id. (internal citations omitted).

Ahn is a review article. Ex. 2291, 1. Ahn states: "Because sumatriptan is hydrophilic, it penetrates the blood-brain barrier poorly, suggesting a peripheral site of action. On the other hand, it has been proposed that the barrier is compromised in migraineurs, so a CNS site of action has not been ruled out." *Id.* Ahn states: "An important model of migraine pathogenesis involves central sensitization, in which peripheral stimulation of dural and vascular afferents by electrical, chemical, or mechanical stimuli cause both excitation and sensitization of neurons in the trigeminal nucleus caudalis (TNC) with dural receptive fields." *Id.* at 2 (citations omitted). "The presence of [triptan] binding sites and triptan receptor mRNA within the CNS, notably in the dorsal raphe and periaqueductal gray of the midbrain, leaves little doubt as to the potential for CNS effects of the triptans. But the relatively low brain penetration of sumatriptan called into question whether CNS effects were at all necessary for its antimigraine activity." *Id.* (citation omitted). Ahn stated that "the greater lipophilicity and better brain penetration of the various triptans do not correlate with significantly greater clinical efficacy over sumatriptan." *Id.* (citation omitted).

That being said, Ahn stated that "[t]wo studies argue for a significant central, presynaptic mechanism. The first used single unit recordings from both presynaptic trigeminal afferents and postsynaptic neurons with dural receptive fields." *Id.* (citation omitted). Sumatriptan was unable to inhibit peripheral sensitization, but recordings of second order neurons showed that sumatriptan had inhibited the transmission of sensitized afferent activity to the central target. *Id.* "Interestingly, central neurons that had already been sensitized were not further modulated by sumatriptan." *Id.* Ahn states that another study showed that sumatriptan dose-dependently reduced the spontaneous firing rate of certain postsynaptic currents. *Id.* Ahn states that in another study, "agonists increased the spontaneous firing rate of TNC neurons with receptive fields in the sagittal sinus; co-administration of pulses of sumatriptan reduced that firing activity." *Id.* (citation omitted). "Perhaps the most direct evidence for multiple CNS sites of triptan action is the report that microinjection of naratriptan into the periaqueductal gray selectively inhibits durally-evoked nociceptive responses of TNC neurons with shared dural and facial receptive fields." *Id.* (citation omitted). One "model of activation-dependent 5-HT_{ID} receptor availability is consistent with the fact that triptans do not prevent the pain of migraine, and predicts that triptans would only be effective in experimental models of pain in which a prior stimulus has activated nociceptors and externalized the triptan receptor to the presynaptic membrane." *Id.* at 3. Ahn concluded that "studies will not only determine which brain regions are targeted by triptans, but taken together with further analysis of the respective contributions of the different triptan receptors, will provide important information on the complex pathophysiology of migraine." *Id.*

Kaube is a research article involving anaesthetized cats. Ex. 2306, 788. Discussing sumatriptan, Kaube states: "Since it has been shown that vasodilatation of cranial vessels may not necessarily be a sufficient stimulus to activate trigeminal neurones, vasoconstriction may, therefore, not be the only mechanism responsible for the clinical efficacy of the drug in migraine." *Id.* (citations omitted). Kaube discusses three proposed sites of action of sumatriptan: (1) at cranial arteries as a highly selective vasoconstrictor, (2) in the periphery at the trigeminovascular innervation of the cranium, and (3) a central locus of action. *Id.* To investigate the effects of systemically administered sumatriptan, Kaube used mannitol as a hyperosmolar agent to disrupt the blood-brain barrier. *See id.* Kaube interpreted its data as demonstrating that "sumatriptan can interact with the transmission of nociceptive input in central trigeminal neurons suggesting inhibitory modulation of synapses at the second order neurone if entry of the drug into the central neurvous system has been facilitated." *Id.* at 790. Kaube states: "[a]s the inhibition of the electrophysiological responses only occurred after the administration of both sumatriptan and mannitol, it is most likely that the disruption of the blood-brain barrier is pivotal in facilitating the inhibitory effect of sumatriptan." *Id.*

Discussing other studies with other agents, Kaube states:

> Such peripheral effects would also not depend on the presence of hyperosmolar infusions. It is not known whether the integrity of the blood-brain barrier is impaired during migraine attacks although it is important to note that drowsiness or sedation are recognized as albeit less common side effects of parenteral sumatriptan administration indicating a possible central site of action.
>
> These data are certainly consistent with a peripheral action of sumatriptan on the as yet unproven assumption that the

> blood-brain barrier is normal in migraine and suggest a further target for future anti-migraine drugs. Future clinical research with better imaging techniques, radiolabelled drugs and tracers will reveal more about the role of supraspinal and spinal structures in the pathophysiology of migraine. These data suggest that the status of the blood-brain barrier in migraine must be studied if the action and site of action of antimigraine compounds is to be understood since these drugs have significant actions in the central nervous system if access to the brain is possible.

Id. at 791.

Araki is a review article. *See* Ex. 2282, 124. Araki states "[s]ince the success of sumatriptan, various triptan agents have been developed by improving the weak points of sumatriptan (the elimination half-life in the blood is short, crossing of the blood-brain barrier is weak, and the metabolites do not have an inhibiting action on migraine.)." *Id.* at 127. Araki states that sumatriptan is effective against the concomitant symptoms of migraine such as nausea, vomiting, and photophobia, but is not very effective when administered during the aura phase and is more effective when administered during the headache phase. *Id.* Araki states that sumatriptan also causes vasoconstriction by binding to 5-HT_{1B} receptors and inhibits release of neuropeptides by binding to 5-HT_{1D} receptors found in the trigeminal nerves around blood vessels and may also act of 5-HT_{1F} receptors. *Id.* at 126–127.

(b) Evidence relied on by Patent Owner's expert

Patent Owner's expert (Dr. Ferrari) additionally relies on Exhibit 2294[79], for which we make factual findings as follows:

[79] J. Olesen et al., *Timing and Topography of Cerebral Blood Flow, Aura, and Headache during Migraine Attacks*, 28 ANN NEUROL 791–98 (1990).

Exhibit 2294 is a research article, which states:

> Further development of this pathological process was accompanied by the aura symptoms. Thereafter headache occurred while regional cerebral blood flow remained decreased. During the headache phase, regional cerebral blood flow gradually changed from abnormally low to abnormally high without apparent change in headache. In some patients headache disappeared while regional cerebral blood flow remained increased. Although regional cerebral blood flow reduction and aura symptoms in the great majority of patients were unilateral, one-third had bilateral headache. . . . Our results suggest a simple model for migraine attacks: A pathological disturbance in one cerebral hemisphere causes the aura symptoms and after a time delay, it also causes the headache by stimulating local vascular nociceptors. Bilateral headache caused by a unilateral cerebral disturbance may be explained by recent neuroanatomical and neurophysiological findings.

Ex. 2294, Abstract.

Dr. Ferrari also opines that, based on observations originally made in the 1930's, migraine was for a long time thought by many to be a vascular disorder caused primarily by vasodilation of intracranial and extracerebral arteries, where the aura was induced by vasoconstriction followed by a rebound vasodilation that caused a headache. Ex. 2268 ¶ 28 (citing Ex. 2289, 374–375). Under this theory, vasodilation was considered to mechanically activate trigeminal nerves which supply blood vessels. *Id.* (citing Ex. 2290, 73). Pain was thought to be associated with activation of nociceptors located in the walls of extracerebral blood vessels, which responded with local release of neuronal messengers from vascular sensory nerve fibers connected to the trigeminocervical complex in the brain stem. *Id.* This theory was supported by the success of ergotamine and triptans,

which had vasoconstrictor effects. *Id.* ¶ 29 (citing Ex. 2291, 1; Ex. 2308, 743; Ex. 2291, 1).

However, Dr. Ferrari opines that by November 14, 2005, "there was a body of evidence to suggest that the vascular theory did not provide a complete answer" because blood vessel dilation alone was insufficient to trigger migraine; headache pain could start when vessels were vasoconstricted; and migraine pain was not always temporally correlated with vasodilation. *Id.* ¶ 30 (citing Ex. 2293, S239; Ex. 2294, Abstract). Dr. Ferrari opines that the evidence at this time suggested that vasodilation was likely not the cause of migraine, although he recognizes that several prominent thought leaders in the field adhered to the theory and a majority of the relevant scientific community would have agreed that vasodilation was associated with migraine. *Id.* ¶ 31.

According to Dr. Ferrari, scientists in the early-2000's were "leaning more in favor of the hypothesis that the central nervous system was at least in part responsible for migraine," i.e., the central neuronal theory. *Id.* ¶ 32 (citing Ex. 1089, 258; Ex. 2308, Abstract; Ex. 2292, 387). This theory suggested that migraine involved activation and sensitization (sometimes referred to as hypersensitization) of the trigeminovascular pathways. *Id.* (citing Ex. 2295, 283; Ex. 2289, 373–375). This theory suggested that headache in migraine resulted from abnormal firing of neurons and neurotransmitter release in the brain. *Id.*

Dr. Ferrari opines that one aspect of the central neuronal theory was a phenomenon called cortical spreading depression ("CSD"). Ex. 2268 ¶ 33. Dr. Ferrari opines that some, but not all, leading researchers were of the view that, at least in some instances, the abnormal activity included a brief

period of neuronal excitation characterized by a transient burst of activity over a period of a few seconds, followed by a depression that involved a complete loss of neuronal activity that could last a few seconds, progressing as a self-propagating wave of neuronal and glial depolarization, with an increase in extracellular potassium and neurotransmitters, associated with cerebral blood flow changes. *Id.* ¶¶ 33–34 (citing Ex. 2296, 1447–1448; Ex. 2289, 375, 377; Ex. 2292, 388). Dr. Ferrari opines that although the theory was not universally accepted, a significant proportion of researchers considered CSD to be the cause of aura experienced by some migraineurs. *Id.* ¶ 34 (citing Ex. 2295, 280–281; Ex. 2308, 742).

Dr. Ferrari further opines that in the 1980's and 1990's, Professor Mike Moskowitz and colleagues at Harvard championed the neurogenic inflammation theory that activation of the trigeminal system causes the release of vasoactive peptides (e.g., Substance P, neurokinin A, and CGRP) onto dural tissues. *Id.* ¶ 35 (citing Ex. 2289, 375; Ex. 2297, Abstract). According to this theory, inflammation was characterized by vasodilation, plasma protein extravasation (PPE), release of pre-inflammatory mediators from mast cells, and white cell adhesion. *Id.* ¶ 36 (citing Ex. 2289, 374; Ex. 2291, 1–2; Ex. 1040, 179). Dr. Ferrari opines that by November 14, 2005, CGRP was considered to be involved in the vasodilation, and to enhance Substance P, but was insufficient alone to drive inflammation. *Id.* (citing Ex. 2298, 702–703; Ex. 1040, 179). Dr. Ferrari further opines that neurogenic inflammation was observed in rodents but by November 14, 2005, there was no evidence for it occurring in humans and also Substance P antagonists were not effective antimigraine agents. *Id.* ¶ 37 (citing Ex. 2299, 1234–1235; Ex. 2300, Abstract).

Dr. Ferrari opines that before November 14, 2005, a person of ordinary skill would have been aware of the existence of the debate among key opinion leaders as to the pathogenesis of migraine and would have regarded it as largely unresolved. *Id.* ¶ 38. Dr. Ferrari opines that sumatriptan was developed as a selective vasoconstrictor blood vessels but was discovered in addition to block neutrally-mediated sensory neurotransmitter release and nociceptive (pain) neurotransmission within the meninges. *Id.* (citing Ex. 2302, 145–146). Dr. Ferrari opines that many researchers believed that the relevant site of action for migraine was behind the BBB. *Id.* ¶ 39 (citing Ex. 2291, 1, 3).

Dr. Ferrari opines that only lipid-soluble solutes that can freely diffuse through the capillary endothelial membrane may passively cross the BBB. *Id.* ¶ 41 (citing Ex. 2303, 253). Dr. Ferrari opines that small molecule drugs typically of 50–1000 daltons can cross the BBB easily. *Id.* (citing Ex. 2304, 260). Dr. Ferrari opines that 98% of small molecule drugs and almost 100% of large molecule drugs (e.g., antibodies) do not cross the blood brain barrier. *Id.* (citing Ex. 2284, 3–4, 8). Dr. Tomlinson opines that the antibody concentration beyond the BBB has been reported to be only about 0.1% of the antibody concentration in the plasma. *Id.*; Ex. 2271 ¶ 68. Dr. Foord opines that this concentration (0.1% of the antibody concentration in the plasma) would have been considered inconsequential and not therapeutically effective given the goal to neutralize all of the CGRP neuropeptides present. Ex. 2265 ¶ 91; *see also* Ex. 2268 ¶ 41.

Dr. Ferrari opines that some migraine animal models can increase the permeability of the BBB. Ex. 2268 ¶ 42 (citing Ex. 2291, 2–3; Ex. 2306, 790). Dr. Ferrari opines that Dreier et al. showed that a subject who had

familial hemiplegic migraine II developed a migraine attack that caused opening of the BBB, and Smith et al. demonstrated that a subject during a migraine attack also had a breakdown of the BBB. *Id.* ¶ 88 (citing Ex. 2222, Abstract; Ex. 2223, 1309). Dr. Ferrari opines on this basis that "there are human case reports showing that there is a transient opening of the BBB during migraine attacks, which would allow drugs, such as triptans, to cross the BBB. *Id.*

Dr. Ferrari opines that a person of ordinary skill would not have contemplated using a full-length CGRP antagonist antibody unable to cross the BBB and would not have expected anti-CGRP antagonist antibodies to be effective in treating migraine. *Id.* ¶ 93. Dr. Ferrari opines that a full-length antibody would not have been contemplated as a therapeutic because it is not sufficiently bioavailable. *Id.* ¶ 100.

Dr. Ferrari also opines that a person of ordinary skill reviewing Exhibit 1241[80] would have realized that the two lipophilic β-blockers (propranolol and metoprolol) both crossed the BBB and "appeared in high concentrations in brain tissue." *Id.* ¶ 86 (citing Ex. 1241, Abstract). Dr. Ferrari also opines that atenolol, a hydrophilic β-blocker, was not found at as high a concentration in the brain as propranolol and metoprolol, but it still crossed the BBB. *Id.*

[80] J.M. Cruickshank et al., *β-Adrenoreceptor-blocking agents and the blood-brain barrier*, 59 CLINICAL SCIENCE 453s–55s (1980) (Ex. 1241, "Cruickshank").

(c) Evidence relied on by Petitioner

Petitioner relies, *inter alia*, on Petersen 2004, Petersen 2005, Edvinsson,[81] Arulmani,[82] Cruikshank, Storer, Healy,[83] Messlinger, Hay,[84] and Ferrari and Saxena,[85] for which we make factual findings as follows[86]:

Petersen 2004 is a research article that studied the effect of CGRP and BIBN on vasodilation in anaesthetized rats. Ex. 1090, 698. Petersen 2004 reports that infused BIBN blocked vasodilation of the middle meningeal artery caused by CGRP and transcranial electrical stimulation but did not significantly reduce or block vasodilation of the cortical pial arteries caused by CGRP or transcranial electrical stimulation. *See id.* at 698 (definitions and methods), 700–701 (results), 701–703 (discussion). Petersen 2004 states: "[BIBN] is a relatively large hydrophilic compound and is therefore unlikely to pass the blood–brain barrier (BBB) in acute experiments.

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[81] Lars Edvinsson, *Clinical Data on the CGRP Antagonist BIBN4096BS for Treatment of Migraine Attacks*, 11(1) CNS DRUG REVIEWS 69–76 (2005) (Ex. 2215, "Edvinsson").

[82] U. Arulmani et al., *Calcitonin gene-related peptide and its role in migraine pathophysiology*, 500 EUROPEAN J. OF PHARMACOLOGY 315–330 (2004) (Ex. 1031, "Arulmani").

[83] Judith M. Healy et al., *Pharmacokinetics and Biodistribution of Novel Aptamer Compositions*, 21(12) PHARMACEUTICAL RESEARCH 2234 (Dec. 2004) (Ex. 1310, "Healy").

[84] D. L. Hay et al., *The Preclinical Pharmacology of BIBN4096BS, a CGRP Antagonist*, 23(1) CARDIOVASCULAR DRUG REVIEWS 31–42 (2005) (Ex. 2068, "Hay").

[85] Michel D. Ferrari and Pramod R.S. Saxena, *Clinical effects and mechanism of action of sumatriptan in migraine*, 94 (Suppl.) CLINICAL NEUROLOGY AND NEUROSURGERY S73–S77 (1992) (Ex. 1281, "Ferrari and Saxena").

[86] Petitioner also discusses Levy, Fischer, and Ahn, which are relied on by Patent Owner, and which are also discussed in this section. Petitioner also relies on Lassen and Vater, which we discuss *supra*.

However, no direct data exist to support this." *Id.* at 702. Petersen 2004 concludes:

> It seems that [BIBN] does not pass the BBB in the rat, but is very effective in preventing CGRP-induced vasodilatation in vessels without a BBB.
>
> The present study strongly suggest that the clinically effective migraine drug [BIBN] (Olesen *et al*., 2004) does not cross the BBB. With the caution of species differences in BBB function or the possible occurrence of transient BBB changes during the migraine attack, this indicates that dural arteries may play an important role in migraine pathogenesis.

Id. at 703.

Dr. Charles opined that Petersen 2004 concluded that BIBN, while proven to be clinically effective in treating migraine, does not cross the blood brain barrier due to its hydrophilicity and size. Ex. 1014 ¶ 151 (citing Ex. 1090, 702–703). However, Dr. Ferrari opines that a person of ordinary skill would have been skeptical of the conclusion that BIBN does not cross the BBB based on Petersen. Ex. 2268 ¶ 70. Dr. Ferrari opines that Petersen did not measure whether BIBN crosses the BBB because Petersen did not measure BIBN levels inside the brain. *Id.* ¶ 62. Dr. Ferrari opines that Petersen 2004 indirectly draws the conclusion that BIBN does not cross the BBB because of the difference in the inhibitory effect of BIBN on the middle meningeal artery and the pial artery. *Id.* ¶ 63. Nevertheless, Dr. Ferrari opines that in the pial artery experiment, the control group increased in diameter by approximately 30% after administration of αCGRP, but with a large amount of variability, and a person of ordinary skill would have noticed that BIBN prevented the majority of vasodilation in the pial artery that is caused by αCGRP (approximately 5% increase in the pial artery diameter compared with approximately 30–35% for control). *Id.* ¶ 64.

Dr. Ferrari opines that Petersen 2004 recognized the decrease in pial artery diameter and local cortical cerebral blood flow, stating "[t]he PA and $LCBF_{Flux}$ responses were attenuated dose-dependently, but not significantly by the antagonist [BIBN]." *Id.* ¶ 66 (quoting Ex. 1090, 700) (alteration to Peterson 2004). Dr. Ferrari opines that Petersen 2004 showed the p-value of 0.08, which was just outside the range of statistical significance and opines that if Petersen had performed the experiment a few more times (i.e., by increasing the power of the experiment), Petersen might have detected a statistical change. *Id.* ¶ 67. Dr. Ferrari also opines that Petersen 2004 admits that "no direct data exist[s] to support" that BIBN does not cross the BBB. *Id.* ¶ 69 (quoting Ex. 1090, 702) (alteration to Peterson 2004). Dr. Ferrari also opines that it was not settled by November 14, 2005, nor is it completely settled today, whether pial arteries possess a BBB. *Id.* ¶ 63 (citing Ex. 2239, Abstract).

Dr. Charles opines that Dr. Ferrari's opinions on Petersen 2004's pial arteries ignore, *inter alia*, Figure 4 of Petersen 2004, which evaluates the effects of transcranial electrical stimulation on endogenous CGRP, and Petersen 2004's remarks on the statistical procedure. *See* Ex. 1338 ¶¶ 39–40. Dr. Charles also opines that pial arteries were understood to be extremely impermeable. *Id.* ¶ 41. Dr. Charles also opines that Dr. Ferrari ignores that Petersen 2005 observed that CGRP infusion causes immediate and delayed headaches in healthy volunteers, which were blocked by pretreatment with BIBN. *Id.* ¶ 44 (citing Ex. 1333, Abstract, 203, 205–206).

Petersen 2005 is a clinical study. Ex. 1333. Petersen 2005 reports that "[BIBN] completely inhibits the effects of CGRP on the superficial temporal and radial artery, as well as its effect on HR [heart rate]. In

contrast, it had no significant effect on the CGRP-mediated CBF [cerebral blood flow] and V_{MCA} [middle cerebral artery blood flow velocity] increase." *Id.* at 211. Petersen 2005 concludes: "Whether the effect takes place in the dura mater or in extracranial arteries and whether areas of the brain stem or hypothalamus devoid of a blood-brain barrier also play a role remain to be determined." *Id*.

Petersen 2005 states that infusion of CGRP in healthy volunteers caused a sensation of fullness in the head or mild headache corresponding to a headache score of 1. Ex. 1333, 209–210. Petersen 2005 then states that a migraine is only induced in migraine patients but not in healthy volunteers. *Id.* at 210.

Dr. Charles opines that BIBN did not block CGRP-induced symptoms in regions protected by the BBB. *Id.* ¶ 45. Dr. Charles opines that Petersen 2004 and Petersen 2005 collectively demonstrate that anti-CGRP drugs like BIBN would treat or prevent migraine predominantly in an extracerebral manner, i.e., without needing to cross the BBB to be therapeutically effective. *Id.* ¶ 47.

Edvinsson is a review article, which reviewed, *inter alia*, Olesen and Petersen 2004. *See* Ex. 2215, 69, 76 (references 21 and 25). Edvinsson states: "In migraine and cluster headache, there is a clear association between the headache and the release of CGRP, but not with any of the other neuronal messengers that are stored to a lower degree in this system." *Id.* at 70. After discussing Petersen 2004, Edvinsson states: "These data on [BIBN] suggest that the blocker does not freely pass the blood-brain barrier in the rat, but is very effective in preventing vasodilatation of vessels without this feature." *Id.* at 72. Regarding a different study of the pain free

rate after BIBN, Edvinsson states: "The response rate to [BIBN] was 44% at 2 h and 56% at 4 h; at the same time the placebo effect was 2% and 10% which leaves us with a good headache-free rate of 42 to 46% (in the meta-analysis it was about 20% for sumatriptan). This would indicate superiority of [BIBN]. In addition, the sustained 24 h headache-free rate was 47% (placebo 15%), which also compares well with the sumatriptan pain-free rate of 20%." *Id.* at 74–75 (citations omitted). Edvinsson concludes:

> In a rat model of vascular headache and in a study of healthy volunteers, [BIBN] does not appear to pass the blood-brain barrier freely and may, therefore, exert its antagonistic actions on extracerebral arteries and neuronal structures (parts of the trigeminovascular system outside the CNS). Although it may be tempting to propose a hypothesis on the site of origin of migraine headache we still need more data to support it. The site of the antimigraine effect of [BIBN], as judged from the available data, suggests that it does not have to reach the CNS to exert its therapeutic action and thereby its side effects may be limited. . . . Future studies may show other mechanisms of action of [BIBN], but at this stage this CGRP antagonist appears to act primarily as a blocker of neuronal transmission in the trigeminovascular system.

Id. at 75 (citations omitted).

Arulmani is a review article. Arulmani states:

> Several studies have reported that inhibition of trigeminal CGRP release may underlie the therapeutic efficacy of triptans. . . . In marked contrast, however, it has been shown that compounds that exclusively inhibit neurogenic inflammation (e.g. tachykinin NK1 receptor antagonists) and the trigeminovascular system (e.g. 5-HT1D receptor agonists) are ineffective in acute migraine treatment. Therefore, it is not yet clear whether the inhibition of trigeminal CGRP release per se is an important mechanism behind the therapeutic efficacy of antimigraine agents. Certainly, the above effect of triptans (inhibition of trigeminal CGRP

> release) may be secondary to the alleviation of headache produced by cranial vasoconstriction. Accordingly, it is tempting to suggest that vasoconstriction of cranial blood vessels, including arteriovenous anastomoses, is the most important effect of the acutely acting antimigraine drugs available thus far. This suggestion gains weight when considering that: (i) sumatriptan, which poorly penetrates the central nervous system, did not have any effect on capsaicin-induced CGRP release (see Fig. 7), while potently constricting arteriovenous anastomoses, (ii) the 5-HT1B/1D receptor agonists . . . are effective in aborting acute migraine attacks due to vasoconstrictor effects via 5-HT1B receptors, and (iii) [BIBN] is reported to be effective in migraine based on its antagonism of CGRP receptors and its failure to block capsaicin-induced CGRP release (see Fig. 5). Therefore, the above lines of evidence support the contention that the therapeutic action of antimigraine compounds is mainly due to cranial vasoconstriction or the preclusion of CGRP-induced cranial vasodilatation rather than inhibition of trigeminal CGRP release. Indeed, several potential sites of action for [BIBN] have been reported, other than blocking cranial vasodilatation, namely, inhibition of neurogenic inflammation and nociceptive pathways. Nevertheless, [BIBN] does not seem to penetrate the blood–brain barrier. . . ; hence, it is important to investigate the effects of [BIBN] on the neuronal receptors (nociceptive pathways).

Ex. 1031, 325–326 (citations omitted).

Cruickshank is a clinical study in which beta-adrenoreceptor blockers (propranolol, metoprolol, and atenolol) were administered to neurosurgical patients, eight with subarachnoid hemorrhage, five with aneurysms, and two with depression/anxiety). *See* Ex. 1241, 453s. The study reported that the cerebrospinal fluid levels of both propranolol and metoprolol in the present study were roughly equivalent to the free drug concentration in the plasma. *See id.* at 454s–55s.

Storer is a research article involving anaesthetized cats. Ex. 2307, 1172. Storer concluded that "[i]ntravenous [BIBN] resulted in a dose-dependent inhibition of trigeminocervical SSS-evoked activity [, that the] data suggest that there are non-presynaptic CGRP receptors in the trigeminocervical complex that can be inhibited by CGRP receptor blockade and that a CGRP receptor antagonist would be effective in the acute treatment of migraine and cluster headache." *Id.* at Abstract. Storer states: "It seems more likely that acute anti-migraine compounds work by blocking trigeminal nociceptive traffic either at the vessel/nerve interface, or in the trigeminocervical complex, or both. The new data establish that for CGRP antagonists the trigeminocervical complex is one possible target, and further suggest that newer compounds should actively target central structures." *Id.* at 1179 (citations omitted).

Healy is a study of aptamers in rats. Ex. 1310, 2236. The purpose of Healy was to "determine plasma pharmacokinetics and tissue distribution in rat of several novel aptamer compositions, including fully 2'-*O*-methylated oligonucleotides and conjugates bearing high-molecular weight polyethylene glycol (PEG) polymers, cell-permeating peptides, and cholesterol." *Id.* at 2234. Healy stated that "[n]one of the aptamer conjugates or compositions showed a propensity to traverse the blood/brain barrier." *Id.* at 2244.

Messlinger is an abstract, reporting on a study of aptamers in an animal model of trigeminovascular activation and meningeal blood flow. Ex. 1240, 923. Messlinger reported that "[t]he Spiegelmer [CGRP-binding aptamer] caused dose-dependent, significant inhibition of the evoked blood flow responses to about 50% of the control. Topical application was most effective." *Id.*

Hay is a review article. *See* Ex. 2068. Hay states: "There is currently no direct data on whether [BIBN] can cross the blood-brain barrier, although it is predicted to be charged at physiological pH, suggesting it probably will not penetrate this structure. Vasodilation may not be the primary mechanism of action of CGRP in migraine. [BIBN] has been used to demonstrate the role of CGRP receptors within the trigeminal pathway." Ex. 2068, 39 (citations omitted).

Ferrari and Saxena is a review article. *See* Ex. 1281. Ferrari and Saxena states: "Important pharmacological actions of sumatriptan are (i) poor penetration of the blood-brain barrier suggesting a peripheral point of action; (ii) 5-HT_1-like /5-HT_{1d} receptor- mediated vasoconstriction of large cerebral arteries and dural vessels; and (iii) blockade of neurogenic durai inflammation via 5 -HT_{1d} autoreceptor-mediated inhibition of vasoactive neuropeptides within the trigeminovascular system." *Id.* at Abstract.

(d) Evidence relied on by Petitioner's expert

Petitioner's expert (i.e., Dr. Charles) additionally relies on Emilien,[87] Humphrey,[88] and Humphrey 1991,[89] for which we make factual findings as follows:

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[87] G. Emilien et al., *Current therapeutic uses and potential of b-adrenoceptor agonists and antagonists*, 53 EUR. J. CLIN. PHARMACOL. 389–404 (1998) (Ex. 1242, "Emilien").

[88] Patrick P. A. Humphrey et al., *Serotonin and Migraine*, 53 ANNALS NEW YORK ACADEMY OF SCIENCES 587–600 (Ex. 1243, "Humphrey"). Petitioner submits this reference as published in 1990, and Patent Owner does not dispute this reference date.

[89] Patrick P. A. Humphrey et al., *Preclinical Studies on the Anti-Migraine Drug, Sumatriptan*, 31 EUR. NEUR. 281–290 (1991) (Ex. 1244, "Humphrey 1991").

Emilien is a review article that discusses therapeutic uses of beta-adrenoceptor agonists and antagonists. Ex. 1242. Emilien states that "[s]ome are lipid soluble (propranolol, oxprenolol, metoprolol, labetalol), while others are only water soluble (nadolol) or partially lipid soluble." *Id.* at 391. Emilien states that "[t]here are high concentrations of both β1- and β2-adrenoceptors in the brain." *Id.* at 395. Emilien states:

> Centrally active β-adrenoceptor blockers, such as propranolol, are effective in the prophylaxis of migraine but seem to have no effect on the symptoms of an acute attack. Although neither the pathophysiological basis of migraine nor the mechanism of action of β- blockers is understood, the therapeutic effect may have to do with inhibition of amine-induced vasodilatation in the early phase of an attack. Therapeutically effective β-adrenoceptor blockers are propranolol, timolol, nadolol and metoprolol. These drugs reduce the frequency of attacks in common as well as classical migraine. . . . The ability of certain β-blockers to modulate serotonergic systems has been postulated to contribute to their antimigraine efficacy.

Id. at 396 (citations omitted).

Humphrey is a review article. Ex. 1243. Humphrey presents two historical hypotheses of migraine:

> Wolff's "vascular hypothesis" of migraine proposed that the head-ache was caused by a period of extracranial vasodilatation while the preceding neurological symptoms (if present) were thought to result from a focal intracranial vasoconstriction. The precipitating factors were considered to be varied, but humoral hypotheses were invariably implicated. However, it was never satisfactorily explained how the headache could be localized to one (sometimes varying) side of the head and why physiologically induced cephalic vasodilation did not induce an attack even in migraineurs. This led to the opposite view that migraine was entirely a central nervous system disorder and that all the symptoms of the disease, including the head pain, could be explained by a derangement of brain function.

Id. at 588 (citations omitted). Humphrey states that intravenous serotonin can ameliorate a migraine attack, likely acting as a vasoconstrictor. *Id.* With respect to sumatriptan, Humphrey states:

> Sumatriptan undoubtedly has a selective cranial vasoconstrictor activity and in the absence of any demonstrable analgesic activity in animals it is the opinion of the authors that this is the mechanism of its anti-migraine action. Others have suggested it may have a central component of action despite the low lipophilicity and high basicity of the compound (like serotonin). Regardless of the relative merits of these arguments, studies, both in the laboratory and in the clinic, should not only lead to a better understanding of the mechanism of action of sumatriptan but also hopefully a greater understanding of the pathophysiological mechanisms involved in the disease itself.

Id. at 591.

Humphrey 1991 is a review article. Ex. 1244. Humphrey states with respect to experiments with sumatriptan: "Although an inhibitory effect on neurotransmitter release from trigeminal nerve endings was implicated, the action of sumatriptan could still predominantly involve a direct vasoconstrictor action on dural blood vessels that itself would be expected to reduce extravasation." *Id.* at 285. Humphrey 1991 concludes: "Sumatriptan is a highly selective agonist at 5-HT_1-like receptors that mediate constriction of some cranial vessels, particularly those in the dura mater which are believed to be distended and inflamed during a migraine headache." *Id.* at 289.

Dr. Charles opines that, in 2005, it was known that migraine drugs did not need to cross the blood brain barrier to produce therapeutic effects. Ex. 1014 ¶ 149. Dr. Charles opines that it was known that intracranial vessels producing pain during migraine attacks are outside the blood brain barrier. *Id.* ¶ 150 (citing Ex. 1094, 228; Ex. 1246, 106). Dr. Charles opines

that other migraine drugs were known to be effective despite poor penetration of the blood brain barrier. *Id.* ¶ 151 (citing Ex. 1241, Abstract, 454s–55s; Ex. 1242, Abstract; Ex. 1243, 591–592; Ex. 1244, 286).[90]

Dr. Charles opines that Dr. Ferrari relies upon animal studies involving invasive manipulations, which are not representative of physiological conditions, including an open cranial window in Fischer and craniotomies in Storer and Levy. Ex. 1338 ¶ 49, 51. Dr. Charles opines that Storer and Fischer did not exclude the periphery as BIBN's site of action. *Id.* ¶ 50. Dr. Charles also opined that Levy used too short a timeframe. *Id.* ¶ 52.

Dr. Charles further opines that Dr. Ferrari appears to apply two different standards in determining whether a drug has limited ability to cross the BBB because a mere 0.006% of an injected dose of sumatriptan was able to cross the BBB. *Id.* ¶ 58 (citing Ex. 2268 ¶ 88; Ex. 1243, Table 3).

Under a section heading titled "Transient Changes in the BBB During Migraine Attacks Were Speculative," Dr. Charles opines that the case studies relied on by Dr. Ferrari were limited to patients with a very severe form of headaches such as familial hemiplegic migraine type II or prolonged migraine (citing Ex. 2268 ¶ 88; Ex. 2222; Ex. 2223), and that it was unclear whether such changes occur in *all* migraine patients. Ex. 1338 ¶ 64.

(e) Analysis

As discussed above, the blood brain barrier (BBB) raised uncertainty, unpredictability, and skepticism in using full-length anti-CGRP antibodies to

[90] We review Dr. Charles's treatment of Petersen and BIBN (Ex. 1014 ¶ 151; Ex. 1338 ¶¶ 36–42) in the discussion of Petersen 2004 and Petersen 2005, *supra*, this section.

reduce incidence of or treat headache such as migraine, i.e., whether anti-CGRP antibodies needed to cross the blood-brain barrier to reduce incidence of or treat headache such as migraine.

Petitioner argues that a person of ordinary skill would have understood that an anti-CGRP antibody would not have been required to cross the BBB. Pet. 32; *see also* Ex. 1014 ¶ 149 (Charles Declaration).[91] Petitioner offers evidence that BIBN was successful in treating migraine in Olesen and related studies. *See* Ex. 1025; Pet. 32 (citing Ex. 1090, 702–703). Petersen 2004 concluded that BIBN does not cross the blood brain barrier because it found an effect, *inter alia*, on the middle meningeal artery but it found an effect on pial arteries was not statistically significant. Ex. 1090, 701–703; Ex. 2268 ¶ 63. However, Petersen 2004 acknowledged that there was no direct evidence that BIBN does not cross the blood brain barrier. Ex. 1090, 702; Ex. 2268 ¶¶ 62–70; Ex. 2298, 698. Also, some researchers believed that there was transient permeability of the BBB in at least some migraine patients. *See* Ex. 1338 ¶ 64.

Petitioner argues that other migraine drugs were known to be effective despite poor penetration of the BBB. Pet. 32–33 (citing Ex. 1241, Abstract, 454s–55s; Ex. 1242, Abstract; Ex. 1243, 591–92; Ex. 1244, 286; Ex. 1014 ¶ 151); Reply 9–10 (citing Ex. 1338 ¶¶ 18–21, 57–62, 63–66; Ex. 1281, S73;

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[91] Dr. Charles also opines that, if required to cross the BBB, an anti-CGRP antibody would have been understood to cross the blood brain barrier (BBB) if and when the BBB is temporarily breached by a migraine attack. Ex. 1338 (Second Charles Declaration) ¶ 65. However, this is not an argument made by Petitioner, and is therefore waived. *See* Reply 7–10. Further, we agree with Patent Owner that Dr. Charles does not provide support for this opinion. Accordingly, even if this argument were not waived, we do not give it weight on this record.

Ex. 1303, 23:22–24:22; Ex. 2291, Abstract; PO Resp. 13, 39 n.11). One such piece of evidence, Ferrari and Saxena, concluded that sumatriptan had poor penetration of the blood-brain barrier suggesting a peripheral point of action. Ex. 1281, Abstract. However, other evidence had a mixed view. Ahn stated "[b]ecause sumatriptan is hydrophilic, it penetrates the blood-brain barrier poorly, suggesting a peripheral site of action. On the other hand, it has been proposed that the barrier is compromised in migraineurs, so a CNS site of action has not been ruled out." Ex. 2291, 1; *see also* Ex. 2268 ¶¶ 39, 42. Ahn noted "[triptan] binding sites and triptan receptor mRNA within the CNS" and, on the other hand, that "greater lipophilicity and better brain penetration do not correlate with significantly greater clinical efficacy over sumatriptan." Ex. 2291, 2. Levy stated that a theory that peripheral CGRP caused migraine headache was lacking direct evidence. *See* Ex. 2298, 698; Ex. 2268 ¶ 36. Accordingly, there were also differences of opinion as to whether other migraine drugs, e.g., sumatriptan, crossed the blood brain barrier.

We determine that in 2005, a POSA would have been aware of the differences of opinion among key opinion leaders as to the pathogenesis of migraine and that it was largely unresolved. *See* Ex. 2268 ¶ 38. Dr. Charles opines that it was known that intracranial vessels producing pain during migraine attacks are outside the blood brain barrier. Ex. 1014 ¶ 150. However, Dr. Ferrari opines that by November 14, 2005, "there was a body of evidence to suggest that the vascular theory did not provide a complete answer" because blood vessel dilation alone was insufficient to trigger migraine; headache pain could start when vessels were vasoconstricted; and

migraine pain was not always temporally correlated with vasodilation. Ex. 2268 ¶ 30 (citing Ex. 2293, S239; Ex. 2294, Abstract).

We find that Dr. Ferrari's opinion is supported by the exhibits cited by Patent Owner. For example, Bussone, a 2004 article, states:

> Migraine has long been regarded as a vascular disorder because of the throbbing nature of the pain. However, vascular changes do not provide sufficient explanation for the pathophysiology of migraine. Up to one third of patients do not have throbbing pain. One of the most powerful arguments against the vascular theory is that it is in absolute conflict with the blood flow data that should be its greatest support. It is clear from Olesen's studies, and reinforced by the more recent studies of Cutrer et al. that the headache phase of migraine with aura starts while blood flow is still reduced. Thus, the headache pain cannot be due simply to vasodilation. There seems to be an increasing body of evidence for the concept of central neuronal hyperexcitability as a pivotal physiological disturbance predisposing to migraine.

Ex. 2293, S239 (citing, *inter alia*, Ex. 2294) (cited in PO Resp. 8). Exhibit 2294 reported that headache appeared during aura while blood flow was still decreased. Ex. 2294, Abstract; *see also* Ex. 1243, 588 (critiquing Wolff's vascular hypothesis).

Further, other articles from 2005, including Fischer and Levy relied on by Petitioner, express doubts as to the hypothesis that migraine had a peripheral cause or peripheral treatment. *See* Ex. 2298, 698, 703; Ex. 2310, 5881. Fischer stated: "Consequently, we cannot exclude a central site of action of the CGRP receptor antagonist." Ex. 2310, 5878. Levy stated "[t]hese findings, together with our present results, support a central site of action for the role of CGRP in promoting migraine, as well as the antimigraine effect of CGRP antagonism by BIBN4096." Ex. 2298, 704.

Regardless of whether there were methodological flaws in any of the research studies relied on by Patent Owner, as argued by Petitioner (Reply 8–10) and as opined by Petitioner's expert (Ex. 1338 ¶¶ 48–53), we determine that these articles serve as evidence that a person of ordinary skill would have been confronted with different viewpoints as to whether migraine was susceptible to a peripheral cause or peripheral treatment. In other words, we consider the journal articles to support Dr. Ferrari's opinion as to the mindset of a person of ordinary skill at the time of the invention in 2005, whether or not the journal articles may have methodological flaws.

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

We determine that the fact pattern in this case resembles an aspect of the fact pattern in *Honeywell International Inc. v. Mexichem Amanco Holding S.A. DE C.V.*, 865 F.3d 1348 (Fed. Cir. 2017). In *Honeywell*, the Court reviewed a Board decision in which the Board found that "'the skilled artisan would *no more have expected failure . . . than would have expected success*.'" *Id.* at 1355 (emphasis in Federal Circuit opinion). The Federal Circuit determined that "the Board erred in dismissing Honeywell's evidence of unpredictability in the art when it stated that one of ordinary skill would no more have expected failure than success in combining the

references." *Id.* The Court found that the Board had improperly shifted the burden in "argu[ing] that Honeywell did not persuasively establish that one of ordinary skill would have expected failure." *Id.* (emphasis omitted). The Court then stated that "[t]he Board made what amounts to a finding that one of ordinary skill would not have expected success, because Honeywell's evidence persuasively established the 'overall unpredictability' in the art, but then glossed over that finding with a 'routine testing' rationale because Honeywell did not persuasively prove an expectation of failure." *Id.* (emphasis omitted). The Court reversed, reasoning that "[u]npredictability of results equates more with nonobviousness rather than obviousness, whereas that which is predictable is more likely to be obvious." *Id.* at 1356.[92]

We recognize that there are other cases in which the Federal Circuit has explained that absolute certainty is not required and some level of unpredictability in the art cannot defeat a showing of a reasonable expectation of success. *See, e.g.*, *Pfizer,* 480 F.3d at 1364 (Fed. Cir. 2007) ("Indeed, a rule of law equating unpredictability to patentability, applied in this case, would mean that any new salt—including those specifically listed in the '909 patent itself—would separately be patentable, simply because the formation and properties of each salt must be verified through testing."). *Honeywell* is nevertheless instructive that, when there is a high enough quantum of unpredictability, e.g., where the chance of failure is equal to the chance of success, a proponent of unpatentability may not have met its

[92] We recognize that in *Honeywell*, the Court also concluded that the Board erred in its treatment of unexpected results, which may be a separate aspect of that case. *Id.* at 1354–55. We thus draw from the *Honeywell* case while recognizing that there may be some differences.

burden of showing a reasonable expectation of success. Petitioner is arguing that a person of ordinary skill would have taken the leap from a small molecule antagonist such as BIBN to a large molecule anti-CGRP antagonist antibody. We determine that Petitioner has not demonstrated that a person of ordinary skill in the art would have had a reasonable expectation of success in using an antibody treatment in view of the level of unpredictability in whether the blood brain barrier would have been an obstacle, i.e., the uncertainty in whether anti-CGRP antibodies needed to cross the blood-brain barrier to reduce incidence of or treat headache such as migraine. We find that, as in *Honeywell*, the expectation of failure would have been at least equal to the expectation of success and determine that Petitioner has not met its burden on this issue.

(5) West-Ward Decision

Patent Owner argues that the recent decision in *Novartis Pharmaceuticals Corp. v. West-Ward Pharmaceuticals International Ltd.*, 923 F.3d 1051 (Fed. Cir. 2019) ("*West-Ward*"), involved facts similar to those here and found that the asserted art would not have given a POSA a reasonable expectation of success. PO Resp. 45–47. Patent Owner asserts that the claims in *West-Ward* were directed to a method of treating renal cell carcinoma (RCC) with everolimus (a rapamycin derivative), an mTOR inhibitor. *Id.* at 45.[93] Patent Owner asserts that as of the filing date of the patent challenged in *West-Ward*, mTOR inhibitors were "hypothesized" to inhibit tumor growth and other mTOR inhibitor, temsirolimus (also a rapamycin derivative), had shown responses against RCC, which was an "unpredictable and difficult to treat cancer," in phase I clinical trials. *Id.* at

[93] Patent Owner's citations to the slip opinion of *West-Ward* are omitted.

45–46. Patent Owner asserts that two phase II clinical trials with temsirolimus were underway at the time. *Id.* at 46.

Patent Owner also asserts that the prior art disclosed everolimus as particularly useful for treating tumors and disclosed formulations and dosage ranges, but that the prior art did not disclose "any pre-clinical or clinical data showing any antitumor activity of everolimus" nor that "everolimus would be effective in treating advanced RCC." PO Resp. 46. Patent Owner relates that the Federal Circuit found no reasonable expectation of success for everolimus to treat RCC. *Id.* Patent Owner highlights the Court's reasoning that temsirolimus phase I data had "diminished weight" because it came from small sample sizes, and was designed to test safety, not efficacy, even though efficacy results were also reported. *Id.* Patent Owner also points to the Court's reasoning that everolimus and temsirolimus were "pharmacologically different," that different binding affinities and different half-lives "would not have given a POSA an expectation of "the same anti-tumor efficacy," that the molecular biology of RCC was "not fully understood," and "[c]learly additional experiments are required to establish the relationship between [e.g., mTOR] activity and rapamycin sensitivity in human cancer cells." *Id.* at 46–47.

Patent Owner argues that *West-Ward* compels a finding of no reasonable expectation of success here. *Id.* at 47. Patent Owner asserts that, similar to *West-Ward*, Olesen's clinical data with a small molecule receptor antagonist holds diminished weight because Olesen's data base was too small (citing Ex. 1025, 1109) and because receptor antagonism is different than ligand antagonism (citing Ex. 2265 ¶¶ 60–65, 130). *Id.* Patent Owner asserts that, similar to *West-Ward*, an anti-CGRP antibody and a small

molecule (BIBN) are pharmacologically different from each other with different affinities and half-lives (citing Ex. 2265 ¶¶ 62, 64–65); no positive pre-clinical or clinical data existed, as of 2005, showing any therapeutic, let alone anti-migraine, activity of anti-CGRP antibodies (citing *id.* ¶¶ 83, 107–108; the art called for "more data from carefully designed studies" (citing Ex. 1096, 567); and there was uncertainty in the field regarding pathophysiology of migraine and whether CGRP was a biomarker for migraine, as discussed in other sections. *Id.*

Petitioner disagrees with Patent Owner's analogy to *West-Ward*. Reply 20–21. Petitioner argues that *West-Ward* involved a narrow species claim covering use of an mTOR inhibitor called everolimus; that the prior art lacked an express disclosure that everolimus "would be effective in treating advanced RCC"; that the claimed disease resisted "all treatment modalities that have been studied"; and that no Phase II clinical data existed for everolimus or other mTOR inhibitors. *Id.* at 20 (citing 923 F.3d. at 1053, 1054, 1057, 1061). Petitioner argues that the subject claims broadly cover use of any humanized anti-CGRP antagonist antibody having functional properties already known in the prior art; that the prior art here taught using humanized anti-CGRP antibodies for treating migraine and confirmed that blocking the CGRP pathway actually treated migraine (citing Pet. 25–28; Ex. 1014 ¶¶ 109–110); and that Olesen reported positive Phase II results and multiple drugs known to antagonize the CGRP pathway had proven clinical efficacy (citing Ex. 1303, 23:22–24:22; Ex. 1282, 1519–20; Ex. 1025, Abstract). Reply 20–21. Petitioner asserts that only a finite number of ways to antagonize the CGRP pathway existed—binding CGRP, binding receptors, or inhibiting CGRP release—and multiple approaches had already

proven clinically efficacious. *Id.* at 21 (citing Ex. 1024, 422 ("we expect that CGRP antagonists will be effective anti-migraine drugs")).

We agree with Patent Owner that the facts at issue here resemble the fact pattern in *West-Ward*. Similar to *West-Ward* where clinical results had been obtained with temsirolimus but not with everolimus, clinical results had been obtained with BIBN (e.g., Olesen, Ex. 1025) but not with anti-CGRP antagonist antibodies. Indeed, the anti-CGRP antibodies are pharmacologically different from BIBN because anti-CGRP antibodies have different half-lives and different sizes than BIBN. *See* Ex. 2265 ¶¶ 60–65, 91, 130; Ex. 2271 ¶¶ 54–56; Ex. 2268 ¶¶ 41, 93, 100. Further, as above, the mechanisms of migraine and its treatment were still uncertain in 2005.

Petitioner appears to attempt to distinguish *West-Ward* by arguing that the CGRP pathway was well-characterized and by arguing that there were a "finite number" of options for blocking the CGRP pathway. *See* Reply 21. However, we have discussed in detail the uncertainty regarding whether the BBB would have been an obstacle to using large molecule treatments. Moreover, even if there were a finite number of ways or approaches to antagonize the CGRP pathway, as argued by Petitioner, that is not a basis to conclude that there were a finite number of *compounds* that could possibly do so, as evidenced by Petitioner's argument that aptamers were also under consideration for treatment of migraine. *See* Pet. 27; Ex. 1014 ¶ 62. In any event, we agree with Patent Owner that *West-Ward* illustrates how a jump from one molecule to another may result in a lack of a reasonable expectation of success in an area with uncertainty, and agree with Patent Owner that this case bears similarities to *West-Ward*.

(6) Binding Affinity

Regarding the binding affinity recited in claim 1 of the '908 patent, we understand Petitioner to argue that a person of ordinary skill would have sought to make an antibody with a binding affinity of 10 nM because antibodies naturally had a certain range of affinities and other therapeutic antibodies had comparable affinities. 1712 IPR Pet. 30, 31, 50. Although it was not argued by the parties *in haec verba*, we also understand Petitioner to be arguing that the skilled artisan would have reached these specific affinities as a matter of routine optimization, i.e., when Petitioner argues that a person of ordinary skill would have sought to increase the affinity to increase biological potency and "a POSA would have targeted a binding affinity of 10 nM or less." *Id.* at 35. Similarly, although it was not argued *in haec verba*, we understand Patent Owner to be arguing that affinity is not a result effective variable, i.e., when Patent Owner contends that increasing affinity does not necessarily increase binding. *See* 1712 IPR Sur-reply 24–25 ("The art teaches a disconnect between binding and activity. Even in Tan 1994, the anti-CGRP antibody MAb Rl.50 'clearly showed the greatest [binding] activity' among the tested antibodies to rαCGRP, yet it 'blocked rat αCGRP poorly.'").

"[T]he discovery of an optimum value of a variable in a known process is normally obvious." *In re Antonie*, 559 F.2d 618, 620 (CCPA 1977); *see also E.I. DuPont de Nemours & Co. v. Synvina C.V.*, 904 F.3d 996, 1006 (Fed. Cir. 2018) (discussing case law). Exceptions to this rule include (1) the results of optimizing a variable were unexpectedly good and (2) the parameter optimized was not recognized in the prior art as one that would affect the results. *Antonie*, 559 F.2d at 620.

We find that affinity is a result effective variable because it can improve binding to CGRP up to a point, and can improve antagonism of CGRP's effect, based on the testimony of Dr. Vasserot and Dr. Tomlinson. Dr. Vasserot opined that "it was known that stronger binding affinities may confer increased efficacy *in vivo* while reducing the administered dosage amounts and/or frequency of administration of an antibody." 1712 IPR Ex. 1236 ¶ 69 (citing Ex. 1023, 2:12–27). Queen discloses that "[l]oss of any affinity is, of course, highly undesirable. At the least, it means that more of the humanized antibody will have to be injected into the patient, at higher cost and greater risk of adverse effects." Ex. 1023, 2:17–20. Queen further discloses that "an antibody with reduced affinity may have poorer biological functions, such as . . . virus neutralization." *Id.* at 2:20–23.

In response to the question whether an ideal drug would have a very high affinity and exquisite specificity for its target, Dr. Tomlinson responded as follows:

> Yes. I mean, obviously, you need to get above a certain level in order to get the efficacy you need, above a cert -- you know, depending on which way you're looking at it, I'll say below a certain affinity. So as the affinity gets better, there's a law of diminishing returns. So there's no point in going better than that because, in fact, you're just making the affinity better, but it's not, in fact, making your product any more useful.

Ex. 1301, 214:12–21; *see also* Ex. 1301, 211:16–21 ("Q. For therapeutic antibodies that act by binding a target antigen, is strong binding affinity to that antigen a desirable characteristic? [Objection to form]. [A]. Yes).

We understand Patent Owner to argue that the art teaches a disconnect between binding and activity because one of the antibodies in Tan 1994, i.e., Mab R1.50, showed the greatest affinity, but blocked αCGRP poorly. 1712

IPR Sur-reply 24–25 (citing Ex. 1021, 707; 1712 IPR Ex. 2273 ¶ 119). However, Tan 1994 in context stated "[t]he use of RIA and a receptor binding assay as biochemical screens was generally successful in predicting blocking MAbs." Ex. 1021, 707. Patent Owner's argument appears to be based on an antibody that was the exception to the general rule. However, binding affinity is not the only variable to be optimized because the antibody must also bind CGRP in a manner that blocks its binding to the CGRP receptor, in order to be useful. For example, Dr. Vasserot explained that a person of ordinary skill would have been motivated to develop an antibody that binds to the C-terminal region of CGRP because amino acid sequences 8–37 and 33–37 are involved in receptor binding. 1712 IPR Ex. 1236 ¶ 145–146. We do not understand Tan 1994's disclosure to mean that affinity is not a result effective variable, all else being equal. That is why Dr. Tomlinson agreed that one needs affinity to be a certain level to get the needed efficacy. *See* Ex. 1301, 214:12–21.

We, therefore, determine that binding affinity is a result effective variable, and as such, a value that can be optimized. *See Antonie*, 559 F.2d at 620.

We also find that binding affinities of 10 nM or less for anti-CGRP antibodies were known in the art prior to 2005. For example, as testified by Dr. Balthasar, Andrew reported K_D values[94] of 4.0 nM to 40 nM for antibodies raised against human CGRP. 1712 IPR Ex. 1341 ¶ 81.

[94] Dr. Balthasar explains that "Andrew reports a K_A range of 2.5×10^7 to 2.5×10^8 M^{-1}, which can be converted to K_D values by taking the inverse (i.e., $K_D = 1/K_A$)." 1712 IPR Ex. 1341 ¶ 81 n.3.

(7) Summary of Reasonable Expectation of Success

(a) Claim 17 of the '045 patent

Claim 17 of the '045 patent recites a method for reducing incidence of or treating headache in a human comprising administering an effective amount of a human or humanized monoclonal anti-CGRP antagonist antibody to the human. Although the term antibody includes fragments, Petitioner has not established a reason or motivation to humanize antibody fragments, as discussed above. The recited term "effective amount" also requires a beneficial or desired result from administration of the antibody.

As discussed above, Olesen shows that use of a different (and significantly smaller) compound and binding of that compound to a different site (CGRP receptor) was shown to effectively treat migraine. However, we determine that Olesen provides no data that would provide a POSA with a reasonable expectation of success in using a full-length anti-CGRP antibody binding to the ligand to treat a vasomotor symptom, specifically including a headache or migraine. In short, the differences between Olesen and claim 17 are too significant for a POSA to have had a reasonable expectation of success in achieving the invention of claim 17.

We also determine that Tan does not provide any data establishing a successful use of a full-length anti-CGRP antibody to achieve immunoblockade of endogenous CGRP. Although Tan suggests an approach for doing so, it relies on Covell for support which likewise provides no data regarding an antibody's penetration of the synaptic cleft or ability to bind CGRP in the synaptic cleft. Moreover, as to claims addressing headache or migraine, concerns and skepticism about crossing

the blood brain barrier with a full-length antibody would have further undermined a reasonable expectation of success.

We also find that the asserted combination of Olesen, Tan, and Queen does not satisfy the reasonable expectation of success requirement. Olesen, Tan, and Queen do not provide any data on whether administration of a full-length anti-CGRP antibody would provide a beneficial or desired result in treating, or reducing incidence of, a vasomotor symptom, such as headache or migraine. Although Tan posits that the failure of its MAb C4.19 to reach the synaptic cleft *should* (not would) be overcome by higher concentrations or longer incubation times, there is no evidence in the record that anyone successfully followed Tan's suggested approach prior to the filing of the challenged patents. *See, e.g.*, Ex. 1001, 55:26–57:12. At most, the combined teachings of Olesen, Tan, and Queen suggest the possibility, but not a reasonable probability, of meeting the limitations of claim 17 of the '045 patent. *See Pfizer*, 480 F.3d at 1364.

In short, Olesen's teachings are distinct from the binding of an anti-CGRP antibody to a CGRP ligand, and the combination of Tan's disclosure does not remedy the deficiencies of Olesen so as to provide a reasonable expectation of success. Neither Olesen nor Tan, singularly or in combination, establish that a person of ordinary skill in the art would have had a reasonable expectation that performing the recited method would bring about the recited result. Although Queen establishes the ability of a POSA to make a humanized anti-CGRP antibody, Queen does not remedy the deficiencies of Tan and/or Olesen because the claims are directed to methods of administering the anti-CGRP antibody and achievement of a beneficial or desired result.

For these reasons, Petitioner fails to establish a reasonable expectation of success as to claim 17 of the '045 patent

(b) Claim 1 of the '045 patent

Petitioner's arguments regarding claim 1 of the '045 patent are cursory and conclusory (Pet. 49–50) and, although Patent Owner may not have challenged those arguments, it is Petitioner's burden to establish obviousness by a preponderance of the evidence. *See Dynamic Drinkware,* 800 F.3d at 1378. Moreover, for reasons discussed above in connection with claim 17 of the '045 patent, Petitioner cannot rely on the argument that claim 1 is broader than claim 17 and "would have been obvious for all of the reasons discussed" in connection with claim 17. Pet. 49–50 (citing Ex. 1014 ¶¶ 11–14, 156–159, 190; Ex. 1015 ¶¶ 12–14, 83–86, 139–140).

As an initial matter, Petitioner's arguments as to claim 1 are necessarily limited to administration of a full-length antibody to humans because Petitioner failed to establish a motivation to humanize antibody fragments or a reason to humanize antibodies for administration to animals. *See generally* Pet.; Reply. Petitioner also argues that Tan "established that murine monoclonal anti-CGRP antagonist antibodies reduced incidence of skin vasodilation in rats," and "previously disclosed reducing incidence of skin vasodilation in an individual with a monoclonal anti-CGRP antagonist antibody." Pet. 50 (citing Ex. 1022, 569; Ex. 1014 ¶¶ 56–58). But, as discussed above, Tan does not "establish" the use of a full-length anti-CGRP antibody to reduce incidence of skin vasodilation in rats, and only "disclosed," at most, the possibility of the antibody reaching the synaptic cleft with dosing protocols that "should" achieve "sufficiently high concentrations required for immunoblockade." Ex. 1022, 571. Moreover,

Tan's intended purpose was "to investigate immunoblockade as an alternative strategy for probing the role of CGRP as a vasodilator *in vivo*," and Tan says nothing about treatment of, or reducing incidence of, any disease or condition in humans. *See id*. at 566.

For these reasons, Petitioner fails to establish a reasonable expectation of success as to claim 1 of the '045 patent

(c) Claim 1 of the '907 patent

Petitioner fails to establish a reasonable expectation of success as to claim 1 of the '907 patent for the same reasons discussed above in connection with claim 17 of the '045 patent.

(d) Claim 1 of the '908 patent

Petitioner fails to establish a reasonable expectation of success as to claim 1 of the '908 patent for the same reasons discussed above in connection with claim 17 of the '045 patent.

5. Summary as to Nonobviousness of the Challenged Claims

Having considered the parties' arguments and evidence, we evaluate all of the evidence together to make a final determination of obviousness. *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1075 (Fed. Cir. 2012) (stating that a fact finder must consider all evidence relating to obviousness before finding patent claims invalid). In particular, we have determined that the cited prior art discloses or suggests every element of the challenged independent claims. We have weighed the reasons to combine and reasons not to combine the cited references and find that, on balance, the reasons to combine outweigh those not to combine.

We have also determined that Petitioner has failed to establish by a preponderance of the evidence that a person of ordinary skill in the art would have had a reasonable expectation of success in achieving the invention of the independent claims of the challenged patents. We have also weighed Petitioner's objective indicia of obviousness and find that such evidence does not outweigh the absence of a reasonable expectation of success. After doing so, we conclude that Petitioner has failed to satisfy its burden of demonstrating, by a preponderance of the evidence, that the independent claims of each of the challenged patents would have been obvious over the combination of Olesen, Tan, and Queen. Having concluded that the challenged independent claims are not unpatentable, we also conclude that Petitioner has failed to satisfy its burden to show that the challenged dependent claims are unpatentable.

III. MOTIONS

A. Motion to Exclude

Patent Owner moves to exclude the entirety of Exhibits 1110, 1247, 1261, 1262, 1264, 1265, 1267–1279, 1281, 1286, 1287, 1293, 1296, 1311, 1313, 1314, 1316, and 1317, and portions of Exhibits 1012, 1013, 1301, 1302, 1303, 1304, 1327, and 1328. Mot. Excl. 1–15. Petitioner opposes. Opp. Excl. 1–15.

1. The Tan Thesis (Ex. 1287)

Patent Owner moves to exclude the Tan Thesis (Exhibit 1287) under Federal Rule of Evidence 901 for lack of foundation and authentication, and because Petitioner has not shown that it was a publicly accessible document. *See* Mot. Excl. 2–7. Petitioner opposes. Opp. Excl. 3.

Whether a reference qualifies as a "printed publication" is a legal conclusion based on underlying factual findings. *Nobel Biocare Servs. AG v. Instradent USA, Inc.*, 903 F.3d 1365, 1375 (Fed. Cir. 2018) (citing *Jazz Pharm., Inc. v. Amneal Pharm., LLC*, 895 F.3d 1347, 1356 (Fed. Cir. 2018)). The underlying factual findings include whether the reference was publicly accessible. *Id.* (citing *In re NTP, Inc.*, 654 F.3d 1279, 1296 (Fed. Cir. 2011)). In an *inter partes* review, the petitioner bears the burden of establishing by a preponderance of the evidence that a particular document is a printed publication. *Id.* (citing *Medtronic Inc. v. Barry*, 891 F.3d 1368, 1380 (Fed. Cir. 2018)); *see also In re Wyer*, 655 F.2d 221, 227 (CCPA 1981) (a party asserting a reference as a prior art printed publication should provide sufficient proof of accessibility).

The determination of whether a document is a "printed publication" under 35 U.S.C. § 102 "involves a case-by-case inquiry into the facts and circumstances surrounding the reference's disclosure to members of the public." *Medtronic*, 891 F.3d at 1380 (citing *In re Klopfenstein*, 380 F.3d 1345, 1350 (Fed. Cir. 2004)).[95] In certain situations, particularly for manuscripts or dissertations stored in libraries, courts may inquire whether a reference was sufficiently indexed or catalogued. *See, e.g.*, *In re Hall*, 781 F.2d 897, 898–99 (Fed. Cir. 1986); *In re Lister*, 583 F.3d 1307, 1315 (Fed. Cir. 2009) (manuscript became publicly accessible once it was placed in a searchable database); *see generally Medtronic*, 891 F.3d at 1380.

[95] As it relates to this proceeding, pre-AIA § 103 provides for obviousness based on the types of prior art set forth in pre-AIA § 102. Further, Section 311 refers to § 102, which also uses the term "printed publication."

Petitioner relies on the declaration of Mr. Carney (Exhibit 1307) for proof of timely cataloguing of the Tan Thesis. Mr. Carney relies on three sources of information for his understanding that the Tan Thesis was publicly available at least as early as 1994, and long before November 2005. *See* Ex. 1307 ¶¶ 15–19.

First, Mr. Carney avers that he accessed the catalogue entry for the Tan Thesis in the Cambridge University Library ("CUL") catalogue, and according to the catalogue, the entry was created in 1994 and the Tan Thesis was approved on July 29, 1994. *Id.* ¶ 15. The CUL catalogue entry is Exhibit C to Exhibit 1307. The record states:

Publisher	1994.
Creation Date	1994.
. . .	
Notes	Date approved: 29 July 1994.

Ex. 1307, 296.

Second, Mr. Carney avers that he downloaded the MARC record from the Cambridge University Library Catalog for its Tan Thesis, and the MARC record indicates that the Tan Thesis was produced in 1994. *Id.* ¶¶ 16–17. The MARC catalogue entry is Exhibit D to Exhibit 1307. *Id.* ¶ 16. Mr. Carney avers that field 008 of the MARC entry lists the first six characters "020506" in "YYMMDD" format, indicating that the MARC record for the Tan Thesis was created on May 6, 2002. We have reviewed Exhibit D to Exhibit 1307 and find that it supports Mr. Carney's opinion. In particular, field 008 states: "020506s1994 enk . . . ." Ex. 1307, 298.

Third, Mr. Carney relies on correspondence from Louise Clarke, in response to an official request for information concerning the date of public

availability of the Tan Thesis, explaining that these are delivered to the Cambridge University Library about one month after they are approved by the Board of Graduate Studies. Ex. 1307 ¶ 18. The response is an email, which is Exhibit E to Exhibit 1307. *Id.*

Patent Owner argues that Petitioner presented Exhibit 1287 to Dr. Ferrari during a deposition and that Patent Owner objected at that time based on lack of foundation among other objections. Mot. Excl. 3. Patent Owner argues that Petitioner filed a copy of Exhibit 1287 with its Reply that was allegedly the same version as that presented during the Ferrari deposition, and that Patent Owner renewed its objections as lacking foundation under FRE 901. *Id.* at 3–4. Patent Owner argues that Petitioner introduced a new version (Ex. 1287A) with the Carney Declaration. *Id.* at 4. However, Patent Owner does not detail whether or how the versions might differ, and whether they would do so in a material fashion.

Patent Owner argues that Mr. Carney does not present any proof that the MARC Records were used by the Cambridge University Library. *Id.* at 5. However, even if they were not, the MARC record would still add support to a finding of public accessibility. Patent Owner argues that, in order to provide a connection between catalog entries and public availability, it is necessary to provide information regarding a library's indexing and cataloguing practice. *Id.* at 5–6. Patent Owner argues that the Clarke email exchange is hearsay; that Petitioner has not established that Ms. Clarke is qualified to testify as to CUL's shelving or indexing practice now or before 2005; that Petitioner has not established that Ms. Clarke is qualified to testify as to when the public would have access to a shelved or indexed thesis; and that the Clarke email does not support Mr. Carney's arguments

about availability because it is unclear who or what "we" refers to and whether such persons have actual knowledge of CUL filing and accessibility practice. *Id.* at 6–7. Patent Owner also argues that Mr. Carney's declaration is devoid of other evidence as to CUL's policy on indexing and cataloguing. *Id.* at 7.

Petitioner argues that the Tan Thesis is self-authenticating as an ancient document under FRE 901(b)(8). Opp. Excl. 1–2. Patent Owner argues that Petitioner has not provided evidence of authenticity nor that the Tan Thesis is an ancient document based on basic facts of Exhibit 1287's identity or date of publication. Mot. Excl. Reply 3. However, we determine that the Library Catalog indicating creation in 1994, and the 1994 date on the title page of the Tan Thesis (Ex. 1287, ii; Ex. 1307, 20), is sufficient to establish the date of creation of the Tan Thesis for purposes of FRE 901(b)(8). *See* Ex. 1307, 296. Further, we find that the document was found in a place of natural custody and is the type of document that falls within the policy of the rule. *See* Ex. 1307 § 18; Wright and Miller, FED. PRACTICE & PROCEDURE § 7113 (the provision has been applied to all manner of written items including office memoranda and scientific reports) (citing *Horne v. Owens-Corning Fiberglass Corp.*, 4 F.3d 276, 283 (4th Cir. 1993) (office memoranda); *Rowan Cty. Bd. of Educ. v. U.S. Gypsum Co.*, 407 S.E.2d 860, 868 (N.C. App. 1991) (scientific reports)). We note the title page states that it is "A dissertation submitted to the University of Cambridge for the Ph.D. Degree" and names "Keith Kwan Cheuk Tan." Ex. 1287, i; Ex. 1307, 20. For these reasons, we conclude that the Tan Thesis is what it purports to be. Further, Patent Owner does not set forth or explain how the versions of the Tan Thesis differ.

Petitioner also argues that proof of the public accessibility of the Tan Thesis is unnecessary for its use to challenge Teva's assertion that the personal (not public) knowledge of the co-authors of the Tan references was to never consider developing therapeutic antibodies, and for the rebuttal purpose of demonstrating that actual researchers in the field before November 2005 were urging humanization and therapeutic uses of anti-CGRP antibodies. Opp. Excl. 2–3.[96] We do not agree with Petitioner that these uses are strictly for a personal viewpoint of the Tan authors inasmuch as they would more properly be understood to reflect the views of a person of ordinary skill, i.e., where Tan is being used as prior art to reflect the state of the art. Further, 35 U.S.C. § 311 contains a requirement that *inter partes* reviews are conducted on the basis of patents and printed publications, i.e., that are publicly available.

Petitioner argues that Patent Owner ignores the MARC record indicating that the Library actually indexed Exhibit 1287 in its electronic MARC records by 2002 and shelved it by 1994. Opp. Excl. 3–4. We agree with Petitioner that the MARC record indicates that the Tan Thesis was indexed by 2002. Ex. 1307, 298. Further, the Cambridge University Library has a catalogue entry indicating a creation date of 1994. Ex. 1307, 296. We find that this entry was sufficient for a person of ordinary skill to have found and accessed the Tan Thesis, at least by 2002, as indicated by the MARC record.

[96] Petitioner also argues that a motion to exclude is not the proper place for Patent Owner's challenge to public availability, which is a substantive issue. Opp. Excl. 2. We take no position on this argument because we find that the Tan Thesis was publicly available.

As to Patent Owner's argument that Petitioner failed to show a connection between shelving and cataloguing, we do not agree because the MARC record indicates that a person could have sufficiently located the Tan Thesis. *In re Lister*, 583 F.3d 1307, 1315 (Fed. Cir. 2009) (manuscript became publicly accessible once it was placed in a searchable database). In this connection, we find that the Clarke email is not necessary.

In any event, we grant the motion to exclude as to the Clarke email because Petitioner does not provide any arguments for its admissibility. *See* Mot. Excl. 2–4.

Thus, although we find that the Clarke email is not necessary for proof that the Tan Thesis was publicly available, we find that the library would have been in possession of the Tan Thesis in 1994, and the Tan Thesis was catalogued by 2002, well before 2005, as established by the Carney Declaration and by the Library Catalogue entry and the MARC Records. We, therefore, conclude that the Tan Thesis was publicly accessible by 2005. We, therefore, deny the motion to exclude as to the Tan Thesis (Ex. 1287).

2. Portions of Deposition Testimony (Exhibits 1301, 1302, 1303, 1304, 1343, and 1345)

Patent Owner moves to exclude portions of the following deposition testimony: Exhibit 1301, 27:25–28:6, 29:21–22, 30:6–9, 115:9–116:21, 154:24–156:21, 211:16–21; Exhibit 1302, 45:20–46:19, 81:9–82:2, 179:14–180:19; Exhibit 1303, 25:11–17, 54:12–23, 61:15–65:12, 69:10–16, 73:8–18, 102:9–106:19, 108:25–133:7, 193:3–10; Exhibit 1304, 59:23–71:17, 74:17–75:12, 82:17–134:18, 119:1–15, 142:1–8; 1343, 33:17–34:6, 76:12–77:8; Exhibit 1345, 61:5–65:2, 52:6–54:7. Mot. Excl. 7–12. Petitioner opposes. Opp. Excl. 4–13.

Patent Owner variously argues that the questions were in improper form, not relevant, vague, mischaracterized the witnesses' prior testimony, called for a legal conclusion, lacked clarity, or contained compound questions. Mot. Excl. 7–12. We consider Patent Owner's arguments in this regard to address issues of weight rather than admissibility, and we deny these aspects of the motion. *See Corning Inc. v. DSM IP Assets B.V.*, IPR2013-00053, Paper 66 at 19 (PTAB May 1, 2014) (sitting as a non-jury tribunal, the Board may assign appropriate weight to evidence presented) (citing *Donnelly Garment Co. v. NLRB*, 123 F.2d 215, 224 (8th Cir. 1941)).

Patent Owner also argues that Petitioner's question at Exhibit 1301, 115:9–116:21, calls for unfounded speculation from the witness about the state of mind of others. Mot. Excl. 8. However, in the deposition, Dr. Tomlinson declined to speculate and merely read from the document that he was asked to review. Accordingly, we consider the deposition objection to be without merit. Further, we understand questions about the purpose of mutations do not go to the state of mind of the scientists who made the mutations, but to inquire from Dr. Tomlinson about what a person of ordinary skill would have understood about the function, if any, of the mutations. *See* Ex. 1301, 115:9–116:21. Were we to reach the issue, we would deny this aspect of the motion as without merit.

Patent Owner seeks to exclude a portion (Ex. 1302, 179:14–180:19) of Dr. Stoner's direct testimony as relating to a legal hypothetical and therefore beyond the scope of direct testimony. Mot. Excl. 9. However, because this is not a jury trial, the Board can separate legal issues from fact issues in rendering interpreting witness testimony. Accordingly, we deny this aspect of the motion.

Patent Owner argues that the discussion of sumatriptan's effects on blood pressure (Ex. 1303, 25:11–17), should be excluded for lack of foundation. Mot. Excl. 9. We disagree with Patent Owner, and determine that counsel for Petitioner adequately laid the foundation for this question by reference to a previous discussion of sumatriptan. *See* Ex. 1303, 24:23–25. Further, we understand the questions to appeal to Dr. Ferrari's "significant experience . . . performing clinical research and treating patients," for which Patent Owner presented no evidence to show that Dr. Ferrari was not qualified to opine on that topic. *See* Ex. 2268 ¶ 4; *see also* Ex. 1303, 16:25–30:4 (discussing experience with sumatriptan); Opp. Excl. 7. We deny this aspect of the motion.

Patent Owner seeks to exclude a portion (Ex. 1303, 61:15–65:12) of the cross-examination of Dr. Ferrari as beyond the scope of Dr. Ferrari's direct testimony. Mot. Excl. 9. Upon review of the Ferrari Declaration, Exhibit 2268, we agree that questions on cyclic AMP were beyond the scope of the Ferrari Declaration. Accordingly, we grant this aspect of the motion.

Patent Owner argues that 25 pages of deposition testimony (Ex. 1303, 108:25–133:7), should be excluded, *inter alia*, "for lack of foundation for discussion of experimental results." Mot. Excl. 10. Because Patent Owner does not point us more specifically to the objectionable material, we deny the motion for lack of specific argument. Nevertheless, from our review of the record, we determine that Patent Owner appears to be arguing based on counsel's objection at Exhibit 1303, 110:5–9, to the following question regarding Exhibit 2151: "Q. There were no significant differences between patients with acute myocardial infarction and normal controls at admission, correct?" Ex. 1303, 110:5–8. We disagree with Patent Owner, and

determine that counsel for Petitioner adequately laid the foundation for this question with the two previous questions regarding Exhibit 2151 at Exhibit 1303, 109:22–110:4 that oriented the witness to further questions on the study. We further observe that Dr. Ferrari cited Ex. 2151 in his declaration. *See* Ex. 2268 ¶ 115; Opp. Excl. 9–10. We deny this aspect of the motion.

Patent Owner seeks to exclude discussion of the meaning of "antibody serum" (Ex. 1303, 69:10–16). Mot. Excl. 9–10. We disagree with Patent Owner because the patents at issue in these proceedings concern antibody preparations, and we deny this aspect of the motion.

Patent Owner seeks to exclude discussion of a portion (Ex. 1304, 119:1–5) of the cross-examination of Dr. Rapoport as beyond the scope of Dr. Rapoport's testimony. Mot. Excl. 11. However, Dr. Rapoport refers to Exhibit 2167, the subject of the questioning, in his declaration. *See* Ex. 2262 ¶ 30. Accordingly, we deny this aspect of the motion.

Patent Owner seeks to exclude discussion of triptans (Ex. 1304, 59:23–71:17) as beyond the scope of Dr. Rapoport's direct testimony and discussing another treatment and disorder. Mot. Excl. 10. However, we agree with Petitioner that the questions related to a paper co-authored by Dr. Rapoport, and that the discussion was relevant to treatment of MOH, which Dr. Rapoport discussed in his declaration. *See* Ex. 1304, 60:5–6; Ex. 2262 ¶¶ 65–69; Opp. Excl. 10–11. Accordingly, we deny this aspect of the motion.

Patent Owner seeks to exclude discussion of toxicity studies in animals (Ex. 1303, 54:12–23) as beyond the scope of Dr. Ferrari's direct testimony. Mot. Excl. 9. The question at issue was directed to whether toxicity studies in animals would show acute safety in humans, and Patent

Owner does not persuasively explain why this would be beyond the scope of Dr. Ferrari's testimony regarding safety in humans. Accordingly, we deny this aspect of the motion.

3. Exhibits Not Cited in the Petition or Reply (Exhibits 1098, 1261, 1262, 1264, 1265, 1267–1279, 1286, 1291–1293, 1296, 1311, 1313, 1314, 1316, 1317, 1331, 1335–1336, 1344, 1347, and 1349)

Patent Owner seeks to exclude the following exhibits as irrelevant or prejudicial because they were not cited in a brief by Petitioner and were only relied on in expert testimony: Exhibits 1098, 1261, 1262, 1264, 1265, 1267–1279, 1286, 1291–1293, 1296, 1311, 1313, 1314, 1316, 1317, 1331, 1335–1336, 1344, 1347, and 1349. Mot. Excl. 12–13. We deny this aspect of the motion. Where, as here, the decision is by an administrative agency, rather than a jury, there is a diminished concern that such exhibits would be prejudicial. *See Corning*, Paper 66 at 19.

4. Portions of Exhibits 1014, 1015, 1337, and 1338

Patent Owner seeks to exclude portions of expert testimony as irrelevant, prejudicial, or lacking probative value because they were not cited in a brief by Petitioner: paragraphs 39–49, 63–66, 74, 79, 85, 114, 138, 143, 145, 147, 153, 155, 162, 165, 169, 174, and 179 in Exhibit 1014; paragraphs 15, 17–20, 23–26, 58, 62–64, 110, 112, and 114 in Exhibit 1015; paragraphs 1–14 in Exhibit 1337; and paragraphs 1–4 in Exhibit 1338. Mot. Excl. 14–15. We deny this aspect of the motion, for similar reasons as for the other uncited evidence.

B. Motion to Strike

Patent Owner moves to moves to strike the following arguments and evidence from Lilly's Reply as impermissible attempts to present new evidence and new theories of invalidity: arguments on pages 6, 10–11, 5;

Exhibits 1287; paragraphs 22, 24–25, and 30–33 of Exhibit 1337. Mot. Strike 1–4 (citing, e.g., 37 C.F.R. § 42.22(a)(2); 37 C.F.R. § 42.23; Trial Practice Guide at 40; *Henny Penny Corp. v. Frymaster LLC*, 938 F.3d 1324 (Fed. Cir. 2019); *Tietex Int'l, Ltd. v. Precision Fabrics Grp., Inc.*, IPR2014-01248, Paper 39 at 14–15 (PTAB Feb. 27, 2016)).

First, Patent Owner seeks to strike portions of the Reply Brief that rely on the Tan Thesis (Exhibit 1287) and the Tan Thesis itself. Mot. Strike 2–3. Patent Owner argues that Petitioner improperly puts forth new Exhibit 1287 for the first time on Reply to supplement its deficient motivation argument to humanize the claimed anti-CGRP antagonist antibodies. *Id.* at 2. Patent Owner argues that any arguments and evidence as to motivation must have been made in the Petition. *Id.* at 3. Patent Owner cites *Intelligent Bio-Systems*, 821 F.3d at 1369–70, for the proposition that a reply or reply evidence may be excluded if it introduces new evidence that is necessary to make out a *prima facie* case of unpatentability. Mot. Strike 3. Petitioner responds, *inter alia*, that it relies on Exhibit 1287 in the Reply to respond to arguments in the Patent Owner response regarding blood pressure data, and to show that Dr. Tan believed humanized antibodies should be developed notwithstanding the blood pressure data. Opp. Strike 3–4. Petitioner cites *Belden Inc. v. Berk–Tek LLC*, 805 F.3d 1064, 1079 (Fed. Cir. 2015) for the proposition that "[e]vidence admitted in rebuttal to respond to the patent owner's criticisms will commonly confirm the prima facie case." We agree with Petitioner that the Reply relies on the Tan Thesis as part of its rebuttal to arguments made in the Patent Owner response. *See* Reply 6 (citing PO Resp. 4), 15 (citing PO Resp. 4). Exhibit 1287 is therefore proper reply evidence, and we deny this aspect of the motion.

Second, Patent Owner seeks to strike the portions of Dr. Balthasar's declaration relating to Tan's full-length antibody (Ex. 1337 ¶¶ 22, 24–25, 30–33) and the portions of the Reply based thereon (Reply 10–11). Mot. Strike 3–4. Patent Owner argues that Petitioner "seeks to introduce the testimony of a brand new expert, Dr. Balthasar, on the same efficacy issue Dr. Charles failed to support in its Petition." *Id.* at 4. However, Patent Owner's argument appears to be an admission that Dr. Balthasar's testimony was on the same subject as the Petition and the testimony of Dr. Charles on which the Petition relied. *See id.* Such evidence is therefore not beyond the scope of the Petition and is merely responsive to the cross-examination discussed in the Patent Owner Response. *See id.* at 3 (citing PO Resp. 3–4). This evidence was not being introduced to supply a limitation but rather to buttress previously presented arguments about motivation to combine. *See Chamberlain Grp., Inc. v. One World Techs., Inc.*, 944 F.3d 919, 925 (Fed. Cir. 2019) ("Parties are not barred from elaborating on their arguments on issues previously raised.").

Further, Patent Owner had the opportunity to depose Dr. Balthasar (Ex. 2239), and also the opportunity to submit a Sur-reply (Paper 43). Therefore, we determine that Patent Owner has failed to meet its burden to show that the arguments and evidence should be stricken. *See* 37 C.F.R. § 42.20; *Genzyme Therapeutic Prods. L.P. v. Biomarin Pharm Inc.*, 825 F.3d 1360, 1367 (Fed. Cir. 2016); *see also Anacor Pharms., Inc. v. Iancu*, 889 F.3d 1372, 1380–81 (Fed. Cir. 2018) (reply may document the knowledge that skilled artisans would bring to bear in reading the prior art identified as producing obviousness). Accordingly, this aspect of the motion is denied.

IV. CONCLUSION

For the foregoing reasons, we conclude that Petitioner has not established by a preponderance of evidence that claims 1, 3, 4, 8–17, 19, 20, and 24–31 of the '045 patent are unpatentable, or that claims 1–18 of the '907 patent are unpatentable, or that claims 1–18 of the '908 patent are unpatentable.

In summary:

IPR2018-01710 U.S. Patent No. 8,586,045 B2				
Claims	**35 U.S.C. §**	**Reference(s)/Basis**	**Claims Shown Unpatentable**	**Claims Not shown Unpatentable**
1, 3, 4, 8–17, 19, 20, 24–31	103(a)	Olesen, Tan, Queen		1, 3, 4, 8–17, 19, 20, 24–31
Overall Outcome				1, 3, 4, 8–17, 19, 20, 24–31

IPR2018-01711 U.S. Patent No. 9,884,907 B2				
Claims	**35 U.S.C. §**	**Reference(s)/Basis**	**Claims Shown Unpatentable**	**Claims Not shown Unpatentable**
1–18	103(a)	Olesen, Tan, Queen		1–18
Overall Outcome				1–18

IPR2018-01712 U.S. Patent No. 9,884,908 B2				
Claims	**35 U.S.C. §**	**Reference(s)/Basis**	**Claims Shown Unpatentable**	**Claims Not shown Unpatentable**
1–18	103(a)	Olesen, Tan, Queen		1–18
Overall Outcome				1–18

V. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that Petitioner has failed to prove by a preponderance of the evidence that claims 1, 3, 4, 8–17, 19, 20, and 24–31 of U.S. Patent No. 8,586,045 B2 are unpatentable;

FURTHER ORDERED that Petitioner has failed to prove by a preponderance of the evidence that claims 1–18 of U.S. Patent No. 9,884,907 B2 are unpatentable;

FURTHER ORDERED that Petitioner has failed to prove by a preponderance of the evidence that claims 1–18 of U.S. Patent No. 9,884,908 B2 are unpatentable;

FURTHER ORDERED that Patent Owner's Notice of Objection to Evidence and Notice of Objection to Petitioner's Demonstrative Exhibits are overruled;

FURTHER ORDERED that Patent Owner's Motion to Strike is denied, as discussed herein (*see* Section III.B);

FURTHER ORDERED that Patent Owner's Motion to Exclude is granted as to Exhibit E to Exhibit 1307 (Clarke email) and questions

directed to Dr. Ferrari on cyclic AMP (Ex. 1303, 61:15–65:12), and otherwise denied, as discussed herein (*see* Section III.A); and

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

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