

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.

IPR2018-01424 (Patent No. 9,346,881 B2)
IPR2018-01426 (Patent No. 9,890,211 B2)
IPR2018-01427 (Patent No. 8,597,649 B2)¹

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

Per Curiam

JUDGMENT
Final Written Decision
Determining All Challenged Claims Unpatentable
35 U.S.C. § 318(a)

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 1–6 and 14–19 of U.S. Patent No. 9,346,881 B2 (“the ’881 patent”) (IPR2018-01424), claims 1–15 of U.S. Patent No. 9,890,211 B2 (“the ’211 patent”) (IPR2018-01426), and claims 1–9 of U.S. Patent No. 8,597,649 B2 (“the ’649 patent”) (IPR2018-01427).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 demonstrated by a preponderance of the evidence that all 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 ’881 patent, the ’211 patent, and the ’649 patent. Teva Pharmaceuticals International GmbH (“Patent Owner” or “Teva”) filed a Preliminary Response to each of the Petitions. Paper 8 (“Prelim. Resp.”).

² All of the respective challenged claims are referred to collectively as the “challenged claims,” and the ’881 patent, the ’211 patent, and the ’649 patent are referred to collectively as the “challenged patents.” IPR2018-01424 (“1424 IPR”), IPR2018-01426 (“1426 IPR”), and IPR2018-01427 (“1427 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 IPR2018-01426. Similar Papers and Exhibits were filed in each of the three *inter partes* reviews.

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We entered our three Decisions on Institution (Paper 14, “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 24, “PO Resp.”), Petitioner filed a substantially similar Reply (Paper 37, “Reply”), and Patent Owner filed a substantially similar Sur-reply (Paper 49, “Sur-reply”).

In each of the three *inter partes* reviews, Patent Owner filed a substantially similar Motion to Strike (Paper 43, “Mot. Strike”) and Petitioner filed a substantially similar Opposition to the Motion to Strike (Paper 45, “Opp. Strike”). In each of the three *inter partes* reviews, Patent Owner also filed a substantially similar Motion to Exclude (Paper 56, “Mot. Excl.”), Petitioner filed a substantially similar Opposition to the Motion to Exclude (Paper 58, “Opp. Excl.”), and Patent Owner filed a substantially similar Reply to Petitioner’s Opposition to the Motion to Exclude (Paper 59).

Petitioner and Patent Owner requested an oral hearing. Papers 50, 51. A combined⁵ oral hearing was granted, and scheduled for November 22, 2019. 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

⁴ IPR2018-01424 was instituted on February 19, 2019, and IPR2018-01426 and IPR2018-01427 were instituted on February 25, 2019. *See also* 1424 IPR Paper 14; 1427 IPR Paper 14.

⁵ In addition to the three *inter partes* reviews addressed in this Decision, the oral hearing included IPR2018-01422, IPR2018-01423, and IPR2018-01425. Those cases are addressed in a separate decision.

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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 67);⁶

Patent Owner’s Petition to Expedite Under 37 C.F.R. § 1.182 (Paper 65); and

Patent Owner’s Petition Under 37 C.F.R. § 1.181(a)(3) Invoking the Supervisory Authority of the Director (Paper 64).

No decision was reached on Patent Owner’s filings (Papers 64, 65, 67) prior to the hearing scheduled for the following day. Accordingly, we held a combined oral hearing on November 22, 2019, and the transcript of that hearing has been entered into the record. Paper 69 (“Tr.”). Patent Owner’s request for rehearing (Paper 67) was denied on February 18, 2020.

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 as issue. *Id.* at 1374. Because Patent Owner argued a presumption of nexus with respect to its proffered evidence of objective indicia of nonobviousness, 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 70. Petitioner filed a substantially similar supplemental brief and responsive brief (Paper 71, “Pet. Supp. Br.,”

⁶ 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 75.

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Paper 74, “Pet. Supp. Rep. Br.”), and Patent Owner filed a substantially similar supplemental brief and responsive brief (Paper 72, “PO Supp. Br.,” Paper 73, “PO Supp. Rep. Br.”) 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. 64.

Patent Owner identifies Teva Pharmaceuticals International GmbH and Teva Pharmaceuticals USA, Inc. as the real parties-in-interest. Paper 4, 1.

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. 65. According to Petitioner, the first DJ action seeks a declaration that Petitioner’s investigational drug galcanezumab will infringe U.S. Patent Nos. 8,586,045; 9,266,951; 9,340,614; the ’649 patent; and the ’881 patent, and Patent Owner filed an amended complaint in the first DJ action on January 16, 2018. *Id.* Petitioner also identifies a declaratory judgment action filed by Patent Owner on February 6, 2018, seeking a declaration that Petitioner’s product will infringe U.S. Patent Nos. 9,884,907 and 9,884,908 (“the second DJ action”). *Id.* Petitioner states that Patent Owner thereafter filed an amended complaint in the second DJ action to incorporate U.S. Patent No. 9,890,210 and the ’211 patent. *Id.*

According to Petitioner, all of the patents in the first DJ action and the second DJ action purport to claim priority to the same provisional application, and two applications (15/883,218 and 15/956,580) also

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purported to be based on the same provisional application are pending before the United States Patent and Trademark Office. *Id.*

Patent Owner identifies the first DJ action, the second DJ action, the three *inter partes* reviews, and six other *inter partes* reviews styled *Eli Lilly and Co. v. Teva Pharmaceuticals International GmbH*, IPR2018-01422, IPR2018-01423, IPR2018-01425, IPR2018-01710, IPR2018-01711, and IPR2018-01712. Papers 4, 7. Patent Owner also identifies U.S. Patent Nos. 9,365,648; 9,328,168; 9,115,194; 8,734,802; 8,007,794, in addition to the patents and patent applications identified by Petitioner. Paper 5. Patent Owner also identifies a litigation styled *Teva Pharmaceuticals International GmbH v. Eli Lilly and Co.*, Civ. No. 1-18-cv-12029 (D. Mass.). Paper 7.

*D. The Challenged Patents*⁷

The '211 patent is titled “Antagonist Antibodies Directed Against Calcitonin Gene-Related Peptide^[8]” and “relates to the use of anti-CGRP antagonist antibodies for the prevention, amelioration, or treatment of vasomotor symptoms, such as CGRP related headaches (e.g., migraine) and hot flushes.” Ex. 1001, [54], 1:30–33.

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 1:37–39. In humans, two forms of CGRP with similar activities (α -CGRP and β -CGRP) exist and exhibit differential

⁷ 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); 1424 IPR Ex. 1001, code (60); 1427 IPR Ex. 1001, code (60). We refer to the '211 patent in this Decision unless otherwise indicated.

⁸ Calcitonin Gene-Related Peptide is abbreviated throughout as CGRP. See Ex. 1001, 1:37.

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distribution. *Id.* at 1:39–42. At least two CGRP receptor subtypes may also account for differential activities. *Id.* at 1:42–43. 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 1:43–47.

CGRP-mediated vasodilation 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 1:47–50. CGRP has been noted for its possible connection to vasomotor symptoms. *Id.* at 1:51–54. Vasomotor symptoms include hot flushes and night sweats. *Id.* at 1:54–55. 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 2:16–19.

According to the Specification, the precise pathophysiology of migraine is not yet well understood. *Id.* at 3:33–34. Dilation of blood vessels is associated with and exacerbates the pain symptoms of migraine. *Id.* at 3:39–40. The variety of pharmacologic interventions that have been used to treat migraine and the variability in responses among patients indicate that migraine is a diverse disorder. *Id.* at 3:4–6. 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 3:7–19. Some patients respond well to sumatriptan, which is a 5HT₁ receptor agonist, which also inhibits release of CGRP; others are relatively resistant to its effects. *See id.* at 2:28–30, 3:24–29, 4:20–22.

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Embodiments described in the '211 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 3:53–4:3. Other embodiments of the '211 patent are also directed to methods of ameliorating, controlling, reducing incidence of, or delaying the development or progression of a migraine headache or cluster headache, using an effective amount of an anti-CGRP antagonist antibody with or without additional agents. *See id.* at 4:4–52. 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 4:56–5:52, 8:18–20. Other embodiments are directed to a polypeptide which may or may not be an antibody. *See id.* at 7:7–8:17. 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 8:30–60. Other embodiments are directed to methods of making the same. *See id.* at 9:4–19.

The '211 patent includes a Table 4 showing amino acid sequences of different variants of human α -CGRP and related peptides. *Id.* at 51:64–52:2; col. 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 10:24–26. Table 6 provides data on binding affinity for G1 variants. *See id.* at cols. 62–67. Another table (cols. 72–103) lists additional antibody sequences.

E. Illustrative Claims

Claim 1 of the '211 patent, the only independent claim, is illustrative and reproduced below:

1. A humanized monoclonal anti-Calcitonin Gene-Related Peptide (CGRP) antagonist antibody, comprising:

two human IgG heavy chains, each heavy chain comprising three complementarity determining regions (CDRs) and four framework regions, wherein portions of the two heavy chains together form an Fc region; and

two light chains, each light chain comprising three CDRs and four framework regions;

wherein the CDRs impart to the antibody specific binding to a CGRP consisting of amino acid residues 1 to 37 of SEQ ID NO:15 or SEQ ID NO: 43, and wherein the antibody binds to the CGRP with a binding affinity (K_D) of about 10 nM or less as measured by surface plasmon resonance at 37° C.

Ex. 1001, 103:32–45.

Claims 2–15 depend, directly or indirectly, from claim 1. *Id.* at 103:46–104:59.

Claim 1 of the '881 patent, the only independent claim, is illustrative and reproduced below:

1. A human or humanized, monoclonal anti-CGRP antagonist antibody that (1) binds human α -CGRP and (2) inhibits human α -CGRP from binding to its receptor as measured by a radioligand binding assay in SK-N-MC cells.

1424 IPR Ex. 1001, 99:14–17.

Claims 2–6 and 14–19 depend, directly or indirectly, from claim 1. *Id.* at 99:18–35, 100:33–49.

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Claim 1 of the '649 patent, the only independent claim, is illustrative and reproduced below:

1. An isolated human or humanized anti-CGRP antagonist antibody with a binding affinity (K_D) to human α -CGRP of 50 nM or less as measured by surface plasmon resonance at 37° C.

1427 IPR Ex. 1001, 101:38–41.

Claims 2-9 depend, directly or indirectly, from claim 1. *Id.* at 101:42-102:49.

F. The Asserted Prior Art and Declaration Evidence

Petitioner's asserted grounds of unpatentability rely on the following references:

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.

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

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

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

Petitioner relies on the Declaration of Dr. Andrew C. Charles, M.D. dated August 7, 2018 (Ex. 1012 “First Charles Declaration”⁹), the

⁹ The First Charles Declaration is Ex. 1006 in the 1424 IPR, and Ex. 1002 in the 1427 IPR.

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Declaration of Dr. Alain P. Vasserot, Ph.D. (Ex. 1013, “Vasserot Declaration”¹⁰), the Declaration of Dr. Andrew C. Charles, M.D. dated September 9, 2019 (Ex. 1328, “Second Charles Declaration”¹¹), and the Declaration of Dr. Joseph P. Balthasar, Ph.D. (Ex. 1327, “Balthasar Declaration”¹²).

Patent Owner relies on the Declaration of Dr. Michael Ferrari, M.D., Ph.D. (Ex. 2214, “Ferrari Declaration”¹³), the Declaration of Dr. Ian M. Tomlinson, M.A., Ph.D. (Ex. 2226, “Tomlinson Declaration”¹⁴), the Declaration of Steven M. Foord, Ph.D. (Ex. 2232, “Foord Declaration”¹⁵), the Declaration of Alan M. Rapoport, M.D. (Ex. 2237, “Rapoport Declaration”¹⁶), and the Declaration of Robert D. Stoner, Ph.D. (Ex. 2243, “Stoner Declaration”¹⁷).

G. The Asserted Grounds of Unpatentability

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

¹⁰ The Vasserot Declaration is Ex. 1007 in the 1424 IPR, and Ex. 1003 in the 1427 IPR.

¹¹ The Second Charles Declaration is Ex. 1324 in the 1424 IPR, and Ex. 1330 in the 1427 IPR.

¹² The Balthasar Declaration is Ex. 1323 in the 1424 IPR, and Ex. 1329 in the 1427 IPR.

¹³ The Ferrari Declaration is Ex. 2210 in the 1424 IPR, and Ex. 2141 in the 1427 IPR.

¹⁴ The Tomlinson Declaration is Ex. 2222 in the 1424 IPR, and Ex. 2137 in the 1427 IPR.

¹⁵ The Foord Declaration is Ex. 2228 in the 1424 IPR, and Ex. 2054 in the 1427 IPR.

¹⁶ The Rapoport Declaration is Ex. 2233 in the 1424 IPR, and Ex. 2165 in the 1427 IPR.

¹⁷ The Stoner Declaration is Ex. 2239 in the 1424 IPR, and Ex. 2123 in the 1427 IPR.

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Claim(s) Challenged	35 U.S.C. §	Reference(s)/Basis
IPR2018-01424 1–6, 14–19	103(a)	Tan, Wimalawansa, Queen, Doods
IPR2018-01426 1–15	103(a)	Tan, Wimalawansa, Queen
IPR2018-01427 1–9	103(a)	Tan, Wimalawansa, 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 proposed a definition of a person of ordinary skill in the art (“POSA”) in its Petition. Pet. 22 (citing Ex. 1013 ¶¶ 84–86; Ex. 1012 ¶¶ 78–80). Patent Owner proposed its own definition of a person of skill in the art in its Preliminary Response. Prelim. Resp. 29.

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

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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 adopt and apply the definition of a person of ordinary skill 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 vitae* at Ex. 1012, Appendix A; Ex. 1013, Appendix A; Ex. 1305, 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

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the specification of the patent in which it appears.¹⁸ 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 on August 8, 2018. Paper 6; 1424 IPR Paper 4, 1427 IPR Paper 6. 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 requested construction of the term “specific binding.” Pet. 23–24. We determined in our Institution Decision that “it is not necessary to construe the term ‘specific binding’ on this record and at this stage of the proceeding.” Inst. Dec. 11. Neither party pursued construction after our Institution Decision, and we decide that it is not necessary to construe the term “specific binding” for purposes of this Final Written Decision.

¹⁸ 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)).

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With respect to the 1424 IPR, Petitioner requests construction of the following terms: “anti-CGRP antagonist antibody” and “humanized antibody” in the ’881 patent.¹⁹ 1424 IPR Pet. 26. Patent Owner in its Preliminary Response requested construction of the claims “according to their plain and customary meaning,” but did not address claim construction further in its Patent Owner Response or Sur-reply. *See* 1424 IPR Prelim. Resp. 29; *see generally* 1424 IPR PO Resp., Sur-reply.

Petitioner argues that the ’881 patent expressly defines “antibody” to encompass “not only intact polyclonal or monoclonal antibodies, but also fragments thereof (such as Fab, Fab’, F(ab’)₂, Fv).” 1424 Pet. 26 (citing 1424 IPR Ex. 1001, 12:39–45, 26:29–39; 1424 IPR Ex. 1006 ¶ 116; 1424 IPR Ex. 1007 ¶ 74). The Specification of the ’881 patent states:

An “antibody” is an immunoglobulin molecule capable of specific binding to a target, such as a carbohydrate, polynucleotide, lipid, polypeptide, etc., through at least one antigen recognition site, located in the variable region of the immunoglobulin molecule. As used herein, the term encompasses not only intact polyclonal or monoclonal antibodies, but also fragments thereof (such as Fab, Fab', F(ab')₂, Fv), single chain (ScFv), mutants thereof, fusion proteins comprising an antibody portion (such as domain antibodies), and any other modified configuration of the immunoglobulin molecule that comprises an antigen recognition site. An antibody includes an antibody of any class, such as IgG, IgA, or IgM (or sub-class thereof), and the antibody need not be of any particular class.

¹⁹ Petitioner also requests construction of these two terms in the 1427 IPR, and we analyze the construction of the terms in the 1427 IPR in the same manner because the ’649 patent shares the same Specification as the ’881 patent.

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1424 IPR Ex. 1001, 12:35–48; *see also id.* at 26:29–50. We agree with Petitioner that this constitutes an express definition of the term “antibody” and we so construe the term. *Paulsen*, 30 F.3d at 1480. We agree with Petitioner that the defined term “antibody” includes antibody fragments. 1424 IPR Ex. 1001, 12:35–48.

Petitioner argues that the ’881 patent expressly defines “humanized” antibodies in the same manner, i.e., encompassing “forms of non-human (e.g., murine) antibodies that are specific chimeric immunoglobulins, immunoglobulin chains, or fragments thereof (such as Fv, Fab, Fab’, F(ab’)₂ or other antigen-binding subsequences of antibodies)” 1424 IPR Pet. 26 (citing 1424 IPR Ex. 1001, 13:15–20; 1424 IPR Ex. 1006 ¶ 116; 1424 IPR Ex. 1007 ¶ 75). The Specification of the ’881 patent states:

As used herein, “humanized” antibodies refer to forms of non-human (e.g. murine) antibodies that are specific chimeric immunoglobulins, immunoglobulin chains, or fragments thereof (such as Fv, Fab, Fab', F(ab')₂ or other antigen-binding subsequences of antibodies) that contain minimal sequence derived from non-human immunoglobulin.

1424 IPR Ex. 1001, 13:15–20; *see also id.* at 26:29–50. We agree with Petitioner that this constitutes an express definition of the term “humanized antibody” and we so construe the term. *Paulsen*, 30 F.3d at 1480. We agree with Petitioner that “humanized antibody” includes antibody fragments. 1424 IPR Ex. 1001, 13:15–20.

We adopt and apply the foregoing constructions for purposes of this Final Written Decision. We determine that no other term requires express construction. *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).

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However, we provide the following additional discussion regarding interpretation of the challenged claims.

The terms “human” and “humanized” as applied to antibodies are defined in the Specification by the structure of the antibody (e.g. amino acid sequence). 1424 Ex. 1001, 13:15–148. Accordingly, we do not construe the claim terms “human” or “humanized” as incorporating a use of the antibody into the claims, such as use in humans.²⁰ See *Senju Pharm. Co. v. Lupin*, 780 F.3d 1337, 1346 (Fed. Cir. 2015) (“In composition claims 12–16 . . . there is no limitation denoting the function of the composition and we decline to import this limitation into the claims.”) (citing *Phillips v. AWH Corp.*, 415 F.3d 1303, 1323 (Fed. Cir. 2005) (stating that the Court has repeatedly warned against confining the claims to particular embodiments in the written description)).

Similarly, we do not construe the claimed antibody as reciting any use of the antibody, such as for treatment or prevention of a disease, disorder, or symptom. See, e.g., *ParkerVision, Inc. v. Qualcomm Inc.*, 903 F.3d 1354, 1361 (Fed. Cir. 2018) (“We explained long ago that ‘[a]pparatus claims cover what a device *is*, not what a device *does*.’”) (quoting *Hewlett-Packard Co. v. Bausch & Lomb Inc.*, 909 F.2d 1464, 1468 (Fed. Cir. 1990))(alteration in original).

Patent Owner argues that “the utility of the claimed antibody must be considered here, namely ‘preventing or treating CGRP associated disorders

²⁰ The record reflects that humanized antibodies were administered to animals as of November 2005. See Ex. 2128, 1, 5 (discussing the humanized monoclonal antibody bevacizumab (Avastin®) and stating that “[t]he safety and pharmacokinetics of bevacizumab were evaluated in young adult cynomolgus monkeys”).

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such as vasomotor symptoms, including headaches (e.g., migraine, cluster headache, and tension headache) and hot flushes.” PO Resp. 14–15 (citing Ex. 1001, Abstract).²¹ Patent Owner bases this argument on *Otsuka Pharmaceutical Co. v. Sandoz Inc.*, 678 F.3d 1280, 1291 (Fed. Cir. 2012). *Otsuka* involved an obviousness challenge in which “the parties’ arguments focus on selecting and modifying particular prior art compounds, designated as lead compounds.” *Id.* Here, the parties’ arguments do not focus on selecting and modifying particular prior art compounds. Moreover, in a lead compound analysis as was at issue in *Otsuka*, “whether a chemist would have selected a prior art compound as a lead . . . is guided by evidence of the compound’s pertinent properties.” *Id.* at 1292 (citing cases). Thus, the pertinent properties in a lead compound analysis are those of a prior art compound, not properties that are read into the claims. *See ParkerVision*, 903 F.3d at 1361.

We also reject Patent Owner’s argument that Petitioner has read “safety and efficacy requirements into the claims” based on arguments in the Petition. Sur-reply 3–5. Patent Owner relies on *Phigenix v. ImmunoGen*, IPR2014-00676, Paper 39 at 16 (PTAB Oct. 27, 2017), that addressed a particular rationale that the patent challenger advanced for combining the teachings of the prior art. *Id.* *Phigenix* does not stand for the proposition that limitations can be read into claims based on arguments by a party that is not the owner of the patent. Here, the challenged claims do not recite any safety or efficacy requirements, and we decline to incorporate such

²¹ Immediately after this statement, Patent Owner states that “Lilly agrees.” PO Resp. 15 (citing Pet. 4). The Petition at page 4 is a description of the ’211 patent and is *not* an agreement by Petitioner that the utility of the claimed antibody must be considered. *See* Pet. 4.

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limitations into the challenged claims. However, in our discussion of the asserted ground below, we address Patent Owner’s “safety” arguments advanced as a reason that a person of ordinary skill in the art would not have combined the teachings of Tan, Wimalawansa, and Queen. *See infra* Section II.D.2.b)(2).

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;

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(3) the level of ordinary skill in the art; and (4) objective evidence of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

An obviousness analysis “need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ.” *KSR*, 550 U.S. at 418; *see Translogic*, 504 F.3d at 1262. “Often, it will be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue.” *KSR*, 550 U.S. at 418.

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

D. Petitioner’s Asserted Obviousness Grounds

Petitioner asserts that the challenged claims would have been obvious over the combination of references set forth above (*see supra* Section I.G). Pet. 24–64; Reply 1–27. Patent Owner opposes. PO Resp. 1–63; Sur-reply 1–28. The thrust of Patent Owner’s position is that (1) a person of ordinary skill in the art would not have combined the cited combinations of references, e.g., because of potential safety concerns, to arrive at the claimed invention, and (2) the objective indicia compel a finding of nonobviousness. *See* PO Resp. 13–46; Sur-reply 3–28.

1. *The Asserted Prior Art*

a) *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 hαCGRP₈₋₃₇. *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* Ex. 1022, 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 565. Tan reports that MAb C4.19 IgG increased MAP [mean arterial pressure] slightly, but MAP was decreased by rαCGRP in a dose-dependent manner. *Id.* at 568. In experiments involving MAb C4.19 Fab' fragment, a control dose of 0.1 nmol/kg rαCGRP decreased MAP by 29.5 mm Hg. *Id.* at 569. The hypotensive response to rαCGRP was accompanied by a dose-dependent tachycardia in some experiments. *Id.* at 568. Tan states that “[t]his study has clearly demonstrated the ability of MAb C4.19 IgG and its Fab' fragment to block the hypotensive effects of exogenous rαCGRP.” *Id.* at 570.

Tan reports that the skin blood flow response to antidromic stimulation of the saphenous nerve was effectively blocked 30 minutes after administration of MAb C4.19 Fab' fragment (2 mg/rat) but not 60 minutes after administration of MAb C4.19 IgG (1 mg/rat). *See id.* at 565, 569–570.

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

b) Wimalawansa (Ex. 1096)

Wimalawansa 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., during parts of the circadian cycle. *See id.* at 543. CGRP has various direct

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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., CGRP₈₋₃₇) 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 CGRP₈₋₃₇ 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 CGRP₈₋₃₇ 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:

CGRP agonists designed specifically for cerebral vascular bed, when available, can be used during the early phase (i.e. vasoconstrictive 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.

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

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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, (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 3Å of the CDRs in a three-dimensional model and capable of interacting with the antigen or CDRs of the donor or humanized immunoglobulin, and/or (5) the amino acid is rare for that position in a human sequence and the corresponding amino acid from the donor sequence is also rare, relative to other human sequences. *See id.* at 2:41–3:26.

d) Doods (Ex. 1024)

Doods 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.

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Doods describes *in vitro* and *in vivo* testing of BIBN4096BS (“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 ¹²⁵I-hCGRP (the radioligand) and BIBN, and a gamma counter was used to measure the inhibition of ¹²⁵I-hCGRP to CGRP receptors. *Id.* at 420. Doods reports that in this assay, BIBN inhibited the binding of ¹²⁵I-hCGRP to rat CGRP receptors. *Id.* at 422; 1424 IPR Ex. 1006 ¶ 86.

SK-N-MC²² cells were used in the second assay, and the results showed that BIBN inhibited the binding of ¹²⁵I-hCGRP to human CGRP receptors in SK-N-MC cells. Ex. 1024, 420–22; 1424 IPR Ex. 1006 ¶ 87. Doods also used SK-N-MC cells to measure BIBN’s antagonistic effects on inhibiting cAMP activation. Ex. 1024, 420–21. Doods confirmed that BIBN antagonizes CGRP because it inhibited CGRP-induced cAMP activation. *Id.* at 422; 1424 IPR Ex. 1006 ¶ 88.

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. Ex. 1024, 421–22; 1424 IPR Ex. 1006 ¶ 89. 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.” Ex. 1024, 422.

²² SK-N-MC, as used by Doods, stands for “neuroblastoma cell line of human origin.” Ex. 1024, Abstract (Abbreviations).

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2. *Independent Claims*

Petitioner sets forth its contentions as to how the limitations of claim 1 of each of the challenged patents is obvious over the combination of Tan, Wimalawansa, and Queen (and Doods regarding the '881 patent). Pet. 23–58; Reply 1–27; 1424 IPR Pet. 27–52; 1424 IPR Reply 1–28; 1427 IPR Pet. 26–49; 1427 IPR Reply 1–27. Patent Owner opposes. PO Resp. 1–59; Sur-reply 1–27; 1424 IPR PO Resp. 11–59; 1424 IPR Sur-reply 1–27; 1427 IPR PO Resp. 12–61; 1427 IPR Sur-reply 1–28.

a) *The asserted prior art discloses or suggests each and every element of the challenged independent claims*

(1) *The '211 patent, claim 1*

(a) *Claim 1*

i. *“A humanized monoclonal anti-Calcitonin Gene-Related Peptide (CGRP) antagonist antibody”*

Petitioner asserts, *inter alia*, that Tan describes murine anti-CGRP antagonist antibodies, including a full-length antibody (MAb C4.19), that blocked the effects of CGRP both *in vitro* and *in vivo* and that an anti-CGRP antagonist antibody with the claimed properties could have been readily prepared by known, established, and conventional techniques. Pet. 18–19, 29 (citing, e.g., Ex. 1022, 567, 569–571; Ex. 1012 ¶¶ 56, 70–71, 118–126; Ex. 1013 ¶ 97). Petitioner asserts that Wimalawansa proposes using humanized anti-CGRP monoclonal antagonistic antibodies as therapeutic agents for several diseases, e.g., migraine, inflammation, and cardiogenic shock. *Id.* at 27 (citing Ex. 1012 ¶ 114; Ex. 1096, 567, 570); *see also id.* at 26 (Ex. 1012 ¶ 111). Petitioner also asserts that Sveinsson, Salmon, and the '438 patent disclose using anti-CGRP antagonist antibodies to treat

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migraine, ameliorate pain, and treat human conditions.²³ *See id.* at 26 (citing Ex. 1026, 7:5–12, 7:19–24, 10:25–30, claims 2, 7; Ex. 1027 ¶¶ 2–3, 12, 39; Ex. 1028, Abstract, 1:16–21; Ex. 1012 ¶¶ 111–113).

Petitioner asserts that Queen describes routine and conventional humanization technologies, using human IgG scaffolds. *Id.* at 24 (citing Ex. 1023; Ex. 1013 ¶ 49).

With respect to Tan’s saphenous nerve assay, Tan reports “that effective immunoblockade was achieved with MAb C4.19 Fab' fragment 30 min after administration, while the IgG was ineffective up to 2h after the dose.” Ex. 1022, 571. Nevertheless, based on Tan’s own studies and the studies of others, Tan also concluded that “[g]iven an adequate incubation period in a tissue bath, Mab C4.19 IgG clearly diffuses into the synaptic cleft since it was effective at blocking CGRP released from primary afferent nerves by capsaicin *in vitro*,” “[t]he slow distribution of whole IgG to the site of immunoblockade could be overcome by . . . chronic administration of IgG,” and “[w]ith repeated administration, IgG should eventually distribute into interstitial space and achieve the sufficiently high concentrations required for immunoblockade.” *Id.*; *see* Pet. 18–19.

Tan also taught mouse anti-CGRP antibodies (Ex. 1022, 565), and Andrew taught anti-human antibodies (*see* Ex. 1055, Abstract, 88, 89, Table 2, Fig. 1; Ex. 1023, 2:41–3:26). For the reasons discussed herein, we find that Petitioner has shown that a person of ordinary skill would have sought to develop antibodies capable of binding and antagonizing human

²³ These other documents are discussed in more detail below. *See infra* Section II.D.2.b)(1)(a).

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CGRP, as taught by Andrew, and would have sought to humanize such antibodies, as taught by Queen. *See infra* Section II.D.2.a.ii.

ii. “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”

Binding affinity describes the strength of the interaction between an antibody and its antigen, and is commonly measured by the equilibrium dissociation constant (K_D), which is expressed in terms of concentration (e.g., nM). Ex. 1013 ¶¶ 60, 61; *see* Pet. 17. Lower K_D values indicate a higher or stronger binding affinity. Ex. 1013 ¶¶ 60, 61; Ex. 1301, 214:22–25; *see* Pet. 17.

Petitioner asserts that, by 2005, surface plasmon resonance (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.” Pet. 17 (quoting Ex. 1084²⁴, Abstract; citing Ex. 1013 ¶¶ 62–67; Ex. 1084, Abstract, 141, 148–49; Ex. 1086, 117).

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 α CGRP or β CGRP with sufficient affinity (i.e., a relatively low K_D) to effectively block its interaction with receptors.” *Id.* (citing Ex. 1012 ¶¶ 127–131; Ex. 1013 ¶¶ 101–103). According to Petitioner, “antibodies with such affinities were known to be associated with increased biological potency” by 2005. *Id.* (citing Ex. 1088, 350; Ex. 1012 ¶ 128; Ex. 1013 ¶ 101). Petitioner also argues that “the prior art demonstrated a

²⁴ M.H.V. Van Regenmortel, *Improving the Quality of BIACORE-Based Affinity Measurements*, IMMUNOGENICITY OF THERAPEUTIC BIOLOGICAL PRODUCTS Dev Biol. Basel, Karger (Brown F, Mire-Sluis AR eds. 2003) 112:141–151.

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clear preference for antibodies with strong binding affinities,” asserting that “all of the FDA-approved antibodies indicated for human therapeutic use before 2005 had binding affinities in the range of 32 nM to 0.08 nM and most had binding affinities less than 10 nM.” *Id.* (citing Ex. 1012 ¶ 128; Ex. 1013 ¶¶ 69, 70, 101; 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 to further improve *in vivo* efficacy.” *Id.* (citing Ex. 1012 ¶ 129; Ex. 1013 ¶¶ 101, 102; 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.* (citing Ex. 1012 ¶ 129; Ex. 1013 ¶ 101). Petitioner specifically argues that “MAb C4.19, which bound both human and rat CGRP, had a binding affinity (K_D) of 1.9 nM to rat α CGRP and an affinity of 2.5 nM to β CGRP,” and “possessed desirable characteristics, such as inhibiting CGRP from binding to its receptors.” *Id.* (citing Ex. 1021, 706, 707; Ex. 1012 ¶ 129; Ex. 1013 ¶ 101).

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.” Pet. 31–32 (citing Ex. 1013 ¶ 108; Ex. 1084,

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Abstract; Ex. 1085). 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 32 (citing Ex. 1012 ¶ 130; Ex. 1013 ¶¶ 68, 108; Ex. 1087, Abstract, 333).

Patent Owner argues that Petitioner “fails to prove that a POSA would have been motivated to arrive at an antibody having the claimed binding affinity (K_D).” PO Resp. 8; *see also id.* at 41. Patent Owner specifically challenges Petitioner’s reliance on Tan 1994’s binding assay demonstrating a K_D of 1.9 nM to rat α CGRP and 2.5 nM to β CGRP for MAb C4.19, and Petitioner’s argument that these K_D values “lead to predictive blocking effects *in vivo*.” *Id.* at 42 (citing Pet. 31). 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 8 (citing Ex. 2226 ¶¶ 104–109); *id.* at 43 (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** α CGRP with unlabeled **rat** α CGRP, and did so at 4 °C, not 37 °C as claim[ed].” *Id.* at 8, 41. 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_D s measured at 4°C are also not instructive as to K_D values at 37°C.” *Id.* at 44–45 (citing Ex. 1087, 331; Ex. 2226 ¶ 108). Patent Owner further argues that Dr. Charles admits that

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human and rat α CGRP are not the same, and that Dr. Vasserot confirms that differences in amino acids and temperature matter. *Id.* at 8, 45 n.9 (citing Ex. 1012 ¶ 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. PO Resp. 45 (citing Ex. 2226 ¶¶ 112, 113; 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 antibody for α and β isoforms of CGRP.” *Id.* (citing Ex. 2226 ¶ 113). 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_D s of 10 nM or less (PO Resp. 42), and “one cannot arrive at the claimed affinity of 10 nM of a humanized antibody absent hindsight” (*id.* at 46).

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 41–42 (citing Ex. 2226 ¶¶ 110, 111). 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 42 (citing Ex. 1021, 707; Ex. 2226 ¶ 110).

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Petitioner replies by arguing that Patent Owner's binding affinity arguments are incorrect. Reply 18–19. 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.” *Id.* at 18 (citing Ex. 1021, 707 (1.9 nM rat CGRP); Ex. 1055, 92; Ex. 1033, 102 (reporting “high affinity” antibody 4901); Ex. 1327 ¶¶ 71–78; Pet. 36–39). 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^[25] was routine.” *Id.* (citing Ex. 1068, 351; Ex. 1327 ¶ 72; Ex. 1013 ¶¶ 120–125; Ex. 1301, 211:22–214:25²⁶).

Patent Owner replies that “the art teaches a disconnect between binding and activity,” citing Tan 1994 and its results for anti-CGRP antibody MAb R1.50. Sur-reply 24 (citing Ex. 1021, 707; Ex. 2137 ¶ 114).

Analysis

We understand Petitioner to argue that a person of ordinary skill would have sought to make an antibody with 10 nM or 1 nM because antibodies naturally had a certain range of affinities and other therapeutic antibodies had comparable affinities. Pet. 30, 31, 50. Although it was not argued by the parties *in haec verba*, we also understand Petitioner to be

²⁵ Affinity maturation is a process by which antibody engineers can further improve the affinity of an antibody. Ex. 1301, 212:24–213:3.

²⁶ In response to counsel's reading from Ex. 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.

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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 30–31. 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 Sur-reply 24 (“Lilly is wrong because the art teaches a disconnect between binding and activity: the anti-CGRP antibody MAb RL50 ‘clearly showed the greatest [binding] activity’ among the tested antibodies to α CGRP, yet it ‘blocked rat α CGRP 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 caselaw). 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.” Ex. 1013 ¶ 69 (citing Ex. 1023, 2:12–27). Queen discloses that “[l]oss of any affinity is, of

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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).

Patent Owner argues 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 α CGRP poorly. Sur-reply 24 (citing Ex. 1021, 707; Ex. 2137 ¶ 114). 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.

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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. Ex. 1013 ¶ 144. 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.

Further, the process of humanizing an antibody would not have prevented a person of ordinary skill from creating an antibody with optimized binding affinity based on known technology. In particular, Queen discloses a humanization process that ideally results in 60–90% of the original affinity of the donor antibody. Ex. 1023, 3:40–43. Further, Maynard²⁷ discloses a process of combining rational design and library screening for antibody humanization to obtain an antibody in this context with 500-fold greater affinity. Ex. 1068, 355; see Pet. 40.

We further determine that, as of 2005, a person of ordinary skill in the art would have had reasons to measure the binding affinity of a human or humanized anti-CGRP antibody using SPR at human body temperature (i.e., 37° C). Ex. 1084, Abstract, 141, 148–49; Ex. 1085; Ex. 1086, 117; Ex. 1087, Abstract 333. In particular, SPR was recognized as the standard technique to measure affinity (Ex. 1084, 141), and it was considered routine

²⁷ Jennifer Maynard et al., *Antibody Engineering*, 2 ANNU. REV. BIOMED. ENG. 339–376 (2000) (Ex. 1068, “Maynard”).

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to measure the affinity at human body temperature, i.e., 37° C, for antibodies designed for *in vivo* use (Ex. 1087²⁸, Abstract). As discussed herein, Wimalawansa and others suggested the use of antibodies in humans to treat various conditions.

Patent Owner also argues that Dr. Vasserot agreed that a lower temperature for observing affinity, e.g., 25° C as opposed to 37° C, resulted in a lower observed affinity and higher K_D . PO Resp. 45 n.9 (citing Ex. 2191, 1[5]5:19–157:10). However, we do not understand this to detract from Petitioner’s case inasmuch as the observed affinity at 37° C would have been higher (with a lower K_D), and does not indicate that a person of ordinary skill would have been unable to make the recited affinity. Further, it might even support Petitioner’s position.²⁹

Tan 1994 discloses an affinity for mouse CGRP with a 1.9 nM for rat α CGRP and 2.5 nM for rat β CGRP, at 4° C measured by fitting to a displacement RIA method. Ex. 1021, 704–705, 707; Ex. 1327 ¶ 72. Regardless, we do not understand Petitioner to argue that a person of ordinary skill would have directly modified Tan’s antibodies through bodily incorporation, but rather relies on Tan for all it teaches. *See In re Etter*, 756 F.2d 852, 859 (Fed. Cir. 1985) (en banc). We understand Petitioner to rely on Tan’s antibodies for an example in the prior art of anti-CGRP

²⁸ R. Johnstone et al., *The Effect of Temperature on the Binding Kinetics and Equilibrium Constants of Monoclonal Antibodies to Cell Surface Antigens*, 27(4) MOLECULAR IMMUNOLOGY 327–333 (1990) (Ex. 1087).

²⁹ Patent Owner also asserts that Dr. Vasserot conceded that there was a difference in the binding of Tan’s antibodies to rat CGRP and human CGRP. PO Resp. 43 n.8 (citing Ex. 2191, 154:21–156:12). However, Andrew raised antibodies that targeted human CGRP in the first instance. Ex. 1055, Abstract, 88, 89, Table 2, Fig. 1; Ex. 1023, 2:41–3:26.

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antibodies and to argue that a person of ordinary skill would have raised antibodies against human CGRP, as did Andrew, and to humanize the framework of the antibody to minimize antigenicity, and in so doing to select antibodies of the desired affinity, in order to optimize the blocking of CGRP.

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 values³⁰ of 4.0 nM to 40 nM for antibodies raised against human CGRP. Ex. 1327 ¶ 72.

We further 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 Ex. 1013 ¶ 69); (2) the parties experts testified that single digit nM affinities are obtained ‘as a general rule’ (Ex. 1327 ¶ 72); 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).

We also determine that a person of ordinary skill in the art would have had a reasonable expectation of success in achieving the nM binding affinity range claimed by Patent Owner because Dr. Tomlinson agreed that “[a]s of 2005, a person of ordinary skill could use affinity maturation techniques to improve binding affinity stronger than one nanomolar.” Ex. 1301, 213:21–

³⁰ Dr. Balthasar explains that “Andrew reports a K_A range of 2.5×10^7 to $2.5 \times 10^8 \text{ M}^{-1}$, which can be converted to K_D values by taking the inverse (i.e., $K_D = 1/K_A$).” Ex. 1327 ¶ 72 n.3.

25. Further, Dr. Balthasar averred that the antibody field recognized a “general rule” that by using animal immunization, one should expect to obtain antibodies that have binding affinities ranging from 1 nM to 1 μ M. Ex. 1327 ¶ 72 (citing Ex. 1068, 351). Maynard discloses that, as 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. See Ex. 1068, 351.

Further, Dr. Vasserot provides a chart showing the K_D range of various therapeutic antibodies to show that affinity below 10 nM or 1 nM would have been routine by 2005. Ex. 1013 ¶ 69. For example, Dr. Vasserot avers that muomonab-CD3 had a K_D of 0.83 nM. *Id.* (citing Ex. 1078³¹, 3618).

Patent Owner argues that the “general rule” does not apply to anti-CGRP antibodies, i.e., because Tan 1994 discloses a high affinity antibody that exhibited poor blocking of CGRP. Sur-reply 24. We have already addressed this argument above, i.e., affinity is not the only variable that needs to be optimized inasmuch as an antibody must also bind the correct site on the CGRP molecule in order to block its function.

Dr. Tomlinson’s testimony that, as of 2005, a person of ordinary skill in the art “could use affinity maturation techniques to improve binding affinity stronger than one nanomolar” (Ex. 1301, 213:21–25), indicates that a person of ordinary skill in the art could have optimized affinity, as reflected in the K_D value, to as strong as necessary to achieve the best efficiency or usefulness of the antibody. For the reasons set forth above, the

³¹ M. Cole et al., *Human IgG2 Variants of Chimeric Anti-CD3 Are Nonmitogenic to T Cells*, 159 J. Immunology 3613–3621(1997).

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prior art suggests a general desire for an optimized, high binding affinity, and we conclude that a person of ordinary skill would have been able to make that binding affinity stronger (i.e., of a lower K_D) than 10 nM or 1 nM. It is well settled that “where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.” *E.I. DuPont*, 904 F.3d at 1006 (quoting *In re Aller*, 220 F.2d 454, 456 (CCPA 1955) and citing cases).

Thus, we determine that a person of ordinary skill in the art would have raised antibodies against human CGRP following a similar process as did Andrew, and humanized them, and would have optimized the affinity based on the properties described by Dr. Vasserot and Dr. Tomlinson, in keeping with the affinity ranges then-common for antibody therapies.

We are persuaded by Petitioner that a person of ordinary skill would have sought to obtain antibodies with the recited affinities and would have tested them at 37° C in order to test them at temperatures that reflect the human body, and to match the affinities of other antibodies that had been developed for therapeutic use. See Ex. 1012 ¶ 128; Ex. 1013 ¶¶ 68–70, 101, 108.

iii. “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”

Petitioner asserts the anti-CGRP antagonist antibodies of the prior art included IgG antibodies. Pet. 13 (citing Ex. 1022, 566; Ex. 1033, 93; Ex. 1055, 89). Petitioner asserts that, as of 2005, IgG was the preferred immunoglobulin class for all therapeutic antibodies, regardless of target antigen. *Id.* (citing Ex. 1012 ¶ 28; Ex. 1013 ¶ 23; Ex. 1062, 43). Petitioner

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asserts that an IgG possesses two heavy chains and two light chains. *Id.* (citing Ex. 1012 ¶ 29; Ex. 1013 ¶ 17; Ex. 1058, 95, 100). Petitioner asserts that each “arm” of an IgG antibody is known as a Fab (“fragment antigen binding”). *Id.* at 14 (citing Ex. 1012 ¶ 30; Ex. 1013 ¶ 18; Ex. 1058, 96–97). Petitioner asserts that the N-terminal regions of the heavy and light chains form the antigen binding site, also referred to as the variable region of an antibody. *Id.* (citing Ex. 1012 ¶ 30). Petitioner asserts that the variable region includes two heavy chain variable domains and two light chain variable domains. *Id.* (citing Ex. 1012 ¶ 30; Ex. 1013 ¶ 19; Ex. 1058, 96).

Petitioner asserts that the heavy and light chain variable domains each contain three CDRs, which are primarily responsible for antigen binding. *Id.* (citing Ex. 1012 ¶ 31; Ex. 1013 ¶ 20; Ex. 1058, 100–101). Petitioner asserts that in both the heavy and light chains, the three CDRs are interspersed between four regions called FRs that support the CDRs. *Id.* (citing Ex. 1012 ¶ 32; Ex. 1013 ¶ 20; Ex. 1058, 100–101). Dr. Charles indicates that “FRs” are framework regions. *See* Ex. 1012 ¶ 32. Petitioner asserts that the remainder of an IgG antibody is referred to as the constant region. *Id.* (citing Ex. 1012 ¶ 33; Ex. 1013 ¶ 21; Ex. 1058, 96–97). Each light chain has one constant domain (“CL”), and each heavy chain has three constant domains (“CH1,” “CH2,” and “CH3”). *Id.* (citing Ex. 1012 ¶ 33; Ex. 1013 ¶ 21; Ex. 1058, 96–97). Petitioner asserts that portions of the CH2 and CH3 domains on the two heavy chains of an IgG antibody form an Fc region. *Id.* (citing Ex. 1012 ¶ 33; Ex. 1013 ¶ 21).

Patent Owner does not dispute this limitation, and we accept Petitioner’s assertions as factual findings. *See generally In re NuVasive*, 841 F.3d 966, 974 (Fed. Cir. 2016). We further observe that Tan, among

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others, disclosed IgG full length antibodies. Ex. 1022, 571; Ex. 1012 ¶ 57. Accordingly, we determine that a person of ordinary skill would have understood Tan to have disclosed this limitation.

iv. “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”

Petitioner asserts that the recited sequence IDs correspond to human α CGRP and β CGRP, respectively. Pet. 6 (citing Ex. 1012 ¶ 85; Ex. 1013 ¶ 72; Ex. 1001, cols. 53–54 (Table 4)). We accept Petitioner’s undisputed assertions as factual findings. *See NuVasive*, 841 F.3d at 974.

Petitioner asserts that Tan discloses antibodies that bind human α CGRP and β CGRP. Pet. 18 (citing Ex. 1021, 706, 709; Ex. 1012 ¶ 69). Petitioner also asserts that Andrew and colleagues used human CGRP as the target antigen to produce antibodies that specifically bound both isoforms of human CGRP. *Id.* at 35 (Ex. 1055, 88, 90; Ex. 1012 ¶ 144; Ex. 1013 ¶ 116). For the reasons discussed above, we find that a person of ordinary skill would have been able to create antibodies that bound both isoforms of human CGRP, as was performed by Tan and Andrew. *See* Ex. 1021, 706, 709; Ex. 1055, 87–88, 90.

v. Conclusion as to the limitations of claim 1 of the ’211 patent

We determine that the asserted prior art taught or suggested each of the limitations of claim 1 of the ’211 patent. Based on the totality of the evidence, we find that Petitioner has shown by a preponderance of the evidence that the prior art discloses or suggests each and every element of claim 1 of the ’211 patent.

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(2) The '649 patent, claim 1

Claim 1 of the '649 is similar to claim 1 of the '211 patent but instead recites an affinity of "50 nM or less." See 1427 IPR Ex. 1001, 101:38–40. We find that if an antibody has an affinity of 10 nM or less, as recited in claim 1 of the '211 patent, it will also have an affinity of 50 nM or less. We note that a higher concentration indicates a lower affinity when expressed as a K_D . 1427 IPR Ex. 1003 ¶¶ 60, 61; Ex. 1301, 214:22–25. Accordingly, the same evidence meets concentrations of 50 nM or less.

Based on the totality of the evidence, we find that Petitioner has shown by a preponderance of the evidence that the prior art discloses or suggests each and every element of claim 1 of the '649 patent.

We, therefore, determine that the asserted prior art taught or suggested each of the limitations of claim 1 of the '649 patent.

(3) The '881 patent, claim 1

Claim 1 of the '881 is similar to claim 1 of the '211 patent but instead of reciting a particular binding affinity, claim 1 of the '881 patent recites that the claimed antibody "inhibits human α -CGRP from binding to its receptor as measured by a radioligand binding assay in SK-N-MC cells." 1424 IPR Ex. 1001, 99:14–17.

Citing Doods, Petitioner asserts that binding assays in SK-N-MC cells had been used routinely in the prior art to assess inhibition of the CGRP pathway. 1424 IPR Pet. 36 (citing Ex. 1024, 420; Ex. 1061, 195; 1424 IPR Ex. 1006 ¶ 68). Patent Owner does not contest that a radioligand binding assay in SK-N-MC cells was known. We find that Doods discloses the recited assay. In particular, Doods discloses using radioligand binding

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studies in SK-N-MC cells to investigate binding of CGRP-receptors. *See* Ex. 1024, 420–422; 1424 IPR Ex. 1006 ¶ 71.

Petitioner asserts that a person of ordinary skill would have confirmed the ability of a humanized anti-CGRP antagonist antibody to inhibit human α CGRP from binding to its receptor using a radioligand binding assay in SK-N-MC cells. 1424 IPR Pet. 36–37 (citing 1424 IPR Ex. 1006 ¶ 139; 1424 IPR Ex. 1007 ¶ 90). Petitioner asserts that SK-N-MC cells were preferred because, unlike animal tissues, they expressed human CGRP receptors and were commercially available. *Id.* at 36 (citing Ex. 1024, 422; 1424 IPR Ex. 1007 ¶ 89; 1424 IPR Ex. 1006 ¶¶ 70, 139).

We conclude that the asserted prior art taught or suggested the humanized anti-CGRP antibodies, as recited in independent claim 1 of the '881 patent, for similar reasons as for independent claim 1 of the '211 patent. We further conclude that a person of ordinary skill would have used a radioligand binding assay in SK-N-MC cells, as taught by Doods, in order to confirm the antibodies' ability to block CGRP from binding to its receptor. *See* 1424 IPR Ex. 1006 ¶ 139; 1424 IPR Ex. 1007 ¶¶ 89–90.

Based on the totality of the evidence, we find that Petitioner has shown by a preponderance of the evidence that the prior art discloses or suggests each and every element of claim 1 of the '881 patent. *See* Ex. 1022; Ex. 1096; Ex. 1023.

b) Suggestion or Motivation to Combine the Asserted References

Petitioner advances arguments and evidence³² regarding reasons why a person of ordinary skill in the art would have combined the teachings of

³² Petitioner's arguments are substantially similar with respect to all of the challenged patents.

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the asserted references to arrive at the claimed invention. Pet. 24–44; Reply 2–19. Patent Owner opposes³³ by advancing reasons why a person of skill in the art would not have combined the teachings of those references in the manner asserted by Petitioner. PO Resp. 11–39; Sur-reply 10–24; *see Artic Cat Inc. v. Bombardier Recreational Prods. Inc.*, 876 F.3d 1350, 1363 (Fed. Cir. 2017) (“Evidence suggesting reasons to combine cannot be viewed in a vacuum apart from evidence suggesting reasons not to combine.”).

(1) Reasons to combine the teachings of the prior art

(a) Other prior art relied on by Petitioner in discussing reasons to combine

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 reasons to combine Tan, Wimalawansa, and Queen (and Doods regarding the ’881 patent³⁴). We discuss those other references here.

The Olesen Abstract³⁵ reports that BIBN was effective in the acute treatment of migraine. Ex. 1029, 119.

³³ Patent Owner’s arguments are substantially similar with respect to all of the challenged patents.

³⁴ In the 1426 IPR and the 1427 IPR, Petitioner also relies on Doods as evidence of what would have been in the knowledge of one of ordinary skill in the art, in assessing the reasons to combine Tan, Wimalawansa, and Queen.

³⁵ 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”). We refer to the page numbers within a reference as opposed to the page numbers designated for the exhibit.

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The Arndt Abstract³⁶ 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.

Arulmozhi³⁷ 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.

Sveinsson³⁸ 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, 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

³⁶ 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”).

³⁷ D.K. Arulmozhi et al., *Migraine: Current concepts and emerging therapies*, 43 VASCULAR PHARMACOLOGY 176–87 (2005) (Ex. 1040, “Arulmozhi”).

³⁸ Sveinsson, WO 2004/014351 A2, pub. Feb. 19, 2004 (Ex. 1026, “Sveinsson”).

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lichens, prurigos, pruriginous toxidermas, severe pruritis, 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., CGRP_{8–37} 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, benzamidazoliny 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. Thus, Sveinsson suggests the use of anti-CGRP antibodies as one of several types of CGRP antagonists.

Salmon³⁹ 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 α CGRP. *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 α CGRP antagonists such as small peptides, small organic molecules, antisense, triple helix molecules, and polyclonal or monoclonal antibodies. *Id.* ¶¶ 13, 39. Salmon concludes that mice lacking α CGRP display an attenuated response to capsaicin, formalin, carrageenin, and acetic acid, and a decreased physical opiate withdrawal precipitated by

³⁹ Salmon, US 2002/0162125 A1, pub. Oct. 31, 2002 (Ex. 1027, “Salmon”).

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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 patent⁴⁰ 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 CGRP₈₋₃₇ and anti-CGRP antibodies are suitable antagonists according to the invention. *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 2:64–66.

Lassen⁴¹ is a study which reports that administered CGRP caused headache in migraine sufferers. Ex. 1047, 55, 59. Lassen suggests that a 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.

⁴⁰ De Lacharriere, US 6,344,438 B1, iss. Feb. 5, 2002 (Ex. 1028, “the '438 patent”).

⁴¹ LH Lassen et al., *CGRP may play a causative role in migraine*, 22 CEPHALALGIA 54–61 (2002) (Ex. 1047, “Lassen”).

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Olesen⁴² discloses that BIBN was effective in treating acute attacks of migraine. Ex. 1025, 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.

Vater⁴³ 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 Spiegelmer⁴⁴ in cell culture. *Id.* at 7.

Messlinger⁴⁵ is a poster presentation abstract that reports that a CGRP-binding Spiegelmer applied topically to exposed rat cranial dura

⁴² Jes Olesen et al., *Calcitonin Gene-Related Peptide Receptor Antagonist BIBN 4096 BS for the Acute Treatment of Migraine*, 350 NEW ENGL J OF MED 1104–10 (2004) (Ex. 1025, “Olesen”).

⁴³ 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”).

⁴⁴ A Spiegelmer is a “mirror image aptamer.” Ex. 1082, Abstract.

⁴⁵ Karl Messlinger et al., *F022 Inhibition of neurogenic blood flow increases in the rat cranial dura mater by a CGRP-binding Spiegelmer*, Poster

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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.

Wong⁴⁶ is a research article, which reports that the authors produced anti-rat CGRP antibodies in mice and administered it to rats. Ex. 1033, 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.*

Andrew⁴⁷ 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.

Lu⁴⁸ is a research article. See Ex. 1288. The abstract reports that “[m]ice lacking α CGRP expression demonstrate no obvious phenotypic differences from their wild-type litter-mates. Detailed analysis of systemic

Presentations F022, 25 CEPHALALGIA 863–1010, 923 (2005) (Ex. 1240, “Messlinger”).

⁴⁶ Wong. et al., *Monoclonal Antibody to Rat α -CGRP: Production, Characterization, and In Vivo Immunoneutralization Activity*, 12(1) HYBRIDOMA 93 (1993) (Ex. 1033, “Wong”).

⁴⁷ 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”).

⁴⁸ 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”).

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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 α CGRP is not required for the systemic regulation of cardiovascular hemodynamics or development of the neuromuscular junction.” *Id.*

Frobert⁴⁹ is a study that raised and analyzed thirty mouse monoclonal antibodies against rat α CGRP. *See* Ex. 1032, Abstract.

Tan 1994⁵⁰ is a study, prior to Tan, which raised and characterized mouse antibodies directed to rat α CGRP, including Mab C4.19. Ex. 1021, 703, 706. This was the same antibody later used in Tan. *See* Ex. 1022, 566 & n.11.

(b) Analysis of Reasons to Combine

Petitioner contends that a person of ordinary skill would have been motivated to humanize anti-CGRP antibodies, as exemplified by the full length antibody MAb C4.19 in Tan, relying on Tan, Wimalawansa, and Queen, and other exhibits reflective of the art as of November 2005. Pet. 24–50; Reply 6–27. Patent Owner opposes. PO Resp. 13–62; Sur-reply 3–25. We review the evidence and arguments relied on by Petitioner, as follows.

⁴⁹ Frobert et al., *A sensitive sandwich enzyme immunoassay for calcitonin gene-related peptide (CGRP): Characterization and application*, 20 PEPTIDES 275–284 (1999) (Ex. 1032, “Frobert”).

⁵⁰ 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”).

Arguments based on Tan

Citing Tan 1994, Petitioner asserts that α CGRP was known to be tied to human diseases such as migraine and increased skin blood flow (a vasomotor symptom). Pet. 30 (citing Ex. 1021, 708; Ex. 1012 ¶¶ 123–124). Citing Tan and Doods, Petitioner asserts that by 2005, researchers had additionally confirmed that prior art anti-CGRP antagonist antibodies were effective *in vivo* and *in vitro* at eliminating or reducing CGRP's biological effects linked to migraine and other diseases involving vasodilation, similar to what had been shown with CGRP-receptor antagonist BIBN before it was successfully tested in the clinic. *Id.* at 28 (citing Ex. 1022, 571; Ex. 1024, 422; Ex. 1012 ¶ 116). Petitioner argues that the prior art's confirmation of the *in vivo* activity of anti-CGRP antagonist antibodies would have further motivated a POSA to prepare a humanized antibody for therapeutic use. *Id.* at 28–29 (citing Ex. 1012 ¶¶ 118–126; Ex. 1013 ¶¶ 95–100). We note that Doods studied BIBN in marmosets, and Tan studied anti-CGRP antibodies in rats. See Ex. 1022, 569; Ex. 1024, 422.

Petitioner argues that Tan's antibodies possessed many of the desirable properties identified by Patent Owner in the Specification of the challenged patents as a prerequisite for anti-CGRP antagonist antibodies, by virtue of their successful immunoblockade, i.e., binding to CGRP, blocking CGRP from binding to its receptors, blocking or decreasing CGRP receptor activation, and inhibiting CGRP biological activity. Pet. 29 (citing Ex. 1001, 26:18–26; Ex. 1012 ¶ 125; Ex. 1022, 571; Ex. 1021, 706–707). Petitioner also argues that Tan and other prior art showed that anti-CGRP antibodies would have been suitable for administration to humans based on

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preferential binding to human α CGRP as compared to amylin. *Id.* at 41 (citing, e.g., Ex. 1013 ¶¶ 90).

Patent Owner responds that Tan's full-length anti-CGRP antibody failed to show any immunoblockade in a rat saphenous nerve assay.⁵¹ PO Resp. 4 (citing Ex. 2226 ¶¶ 10–11, 66, 86–88; Ex. 2214 ¶¶ 60–61). 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* Ex. 1022, 565, 569–570. We agree with Patent Owner that Tan's full length antibody (at 1 mg/rat) in the saphenous nerve assay did not achieve immunoblockade at 60 minutes after administration. *See* Ex. 1022, 569; PO Resp. 24.

Petitioner replies that a person of ordinary skill, based on Tan, would have used longer distribution times or a higher concentration of antibody in order to overcome this deficiency with respect to the full-length antibody, in part because Tan reported a 16% response when a higher antibody dose and two-hour incubation was used. *See* Reply 20 (citing, e.g., Ex. 1022, 569, 571; Ex. 1012 ¶¶ 93–105; Ex. 1013 ¶ 97; Ex. 1305 ¶¶ 24–29, 33–34). Tan reported no significant difference with an increased dose of 3 mg/rat after 60

⁵¹ *See* K.J. Escott et al., *Effect of a calcitonin gene-related peptide antagonist (CGRP₈₋₃₇) on skin vasodilation and oedema induced by stimulation of the rat saphenous nerve*, BR. J. PHARMACOL. 110, 772–76 (1993) (Ex. 1052, “Escott”). Both Tan and the challenged patents cite to Escott in connection with a rat saphenous nerve assay. Ex. 1022, 565, 572; Ex. 1001, 32:17–20, 54:46–52. Escott describes a study wherein short electrical stimulation of the saphenous nerve in rat induced release of CGRP from nerve endings, resulting in an increase in skin blood flow. Ex. 1052, 772. The results in Escott showed that CGRP₈₋₃₇ inhibits vasodilation induced by saphenous nerve stimulation. *Id.* at 775.

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minutes, but at 2 hours produced an area under the curve (AUC)⁵² which was “slightly smaller compared with baseline stimulation, but not by more than 16 % (n=2).” Ex. 1022, 569. Petitioner also points to Dr. Tomlinson’s testimony that the statement in Exhibit 2084⁵³ that “although reliable statistical results cannot be obtained with a sample size of two rats, distinct trends can be seen” was “accurate.” Reply 20; Ex. 1301, 164:21–25, 166:7–20. Petitioner further cites to Dr. Vasserot’s testimony that “[w]e have started projects with less data than [Tan].” Reply 5 (citing Ex. 2191, 100:8–15, 97:15–100:1).

As pointed out by Patent Owner, Dr. Vasserot opined that it was unlikely that the latter full-length antibody result could be statistically evaluated, and if not, that would mean that the result would have to be taken with caution. Ex. 2191, 118:12–119:2; *see* PO Resp. 16. Dr. Foord opined that a person of ordinary skill in the art would not have been able to draw any conclusions from Tan’s administration of 3 mg/rat measured at 2 hours after stimulation. *See* Ex. 2230 ¶ 52.

We agree with Patent Owner that Tan’s antibody fragment was advantageous over its full length antibody. *See* PO Resp. 5. For example, Tan states “[t]his study has demonstrated the superiority of Fab' fragment over IgG for the immunoblockade of endogenous CGRP after systemic administration.” Ex. 1022, 572.

⁵² Tan states that AUC “may relate to the period over which CGRP is released after nerve stimulation and the duration of action of the CGRP released.” Ex. 1022, 571.

⁵³ S. Tjen-A-Looi et al., *CGRP and somatostatin modulate chronic hypoxic pulmonary hypertension*, AM. J. PHYSIOL. 263(3): H681-H690 (1992) (Ex. 2084, “Tjen-A-Looi”).

At the hearing, counsel for Petitioner stated that Petitioner was principally relying on humanization of the full-length antibody. Tr. 7:6–21 (“We’re principally relying on the antibody, not the fragment. We have arguments in our petition relating to the fragment that we’ll stand on, but our argument relates to the full-length antibody.”). We do not view these statements as a withdrawal of any argument based on an antibody fragment when counsel states that they “stand” on arguments relating to the fragment in the Petition.⁵⁴

We determine that Petitioner’s arguments for humanizing antibodies would apply to antibody fragments, albeit with less emphasis by Petitioner than with respect to full-length antibodies. Dr. Tomlinson explains that a fragment might lack an Fc portion of an antibody (*see* Ex. 2226 ¶ 55), but Dr. Vasserot indicates that modern humanized antibodies do not have humanization limited to the Fc portion. *See* Ex. 1013 ¶ 39. We observe that an antibody fragment may be less desirable than a full length antibody inasmuch as it would require more frequent administrations. *See* Ex. 2226 ¶ 105.

As to the use of full-length antibodies and possible treatments, Dr. Charles states that Tan “provides guidance to a POSA to use anti-CGRP antagonist antibodies, including full-length antibodies, to treat vasomotor symptoms, which include migraine.” Ex. 1012 ¶ 124. Patent Owner disagrees, arguing that Dr. Charles’s statement is unsupported and that Petitioner’s experts admitted that Tan does not involve humans or treatment

⁵⁴ As discussed above in our claim construction section, the claim term “antibody” includes antibody fragments as well as full-length antibodies.

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of conditions. PO Resp. 2–4 (Ex. 2191, 118:2–119:1, 122:16–123:13; Ex. 2192, 154:21–156:9; Ex. 2232 ¶¶ 49, 52–55).

We agree with Patent Owner inasmuch as Tan does not purport to be a clinical study of human treatment and is essentially a research article relating to a study of physiological parameters in rats. See Ex. 2191, 122:16–123:15. Dr. Vasserot testified that Tan only mentions treating diseases in the context of skin vasodilation (*id.* at 122:16–123:15), and Dr. Charles agreed that the reference to skin vasodilation was “talking about experiments, not actually treating any disease” (Ex. 2192, 154:21–156:9). This portion of Tan states: “the routine use of Fab' fragment should be advocated for acute immunoblockade experiments *in vivo*. The immunoblockade of exogenous and endogenous CGRP *in vivo* by an anti-CGRP MAb Fab' fragment in this study has provided further evidence for the role of CGRP as a mediator of skin vasodilatation.” Ex. 1022, 572. Thus, although Tan does not discuss migraine, Tan suggests further study of antibody fragments for treating skin vasodilation.

We consider the teachings and suggestions of Tan as a whole. In one set of experiments Tan analyzed blood pressure after administration of additional (exogenous) CGRP, and found that the full-length anti-CGRP antibody shifted the dose-response relationship curve (i.e. reduced vasodilation caused by the additional CGRP). Ex. 1022, 568, 570 (“This study has clearly demonstrated the ability of MAb C4.19 IgG and its Fab' fragment to block the hypotensive effects of exogenous α CGRP.”). In another study with MAb C4.19, Tan found that an increased dose of 3 mg/rat at 2 hours produced an area under the curve (AUC) which was “slightly smaller compared with baseline stimulation, but not by more than 16 %

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(n=2).” *Id.* at 569. That is, Tan found a slight decrease in the duration of action of endogenous CGRP over the period it is released (e.g., slight inhibition of skin vasodilation) by increasing the dose of MAb C4.19 IgG from 1 mg/rat to 3 mg/rat and measuring nerve stimulation at 2 hours after the 3 mg/rat dose rather than 1 hour. *Id.*

Petitioner argues that Tan indicates that repeated administration of a full length antibody should achieve sufficiently high concentrations. Pet. 19 (citing Ex. 1022, 571; Ex. 1008 ¶ 58). 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”). In other words, although Tan provides a trend in results that requires some caution in its interpretation for its full length antibody’s ability to block an animal’s own CGRP in the context of the nerve stimulation assay, Tan nevertheless shows that its full length antibody has anti-CGRP activity. In terms of suggestions in the prior art to study or use anti-CGRP antibodies, Tan “advocate[s]” for its antibody fragment for further study (*id.* at 572) and also expresses optimism that the obstacles for using the full length antibody (whole IgG) in the rat’s saphenous nerve “should” be overcome (*see id.* at 571).

Arguments based on Wimalawansa

Petitioner asserts that Wimalawansa proposes using humanized anti-CGRP monoclonal antibodies as therapeutic agents for CGRP-related diseases. Pet. 24–25, 27 (citing Ex. 1096, 567, 570; Ex. 1012 ¶¶ 73, 114). Patent Owner argues that Wimalawansa does not recommend pursuing

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anti-CGRP antibodies as a therapeutic, but that instead Wimalawansa states 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. 4, 7 (quoting Ex. 1096, 567; citing Ex. 2226 ¶¶ 80–85; Ex. 2232 ¶ 59). Patent Owner also points to statements in Wimalawansa that “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,” and “[s]ome of the potential side effects of CGRP antagonists could possibly be minimized by being designed specifically to act on only one subtype of receptor.” *Id.* at 11 (quoting Ex. 1096, 567, 568) (emphasis omitted).

In view of the cited portions of Wimalawansa, we find that Wimalawansa both suggests further study of CGRP antagonists and antibodies, and at the same time cautions that further study is necessary before they can be evaluated in humans and suggests the use of “extremely specific” receptor antagonists. *See* Ex. 1096, 567, 568. Wimalawansa states that “[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 particular, Wimalawansa also state that “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.” *Id.* at 568.

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Patent Owner argues that Wimalawansa is referring to antibodies targeting the CGRP receptor and not targeting CGRP itself. *See* PO Resp. 49–50 (citing Ex. 2232 ¶¶ 56–59, 84; Ex. 2224 ¶¶ 80–85; Ex. 2214 ¶¶ 21–26). We agree with Patent Owner that there could be some contextual ambiguity inasmuch as Wimalawansa is also discussing anti-CGRP receptor antagonists and is advocating for receptor-specific effects. *See* Ex. 1096, 567–570. However, Wimalawansa’s statement regarding “carefully designed studies” refers to (1) CGRP antagonists, (2) humanized anti-CGRP monoclonal antibodies, or (3) both. *See id.* at 567. This statement indicates that the teachings and suggestions of Wimalawansa are not limited to the class of CGRP receptor antagonists, as confirmed by its latter statement that “CGRP antagonists *and* humanized monoclonal antibodies should be explored.” *Id.* at 570 (emphasis added). We thus find that Wimalawansa is not limited to antibodies targeting the CGRP receptor, but includes humanized anti-CGRP monoclonal antibodies that target CGRP itself.

Arguments based on Queen

Petitioner asserts that Queen describes routine and conventional humanization technologies, using human IgG scaffolds. Pet. 20–21, 24 (citing Ex. 1023, 1:19–23; Ex. 1012 ¶ 76; Ex. 1013 ¶ 49). Relying on Queen, Petitioner argues that the prior art had embraced humanized IgG antibodies for treating human patients because non-human antibodies were known to be immunogenic in humans. *Id.* at 21 (citing Ex. 1013 ¶¶ 49; Ex. 1023, 1:36–56; Ex. 1056, 1074, 1075 (Table 1); Ex. 1012 ¶ 76; Ex. 1077, 53). We determine that Queen primarily informs the issue of reasonable expectation of success in humanizing an antibody and retaining anti-CGRP activity, and further supports a reason to humanize antibodies in general, i.e.,

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to avoid immune reactions from the use of antibodies from other species. Ex. 1023, 1:36–56; Ex. 1012 ¶ 75 (“Queen describes methods for humanizing monoclonal antibodies that ‘will be substantially non-immunogenic in humans and retain substantially the same affinity as the donor immunoglobulin to the antigen.’” (citing Ex. 1023, Abstract, 1:19–23)); Ex. 1013 ¶¶ 47–50.

*Arguments based on other prior art after
Wimalawansa*

Petitioner asserts that Wimalawansa appreciated the need for further studies as of 1996, but asserts that sufficient studies had been conducted by 2005 to support a person of ordinary skill in the art’s motivation to combine the asserted references (e.g., to provide motivation for a person of ordinary skill in the art to pursue humanizing an anti-CGRP antibody). Pet. 26. Petitioner’s arguments as to why a person of ordinary skill would have humanized an antibody based on existing research fall into four general categories: (1) Petitioner argues that the CGRP pathway was a known target; (2) Petitioner argues that a person of ordinary skill could extrapolate from studies of BIBN (a receptor antagonist) to anti-CGRP antibodies; (3) Petitioner argues that prior art explicitly suggested anti-CGRP antibodies; and (4) Petitioner argues that a person of ordinary skill would have sought to create humanized antibodies to create a therapeutic agent with a longer half-life and to avoid immunogenicity.

*Petitioner argues that the CGRP pathway was a
known target*

Petitioner argues that researchers had already recognized the clinical value of antagonizing CGRP’s biological effects, that CGRP’s strong vasodilatory properties were well-known, and that CGRP had been

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implicated in human diseases associated with vasodilation, such as migraine and inflammation. Pet. 25 (citing Ex. 1096, 567, 570; Ex. 1047, 60; Ex. 1026, 7:5–12, 7:19–24, 10:25–30, claims 2, 7; Ex. 1025, 1104, 1108–09; Ex. 1012 ¶¶ 110–117). Petitioner asserts that researchers had confirmed that anti-CGRP antagonist antibodies were effective in vivo at eliminating or reducing CGRP’s biological effects related to migraine. *Id.* at 28, 30 (Ex. 1012 ¶¶ 126; Ex. 1013 ¶¶ 91–92).

We find that the Olesen Abstract, Olesen, and Arndt report that BIBN (a CGRP receptor antagonist) was effective in treating migraine. Ex. 1025, 1104, 1108–1109; Ex. 1029, 119; Ex. 1030, 129. We also find that Lassen reports that administration of CGRP caused headache in migraine sufferers, some of which headaches met the criteria for migraine, particularly after a delayed onset. Ex. 1047, 55, 56, 59.

Petitioner argues that a person of ordinary skill could extrapolate from studies of BIBN (a small molecule receptor antagonist) to antibodies targeting CGRP itself (antibody ligand antagonists)

Petitioner contends that a person of ordinary skill would have had reason to make anti-CGRP antibodies based on the BIBN studies. Petitioner argues that Olesen’s study showed inhibition of the CGRP pathway to be effective in treating migraine in human patients, and refers to a statement in Olesen for the proposition that the study suggests inhibition of the CGRP pathway more generally. Pet. 27–28 (citing Ex. 1025, 1108–1109). Olesen states that “we therefore hypothesize that CGRP antagonists might be effective in the treatment of acute migraine.” Ex. 1025, 1105. Petitioner also points to a statement in Doods that “we expect that CGRP antagonists will be effective anti-migraine drugs” (citing Ex. 1024, 422). Pet. 27–28;

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Ex. 1008 ¶ 116. Doods reports that in this assay BIBN inhibited the binding of ¹²⁵I-hCGRP to cell membranes *in vitro*, and with an *in vivo* animal model reports that BIBN inhibits an evoked facial blood flow response in marmosets. Ex. 1024, 421–422.

We agree with Petitioner that a person of ordinary skill in the art, considering the problem of migraine and seeing the success of BIBN in Olesen, would have been motivated to study other CGRP antagonists in the CGRP pathway, including anti-CGRP antibodies, i.e., as also suggested by Wimalawansa. See Ex. 1096, 570 (“The role of CGRP antagonists and humanized monoclonal antibodies should be explored with respect to control of pain and inflammation, type 11 diabetes, and in conditions with intractable hypotension, such as septic shock syndrome.”).

As we discuss in more detail below (*see infra* Section II.D.2.b)(2)), Patent Owner argues that Olesen does not rule out safety concerns regarding the use of a receptor antagonist such as BIBN or the use more generally of a less specific CGRP pathway antagonist and does not establish BIBN as an adequate proxy for an anti-CGRP antibody. PO Resp. 28–34. We assess the extent to which the safety concerns might constitute a teaching away, or reasons not to combine the teachings of the prior art, below.⁵⁵

⁵⁵ There are certain cases where the court may inquire whether a new chemical entity would have been expected to possess certain activity. For example, in *Procter and Gamble Co. v. Teva Pharms.*, 566 F.3d 989 (Fed. Cir. 2009), the motivation to create a new chemical entity (risendronate) was closely tied to the question of whether a newly synthesized chemical structure gave rise to a reasonable expectation of success in having metabolic activity for treatment of bone disease. Here, to find the challenged claims obvious, we must conclude the skilled artisan would have had a reasonable expectation of success that the humanized antibody retains anti-CGRP activity. However, where, as here, there had already been

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Petitioner makes certain arguments as to whether a person of ordinary skill would have understood BIBN to act peripherally or centrally. *See* Pet. 28. At the same time, Petitioner argues that any arguments that Patent Owner may present regarding possible uses or methods of treatment for the subject antibodies are irrelevant to analyzing reasonable expectation of success because that inquiry focuses on what is claimed. *See id.* at 43 n.2 (citing *Senju Pharm. Co. v. Lupin Ltd.*, 780 F.3d 1337 (Fed. Cir. 2015); *Akorn, Inc. v. Senju Pharm. Co.*, IPR2015-01205, Paper 39 at 8–9 (PTAB Nov. 22, 2016)); Reply 4 (citing *Alcon Research Ltd. v. Apotex Inc.*, 687 F.3d 1362, 1369 (Fed. Cir. 2012)). Patent Owner argues that to prove motivation to humanize the anti-CGRP antibody based on the potential for human therapeutic use, which Patent Owner understands to be Petitioner’s argument, would require both efficacy and safety. PO Resp. 7 (citing Ex. 2191, 65:2–71:19, 75:4–13, 97:15–106:19), 14 (Ex. 2192, 73:6–74:11; Ex. 1012 ¶¶ 3, 12, 104–105, 107–108, 111, 114; Ex. 1013 ¶¶ 85–86, 96, 138; Ex. 2230 ¶¶ 61–68), 47; Sur-reply 3–4 (citing *Phigenix v. ImmunoGen*, IPR2014-00676, Paper 39 at 16 (PTAB Oct. 27, 2017)). Petitioner replies that the prospect of creating a potential therapeutic is sufficient motivation to humanize. Reply 5 (citing *Abbott GmbH & Co., KG v. Centocor Ortho*

explicit suggestions in the prior to study or use antibodies with anti-CGRP activity, which provided a reason to study or use these compounds in humans, we determine that it is not necessary to inquire in these proceedings whether there would have been a reasonable expectation of success for treatment in order to provide a motivation to use the compound. Other patents in the family contain claims directed to treatment of headaches, and the question of whether the success of BIBN would have led a person of ordinary skill in the art to believe that an anti-CGRP antibody would also be effective in treating migraine may be relevant to other pending proceedings in the family of related cases.

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Biotech, Inc., 971 F. Supp. 2d 171, 185 (D. Mass. 2013); *Sanofi-Aventis U.S. LLC v. Immunex Corp.*, IPR2017-01884, Paper 96 at 17 (PTAB Feb. 14, 2019)).

In these proceedings, we do not reach the question of whether the success of BIBN would have led a person of ordinary skill in the art to believe that an anti-CGRP antibody would also be effective in treating specifically migraine or another disease. We determine that this question is not relevant to these proceedings because the issue of a reasonable expectation of success is limited to the scope of the claims. *Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1367 (Fed. Cir. 2016).⁵⁶ The claims at issue are directed to antibodies. We conclude that the relevant question for these proceedings for the issue of reasonable expectation of success is whether a person of ordinary skill in the art would have had a reasonable expectation of humanizing an anti-CGRP antagonist antibody, such as MAb C4.19 disclosed in Tan, while retaining anti-CGRP activity, as recited, based on the suggestions in Wimalawansa, Sveinsson, Salmon, and the '438 patent, among other prior art, to study or use anti-CGRP antibodies.

Patent Owner cites Dr. Charles's statement in an article that "[t]he notion that we would be using antibodies to treat migraine is really quite a radical concept." PO Resp. 9 (citing Ex. 2053, 23) (emphasis omitted).

⁵⁶ "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).

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However, in context, Dr. Charles was expressing his view that the use of antibodies to treat migraine was based on rational drug development (drug development by virtue of understanding the pathways) and that the use of rational drug development was what was radical. *See* Ex. 2053, 23.

In sum, we agree with Petitioner that the success of the BIBN antagonists would have motivated a person of ordinary skill in the art to study antagonism of other parts of the CGRP pathway.

Petitioner argues that prior art explicitly suggested anti-CGRP antibodies

Petitioner asserts that by November 14, 2005, the art described anti-CGRP antagonist antibodies for treating migraine. Pet. 27 (citing Ex. 1026, 7:5–19; Ex. 1040, 182; Ex. 1012 ¶ 115). Petitioner asserts that the prior art was replete with exemplary disclosures of anti-CGRP antagonist antibodies, including humanized antibodies, to treat human diseases and conditions, that provided express motivation to prepare a humanized anti-CGRP antagonist antibody against human CGRP suitable for administration to humans. *Id.* (citing Ex. 1012 ¶¶ 110–117; Ex. 1013 ¶¶ 104–109). Petitioner argues that by 2005, a person of ordinary skill in the art would have been motivated to make an anti-CGRP antibody that binds human α CGRP for therapeutic use because the prior art had expressly proposed generating anti-CGRP antibodies for treating human diseases such as migraine and other conditions, validated blocking the CGRP pathway as a therapeutic target for treating conditions such as migraine, and confirmed that such antibodies effectively inhibit CGRP’s biological activity *in vivo*. *Id.* at 29–30 (citing Ex. 1012 ¶ 126; Ex. 1013 ¶ 91). We agree with Petitioner that Wimalawansa suggests study of anti-CGRP antibodies in migraine and other prior art of record after Wimalawansa discusses

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anti-CGRP antibodies in other contexts, which we discuss in more detail below.

Petitioner asserts that Sveinsson discloses using anti-CGRP antagonist antibodies to treat migraine and psoriasis in human patients. Pet. 26 (citing Ex. 1026, 7:5–12, 7:19–24, 10:25–30, claims 2, 7; Ex. 1012 ¶ 111).

Petitioner asserts that Sveinsson acknowledges that antibodies against CGRP have been described in the art and that “[k]nown CGRP antagonist compounds which are useful in the current invention include . . . anti-CGRP antibodies.” *Id.* (citing Ex. 1026, 7:19–24; Ex. 1012 ¶ 111). Patent Owner argues that Sveinsson refers broadly to anti-CGRP antibodies but provides no actual evidence that an anti-CGRP antibody can be used safely in humans. PO Resp. 35 (citing Ex. 1026, 7:19, Ex. 2232 ¶ 97; Ex. 2226 ¶ 84; Ex. 2211 ¶¶ 73; Ex. 2192, 79:1–80:2, 82:11–83:8, 85:6–13). Both parties are essentially in agreement that Sveinsson suggests anti-CGRP antibodies. Patent Owner argues that this is a “prophetic disclosure.” *See id.* at 33. We agree with Patent Owner that Sveinsson does not disclose safety information for anti-CGRP antibodies, and does not discuss the possibility of stroke. *See* Ex. 2232 ¶ 97. We also agree with Patent Owner that Sveinsson provides a list of multiple “candidate compounds” that might be used as CGRP antagonists, focusing on small molecule inhibitors. *See* Ex. 2226 ¶ 84 (citing Ex. 1026, 10:37–14:19). Dr. Tomlinson also avers that Sveinsson does not discuss humanizing antibodies. *Id.* Nevertheless, we find that Sveinsson suggests the use of anti-CGRP antibodies in the context of treatment of *psoriasis*, e.g., in humans. *See* Ex. 1026, 7:1–3, 7:19, 10:25–30

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(“Known CGRP antagonist compounds which are useful in the current invention include . . . anti-CGRP antibodies.”).⁵⁷

Patent Owner argues that when Sveinsson refers to antibodies, Sveinsson is referring to anti-receptor antibodies (i.e., to anti-CGRP-receptor antibodies) and not to anti-ligand antibodies (i.e., not to anti-CGRP antibodies). *See* PO Resp. 35 n.7 (citing, e.g., Ex. 1026, 7:5–12). Although Sveinsson discusses antibodies in the context of compounds that selectively inhibit the CGRP receptor (*see* Ex. 1026, 7:5–6), Sveinsson proceeds in a subsequent paragraph to disclose that “[a]ntibodies against CGRP have also been described” (*see id.* at 7:19). We, therefore, find that Sveinsson discloses antibodies against both the CGRP receptor and against CGRP itself. *See also* Ex. 1012 ¶¶ 64, 111 (discussing Sveinsson).

Petitioner asserts that Salmon disclosed in 2002 that α -CGRP is involved in modulating neurogenic inflammatory pain and/or physical opiate withdrawal. Pet. 26 (citing Ex. 1027 ¶¶ 2–3; Ex. 1012 ¶ 112). Petitioner asserts that Salmon discloses methods for ameliorating pain caused by neurogenic inflammation by inhibiting the CGRP pathway and identifies anti- α CGRP antibodies for use in such methods. *Id.* (citing Ex. 1027 ¶¶ 12, 39, claim 8; Ex. 1012 ¶ 112). Patent Owner argues that Salmon mentions

⁵⁷ Although Sveinsson states that CGRP antagonists (and in particular receptor antagonists) have been suggested to treat migraine and other diseases, this is not the focus of Sveinsson and Sveinsson does not discuss antibodies in the same paragraph. *See* Ex. 1026, 7:5–12. Nevertheless, we find that Sveinsson explicitly suggests the use of anti-CGRP antibodies for treatment of psoriasis. *See id.* at 21:24–30 (claim 7, which depends from claim 6). In particular, claim 6 recites the use of a CGRP antagonist compound to treat psoriasis, and claim 7 further recites that the compound is selected from a group including “anti-CGRP antibodies.” *See id.*

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only in passing that CGRP antagonists could be used to inhibit the effect of CGRP in inflammatory pain or opiate withdrawal but provides no human safety information for anti-CGRP antibodies. PO Resp. 35–36 (citing Ex. 1027 ¶ 38; Ex. 2214 ¶ 74; Ex. 2232 ¶ 98). Patent Owner argues that Salmon’s focus was on screening methods for CGRP antagonists using α CGRP knockout and knock-in mice. *Id.* (citing Ex. 1027 ¶ 10; Ex. 2232 ¶ 98).

We agree with Patent Owner that Salmon’s focus, in terms of the experiments that Salmon reports, was on CGRP knockout mice. *See* Ex. 2232 ¶ 98; Ex. 1027 ¶¶ 7–37, 68–86. We also agree with Patent Owner that Salmon does not discuss safety considerations for the administration of anti-CGRP antibodies in humans. Ex. 2232 ¶ 98; Ex. 1027 ¶¶ 7–37, 68–86. Nevertheless, we find that Salmon suggests the use of an anti-CGRP antibody *in screening for a compound* and Salmon, which is a published patent application, claims such a compound. *See* Ex. 1027 (claim 8, which depends from claim 6, which depends from one of claims 1–5). Further, Salmon discloses that pharmaceutical compounds can be used for amelioration of neurogenic inflammatory pain or opiate withdrawal including α CGRP antagonists such as small peptides, small organic molecules, antisense, triple helix molecules, and polyclonal or monoclonal antibodies. *Id.* ¶ 39; *see also id.* ¶ 13.

Petitioner asserts that the ’438 patent is directed to the use of an antagonist of CGRP to treat eye discomfort and pain and specifically recommends using anti-CGRP antagonist antibodies for treating human conditions and diseases. Pet. 26 (citing Ex. 1028, Abstract, 1:16–21, 2:7–10, 2:66–67, 3:21–22, Example 2, claim 2; Ex. 1012 ¶ 113). Patent Owner

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argues that the '438 patent provides no information on human safety of anti-CGRP antibodies. PO Resp. 36 (citing Ex. 1028, 2:17–55; Ex. 2214 ¶ 75; Ex. 2232 ¶ 99). We agree with Patent Owner that the '438 patent does not disclose safety information. Nevertheless, we find that the '438 patent discloses the use of anti-CGRP antibodies *in the context of topical or systemic treatment of eye or eyelid pain*. See Ex. 1028, codes (54), (57), 1:16–21, 2:7–10, 2:66–67, 3:21–22, 5:37–49 (Example 2), claim 2. In particular, the '438 patent discloses an ointment with anti-CGRP antibody and claim 2 is a method claim for therapeutically treating eye pain using CGRP_{8–37} or an anti-CGRP antibody. See *id.* at 5:37–49 (Example 2), 6:13–20 (claim 2, which depends from claim 1).

Petitioner also asserts that by 2005, several publications had described anti-CGRP antagonist antibodies. Pet. 11, 12 (citing Ex. 1021; Ex. 1022; Ex. 1033; Ex. 1055). Dr. Charles avers that researchers had already made several anti-CGRP antagonist antibodies. Ex. 1328 ¶ 17 (citing Exs. 1021, 1022, 1032, 1033, 1055; Ex. 1012 ¶¶ 119–125). Although these exhibits (Tan, Tan 1994, Frobert, Wong, and Andrew) refer to anti-CGRP antibodies that target rat or human CGRP, Petitioner does not assert that these antibodies themselves were humanized. See Pet. 12–13; Ex. 1021; Ex. 1022; Ex. 1032; Ex. 1033; Ex. 1055.

Petitioner also cites Arulmozhi for the proposition that the prior art suggested the use of anti-CGRP antibodies for the treatment of migraines. Pet. 27 (citing, e.g., Ex. 1040, 182). Although Arulmozhi suggests inhibition of CGRP or antagonism of CGRP receptors, Arulmozhi does not mention anti-CGRP antibodies. Ex. 1040, 182.

In any event, based on the disclosures discussed above, we conclude that the prior art explicitly suggested the use of anti-CGRP antibodies to treat various human disease conditions.

Petitioner argues that a person of ordinary skill would have sought to create humanized antibodies to create a therapeutic agent with a longer half-life and to avoid immunogenicity

Petitioner argues that a person of ordinary skill in the art would have been specifically motivated to humanize an anti-CGRP antagonist antibody for human use because migraine, psoriasis, neurogenic inflammation, and vasomotor symptoms—known targets for anti-CGRP antagonist antibodies—are chronic conditions requiring repeat administration of therapeutic agents. Pet. 33 (citing Ex. 1012 ¶ 134). Petitioner asserts that a person of ordinary skill would have humanized an antibody to avoid immunogenicity associated with repeat administration of a therapeutic agent. *Id.* (citing Ex. 1013 ¶¶ 104–105; Ex. 1023, 1:44–57, 1:19–21).

Petitioner asserts that researchers developed anti-ligand antagonists in the form of aptamers that bound CGRP for treating migraine, with unchanged basal blood flow and systemic arterial pressure. Reply 9 (citing Ex. 1082, Abstract, 2 (ref. 9); Ex. 1240, 923; Ex. 1305 ¶¶ 38, 54). Petitioner asserts that aptamers have a relatively longer half-life and “can be thought of as . . . *analogous to antibodies*.” *Id.* (citing Ex. 1309, Abstract; Ex. 1240, 923; Ex. 1082, Abstract, 7). Petitioner asserts that the prior art demonstrated that longer acting anti-CGRP drugs were desirable and indicated as safe. *Id.* (citing Ex. 1328 ¶¶ 5–17, 41–51; Ex. 1327 ¶¶ 48–55).

Dr. Balthasar opines that half-life differences between BIBN and antibodies would not have deterred a person of ordinary skill from

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developing humanized antagonist antibodies, and would instead have been viewed as a therapeutic benefit for treating chronic diseases such as migraine. Ex. 1327 ¶ 52. Dr. Balthasar cites the aptamer studies (Vater and Messlinger) as evidence that half-life differences did not deter the development of longer acting CGRP ligand antagonists. *Id.* (citing Ex. 1082, Abstract; Ex. 1240, 923). Dr. Balthasar refers to Dr. Foord's contention that BIBN would persist in the human body for about 24 hours and avers that aptamers were disclosed as having longer half-lives, potentially requiring only weekly or biweekly dosing. *Id.* ¶¶ 50–51, 54 (citing Ex. 1309, 231). Dr. Charles avers that aptamers have half-lives ranging from hours to days. Ex. 1328 ¶ 17 (citing Ex. 1309, Abstract).

Patent Owner argues that Petitioner's argument regarding aptamers is untimely in its Response. Sur-reply 18 (citing, e.g., *Henny Penny Corp. v. Frymaster LLC*, 938 F.3d 1324 (Fed. Cir. 2019)). We decline to strike Petitioner's arguments regarding aptamers as untimely for the reasons given below in the section addressing the motions to strike and exclude. *See infra* Section III.B. On the merits, Patent Owner argues that the aptamers would not have been informative on the safety of antibodies because they have shorter half-lives and are not analogs to antibodies. Sur-reply 18–19 (citing Ex. 1309, Abstract; Ex. 1240; Ex. 2272, 114:6–115:5, 115:19–117:7, 118:9–120:24).

We agree with Petitioner that the aptamer studies show additional teachings in the prior art to antagonize the CGRP pathway, and further to antagonize the CGRP ligand itself. For example, Vater discloses an aptamer that inhibits the action of α -CGRP in cell culture. Ex. 1082, Abstract. Vater in this context refers to α -CGRP as a “migraine-associated target” peptide.

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Id. Messlinger discloses that an anti-CGRP aptamer provided dose-dependent inhibition of the evoked meningeal blood flow responses evoked by periodic local electrical stimulation in rats. Ex. 1240, 923.⁵⁸

Petitioner also argues that a person of ordinary skill in the art would have been motivated to generate an antibody that bind to the α or β isoform of human CGRP. Pet. 34–35 (citing Ex. 1021, 704; Ex. 1012 ¶¶ 141–146; Ex. 1013 ¶¶ 116, 119). Petitioner asserts that the claims do not preclude the claimed anti-CGRP antagonist antibodies from binding to peptides or proteins other than CGRP. *See* Pet. 41.

(2) Safety concerns as a reason not to combine the teachings of the prior art

Patent Owner argues that Petitioner “ignored the known potentially deleterious effects of anti-CGRP antibodies,” and failed to fully consider safety factors in its motivation analysis. PO Resp. 21–41. Patent Owner further argues that the safety concerns overlooked by Petitioner provide reasons a person of ordinary skill in the art would not have humanized an anti-CGRP antibody. *Id.* at 36–38. According to Patent Owner, given the known safety concerns, a person of ordinary skill would not have undertaken the costly and burdensome task of humanizing an anti-CRRP antibody. *Id.* at 7. Patent Owner’s safety arguments can be divided into to the following categories: (1) safety concerns from blocking the CGRP pathway, (2) safety concerns specifically raised by Tan and Wimalawansa, (3) the relationship

⁵⁸ As above, we do not reach any arguments as to whether studies with aptamers would indicate that anti-CGRP antibodies, in particular, would have been successful for treating migraine. We address Patent Owner’s arguments on safety in the section that follows with respect to the teaching away argument.

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between migraine and stroke, and (4) differences between blocking a CGRP receptor (e.g., with BIBN) and an antibody against the CGRP ligand.

In analyzing the alleged safety concerns, we are mindful that a reference “does not teach away . . . if it merely expresses a general preference for an alternative invention but does not ‘criticize, discredit, or otherwise discourage’ investigation into the invention claimed.” *See DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1327 (Fed. Cir. 2009) (citation omitted). We are also mindful that that “prior art need not explicitly ‘teach away’ to be relevant to the obviousness determination.” *See Arctic Cat*, 876 F.3d at 1360. Our analysis is also guided by the principles that “[a] given course of action often has simultaneous advantages and disadvantages, and this does not necessarily obviate motivation to combine,” and that “there is no rule that a single reference that teaches away will mandate a finding of nonobviousness.” *Medichem, S.A v. Rolabo, S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006).

(a) Safety Concerns from Blocking the CGRP Pathway

Patent Owner argues that, as of 2005, CGRP was known to have an important vasoprotective role in humans. PO Resp. 23–24 (citing Ex. 2003⁵⁹, 923; Ex. 2232 ¶ 23). Patent Owner addresses the various roles of CGRP in cardiovascular regulation, such as protecting against persistently-elevated arterial blood pressure (hypertension) and exacerbation of pulmonary hypertension. *Id.* (citing Ex. 2214 ¶¶ 36, 37, 48–54; Ex. 2232

⁵⁹ S.D. Brain et al., *Vascular Actions of Calcitonin Gene-Related Peptide and Adrenomedullin*, AM. PHYSIOLOGICAL SOC’Y 84, 903–934 (2004) (Ex. 2003).

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¶¶ 80, 81; Ex. 2061⁶⁰, 4–6; Ex. 2084, Abstract H687). Patent Owner further asserts, relying on the Ferrari Declaration, that CGRP was a “safeguard against acute ischemic vascular events by countering excessive vasoconstriction during the ischemic attack.” *Id.* at 23 (citing Ex. 2214 ¶¶ 28–41; Ex. 2058⁶¹, Abstract; Ex. 2009⁶², 614–15; Ex. 1035⁶³, 293).

Patent Owner also relies on the Ferrari Declaration to argue that, by 2005, CGRP was known to regulate blood pressure, modulate hypotension, safeguard against acute ischemic vascular events, and serve a myocardial protective function. PO Resp. 23 (citing Ex. 2214 ¶¶ 28–47; Ex. 2058, Abstract; Ex. 2009, 614–615; Ex. 1035, 293). 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.* at 24 (citing Ex. 2214 ¶¶ 28, 42–47).

Patent Owner argues that Petitioner’s cited art, such as Tan and Wimalawansa, does not overcome the known safety concerns associated with anti-CGRP antibodies in 2005. PO Resp. 24–26. Patent Owner specifically argues that BIBN, a small-molecule receptor antagonist discussed in Olesen, would not have served as a proxy for safety of

⁶⁰ A. Franco-Cereceda et al., *Potential of Calcitonin Gene-Related Peptide in Coronary Heart Disease*, PHARMACOLOGY 60, 1–8 (2000) (Ex. 2061).

⁶¹ N.G. Uren et al., *Effect of intravenous calcitonin gene related peptide on ischaemia threshold and coronary stenosis severity in humans*, CARDIOVASCULAR RESEARCH 27, 1477–81 (1993) (Ex. 2058).

⁶² Edvinsson, *Blockade of CGRP receptors in the intracranial vasculature: a new target in the treatment of headache*, CEPHALALGIA 24, 611–22 (2004) (Ex. 2009).

⁶³ L. Edvinsson et al., *CGRP Involvement in Migraines*, THE HEADACHES 3rd ed., 289–99 (2006) (Ex. 1035).

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anti-CGRP antibodies. *Id.* at 27–33. Patent Owner further argues that “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.” *Id.* at 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 of BIBN. *Id.* (citing Ex. 1025, 1109; Ex. 2214 ¶ 22). Patent Owner thus argues that a person of ordinary skill could not draw any conclusion from Olesen regarding cerebrovascular or cardiovascular safety of CGRP antagonism in humans.” *Id.* at 30, 33 (citing Ex. 1025, 1109; Ex. 2214 ¶ 22).

Patent Owner also argues that there are differences between BIBN and full-length antibodies. *Id.* at 29–31. Patent Owner specifically asserts that BIBN is a synthetic small molecule, not an antibody, that BIBN is a receptor antagonist and does not antagonize the CGRP ligand, that BIBN has a molecular weight that is much smaller than the typical antibody, and that BIBN’s half-life is about 2.5 hours and thus any associated side effects would thus be cleared from the body in less than 24 hours. *Id.* at 29–30 (citing Ex. 2232 ¶ 84; Ex. 1024, 420, 421; Ex. 2068, 32; Ex. 2226 ¶¶ 21, 50, 54; Ex. 2090, 9; Ex. 1059, 143; Ex. 2214 ¶ 22; Ex. 1042, 645). Patent Owner further argues that, in contrast, full length antibodies have a much longer half-life of several weeks to months, and any serious side effects produced by the antibody will persist much longer than any produced by BIBN. *Id.* at 30 (citing Ex. 2224 ¶¶ 50–55, 67–71; Pet. 34; Ex. 1059, 143, Fig. 4.16; Ex. 2232 ¶¶ 76, 84). Thus, according to Patent Owner, “Olesen

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would not have been helpful to a POSA in assessing these risks,” such as myocardial infarction or stroke. *Id.* at 28–29 (citing Ex. 2226 ¶¶ 67–71; Ex. 2214 ¶¶ 12, 27, 28, 67–70; Ex. 2232 ¶¶ 76, 84).

In response, Petitioner argues that “[b]y November 2005, the prior art had established that antagonizing the CGRP pathway was understood to be safe and effective.” Reply 6 (citing Ex. 1328 §IV, ¶¶ 76, 77; Ex. 1303, 70:13-75:11, 84:13–22; Ex. 1304, 91:6–10; Exs. 1291, 1292). Petitioner supports this argument by citing the results of multiple studies of compounds that inhibited or blocked CGRP (discussed below), including Olesen’s study and BIBN. *Id.* at 6–12.

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 13–15 (citing Ex. 1328 ¶ 21). Petitioner further argues that 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 vaso peptides.” *Id.* (citing Exs. 2150, 2151, 2154, 2070, 2089, 2209; Ex. 1328 ¶¶ 22, 23). Petitioner also argues that “[i]n the one study that used CGRP₈₋₃₇ (a receptor antagonist) under physiological conditions, *no* vascular changes were observed.” *Id.* (citing Ex. 2152, 165; Ex. 1328 ¶ 24; Ex. 1303, 111:23–119:13). Patent Owner replies that “Lilly’s ‘more recent’ references involve either [BIBN] or CGRP₈₋₃₇ . . . neither of which is informative as to the safety of anti-CGRP antibodies, given their short half-lives and different mechanism of action (both are receptor antagonists).” Sur-reply 13 (citing Reply 13–14;

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

We provide more detail regarding each of the parties' arguments related to the safety of blocking the CGRP pathway in more detail below.

Olesen and BIBN

Petitioner argues in response to Patent Owner's safety arguments that "Olesen again confirmed that antagonizing the CGRP pathway produced *no serious side effects and no cardiovascular events.*" Reply 7 (citing Ex. 1025, 1109; Ex. 1328 ¶¶ 33–34; Pet. 27–28; Ex. 1303, 84:13–22).

Petitioner also contradicts Patent Owner's argument that "Olesen says nothing about cerebrovascular safety" (citing 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 7 (citing Ex. 1025, 1108).

Petitioner also cites to Olesen's description of BIBN as the "first migraine-specific medication that is not a vasoconstrictor." *Id.* at 8 (citing Ex. 1025, 1108; Ex. 2010, 2561).

Petitioner supports its arguments regarding BIBN by citing studies other than Olesen demonstrating "a very favorable safety profile" for BIBN in human volunteers. Reply 7–8 (citing Ex. 1042, Abstract (reporting *no* "clinically relevant, drug-induced changes" in blood pressure, pulse rate, blood flow, or vital signs); Ex. 2019, Abstract (reporting "no effect of CGRP-receptor blockade on the cerebral or systemic circulation in humans")); Ex. 1328 ¶¶ 35–38; Ex. 1303, 84:23–85:7, 87:1–11, 90:22–92:20.

Petitioner also cites to a report co-authored by Dr. Ferrari that discusses BIBN and states that “CGRP antagonists [seem] promising, new antimigraine drugs without vascular side effects.” Reply 8 (citing Ex. 1290, 657) (emphasis omitted). Petitioner further cites to report co-authored by Dr. Rapoport stating that “[r]ecent data suggests that antagonizing the effect of CGRP may provide acute relief of migraine headache [citing Olesen]. Preventative drugs might be developed on the same principle.” *Id.* (citing Ex. 1297⁶⁴, S119). Petitioner thus argues that “the prior art recognized that ‘inhibition of CGRP or antagonism of CGRP receptors could be a viable therapeutic target’ for treating migraine—and researchers were already targeting both CGRP and its receptor.” *Id.* at 8–9 (citing Ex. 1040, 182 (emphasis added by Petitioner); Ex. 1328 ¶¶ 37, 15–17).

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 14 (citing Ex. 1263, Abstract; Ex. 1303, 97:10–98:2). Petitioner argues that Dr. Saxena’s study demonstrated “[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.* (citing Ex. 1263, 296 (emphasis added by Petitioner); Ex. 1303, 102:9–106:19).

Petitioner argues that a longer half-life is one of the benefits of IgG antibodies, and that “the prior art had embraced humanized IgG antibodies for treating human patients because non-human antibodies were known to be

⁶⁴ A.M. Rapoport et al., *Migraine preventative therapy: current and emerging treatment options*, NEUROL. SCI. 26, S111–20 (2005). Ex. 1297.

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immunogenic in humans.” Pet. 34 (citing Ex. 1013 ¶¶ 104–111; Ex. 1023, 1:44–47; Ex. 1012 ¶ 133; Ex. 1077, 53; Ex. 1056, 1074, 1075 (Table 1) (listing numerous humanized monoclonal antibodies approved prior to November 2005)). Petitioner also responds to Patent Owner’s argument that the relatively long half-life of antibodies would have been expected to exacerbate any potential CGRP-blocking side effect (PO Resp. 28–29) 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 9–10 (citing Ex. 1328 ¶¶ 5–17, 46–50; Ex. 1327 ¶¶ 48–55; Pet. 32–34).

Patent Owner argues in reply that references discussing BIBN are not probative of the safety of an anti-CGRP antibody because BIBN is a small-molecule receptor antagonist with a “significantly” shorter half-life than a full-length antibody, and that each of Petitioner’s BIBN references were short-term studies, such that they would not have informed a person of ordinary skill of the risks of an antibody that circulates in the body for weeks. Sur-reply 15–16 (citing Ex. 2272, 83:22–88:12, 86:13–87:9; Ex. 2232 ¶¶ 76, 84; Ex. 2226 ¶¶ 50–55, 60–71, 74–76; Ex. 2214 ¶¶ 22, 62, 68; Ex. 1042, 645, 647; Pet. 32; Ex. 1059, 143, Figure 4.16; Ex. 1025, 1104; Ex. 1290, 657; Ex. 1297, S119). Furthermore, according to Patent Owner, if any of Petitioner’s cited studies tested cerebrovascular or cardiovascular safety of BIBN, “they were all done in ‘healthy volunteers,’ which, according to Dr. Ferrari, ‘are the wrong experiments to assess cardiovascular safety of any drug interacting with CGRP’ because they do not study whether the antagonist would ‘block rescue mechanisms in the times of ischemia.’” *Id.* at 16 (citing PO Resp. 22; Ex. 1303, 87:5–17, 89:21–90:3;

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Ex. 2214 ¶¶ 48–59; Ex. 2193, 222; Ex. 2157, 533; Ex. 1025, 1108; Ex. 1042, 647; Ex. 2272, 83:22–84:13).

Triptans and Aptamers

Petitioner also responds to Patent Owner’s safety arguments by pointing to studies or uses of CGRP inhibitors other than Olesen, such as triptans and aptamers. Reply 6–14. Petitioner points to the triptan known as sumatriptan, FDA-approved since the early 1990s, as “a safe and effective migraine-specific treatment that inhibited CGRP.” *Id.* at 6–7 (citing Ex. 1328 ¶¶ 11, 44; Ex. 1282, 1519–20; Ex. 1303, 18:7–19:3 (“Q: So you agree . . . that “Sumatriptan was a novel, highly-effective drug against migraine and cluster headache attacks?” [quoting from Ex. 1281] A. Yes.”); Ex. 1303, 211:2–9 (“a person of ordinary skill in the art [as defined] . . . would consider Triptans safe enough to prescribe it.”)). Moreover, by 2005, “inhibiting CGRP release was understood as one of ‘the most important contribution[s]’ to sumatriptan’s anti-migraine effects.” *Id.* (citing Ex. 1303, 23:22–24:22; Ex. 1304, 90:10–15).

Petitioner further argues that sumatriptan was considered “very safe” notwithstanding “transient” blood pressure increases observed in some patients. *Id.* at 7 (citing Ex. 1282, 1521; Ex. 1308, 1673; Ex. 1328 ¶ 44). Petitioner also cites to studies and corresponding papers co-authored by Patent Owner’s expert, Dr. Rapoport, that Petitioner asserts “advocated *daily* triptan administration for up to a year for preventative migraine treatment.” *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. 1328 ¶ 12).

Petitioner also argues that researchers, citing Wimalawansa, “had developed prior art α CGRP ligand antagonists—e.g., aptamers that bound CGRP—for treating migraine.” Reply 9 (citing Ex. 1082, Abstract, 2 (ref. 19)).⁶⁵ Petitioner argues that “researchers reported that ‘[b]asal blood flow and systemic arterial pressure were unchanged’” upon anti-CGRP aptamer administration. *Id.* (citing Ex. 1240, 923; Ex. 1327 ¶¶ 38, 54). Petitioner asserts that “[t]he prior art explained that ‘aptamers can be thought of as . . . *analogous to antibodies*,’ and recognized their relatively longer half-life.” *Id.* (citing Ex. 1309, Abstract (emphasis added by Petitioner)⁶⁶; Ex. 1240, 923; Ex. 1082, Abstract, 7; Ex. 1327 ¶ 51). Thus, according to Petitioner, “the prior art demonstrated that longer acting anti-CGRP drugs were desirable and indicated as safe.” *Id.* (citing Ex. 1328 ¶¶ 5–17, 41–51; Ex. 1327 ¶¶ 48–51).

Patent Owner replies that triptans are small-molecule therapeutics with a half-life of about two-hours, such that any adverse effects of triptans are eliminated from the body within hours. Sur-reply 17 (citing Ex. 1282, 7; Ex. 2272, 99:1–4). Furthermore, according to Patent Owner, triptans operate by a mechanism very different from anti-CGRP antibodies, and that

⁶⁵ Ex. 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.

⁶⁶ “[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. . . . aptamers 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.

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“researchers were not discussing CGRP as being the source of the triptans’ anti-migraine activity before 2005.” *Id.* (citing Ex. 1040, 180; Ex. 2213 ¶ 21; Ex. 2272, 99:20–100:1; Ex. 1303, 23:22–24:18). Moreover, according to Patent Owner, “because triptans were used as a treatment for *acute* migraine, physicians would not have been concerned with triptans’ long term effects.” *Id.* at 17–18 (citing Ex. 2212 ¶ 21; Ex. 1031, 322; Ex. 1040, 176). Patent Owner also argues that “aptamers have a short half-life—‘hours to days,’ not ‘weeks,’” are not “analogs to antibodies,” have many characteristics that are similar to small molecules,⁶⁷ and that there is no evidence on the record that aptamers would have been safe in humans. *Id.* at 18 (citing Ex. 1309, Abstract; Ex. 2272, 114:6–115:5).

Ischemic Events

Patent Owner argues that CGRP “counter[s] excessive vasoconstriction during [an] ischemic attack,” and that “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.” PO Resp. 23–24 (citing Ex. 2214 ¶¶ 28, 42–47; Ex. 2058, Abstract; Ex. 2009, 614–15; Ex. 1035, 293).

Petitioner responds that Patent Owner ignored prior-art studies “demonstrating that blocking the effects of endogenous CGRP with specific antagonists does *not* worsen ischemic events.” Reply 13–14 (citing Ex. 1328 ¶¶ 26–32). Petitioner cites to “a 1998 publication report[ing] that blocking endogenous CGRP did not worsen myocardial ischemia in pigs”

⁶⁷ Patent Owner refers to the statement that “[l]ike small molecules, aptamers can be rationally engineered and optimized, are nonimmunogenic, and are produced by scalable chemical procedures at moderate cost.” Ex. 1309, Abstract.

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(Ex. 1283, 498), a 2001 study investigating BIBN in ischemic rats “report[ing] that CGRP antagonism produced *no effect* on infarct size” (Ex. 1284, Abstract; Ex. 1303, 140:5–7, 142:2–7), a 2003 study antagonizing CGRP in dogs with chronic heart failure reporting that “endogenous α -CGRP does not appear to play a major role in the regulation of cardiac and peripheral vascular dynamics in the late stage of heart failure” (Ex. 1285, Abstract; Ex. 1303, 142:24–143:22), and a “2003 publication involving repeated administration of [BIBN] concluded that CGRP played *no* major role in cardiovascular regulation” (Ex. 1318, 76). Reply 13–14 (emphases added by Petitioner). Petitioner also cites to an article co-authored by Dr. Saxena, stating that “[a]n important advantage of CGRP antagonists over the triptans can be their use in patients with coronary artery disease.” *Id.* (citing Ex. 1031, 326; Ex. 1328 ¶¶ 39–40).

Patent Owner 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.” Sur-reply 13 (citing Ex. 2214 ¶ 46).

Analysis

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 focuses on the role of CGRP in the vascular system to argue that Petitioner “ignored the known *potentially* deleterious effects of anti-CGRP antibodies in its ‘motivation’ analysis.” PO Resp. 21 (emphasis added); *see also id.* at 5 (“potential for substantial safety risks”).

Patent Owner’s substantial focus on the “potential” side effects of blocking the CGRP pathway is reflected in the testimony of Patent Owner’s

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experts. *See, e.g.*, Ex. 2226 (emphases added): “the antibody *may* cause catastrophic effects” (*id.* ¶ 45); “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.* ¶ 48); “[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.* ¶ 67); “a POSA also would have considered all *potential* side effects in analyzing CGRP as a therapeutic antibody target” (*id.* ¶ 72); *see also* Ex. 2214 (emphases added): “use of those antibodies would have raised concerns about *potential* side effects because of their long half-lives and long duration of action” (*id.* ¶ 26); “sequestering CGRP for long periods of time had the *potential* to cause deleterious side effects on the vascular system” (*id.* ¶ 37); “*potential* negative consequences” (*id.* ¶ 77).

Patent Owner also relies on the statement in Edvinsson⁶⁸ that “blockade of a strong endogenous vasodilator such as CGRP carries the inherent risk of causing unwanted side effect such as local vasoconstriction, if there is a tonic influence on any particular system.” PO Resp. 22, 25–26 (citing Ex. 2212 ¶ 48 (citing Ex. 2215, 72)). But immediately after that statement, Edvinsson reports on the studies of Peterson, and that Peterson “did not observe any vasoconstriction effect of [BIBN] in cerebral or

⁶⁸ Edvinsson. L., *Clinical Data on the CGRP Antagonist BIBN4096BS for Treatment of Migraine Attacks*, CNS DRUG REVIEWS 11:69–76 (2005) (Ex. 2215, “Edvinsson”).

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systemic circulations during infusions of the drug at 2.5 or 10 mg over a 10-min period. Thus, in agreement with animal data CGRP does not appear to have a tonic influence on the circulation.”⁶⁹ Ex. 2215, 72.

In contrast, Petitioner focuses on evidence of actual studies of inhibiting 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 6–12. These include, in addition to Olesen and BIBN, the anti-CGRP antibody studies of Wong (“[t]he monoclonal antibody had no significant effect on MAP 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 a “safe and effective” migraine specific treatment for humans, and aptamers (α CGRP ligand antagonists having a long *in vivo* half-life) that maintained basal blood flow and systemic arterial pressure upon administration. Ex. 1282, 1519–20; Ex. 1240, 923.

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. 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 do 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

⁶⁹ This statement seemingly answers Peterson’s “potential concern . . . if CGRP exerts a tonic influence on the cerebral arteries.” Ex. 2019, 139–40.

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standard to find a motivation to combine is far below what is sufficient to prove safety and efficacy to the FDA.”).

We agree with Patent Owner that BIBN is a different molecule than an anti-CGRP antibody and operates by a different mechanism of action (e.g. receptor binding rather than ligand binding), but we also find that the prior art shows that both BIBN and anti-CGRP antibodies are able to block the CGRP pathway. Ex. 1025; Ex. 1022; Ex. 1033. Moreover, we find that the safety information provided in Olesen, on balance, and the additional studies cited by Petitioner, including articles by Patent Owner’s experts, 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 humanizing an anti-CGRP antagonist antibody. Ex. 1025; Ex. 1042, Abstract; Ex. 2019, Abstract; Ex. 1290, 657.

Patent Owner also argues that studies of BIBN are not probative of the safety of an anti-CGRP antibody because BIBN has a significantly shorter half-life (about 2.5 hours) than a full-length antibody. PO Resp. 28.

Petitioner argues that anti-CGRP drugs with longer half-lives would have been viewed by a person of ordinary skill in the art “as desirable for preventative migraine treatments, without posing safety concerns.” Reply 9–10 (citing Ex. 1328 ¶¶ 5–17, 46–50; Ex. 1327 ¶¶ 48–55; Pet. 32–34). Moreover, we find that the prior art demonstrated that blocking the CGRP pathway for substantially longer periods of time than BIBN (longer half-life) resulted in few (if any) side effects. Ex. 1055, 93; 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 also* Ex. 1056,

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1075. Stated differently, we find that the advantages of 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*, 437 F.3d at 1165.

Patent Owner also advances the safety concern of inadequate CGRP during an ischemic attack. *See* PO Resp. 23 (citing Ex. 2214 ¶¶ 28, 42–47). Petitioner responds by citing multiple studies showing that blocking the CGRP pathway with a CGRP antagonist does not worsen ischemic events. Reply 17–19; Ex. 1283, 498; Ex. 1284, Abstract; Ex. 1285, Abstract; Ex. 1031. Although those studies may not have involved anti-CGRP antibodies, we find that, based on those studies, a person of ordinary skill in the art as of November 2005 would not have been deterred or discouraged from humanizing an anti-CGRP antagonist antibody, due to the potential risk during an ischemic attack, because Andrew, Lu, and Olesen indicated that the drugs were acceptable to administer in the first instance and “the standard to find a motivation to combine is far below what is sufficient to prove safety and efficacy to the FDA.” *Persion Pharms.*, 945 F.3d at 1192.

(b) Tan and Wimalawansa

Patent Owner argues that Tan and Wimalawansa also raised substantial safety concerns. PO Resp. 24–26. Patent Owner specifically argues that “Wimalawansa recognizes that reduced levels of circulating CGRP causes systemic vasoconstriction and potential deleterious consequences to the cerebrovascular and cardiovascular system.” *Id.* at 24 (citing Ex. 2214 ¶¶ 72, 77). 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.

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cerebrovascular accidents and myocardial infarctions).” *Id.* (citing Ex. 1096, 543). 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.* at 24–25 (citing Ex. 2214 ¶¶ 71, 72).

Patent Owner also argues that Tan “actually demonstrates that anti-CGRP antibodies increase baseline mean arterial pressure (MAP)—the precise response with which Wimalawansa, and the field were concerned.” PO Resp. 25 (citing Ex. 2214 ¶ 51; Ex. 2232 ¶ 78). 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, leading to adverse consequences, well before it might have any local anti-CGRP effect (as in the saphenous nerve assay) for any therapeutic benefit, *e.g.*, treating migraine.” *Id.* at 24 (citing Ex. 2230 ¶ 79; Ex. 2212 ¶ 62) (emphasis omitted). Patent Owner also argues that Tan’s suggestion for “chronic administration” 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 26 (citing Ex. 2214 ¶¶ 60–64; Ex. 2232 ¶¶ 53–55).

Petitioner specifically responds to Patent Owner’s argument regarding the blood pressure increase observed in Tan by describing it as “transient and mild,” and, relying on the testimony of Dr. Balthasar, argues 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.” Reply 10 (citing Ex. 1327 ¶¶ 56–60; Ex. 1022, 568). Petitioner also

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contends that Patent Owner exaggerated Tan's blood pressure effects by alleging a "13-fold" increase, whereas Dr. Foord testified it was only "1.1-fold." *Id.*

Petitioner further argues that a POSA would not have viewed Tan's minor, transient blood-pressure increase as a safety concern because a similar blood pressure increase was observed with the CGRP-receptor antagonist CGRP₈₋₃₇, but that did not deter development of BIBN or other receptor antagonists. *Id.* at 11 (citing Ex. 1022, 569; Ex. 1025, 1109). Petitioner also argues that "Teva omits that Tjen-A-Looi observed a stronger blood pressure increase with CGRP₈₋₃₇ than an anti-CGRP antisera, which similarly did not deter development of CGRP-receptor antagonists." *Id.* (citing Ex. 2084, H687).

Petitioner also cites to other prior art that it contends "further confirms that anti-CGRP antagonist antibodies did not have any chronic blood-pressure or vascular effects." *Id.* at 11–12 (citing Ex. 1327 ¶¶ 61–65; Ex. 1328 ¶¶ 43–53). Petitioner cites to Wong's "*in vivo* pressure testing on the same antibody (#4901) that Teva evaluated in its specification and concluded that it 'had no significant effect on MAP [mean arterial pressure] and heart rate.'" *Id.* at 11–12 (citing Ex. 1033, 101; Ex. 1001, 52:41) (emphasis omitted). Petitioner also cites to Andrew's evaluation of "immunized animals with 'high levels of circulating antibodies to rat CGRP' after 10-15 weeks and confirmed that 'they did not show any signs of physical or behavioral abnormality.'" *Id.* (citing Ex. 1055, 88, 93). Petitioner further cites to Salmon and other researchers for "disabl[ing] α CGRP production entirely in knockout mice, and rather than experiencing any safety concerns, they *claimed* therapeutic uses of anti-CGRP antagonist

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antibodies.” *Id.* (citing Ex. 1027 ¶ 69, claims 8, 9; Ex. 1026, claim 2; Ex. 1288, Abstract).

Patent Owner replies by repeating its argument that Tan “demonstrated that anti-CGRP antibodies increased baseline mean arterial pressure (MAP),” further arguing that “Tjen-A-Looi demonstrated that an anti-CGRP antibody increased pulmonary arterial pressure in rats,” and that “Wong showed that an anti-CGRP antibody blocked CGRP-induced decrease in blood pressure and heart rate in rats.” Sur-reply 12 (citing Ex. 1022, 568, Fig. 2; Ex. 2214 ¶ 51; Ex. 2232 ¶¶ 78, 81; PO Resp. 23, 25; Ex. 2084, H687; Ex. 1033, 102, Table 2). Patent Owner also challenges Petitioner’s reliance on the statement in Wong that “[t]he monoclonal antibody had no significant effect on MAP and heart rate (n=6)” (Reply 12) by arguing that “Dr. Balthasar admitted that he could not ‘draw direct inference from the sentence [referring to MAP and heart rate] alone to which study it refers to.” See Sur-reply 12 n.6 (citing Ex. 2273, 158:17–20); Ex. 1033, 101.

Analysis

We find, based on Patent Owner’s citations, that Wimalawansa states that “there is a diurnal and circadian rhythm of CGRP in the circulation, its level being lowest at early morning.” Ex. 1096, 543. We also find that Wimalawansa states that “elderly and hypertensive patients have a sharp rise in blood pressure when awakening in the morning. This rise is associated with an increased incidence of cardiovascular disorders, particularly the strokes documented in these groups of vulnerable patients.” *Id.* We further find that Wimalawansa states that “[t]he tendency to have a relative deficiency of circulatory CGRP levels during early hours of the morning []

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may correlate with the increased incidence of early morning cardiovascular episodes . . . in the elderly.” *Id.*

We find that the foregoing statements, cited by Patent Owner, address the levels of circulatory CGRP at a particular time of day and/or in a subpopulation of individuals. *See* Ex. 1096, 543. Moreover, we find that Patent Owner’s arguments regarding Wimalawansa refer to potential adverse effects (“*potential* deleterious consequences” and “*may correlate* with the increased incidence of”). PO Resp. 11, 20, 24 (citing Ex. 2214 ¶¶ 72, 77; Ex. 1096, 543) (emphases added). We determine, however, that Wimalawansa does not suggest that anti-CGRP antagonists presented substantial risk of adverse events, as Patent Owner contends. That is because, although cautioning that certain studies should be undertaken prior to administering anti-CGRP antagonists to humans, Wimalawansa specifically concludes that “humanized monoclonal antibodies should be explored.” Ex. 1096, 570. We thus find that Wimalawansa does not criticize, discredit or otherwise discourage humanization of a monoclonal anti-CGRP antagonist antibody.

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. We thus find that Tan

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does not criticize, discredit, or otherwise discourage humanization of a monoclonal anti-CGRP antagonist antibody.

Based on the foregoing, we find that neither Wimalawansa nor Tan teach away from the challenged claims, and would not have deterred or discouraged a person of ordinary skill in the art in November 2005 from humanizing an anti-CGRP antagonist antibody.

(c) Migraine and Stroke

Patent Owner argues that migraine patients present even greater safety concerns with using antibodies. PO Resp. 27–28. Patent Owner 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.’” *Id.* at 27 (citing Ex. 2157, 533; Ex. 2214 ¶¶ 38–47). Patent Owner supports this argument with the 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.* (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 migraine sufferers also had a higher rate of hypertension, and “[a] POSA likely would have been concerned with treating migraine by antagonizing CGRP.” *Id.* at 27–28 (citing Ex. 2214 ¶¶ 48–54; Ex. 2193, 222; Ex. 2195, 259).

Petitioner contends that Patent Owner’s arguments directed to the specific subpopulation of migraine patients are legally irrelevant. Reply 14

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(citing *Bayer Healthcare Pharm., Inc. v. Watson Pharm., Inc.*, 713 F.3d 1369, 1376 (Fed. Cir. 2013) (rejecting patient sub-population arguments where “the [drug] product claims at issue do not distinguish between target patient populations”)). Petitioner also argues that Patent Owner’s migraine arguments are irrelevant for most migraine patients, citing evidence and the testimony of Dr. Ferrari to argue that “over two-thirds of migraine patients experience migraine without aura, for which no correlation between migraine and stroke was known to exist.” *Id.* at 14–15 (citing Ex. 1040, 177; Ex. 1303, 193:3–10 (“[i]n 2005 there was no known association [between migraine without aura and ischemic stroke].”)). Petitioner also asserts (1) that, with respect to young women, an increased relative risk of stroke was observed compared to the general populace, (2) that “the absolute risk of stroke in young women with migraine is low: 18 per 100,000 per year,” and (3) that “a similarly low absolute risk of myocardial ischemia among young women was also known as of 2005.” *Id.* (citing Ex. 2157, 535–36; Ex. 1303, 190:3–193:12). Petitioner thus argues that “there is no significant overlap between migraine patients and individuals at high risk of stroke or myocardial infarction.” *Id.*

Petitioner further argues that even if there had been potential safety concerns in patients with migraine, it would not have discouraged researchers from pursuing anti-CGRP therapies because “[a]nti-migraine treatments could be contraindicated in patients with particular risk factors, as

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had been done with sumatriptan^[70] and ergots ^[71].” Reply 15 (citing Ex. 1282, 1520; 1290, 564–65; Ex. 1328 ¶¶ 63–64).

Patent Owner replies that safety considerations of anti-CGRP antibodies in migraine patients is legally relevant because Petitioner focused on migraine in its Petition as part of its motivation analysis, citing to the testimony of Dr. Charles. Sur-reply 19 (citing Pet. 28–30; Ex. 2192, 73:6–74:11⁷²). Patent Owner further challenges statements in the Charles Declaration and the testimony of Dr. Charles regarding the link between stroke and migraine. *Id.* at 20–21. Patent Owner further addresses stroke and migraine by arguing that “CGRP played a key role in preventing escalation of mild ischemic events into full-blown infarctions, such as stroke and heart attack,” that 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, e.g., stroke or myocardial infarction,” and that “TIAs are common . . . and are known to be a precursor to stroke in about 5,000–12,500 patients annually.” *Id.* (citing Ex. 2214 ¶¶ 31–33, 37–

⁷⁰ 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.

⁷¹ The term “ergots” refers to ergotamine and its derivatives, which have reportedly been used to treat acute migraine since 1926. Ex. 1316, 1.

⁷² Dr. Charles actually testified that, for purposes of his declaration, he “was asked specifically to provide an opinion about migraine,” and that understanding of migraine is relevant to designing anti-CGRP antibodies. Ex. 2192, 73:4–74:11. Dr. Charles did not admit that Petitioner “specifically focused on migraine in its Petition.” Sur-reply 19; *see also* Pet. 29–30 (referring to “treating human diseases such as migraine and other conditions.”).

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47; PO Resp. 10; Ex. 2144, 1665; Ex. 2272, 65:12–68:6; Ex. 2265, 2901) (footnote omitted). Patent Owner thus concludes that Dr. Charles “has offered no rebuttal to Dr. Ferrari’s testimony about the likelihood that CGRP inhibition would worsen common ischemic episodes in migraineurs.” *Id.* at 21.

Analysis

Patent Owner focuses its arguments on the relationship of migraine and stroke, asserting that safety considerations of anti-CGRP antibodies in migraine patients is legally relevant because Petitioner “focused” on migraine as part of its motivation analysis, and the likelihood that, in patients with migraine, CGRP inhibition would worsen common ischemic episodes. PO Resp. 22–28; Sur-reply 19–21. Petitioner responds that the relative incidence of stroke in migraine patients is low, and that, even if potential safety concerns existed, they would not discourage the pursuit of anti-CGRP therapies because anti-migraine therapies could be contraindicated in patients with particular risk factors. Reply 14–15.

We find that the challenged claims are not directed to treating migraine, or subpopulations of migraine patients. Petitioner presents evidence that as of November 2005 a person of ordinary skill would have understood the relationship between migraine and stroke to be relatively isolated and thus any concerns could be addressed by appropriate contraindications. Ex. 2157, 533; Ex. 1040, 177; Ex. 1303, 190:3–193:12; Ex. 1315, Abstract; Ex. 2157, 536. Patent Owner does not rebut that evidence other than by arguing CGRP’s role in “preventing escalation of mild ischemic events” and that “CGRP inhibition would worsen common

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ischemic episodes in migraineurs.” Sur-reply 20–21. This issue of ischemic events is addressed above.

We find that the relationship between migraine and stroke, to the extent it may be relevant to the challenged claims, would not have deterred or discouraged a person of ordinary skill in the art from humanizing and anti-CGRP antagonist antibody in November 2005.

(d) Differences Between Blocking a CGRP Receptor and an Antibody Against the CGRP Ligand

Patent Owner argues that Petitioner has not demonstrated that BIBN can serve as a proxy for an antibody against the ligand, and specifically argues that antagonism of CGRP receptors is pharmacologically different than antagonizing the CGRP ligand. PO Resp. 28–34. 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 of Teva’s claimed compounds.” *Id.* at 31 (citing Ex. 2232 ¶¶ 83, 84, 96–101). 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 only be expected to have an effect on the downstream CGRP pathway,” but “antagonizing CGRP itself would evoke multiple other physiological responses, because CGRP was known to exhibit a large amount of cross-reactivity with the receptors for calcitonin, amylin, and adrenomedullin” (i.e. “cross-binding”). PO Resp. 31–32. (citing Ex. 2232 ¶¶ 23–37, 85–87; Ex. 2187, 240; Ex. 2140, 237, 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

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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.” *Id.* at 32 (citing Ex. 2232 ¶¶ 22–28, 85–87; Ex. 2059, 63; Ex. 2003, 903–906).

In response, Petitioner argues that “CGRP is a secondary or worse binding ligand to non-CGRP receptors,” citing to Dr. Foord’s testimony. Reply 18 (citing Ex. 2232 ¶ 34; Ex. 2059, 63). Petitioner also argues that, to the extent it is deemed relevant at all, ligand cross-binding favors targeting CGRP rather than its receptor. *Id.* at 17–18 (citing Ex. 1328 ¶ 74). According to Petitioner, that is because adrenomedullin was reported to bind CGRP receptors and elicit similar cardiovascular responses as CGRP without having any implicated role in migraine, and under Patent Owner’s cardiovascular safety theory, “blocking the CGRP receptor would have been viewed as a potentially riskier approach because it would reduce both CGRP’s and adrenomedullin’s purported cardiovascular effects.” *Id.* (citing Ex. 2003, 912–914, 919–921).

Patent Owner replies that “cross-reactivity is one of the reasons why a POSA would not have considered CGRP receptor antagonism to be simply ‘alternative, complementary strategies,’” and that “one cannot equate receptor and ligand antagonism without considering the differences between the two.” Sur-reply 23–24 (citing Ex. 2232 ¶ 85).

Second, Patent Owner argues that the “spare receptor” theory would have further diminished any correlation a POSA would have drawn between CGRP receptor blockade and CGRP ligand blockade. PO Resp. 32–34 (citing Ex. 2232 ¶¶ 38–42, 88–95; Ex. 2062, 74; Ex. 2063, 15; Ex. 2064, 537). That theory posits that “a significantly higher percentage of ligands

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than receptors need 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 33 (citing Ex. 2232 ¶¶ 41, 42, 92–94). Thus, according to the Foord Declaration, “Olesen’s receptor antagonism study would not have allowed a POSA to draw conclusions regarding safety of an anti-CGRP antibody.” *Id.* at 33 (citing Ex. 2232 ¶ 86).

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 would need to be bound to elicit a full biological response, contrary to Teva’s hypothetical.” Reply 16–17 (citing Ex. 1327 ¶¶ 40–47). Petitioner further argues that “[s]uccessfully treating migraine does not require antagonizing 99.999% of CGRP ligands to effectively abolish all CGRP activity, as Teva contends.” *Id.* at 16 (citing PO Resp. 32–33; Ex. 1328 ¶¶ 65–69). Rather, according to Petitioner, “only *elevated* or *inappropriate* levels of CGRP were recognized as a cause of migraine, while *normalizing* CGRP levels was accompanied by subsidence of migraine headache.” *Id.* at 16–17 (citing Ex. 1044, Abstract; Ex. 1096, 567; Pet. 27–28). Petitioner also argues that “[b]y 2005, researchers had already targeted the CGRP ligand to treat migraine, further confirming that Teva’s hypothetical ‘spare receptor’ theory did not, in fact, deter targeting CGRP.” *Id.* (citing Ex. 1328 ¶¶ 17 (citing Exs. 1021, 1022, 1033, 1055, 1082, 1240), 69; Pet. 25–28).

Patent Owner replies that “Dr. Foord’s testimony that CGRP ligand antagonism is not an ‘alternative’ to receptor antagonism because of the

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CGRP receptor reserve remains sound and effectively unrebutted.”

Sur-reply 22 (citing Ex. 2232 ¶¶ 86).

Third, Patent Owner points to three examples that it asserts show that receptor antagonism is not a proxy for ligand antagonism. PO Resp. 28–34. 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.* at 33–34 (citing Ex. 2226 ¶¶ 46, 75; 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. 2226 ¶ 75; Ex. 2129, 4880). The third example cited by Patent Owner is the anti-CGRP receptor antibody Aimovig® that “can cause constipation in patients, but the same side-effect is not observed with the anti-CGRP antibody Ajovy®.” *Id.* (citing, e.g., Ex. 2226 ¶ 75; Ex. 2238, 1; Ex. 2237 ¶¶ 53, 54). 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. 2226 ¶ 75).

Analysis

We determine that Patent Owner’s arguments regarding cross-binding and the spare receptor theory are advanced by Patent Owner to rebut the argument that ligand antagonism is an “alternative” to receptor antagonism. But receptor antagonism and ligand antagonism can be “pharmacologically different” and also be “alternative” approaches to blocking the CGRP pathway. *See* Ex. 1022, 571; Ex. 1021, 709. We thus find that ligand

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antagonism and receptor antagonism are different in certain respects, but also alternative approaches to blocking the CGRP pathway. *See* Ex. 1022, 571; Ex. 1021, 709.

Regarding cross-binding specifically, Patent Owner argues that “a POSA would have understood that antagonizing CGRP would potentially alter” physiological responses regulated by receptors other than CGRP receptors, whereas Petitioner argues that ligand cross-binding favors targeting CGRP rather than its receptor. PO Resp. 32; Reply 17–18. We again note that Patent Owner is asserting a potential concern, but that Petitioner cites to prior art evidence of actually inhibiting or binding the ligand without resulting in adverse events, such as the case with aptamers. *See* discussion above. For this reason, we find that potential cross-binding concerns would not have provided a reason for a person of ordinary skill in the art not to humanize an anti-CGRP antibody because prior art studies of antagonizing CGRP do not reflect cross-binding issues.

Specifically regarding the spare receptor theory, we find that the potential necessity of requiring a higher concentration of ligand antagonist to obtain the same effect as a receptor antagonist would not have provided a reason for a person of ordinary skill in the art not to humanize an anti-CGP antibody because, as discussed above, Petitioner cites to prior art evidence of actually inhibiting or binding the ligand without resulting in adverse events.

We also find that Patent Owner’s examples of FDA approved drugs would not have provided a reason for a person of ordinary skill in the art not to humanize an anti-CGRP antibody because “the standard to find a motivation to combine is far below what is sufficient to prove safety and efficacy to the FDA.” *Persion Pharms.*, 945 F.3d at 1192. Moreover, the

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Erbitux® and Aimovig® examples argued by Patent Owner rely on post-filing date art, and there is no evidence that a person of ordinary skill in the art would have been aware of that information as of November 2005. Again, we find that CGRP ligand antagonists and CGRP receptor antagonists differ in certain respects, but we also find that both block the CGRP pathway. See discussion above.

(3) Other Considerations

(a) Hindsight

Patent Owner argues that Petitioner relies on impermissible hindsight. PO Resp. 46–51. We are not persuaded by those arguments. As we found above, Tan, Wimalawansa, and Queen establish reasons that a person of ordinary skill in the art would have combined their respective teachings and would have had a reasonable expectation of achieving the claimed invention. Ex. 1022; Ex. 1023; Ex. 1096. Petitioner’s challenge is fully supported by the prior art, thus rebutting Patent Owner’s hindsight arguments.

(b) Articulation of Prior Art Antibody to Humanize⁷³

Patent Owner argues that Petitioner never articulated which prior art antibody to humanize, that Petitioner “did not specifically argue that a POSA would have humanized [Tan’s] C4.19,” and that Petitioner “falls short in articulating its reasons for unpatentability with sufficient particularity.” Sur-reply 25–26. We are not persuaded because a prior art reference may be relied upon for all that it teaches, and is not limited to its preferred embodiments or working examples. See *Merck & Co., Inc. v. Biocraft Labs., Inc.*, 874 F.2d 804, 807 (Fed. Cir. 1989). Tan’s C4.19

⁷³ This argument is raised in the Sur-reply, and we find no corresponding argument in Patent Owner’s Response. We address it nevertheless.

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antibody is a working example of an anti-CGRP antagonist antibody.

Wimalawansa also refers to “humanized anti-CGRP monoclonal antibodies” without limitation to any particular anti-CGRP monoclonal antibody.

Ex. 1096, 567.

(4) Conclusion regarding Suggestion or Motivation to Combine the Asserted References

For the reasons stated above, we find that there are clearly reasons that a person of ordinary skill in the art would have combined the teachings of Tan, Wimalawansa, and Queen to arrive at claim 1 of each of the challenged patents. *See supra* Section II.D.2.b)(1). In particular, we find that anti-CGRP antagonist antibodies were well known in the art, and that the art encouraged the development of humanized anti-CGRP antibodies. *See* Ex. 1022, Ex. 1096, Ex. 1023.

For the reasons stated above (Section II.D.2.b)(2)), we also find no evidence that making a humanized anti-CGRP antagonist antibody would raise any safety concerns sufficient to discourage a person of ordinary skill in the art from making a human or humanized anti-CGRP antagonist antibody. We also find that none of the evidence advanced by Patent Owner criticizes, discredits, or otherwise discourages making a humanized anti-CGRP antagonist antibody for potential therapeutic purposes.

In *Sanofi-Aventis*, Paper 96 at 20, 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 this case, Patent Owner relies heavily on potential safety concerns based on the role of

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CGRP in the body and general characteristics of antibodies *in vivo*.⁷⁴

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. 1327 ¶¶ 61–64.

For the reasons stated, we find that any alleged safety concerns would not have deterred or discouraged the combination of prior art teachings to achieve the invention of the challenged claims, as advanced by Petitioner.

c) Reasonable Expectation of Success

Petitioner argues that a POSA would have had a reasonable expectation of successfully making a humanized anti-CGRP antagonist antibody as claimed. Pet. 34–40. Petitioner asserts that a POSA would have reasonably expected to succeed in making an anti-CGRP antagonist antibody that bound human α CGRP like those reported in Tan and elsewhere. *Id.* at 34–35 (citing Ex. 1012 ¶¶ 141–146; Ex. 1013 ¶¶ 116–119; Ex. 1021, 706; Ex. 1055, 88, 90, 93). According to Petitioner, generating anti-CGRP antagonist antibodies against human α CGRP instead of rat CGRP would have been straightforward because (1) rat CGRP and human CGRP are similar neuropeptides with highly homologous amino acid sequences, such that a POSA would have expected human α CGRP to be similarly antigenic in mice, (2) researchers had already generated anti-CGRP antagonist antibodies against human CGRP, and (3) human α CGRP was readily available for use in the laboratory and commercially available. *Id.* at 33

⁷⁴ Patent Owner’s arguments regarding Tan, Wimalawansa, and Olesen, and blocking CGRP, are addressed above.

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(citing Ex. 1012 ¶¶ 142–144; Ex. 1013 ¶¶ 116–119; Ex. 1033, 93–95; Ex. 1021, 706; Ex. 1055, 87, 93).

Petitioner further argues that a POSA would have had a reasonable expectation of successfully producing a humanized monoclonal anti-CGRP antagonist antibody of claim 1. Pet. 34–48. Petitioner contends that by 2005, conventional humanization techniques were routinely used that preserved the affinity and specificity of the donor antibody. *Id.* at 39 (citing Ex. 1023, 2:28–34; Ex. 1012 ¶ 151; Ex. 1013 ¶¶ 126–128). Petitioner further asserts that a POSA that followed Queen’s teachings “would have readily been able to graft CDRs from a donor murine anti-CGRP antagonist antibody onto a human IgG scaffold, while maintaining the binding affinity and specificity for human CGRP.” *Id.* at 36 (citing Ex. 1013 ¶ 127; Ex. 1023, Abstract, 2:28–34). Petitioner also asserts that humanized anti-CGRP antagonist antibodies would be expected to have specific binding to human α CGRP or β CGRP. *Id.* at 33–34 (citing Ex. 1012 ¶ 127–139; Ex. 1013 ¶¶ 101–112).

Patent Owner argues that Petitioner “has not demonstrated that a POSA would have had any reasonable expectation that as of November 2005 such humanized anti-CGRP antibodies would be safe and effective” for use “in treating various diseases.” PO Resp. 39–40. Patent Owner relies on *DuPuy Spine*, 567 F.3d at 1326 arguing that the combination would be expected to work for its intended purpose. *See id.* at 38.

According to Patent Owner, Tan’s full-length antibody “demonstrated no efficacy and did not achieve immunoblockade.” *Id.* at 39. Patent Owner argues further that Tan’s results “from the saphenous nerve assay with the full-length antibody would have negated any reasonable expectation of

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success that the C4.19 antibody, humanized or not, could be used to treat vasomotor conditions in humans.” *Id.* (citing Ex. 2232 ¶ 102; Ex. 2226 ¶¶ 66, 82; Ex. 2214 ¶¶ 60, 61). Patent Owner also argues that Tan’s “failure to suggest any therapeutic utility or efficacy of the full-length anti-CGRP antibodies would have negated any reasonable expectation of success in the POSA.” *Id.* at 41 (citing Ex. 2230 ¶ 102). Patent Owner thus argues that Petitioner “failed to prove reasonable expectation of efficacy,” and that Tan showed “that the full-length antibody failed to immunoblockade, such that a POSA would have had a reasonable expectation of success.” Sur-reply 10.

Patent Owner also argues that a person of ordinary skill in the art would not have been persuaded of therapeutic success in view of “Tan’s demonstrated potential for side effects.” PO Resp. 40; *see also id.* at 7 (arguing there was no “reasonable expectation of humanizing and anti-CGRP antibody to provide a therapeutic benefit that outweighed the substantial and expected cerebrovascular and cardiovascular risks”).

Petitioner replies that “there is no dispute that a POSA would have reasonably expected to successfully make the claimed antibody.” Reply 19 (citing Ex. 1301, 204:16–205:9 (Q. “A person of ordinary skill would have been able to succeed in humanizing an anti-CGRP antagonist antibody within the scope of TEVA’s patent claims by following these four general steps, correct?” A. “Provided that sufficient motivation, they would, but it’s not a process to be taken lightly . . . you’re not guaranteed to be successful, although I think there’s a reasonable expectation that you would be.”)). Based on this expert testimony, we agree with Petitioner that a person of ordinary skill would have considered it routine and would have had a

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reasonable expectation to make the claimed antibody. *See* Ex. 1301, 204:16–205:9.

Petitioner also argues that “[t]o the extent that demonstrating safety and efficacy are nevertheless considered, the prior art provides a reasonable expectation of success.” *Id.* at 19 (citing Pet. 29, 43–48). Above, in the discussion of binding affinity, we find that Queen and related prior art taught how to humanize an antibody without loss of affinity or function. *See* Section II.D.2.a.ii., *supra*.

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-Sys.*, 821 F.3d at 1367; *see also Allergan, Inc. v. Sandoz Inc.*, 726 F.3d 1286, 1292 (Fed. Cir. 2013) (“[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).

We find that none of the challenged claims recite safety or efficacy limitations, and none recite an intended therapeutic use. We also find that Patent Owner’s expert, Dr. Tomlinson, has acknowledged a reasonable expectation of success “humanizing an anti-CGRP antagonist antibody within the scope of” the challenged claims. Ex. 1301, 204:16–205:9.

We do not agree with Patent Owner’s assertions regarding Tan, including its potential for side effects, for the reasons discussed above. We also find that Patent Owner’s reliance on *DuPuy Spine* is inapposite. Patent Owner contends that “a reasonable expectation of success ‘refers not only to the expectation that prior art elements are capable of being physically

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combined, but also that the combination would have worked for its intended purpose,” citing *DuPuy Spine*. PO Resp. 39. Rather than addressing the standard for a reasonable expectation of success, the quote from *DuPuy Spine* is taken from a discussion of the “predictable result” discussed in *KSR*,⁷⁵ and the implications of a prior art reference teaching away from a claimed combination. *DuPuy Spine*, 567 F.3d at 1326. As discussed above, we do not find that Tan, or any other prior art, teaches away from the claimed combination.

Accordingly, we find that Petitioner has established by a preponderance of the evidence that a person of ordinary skill in the art would have had a reasonable expectation of success in combining the cited references to meet the limitations of claim 1 of the challenged claims.⁷⁶

d) Objective Indicia of Nonobviousness

Patent Owner argues that “[s]trong objective evidence compels finding non-obviousness of the challenged claims,” and submits evidence of industry praise, long-felt need, unexpected results, industry skepticism, commercial success, and licensing. PO Resp. 51–61; Sur-reply 25–27. Patent Owner argues that “there is a presumption of nexus for objective considerations when the patentee shows that the asserted objective evidence is tied to a specific product and that product ‘is the invention disclosed and claimed in the patent.’” PO Resp. 51–52 (citing *WBIP, LLC v. Kohler Co.*,

⁷⁵ “The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.” *KSR*, 550 U.S. at 416 (2007).

⁷⁶ The limitations specific to claim 1 of the ’881 patent and the ’649 patent are addressed above. See *supra* Sections II.D.2.a)(3) and II.D.2.a)(2), respectively.

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829 F.3d 1317, 1329 (Fed. Cir. 2016)). Here, the “specific product” relied on by Patent Owner is its Ajovy® (fremanezumab-vfrm) antibody and Petitioner’s Emgality® (galcanezumab-gnlm) antibody, both of which have received FDA approval.⁷⁷ PO Resp. 52.

Patent Owner argues that the Ajovy® and/or Emgality® products (1) have received industry wide acclaim, (2) satisfied a long-felt, previously unmet need for a safe, effective, well-tolerated disease-specific, preventative treatment for migraine, (3) achieved unexpected results, (4) faced industry skepticism, and (5) achieved commercial success in the form of rapid commercial growth since their launch in the third quarter of 2018. *Id.* at 52–60. Patent Owner also argues that the challenged patents were included in a group of patents in a royalty-bearing non-exclusive license agreement to AlderBio Holdings, LLC and Alder Biopharmaceuticals, Inc. (collectively “AlderBio”) in January 2018 (“AlderBio License”), and that the AlderBio License “has nexus to the challenged claims because the challenged patent is part of the license.” *Id.* at 60–61.

(1) The Law of Secondary Considerations

Notwithstanding what the teachings of the prior art would have suggested to one skilled in the art, objective evidence of nonobviousness (so-called “secondary considerations”) may lead to a conclusion that the challenged claims would not have been obvious. *In re Piasecki*, 745 F.2d 1468, 1471–72 (Fed. Cir. 1984). Objective evidence of non-obviousness “may often be the most probative and cogent evidence in the record” and

⁷⁷ Ajovy® is indicated for the preventive treatment of migraine in adults. Ex. 2168, 1; see PO Resp. 2. Emgality® is also approved for a similar purpose. See Ex. 2237 ¶ 23.

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“may often establish that an invention appearing to have been obvious in light of the prior art was not.” *Transocean Offshore Deepwater Drilling, Inc. v. Maersk Drilling USA, Inc.*, 699 F.3d 1340, 1349 (Fed. Cir. 2012).

In order to accord substantial weight to secondary considerations in an obviousness analysis, “the evidence of secondary considerations must have a ‘nexus’ to the claims, *i.e.*, there must be ‘a legally and factually sufficient connection’ between the evidence and the patented invention.” *Henny Penny*, 938 F.3d at 1332 (quoting *Demaco Corp. v. F. Von Lang-sdorff Licensing Ltd.*, 851 F.2d 1387, 1392 (Fed. Cir. 1988)). “The patentee bears the burden of showing that a nexus exists.” *WMS Gaming Inc. v. Int’l Game Tech.*, 184 F.3d 1339, 1359 (Fed. Cir. 1999).

A patent owner may establish nexus, either through (1) the use of a rebuttable presumption that arises when certain conditions are met or (2) a direct showing of nexus. We discuss each in turn.

First, a patent owner may rely on a rebuttable presumption of nexus as follows:

As first recognized in *Demaco* . . . , a patentee is entitled to a rebuttable presumption of nexus between the asserted evidence of secondary considerations and a patent claim if the patentee shows that the asserted evidence is tied to a specific product and that the product “*is the invention disclosed and claimed.*” 851 F.2d at 1392 (emphasis added). That is, presuming nexus is appropriate “when the patentee shows that the asserted objective evidence is tied to a specific product and that product ‘embodies the claimed features, and is coextensive with them.’” *Polaris Indus., Inc. v. Arctic Cat, Inc.*, 882 F.3d 1056, 1072 (Fed. Cir. 2018) (quoting *Brown & Williamson Tobacco Corp. v. Philip Morris Inc.*, 229 F.3d 1120, 1130 (Fed. Cir. 2000)). . . .

. . . Whether a product is coextensive with the patented invention, and therefore whether a presumption of nexus is appropriate in a given case, is a question of fact.

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Fox Factory, 944 F.3d at 1373.

The court in *Fox Factory* further explained, with respect to a presumption of nexus, that “the degree of correspondence between a product and a patent claim falls along a spectrum,” and that “[a]lthough we do not require the patentee to prove perfect correspondence to meet the coextensiveness requirement, what we do require is that the patentee demonstrate that the product is essentially the claimed invention.” *Id.* at 1374. The court rejected the patent owner’s argument that the coextensiveness requirement is simply an inquiry into “whether the patent claims broadly cover the product that is the subject of the evidence of secondary considerations.” *Id.* at 1377. The court found, on the facts of that case, that “nexus may not be presumed” because “there are one or more features not claimed by the [challenged patent] that materially impact the functionality” of the products on which patent owner’s presumption argument is based. *Id.* at 1376.

Second, for a direct showing of nexus, a patent owner may demonstrate a “correspondence between the objective evidence and the claim scope.” *Henny Penny*, 938 F.3d at 1332; *see Fox Factory*, 944 F.3d at 1373–74.

(2) Presumption of Nexus

Patent Owner asserts a presumption of nexus, e.g., in the context of its assertions of commercial success, arguing that the commercial success of the Ajovy®, Emgality®, and Alder products enjoy a presumption of nexus to the claims at issue because, according to Patent Owner, the Ajovy® and Emgality® antibodies are embodiments of the claimed invention and Alder has licensed Patent Owner’s patents. PO Resp. 51–52, 59–60 (citing *Crocs*,

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Inc. v. Int’l Trade Comm’n, 598 F.3d 1294, 1310–11 (Fed. Cir. 2010)).

Patent Owner also argues more generally for a presumption of nexus for its secondary considerations. See PO Resp. 51–52; PO Supp. Br. 2–3 (citing, e.g., Ex. 2226 ¶ 114; Ex. 2237 ¶¶ 21–24; Ex. 2241 ¶¶ 19–24, 25; Ex. 2257, 5). Patent Owner further argues that Petitioner “fails to rebut the presumption of nexus between [Patent Owner’s] objective indicia and the claimed antibodies (e.g., Ajovy and Emgality).” Sur-reply 25.

In the first instance, Patent Owner asserts that expert testimony demonstrates a nexus between the challenged claims and objective indicia from a representative number of species (the Ajovy®, Emgality®, and Alder products) and the challenged claims. PO Supp. Br. 2 (citing Ex. 2226 ¶ 114 Ex. 2243 ¶ 20; Ex. 2257, 5). Patent Owner further argues that it has “presented strong evidence that the relevant properties of Ajovy® and Emgality® are due to the claimed features and have nexus to each of the challenged claims.” Sur-reply 25 (citing Ex. 2226 ¶ 114). However, Patent Owner does not explain in its briefs how the Ajovy® and Emgality® products are covered by the claimed invention. At most, the Tomlinson Declaration at paragraph 106 contains a claim chart. We consider this to be inappropriate incorporation by reference of a declaration into a brief. See 37 C.F.R. § 42.6(a)(3). Therefore, we consider this argument waived, notwithstanding the arguments made in the supplemental briefing. See Paper 15 (Scheduling Order), 5 (“Patent Owner is cautioned that any arguments for patentability not raised in the response may be deemed waived”).

Even so, for completeness of discussion, we analyze Patent Owner’s arguments as follows. For purposes of this discussion, and based on the

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presentation in the Tomlinson Declaration (Ex. 2226 ¶ 114), we find that Patent Owner's Ajovy® product is broadly covered by claim 1 of the challenged patents. For example, fremanezumab-vfrm is a humanized monoclonal antibody that binds to CGRP ligand and blocks its binding to the receptor, and specifically binds to human α -CGRP with a picomolar affinity. Ex. 2168⁷⁸, 2 (12.1), 70; Ex. 2218⁷⁹, 11.

Petitioner disputes that the Emgality® product is claimed in the challenged patents. Reply 21 n.4. We find that the Emgality® product is an anti-CGRP antibody. Ex. 2216, 13. We note that Patent Owner has not provided us with any adjudication showing that the Emgality® product is covered by any of the challenged claims, and we expressly do not decide whether the Emgality® product is covered by any of the challenged claims because issues of infringement are beyond the scope of our jurisdiction.

Regardless of whether or not any of the challenged patents broadly cover the Ajovy® or Emgality® products, Petitioner argues (with respect to the *Fox Factory* test for presumption of nexus) that Patent Owner has failed to meet its burden of establishing that the Ajovy® and Emgality® products are coextensive with the challenged claims. Reply 21–22; Pet. Supp. Br. 3–6. Petitioner further argues that Patent Owner's secondary considerations lack nexus to the challenged claims because the "relevant or important properties of Ajovy® and Emgality®" products were already known in the prior art or are unclaimed features. Reply 23.

⁷⁸ Highlights of Prescribing Information, Ajovy® (Rev. 1/2019) (Ex. 2168).

⁷⁹ Non-Clinical Review(s), Center for Drug Evaluation and Research, Application No. 761089Orig1s000, Drug: Fremanezumab (a calcitonin gene-related peptide receptor antagonist), Applicant: Teva (Ex. 2218).

Petitioner argues that Patent Owner’s secondary considerations evidence is not commensurate with the scope of the challenged claims, arguing that the Ajovy® and Emgality® antibodies are “two highly specialized antibodies,” whereas the challenged claims “encompass a vast array of antibodies and antibody fragments that would have far inferior properties compared to the unique, highly optimized fremanezumab and galcanezumab antibodies.” Reply 21–23. Petitioner argues that the Ajovy® and Emgality® antibodies have the following unclaimed features that materially impact the functionality: (1) specific sequences that affect binding affinity and inhibit the ability of the antibody to kill cells; (2) picomolar binding affinities; (3) full-length antibodies (as opposed to fragments); and (4) IgG antibody classes. *Id.* at 2–23; Pet. Supp. Br. 2–6. We analyze each in turn.

(a) Discussion of Alleged Unclaimed Features

Specific sequences that affect binding affinity and inhibit ability to kill cells

Petitioner asserts that Teva represented to the FDA that multiple mutations were introduced into the Ajovy® antibody that materially impact functional properties including binding affinity, e.g., residues 99 and 100. Reply 22; Pet. Supp. Br. 3–4 (citing Ex. 2217, 8–9 (“A99L” and “R100A”); Ex. 1301, 115:9–116:21). Petitioner also asserts that the Emgality® antibody has specific amino acid sequences that are critical for functionality. Reply 22 (citing Ex. 2216, 17); Pet. Supp. Br. 3. Petitioner asserts that binding affinity materially impacts functionality. Pet. Supp. Br. 4 (citing Ex. 1023, 2:12–27 (affinity is “critical[]” for an antibody’s biological function)); *see also id.* at 3 (citing Ex. 1062, 41; Ex. 1063, 63; *MorphoSys*

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AG v. Janssen Biotech Inc., 358 F. Supp. 3d 354, 366 (D. Del. Jan. 25, 2019); Ex. 1013 ¶¶ 20, 41; Ex. 1301, 81:11–22).

Petitioner asserts that Patent Owner also represented to the FDA that specific mutations were introduced into the Ajovy® product’s sequence to eliminate antibody dependent cell toxicity (ADCC) and complement dependent cytotoxicity (CDC), i.e., its ability to kill cells. Pet. Supp. Br. 3–4 (citing Ex. 2217, 8–9 (“A330S” and “P331S”); Ex. 1301, 116:11–21).

Petitioner asserts that the Emgality® antibody contains analogous mutations that disable the antibody’s ability to kill cells. *Id.* (citing Ex. 2216, 17).

Petitioner asserts that killing cells is undesired for antibodies used to antagonize CGRP in treating migraine, and thus these disabling mutations also “materially impact” functionality. *Id.* (citing Ex. 1013 ¶¶ 139, 149–150; Ex. 1012 ¶ 167, 178–179; Ex. 1062, 43; Ex. 2098, 646).

Petitioner asserts that the challenged claims do not recite these limitations but other unchallenged patent claims do claim the above-referenced mutations in the Ajovy® antibody. Pet. Supp. Br. 5. Petitioner asserts that claims 3 and 5 of the ’794 patent⁸⁰ recite SEQ ID NO: 1, which includes the affinity-conferring A99L and R100A mutations discussed above. *Id.* (citing Ex. 2024, col. 73). Petitioner asserts that claim 7 of the ’794 patent is limited to a heavy chain produced from Accession No. PTA-6867, which includes the mutations to residues 330 and 331 that eliminate ADCC and CDC. *Id.* (citing Ex. 2024, 58:3–17). Petitioner asserts that it also did not challenge claims the sequence specific claims of the ’614, ’951, and ’881 patents. *Id.* Petitioner further argues that Dr. Tomlinson testified

⁸⁰ U.S. Patent No. 8,007,794 B2, iss. Aug. 30, 2011 (Ex. 2024, “the ’794 patent”).

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that there are 20²⁰ possible mutations, i.e., “an unfathomable number,” in the variable region of the antibody, none of which are excluded by the challenged claims. *Id.* at 4 (citing Ex. 1301, 91:25–92:22). Petitioner asserts that Patent Owner represented that the unchallenged ’794 patent, directed to specific sequences, “protect[s]” the Ajovy® product. *Id.* at 5 (citing Ex. 2224, 78 n.1; Ex. 2168, 4). Petitioner argues that no presumption of nexus applies because the challenged claims do not recite any amino acid sequences, let alone the ones conferring functionality in the Ajovy® and Emgality® products. *Id.* at 4–5 (citing *Fox Factory*, 944 F.3d at 1375–77; *Celltrion, Inc. v. Genentech, Inc.*, IPR2017-01374, Paper 85 at 48 (PTAB Nov. 29, 2018); *Therasense, Inc. v. Becton, Dickinson and Co.*, 593 F.3d 1289, at 1299 (Fed. Cir. 2010)).

Patent Owner does not contest Petitioner’s assertions that the Ajovy® antibody has unclaimed sequences that materially affect binding and eliminate the antibody’s ability to kill cells. *See* Sur-reply 25–27. Nor does Patent Owner contest that the Emgality® antibody has unclaimed sequences that materially affect binding and eliminate the antibody’s ability to kill cells. *Id.* Rather, Patent Owner argues that these unclaimed features are not critical to the objective indicia. *See* PO Supp. Br. 3–4 (distinguishing *Fox Factory*, arguing that “where a Patent Owner concedes that objective indicia are due to something other than the claimed invention, it is common sense that a nexus cannot be presumed” and that “in stark contrast to *Fox Factory*, the record here is devoid of evidence that the praise for and success of the antibody products depends critically on any subsidiary features not recited in the claims”).

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We find, based on the undisputed evidence, that the Ajovy® and Emgality® products have sequences (including specific mutations), not recited in the challenged claims—some of which are claimed in other unchallenged patent claims. *See NuVasive*, 841 F.3d at 974. For example, the challenged claims of the '211 patent do not recite the affinity-conferring A99L and R100A mutations, which is the subject of claims 3 and 5 of the '794 patent and are part of the Ajovy® antibody. Furthermore, the challenged claims do not recite the mutations to residues 330 and 331 that eliminate ADCC and CDC, which are the subject of claim 7 of the '794 patent and are part of the Ajovy® antibody. Further, it is undisputed that the challenged claims do not recite the mutations of the Emgality® antibody.

Picomolar binding affinities

Petitioner further asserts that other unclaimed features materially impact function. Reply 22–23; Pet. Supp. Br. 5. Petitioner asserts that Dr. Tomlinson admitted that the 2.2 pM and 31 pM binding affinities of the Ajovy® and Emgality® antibodies “do not represent” the range of 10 nM or less binding affinity. Pet. Supp. Br. 5 (citing Ex. 1301, 103:16–104:19). Petitioner asserts that binding affinity materially impacts an antibody’s functionality. *Id.* (citing Ex. 1013 ¶¶ 41, 69; Ex. 1023, 2:12–27; Ex. 1266, 521).

Patent Owner does not dispute Petitioner’s assertions, and we adopt them as factual findings. *See NuVasive*, 841 F.3d at 974.

Full-length antibodies (as opposed to fragments)

Petitioner further asserts that Dr. Tomlinson admitted that the challenged claims broadly cover all types of antibody fragments even though he testified that a “fragment is not going to be effective as a human

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therapeutic,” in contrast to the Ajoovy® and Emgality® antibodies, which are not fragments. *See* Reply 23; Pet. Supp. Br. 6 (citing Ex. 1301, 27:25–28:6, 29:21–22, 30:6–9, 134:14–135:21). Petitioner asserts that antibody format materially impacts performance. Pet. Supp. Br. 6 (citing Ex. 1009 ¶ 57; Ex. 1008 ¶ 159).

Patent Owner does not dispute Petitioner’s assertions, and we adopt them as factual findings. *See NuVasive*, 841 F.3d at 974.

IgG antibody classes

Petitioner further asserts that Ajoovy® is an IgG₂ antibody and Emgality® is an IgG₄ antibody, but the challenged claims also encompass IgG₃, IgA, IgD, IgE, and IgM antibody classes.⁸¹ Pet. Supp. Br. 6 (citing Ex. 2217, 8; Ex. 2216, 17). Petitioner asserts that antibody class materially impacts performance. *Id.* (citing Ex. 1013 ¶ 27, 45; Ex. 1012 ¶ 167). Petitioner asserts that Dr. Tomlinson admitted that he is unaware of anyone ever successfully making an FDA-approved antibody using those classes. *Id.* (citing Ex. 1301, 34:9-35:1; 36:16–39:11; 109:7–115:1).

Patent Owner does not dispute Petitioner’s assertions, and we adopt them as factual findings. *See NuVasive*, 841 F.3d at 974.

(b) Analysis and conclusion as to asserted presumption of nexus

Patent Owner argues that Petitioner is applying the wrong test for determining whether there is a presumption that the objective indicia, such as praise and success of the Ajoovy® and Emgality® antibodies, have a

⁸¹ There are exceptions for certain dependent claims, and claims that depend from those claims, that specifically refer to IgG₁ (e.g. claim 3 of the ’211 patent), IgG₂ (e.g. claim 7 of the ’211 patent and claim 14 of the ’881 patent), and IgG₄ (e.g. claim 12 of the ’211 patent).

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nexus to the challenged claims. PO Supp. Rep. Br. 1–2. Patent Owner argues that in *Fox Factory*, the successful chainring products had features that (i) materially affected functionality and also (ii) indisputably were responsible for the chainring’s success. *Id.* at 2–3. Patent Owner argues that Petitioner points to no evidence that the unclaimed sequence mutations were responsible for the praise and success of the Ajoy® and Emgality® antibodies. *Id.* at 3. Patent Owner argues that Petitioner’s assertions that the products’ different mutations are equally praised and successful support Patent Owner’s position because no evidence shows that any one or combination of unclaimed features is responsible for the objective indicia. *Id.* at 1.

We do not agree with Patent Owner’s proposed test for co-extensiveness. In *Fox Factory*, it was undisputed that the product (chainrings) included unclaimed features, specifically wide and narrow teeth and >80% gap filling, that the patentee admitted were critical to the product’s ability to better retain the chain, that led the court to determine that “no reasonable fact finder could conclude that these features are insignificant.” *Fox Factory*, 944 F.3d at 1374–75. Nevertheless, that fact pattern was more than what is required to find a lack of coextensiveness. In the same paragraph, the court states that “[a] patent claim is not coextensive with a product that includes a ‘critical’ unclaimed feature that is claimed by a different patent and that materially impacts the product’s functionality by ‘lead[ing] to a chainring that will retain a chain in even the worst conditions.’” *Id.* at 1375. Immediately following that statement, the court stated that “[i]n short, because the independent claims do not include the

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>80% gap filling feature, we cannot say that the X-Sync chainrings *are* the invention claimed by the independent claims.” *Id.*

Contrary to Patent Owner’s arguments, we do not understand *Fox Factory* to be making a distinction between features that are “critical” and features that “materially impact” the functionality of the product. In other words, on the facts of these cases, we understand an unclaimed feature of the Ajovy® or Emgality® product to be critical or significant, as used in *Fox Factory*, if it materially impacts the functioning of the product. *See id.* at 1374–75; *see also Merck & Cie v. Gnosis S.p.A.*, 808 F.3d 829, 837–38 (Fed. Cir. 2015) (affirming the Board’s finding that products “have material features beyond those disclosed and claimed”). *Fox Factory* also explains that where the patented invention is only a component of the commercially successful product, the patentee is not entitled to a presumption of nexus. *Id.* at 1373 (citing *Demaco*, 851 F.2d at 1392). Accordingly, we do not agree with Patent Owner that *Fox Factory* requires more than a showing that the unclaimed feature materially affects the functioning of the product that is alleged to be coextensive with the claim.

Further, Patent Owner did not contest the materiality of these unclaimed features. *See* Reply 20–22; Sur-reply 25–27. As to Patent Owner’s arguments that none of the unclaimed features are critical to objective indicia because drugs with different mutations had similar beneficial effects (PO Supp. Rep. Br. 1), we are not persuaded that this means that the individual mutations lacked criticality or otherwise did not materially affect the functioning of the antibody. We understand this to indicate that one has a group of material mutations to choose from, none of which were claimed. We are also persuaded by Petitioner that antibody

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format materially impacts performance. *See, e.g.*, Ex. 1013 ¶¶ 20–41, 139–141; Ex. 1012 ¶ 167, 178–179.

Based on the evidence before us, we find that Patent Owner has not shown that the Ajovy® and/or Emgality® antibodies are coextensive with the challenged claims. In particular, we determine all of the challenged claims fail to recite one or more of (1) specific sequences that affect binding affinity and/or the ability of the antibody to kill cells, (2) less than 1 nM binding affinities,⁸² (3) full length antibodies, or (4) specific antibody class, each of which materially affect the functioning of the Ajovy® and Emgality® antibodies. We, therefore, find that Patent Owner has not established a presumption of nexus between the asserted evidence of secondary considerations based on the Ajovy® and/or Emgality® antibodies. Moreover, we find in the alternative that Petitioner has rebutted any alleged presumption of nexus by persuasively establishing that the Ajovy® and Emgality® antibodies include one or more features not claimed by the challenged patent that materially impact the functionality of the antibodies.

For these reasons, we conclude that Patent Owner has not established a presumption of nexus between the challenged claims and the objective indicia based on asserted ties between the challenged claims and the Ajovy® or Emgality® antibodies. In this connection, the Ajovy® or Emgality® antibodies have additional, material, unclaimed features that result in a lack of coextensiveness with the challenged claims.⁸³

⁸² 2.2 pM equals 0.0022 nM and 31 pM equals 0.031 nM.

⁸³ We address the Alder product, Aimovig®, separately below with respect to licensing.

(3) Patent Owner’s asserted direct showing of nexus between the claims and the objective indicia

We separately consider the issue of nexus between the challenged claims and Patent Owner’s licensing evidence below. As to the other categories, Patent Owner does not advance any basis for nexus in connection with its asserted evidence of industry praise, long-felt need, unexpected results, industry skepticism, or commercial success, other than its “presumption of nexus” argument until its Supplemental Brief. *See* PO Resp. 47–57, Sur-reply 25–27, PO Supp. Br. 6–7. Accordingly, we find any arguments as to a direct showing of nexus are waived.

We observe that, although Dr. Tomlinson has claim charts that allegedly show how the Ajovy® or Emgality® products are covered by the claimed invention (Ex. 2226 ¶ 114), Dr. Tomlinson’s claim charts do not show how the objective indicia have a direct nexus to the claimed invention. Nevertheless, for completeness of discussion, we review Patent Owner’s proffered evidence of objective indicia and analyze any relationship to the claimed invention to determine whether there is a direct nexus between the challenged claims and the objective indicia.

(4) Discussion of Patent Owner’s asserted secondary considerations of nonobviousness

(a) Industry Praise

Factual Findings

Patent Owner relies on certain testimony and documentary evidence for praise (“industry-wide acclaim”) of the claimed antibodies. *See* PO Resp. 52–55. We have reviewed the evidence relied on by Patent Owner and make the following factual findings.

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Only two pieces of evidence are focused on Patent Owner's product Ajovy®, i.e., Exhibit 2167 which anecdotally discusses one superresponder patient, and Dr. Rapoport's testimony (Ex. 2237), which discusses the Ajovy® product as a desirable alternative to patients who experienced constipation on the Aimovig® product. The remaining evidence of praise largely discusses the group of antibodies directed at CGRP or CGRP receptors, including Amgen's Aimovig®, Teva's fremanezumab, Lilly's galcanezumab, and Alder's eptinezumab products.

Evidence that specifically addresses the Ajovy® antibodies

Exhibit 2167⁸⁴ is an article in the "News" section of Science magazine which discusses anti-CGRP antibodies, and in particular, discusses Teva's TEV-48125 *on its own*, while another part of the article also refers to drugs by Alder, Lilly, and Amgen. *Id.* at 118–119. The article states that there are a category of "'superresponders,' whose attacks cease for 6 months after a single injection of a CGRP-blocking antibody." *Id.* at 117. The article quotes Dr. Dodick, a neurologist who has consulted for some of the companies developing CGRP blockers, stating that "I've been in this field now for 21 years, and this is the most exciting thing we've seen so far." *Id.*

The article proceeds to tell the story of one superresponder who had no success with countless other treatments but who had the migraines disappear after she received four shots of Teva's antibody containing solution. *Id.* She said that the difference was "mindblowing" and related that she no longer had to spend her days avoiding small disturbances that

⁸⁴ Emily Underwood, *A Shot at Migraine*, 351:6269 SCIENCE 116 (Jan 8, 2016) (Ex. 2167).

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might have otherwise made her migraines worse and that others noticed she had a change in demeanor. *Id.*

The article discloses that each of the four drugs have “similarly encouraging results” in phase II clinical trials with about 15% of participants getting complete relief. *Id.* The article quotes Corey Goodman of VenBio, which bought the rights to TEV-48125, and who had previously overseen the team at the company which previously developed the drug. *See id.* at 118–119. Goodman states that Teva’s compound had “the most beautiful phase II data I’ve ever seen.” *Id.* We determine that this particular praise may be given less weight because it is coming from a party with an ownership stake. The article relates that Dr. Russo, a neurologist who consults for Alder, stated that it was a “really cool finding” that CGRP antibodies can prevent migraine in some fraction of patients. *Id.*

However, the article proceeds to quote Dr. Ferrari as saying that “you would expect a much higher proportion of patients to be completely free of attacks” if CGRP really is a fundamental mechanism. *Id.* The article also relates that Dr. Ferrari stated that safety concerns him because of CGRP’s role in dilating arteries and maintaining blood supply in the heart and brain and that there was a theoretical possibility that “if you block CGRP you could translate a minor stroke or cardiac ischemia . . . into a full blown stroke or heart attack.” *Id.*

Dr. Rapoport provides testimony regarding his own practice, and stated that approximately 3–5% of his 40 patients on the Aimovig® product experienced constipation; that when the Ajovy® product was available, he would switch his patients with constipation to the Ajovy® product; and that he had approximately 20 patients on the Ajovy® product, and that these

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patients reported a reduction in symptoms and a reduction of one migraine day per week. See Ex. 2237 ¶¶ 59–64. He stated that he agreed with the praise that the claimed humanized anti-CGRP antibodies offered a novel, safe, and effective target-preventive specific treatment for migraine. *Id.* ¶ 64 (citing Ex. 2169, 926).

Evidence that addresses the group of CGRP antibodies as a whole, or praises other products in the group

Exhibit 2182⁸⁵ is an article in the “News” section of Nature Biotechnology, which discusses monoclonal antibodies that block CGRP and in particular, discusses Amgen’s Aimovig®, Teva’s fremanezumab, Lilly’s galcanezumab, and Alder’s eptinezumab products. *Id.* at 207. The article proceeds to quote Dr. Charles as saying “These are really the first therapies, ever, that have been designed based on a specific laboratory understanding of the mechanisms of migraine . . . That, to me, is very exciting and compelling.” *Id.* Dr. Rapoport also quotes this portion of this exhibit. See Ex. 2237 ¶ 57.

Exhibit 2052⁸⁶ is an article from neurologylive.com. Dr. Rapoport quotes a portion of this exhibit which quotes Dr. Charles as stating: “This may be irrational exuberance at this point, but I think that these therapies have the possibility to transform our clinical approach to migraine and

⁸⁵ Elie Dolgin, *Migraine drug race turns its final corner*, FDA decisions in sight, 36(3) NATURE BIOTECHNOLOGY 207 (March 2018) (Ex. 2182).

⁸⁶ S. Inman, *Anti-CGRP Monoclonal Antibodies Transforming Migraine Treatment*, available at <https://www.neurologylive.com/print.php?url=/conferences/ana-2018/anticgrp-monoclonal-antibodies-transforming-migraine-treatment> (Oct. 22, 2018) (Ex. 2052).

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cluster headache,’ said Charles, from the University of California, Los Angeles.’” Ex. 2052, 1 (quoted in Ex. 2237 ¶ 57).⁸⁷ The article discloses that the CGRP-targeting antibodies were shown to work rapidly, with a reduction in migraine days compared with placebo observed within the first week following treatment. *Id.* The article states that “nearly half of patients in the trials experienced a >50% reduction in migraine days, a third had a 75% response, and a portion even had a 100% response.” *Id.* The article quotes Dr. Charles for the proposition “around 50% of patients have a 50% responder rate,” “between 30% and 40% of patients have a 75% response rate,” and “10% and even up to 20% of patients in the trials are showing at least 1 month where they are completely headache free.” *Id.*

Exhibit 2053⁸⁸ is an article in UCLA Magazine. Dr. Rapoport quotes a portion of this exhibit which quotes Dr. Charles as stating: “‘We have seen remarkable results from the [anti-CGRP antagonist antibody] clinical trials, with a subset of patients for whom the response is a dramatic reduction in the number of migraine attacks . . . A smaller percentage have shown complete remission, which is unlike what we’ve seen with other therapies.’” *Id.* at 26 (quoted in Ex. 2237 ¶ 57).

Ex. 2186⁸⁹ is an article from Healthline. Dr. Rapoport quotes a portion of the article which quotes Dr. Charles as stating: “‘We’ve identified some targets for preventive therapy that are specific for migraines, and the

⁸⁷ In some instances, we have excerpted more of the article than was quoted in the Rapoport Declaration to provide additional context, even while using ellipses.

⁸⁸ Veronique De Turenne, *Pain Like No Other*, U MAGAZINE 21 (UCLA Spring 2018) (Ex. 2053).

⁸⁹ C. Cassata, *Kristin Chenoweth: Migraine Is More Than a Bad Headache*, HEALTHLINE (Apr. 3, 2019) (Ex. 2086).

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most exciting ones that have been introduced just the last year are these monoclonal antibodies that target a molecule called CGRP . . . For some patients, these are absolutely life-changing medications because they are spectacular at stopping migraine attacks from happening.’” Ex. 2237 ¶ 57 (quoting Exhibit 2186, 4⁹⁰).

Exhibit 2188⁹¹ is an article from U Magazine of UCLA. Dr. Charles is quoted as follows: “‘The notion that we would be using antibodies to treat migraine is really quite a radical concept . . . This is a very different approach because, in contrast to other treatments that we’ve used in the past, which often have been developed for other reasons and we’ve borrowed them as migraine treatments, this has been developed based on our understanding of the chemistry of migraine and what is going on during a migraine attack.’” *Id.* at 25; *see also* Ex. 2237 ¶ 57 (quoting subportion of article).

Exhibit 2205⁹² is an article from migraineagain.com, cited in the Rapoport Declaration. *See* Ex. 2235 ¶ 48. The article states that “Phase 3 results [with the Emgality® antibody] showed that patients with Chronic Migraine who did not respond to Botox and who were treated with 120 mg of Emgality® antibody had an average of 3.91 fewer Migraine days compared to the placebo. Those who received the larger dose, 240 mg, had 5.27 fewer Migraine days compared to placebo.” Ex. 2205, 2. The article

⁹⁰ Part of this quotation is not legible in the version of the exhibit filed with the Board. However, Petitioner has not moved to exclude Dr. Rapoport’s testimony on this basis.

⁹¹ Veronique De Turenne, *Game Changer*, U MAGAZINE 23 (UCLA Spring 2018) (Ex. 2188). This article is also found in Exhibit 2053.

⁹² A. Glaser, *Emgality Approval Brings New Hope For Preventing Migraines*, MIGRAINE AGAIN 1 (Nov. 20, 2018) (Ex. 2205).

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also reported that the Emgality® antibody prevents episodic cluster headaches but less success with chronic cluster headaches. *See id.* at 4.

Exhibit 2162⁹³ is an article labeled as “Current Opinion,” which discusses CGRP, CGRP receptor antagonists, and CGRP monoclonal antibodies and in particular, discusses Lilly’s LY2951742; Alder’s ALD-403; Teva’s TEV-48125 LBR-101; and Amgen’s AMG 334. *Id.* at Abstract, 447. The article concludes that “We have entered a new era for the treatment of migraine that marks the evolution from ergotamines and triptans to new compounds that may offer similar or even better efficacy without the vasoconstrictive risk factors caused by previous ones.” *Id.*

Exhibit 2174⁹⁴ is an article in the “News” section of Nature Biotechnology which discusses anti-CGRP antibodies, and in particular, discusses Teva’s LBR-101, Lilly’s LY2951742; Alder’s ALD-403; and Amgen’s AMG 334 I. *Id.* at 707. The article states that “Anti-CGRPs offer a novel solution, although CGRP, a neuropeptide, has long been known to be active in the pathophysiology of migraine pain.” *Id.* The article quotes Mark Weatherall, a neurologist as opining that ““We have been waiting for a breakthrough in migraine since the triptans . . . These monoclonal antibodies are a vindication of 25–30 years work on this pathway.”” *Id.* The article also quotes a venture capitalist as saying that it saw Teva’s drug⁹⁵ as a “best-in class opportunity.” *Id.*

⁹³ Stephanie Wrobel Goldberg et al., *Targeting CGRP: A New Era for Migraine Treatment*, 29 CNS DRUGS 443–452 (July 3, 2015) (Ex. 2162).

⁹⁴ Suzanne Elvidge, *Anti-CGRP antibodies for migraine turn industry heads*, 32(8) NATURE BIOTECHNOLOGY 707 (Aug. 2014) (Ex. 2174).

⁹⁵ The quote refers to the company Labrys, which was acquired by Teva along with Labrys’s LBR-101. Ex. 2174, 707.

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Exhibit 2172⁹⁶ is labeled as a “Blog” and discusses “[a]ntibodies [that] are designed to block the action of CGRPs,” and in particular, discusses products by Eli Lilly, Amgen, Teva, and Adler Pharmaceuticals. *Id.* at 1–2. The article quotes Dr. Peter Goadsby as stating that “Here, for the first time ever, is a specific treatment for migraine prevention . . . It’s an enormous step forward.” *Id.*

Exhibit 2179⁹⁷ is an article, labeled as being “[p]osted” on migraineagain.com, which discusses new CGRP therapies, and in particular, discusses therapies in development by Alder (partnering with Novartis), Amgen, Lilly, and Teva, noting four drugs anticipating FDA review—erenumab, which blocks the CGRP receptor, and eptinezumab, fremanezumab and galcanezumab, which block the ligand. *Id.* at 1–3. In discussing Phase III clinical trials of the four compounds, Dr. Goadsby agreed that “it” was a “game changer.” *See id.* at 3–4.

Exhibit 2180⁹⁸ is an article, which discusses monoclonal antibodies for migraine, and in particular, discusses three against CGRP itself: galcanezumab (LY2951742), eptinezumab (ALD403), and fremanezumab (TEV-48215) and one against the CGRP receptor, erenumab (AMG-334). *Id.* at 3–7. The article contains an “Opinion Statement,” which concludes

⁹⁶ Jim Carleton, *CGRP Antibodies: A Potential Game Changer in Migraine Prevention*, Blog, available at <https://www.migrainedisorders.org/news-and-updates/blog/cgrp-antibodies-a-potential-game-changer-in-migraine-prevention> (appears to be dated July 11, 2015) (Ex. 2172).

⁹⁷ Paula Dumas, *CGRP Drugs Offer More Freedom to People with Migraine - for \$8500*, MIGRAINE AGAIN, available at <https://migraineagain.com/cgrp-medications-migraine/> (June 28, 2017) (Ex. 2179).

⁹⁸ Amy R. Tso and Peter J. Goadsby, *Anti-CGRP Monoclonal Antibodies: the Next Era of Migraine Prevention?* 19 CURR. TREAT. OPTIONS NEUROL. 27 (2017) (Ex. 2180).

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that “While we must await the results of all the phase III trials, cautious excitement seems warranted as we enter a new era of better tolerated, well-understood, bespoke migraine treatment for this common and disabling neurological disorder.” *Id.* at 1.

Exhibit 2163⁹⁹ is an article, which discusses CGRP, CGRP antagonists, and monoclonal antibodies for migraine, and in particular, discusses 3 humanized monoclonal antibodies (mAbs) directed against CGRP (ALD403/eptinezumab, TEV-48125/fremanezumab, and LY2951742/galcanezumab) and 1 human mAb targeting the CGRP receptor (AMG 334/erenumab). *Id.* at 535–536. The article concludes that “[t]oday, monoclonal antibodies appear to offer a new and effective strategy for migraine prevention, representing more than hope for millions of chronic migraineurs who are not currently taking any prophylactic therapy.” Ex. 2163, 543–544.

Exhibit 2166¹⁰⁰ is an article, which discusses monoclonal antibodies directed at CGRP and its receptor, and in particular, discusses Lilly’s Galcanezumab/LY2951742, Alder’s ALD403, Teva’s TEV48125, and Erenumab/AMG334. *Id.* at 21–22, 27–28. The article states that “the recent development of monoclonal antibodies for the treatment of migraine may have a significant impact on the field and mark a new chapter in patient care.” *Id.* at 21. The article concludes that “[t]he large amount of publicity

⁹⁹ L. Pellesi et al., *Spotlight on Anti-CGRP Monoclonal Antibodies in Migraine: The Clinical Evidence to Date*, 6(6) CLINICAL PHARMACOLOGY IN DRUG DEVELOPMENT 534–547 (2017) (Ex. 2163).

¹⁰⁰ C. Lauritsen et al., *Calcitonin Gene-Related Peptide, Monoclonal Antibodies, and Migraine*, PRACTICAL NEUROLOGY 21 (Nov./Dec. 2016) (Ex. 2166).

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generated by the success of these agents may lead to a heightened awareness and accelerated development of preventive migraine therapies designed for specific biological targets.” *Id.* at 29.

Exhibit 2173¹⁰¹ is an article, which discusses monoclonal antibodies directed at CGRP and its receptor, and in particular, discusses Alder’s eptinezumab, Amgen’s erenumab, Lilly’s galcanezumab, and Teva’s fremanezumab. *Id.* at 19–20. The article states “[a]s a new age in headache medicine is set to begin, it is incumbent upon neurologists to become better familiarized with and explore the implications of monoclonal antibodies in patient care.” *Id.* at 18. The articles indicates that CGRP monoclonal antibodies are good “but not extraordinary,” with a drop of several headache days per month, and it was unclear who were the superresponders and why more people are not getting a lot better. *Id.* at 22. The article related a suggestion that the days between headaches resulted in an increase in quality of life and ability to perform activities of daily living. *Id.*

Exhibit 2183¹⁰² is an article, which discusses monoclonal antibodies that block the activity of CGRP or its receptor, and in particular, discusses the injectables Aimovig® (erenumab-aooe, Amgen), Ajovy® (fremanezumab-vfrm, Teva), and Emgality® (galcanezumab-gnlm, Eli Lilly

¹⁰¹ Peter McAllister, *Monoclonal Antibodies and Migraine: What the Neurologist Needs to Know*, PRACTICAL NEUROLOGY 18 (May 2017) (Ex. 2173).

¹⁰² *American Headache Society president: ‘Exciting, cautious’ time for patients with migraine*, (Oct. 11, 2018), <https://www.healio.com/family-medicine/neurology/news/online/%7Be3e75c0f-21c7-4de1-a78c-5e3a2f0ba8d6%7D/american-headachesociety-president-exciting-cautious-time-for-patients-with-migraine> (Ex. 2183).

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and Company). *Id.* at 1. The article relates that Dr. Kathleen Digre, president of the American Headache Society, said that it was an “exciting time” and not everyone will respond to these medications. *Id.* at 1–2.

Analysis

We find that the FDA-approved Ajovy® and Emgality® products have received praise as detailed above.

Patent Owner argues that “[i]ndustry-wide praise provides ‘probative and cogent evidence’ of nonobviousness.” PO Resp. 52. Patent Owner supports that argument with statements by Dr. Charles, the field as a whole, and Dr. Rapoport’s experience in administering Ajovy® antibodies to patients with migraine symptoms. *Id.* Dr. Rapoport testified that he has switched patients from the anti-CGRP receptor antibody Aimovig® to the Ajovy® antibody to avoid constipation side effects of the Aimovig® antibody, and that the Ajovy® antibody has the ability to treat medication-overuse headache (MOH). *Id.* at 54–55.

Petitioner argues that Patent Owner’s “reliance of praise of Ajovy® and Emgality® fails to support nonobviousness because those products lack the required nexus to the full scope of the challenged claims,” as discussed above. Reply 23–24. Petitioner further argues that Patent Owner’s evidence of acclaim includes drugs outside the scope of the claims, including small molecules and a commercial antibody targeting the CGRP receptor (Aimovig®), and statements that relate generally to antagonizing the CGRP pathway rather than specifically to the challenged claims. *Id.* at 25.

Patent Owner’s replies that Petitioner “does not dispute that Ajovy® and Emgality® are covered by the claims and have both received widespread industry praise.” Sur-reply 25–26.

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As discussed above, Patent Owner has not shown an entitlement to a presumption of nexus based on the Ajovy® or Emgality® products, nor has Patent Owner made a direct showing of nexus between the praise of the Ajovy® antibody or other CGRP antibodies and the claims of the subject patents. *See supra* Sections II.D.2.d)(2), (3).

Even assuming that praise of CGRP antibodies bears a nexus to the claims of the subject patents, we determine that the praise would be given somewhat less weight where the praise is assigned to a group of antibodies that includes antibodies directed to the CGRP receptor, as opposed to CGRP itself. In this connection, we note that where the praise is equally directed to the Aimovig® antibody, a CGRP receptor antagonist, it is more difficult to determine whether the praise is due to the claimed invention that targets CGRP itself. At most, we would give this praise less weight because there would be a diminished nexus to the claimed invention for praise of the entire group of antibodies.

We observe that nearly half of patients treated with CGRP antibodies experienced a ~50% reduction in migraine days, a third had a 75% response, and a portion even had a 100% response, where 50% of patients have a 50% responder rate, between 30% and 40% of patients have a 75% response rate, and 10% and even up to 20% of patients in the trials are showing at least 1 month where they are completely headache free. Ex. 2052, 1. Thus, there are patients who benefit greatly from these treatments, but Exhibit 2052 refers to 4 drugs and does not specify that the patients were benefiting only from Ajovy® as opposed to Aimovig®. Similarly, Exhibits 2182, 2162, 2174, 2172, 2179, 2180, 2163, 2166, 2173, 2183 praise both Ajovy® and Aimovig® products. Nevertheless, it is difficult to assign the success of the

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treatments to the features of the claimed invention, as opposed to the prior art.

In any event, the exhibits largely praise the Ajovy® antibody as part of a group of drugs. Further, we are cognizant that there is specific praise of the Ajovy® antibody by the superresponder who termed it “mindblowing” and who was free of migraine, and by Dr. Rapoport who prescribed it with success to patients in his practice, e.g., who could not tolerate other medicines due to constipation. *See* Ex. 2167, 119; Ex. 2237 ¶¶ 59–64.

Because Patent Owner has not explained why there is a direct nexus between the praise and the claimed invention (as opposed to unclaimed features of the Ajovy® antibody), we do not give this praise weight. We are mindful that Patent Owner’s attempt to rely on a presumption of nexus by relying on the Ajovy® product was insufficient because Patent Owner was arguing that the claims broadly cover the Ajovy® product without a showing that the Ajovy® product was coextensive with the claims. *See Fox Factory*, 944 F.3d at 1373–74. We reason that if Patent Owner cannot presume a nexus to the Ajovy® product, then more would be required for a direct showing of nexus between the praise and the claimed invention than praise of the Ajovy® product. Even if we considered the praise of the Ajovy® product, we would accord this praise less weight. *See, e.g., ClassCo, Inc. v. Apple, Inc.*, 838 F.3d 1214, 1221–22 (Fed. Cir. 2016) (“because [the claims at issue] are considerably broader than the particular features praised in the articles, it would be reasonable for the Board to assign this evidence little weight.”).

(b) Long-felt Need

Factual Findings

Patent Owner relies on certain testimony and documentary evidence for showing long-felt, unmet need for the claimed antibodies. *See* PO Resp. 55–56. We have reviewed the evidence relied on by Patent Owner and make the following factual findings.

Exhibit 2167, an article discussed above with respect to praise, states that, according to the Migraine Research Foundation, U.S. employees take 113 million sick days per year because of migraines, creating an annual loss of \$13 billion. *Id.* at 117. The article states that this underscores how little then-existing treatments could help people. *See id.*

Dr. Rapoport opines that, in his experience, the great majority of patients were unable to stay on a preventive medicine for 12 months and that, in his view, the literature supports this finding. Ex. 2237 ¶¶ 26–28; *see also* PO Resp. 56 (citing Ex. 2171, 1159–62; Ex. 2163, 543–544). Dr. Rapoport cited one study, which showed that 86 % of patients discontinued their first, second, or third migraine preventive oral medication. Ex. 2237 ¶ 36 (citing Ex. 2245¹⁰³, 476; Ex. 2180, 2). Exhibit 2245 is a study that reports that persistence to oral migraine preventive medicine (OMPM) was 25% at 6 months and 14% at 12 months. *Id.* at Abstract. The article reports that similar trends in time-to-discontinuation were seen following the second or third OMPM. *Id.*

¹⁰³ C. Hepp et al., *Persistence and switching patterns of oral migraine prophylactic medications among patients with chronic migraine: A retrospective claims analysis*, 37(5) CEPHALALGIA 470 (2017) (Ex. 2245).

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Dr. Rapoport listed, from the year 2000, options for preventive medicines, which had been developed for other medical conditions, e.g., tricyclic antidepressants (TCAs), beta blockers, calcium channel blockers, and anti-epilepsy drugs. Ex. 2237 ¶¶ 29–30 & Table 3. Dr. Rapoport averred that these medicines had side effects such as lowering the seizure threshold, drowsiness, weight gain, cardiac arrhythmias, and orthostatic hypotension (for tricyclic antidepressants); weight gain, increased cholesterol, depression, and trouble exercising (for beta blockers); cardiac effects, constipation, and edema (for calcium channel blockers); hepatotoxicity and birth defects (for valproate); glaucoma, hyperchloremic acidosis, nephrolithiasis, oligohydrosis, hyperthermia, and sometimes troublesome paresthesias (for gabapentin); and weight gain and drowsiness (for antiserotonin drugs). *Id.* ¶¶ 30–33.

Exhibit 2190¹⁰⁴ is a review article. The article predicts that the longer half-lives of the anti-CGRP antibodies ALD403 and LY2951742 should improve patient compliance because of the dosing frequency, e.g., every two weeks for LY2951742. *Id.* at 987.

¹⁰⁴ S. Silberstein, *Preventive Migraine Treatment*, 21(4) CONTINUUM 973 (2014) (Ex. 2190).

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Dr. Rapoport opined, based on his experience with patients, and based on the studies in Exhibits 2175¹⁰⁵, 2176¹⁰⁶, and 2177¹⁰⁷, that the claimed antibodies met the need for a disease-specific and mechanism-based migraine preventive treatment. Ex. 2237 ¶¶ 42–44.

As above, Ex. 2172 quotes Dr. Goadsby as stating that “for the first time ever, is a specific treatment for migraine prevention.” Ex. 2172, 2.

Exhibit 2161¹⁰⁸ is an article co-authored by Dr. Scherer of Lilly, which reports on a phase II double-blind, randomized, controlled study of Lilly’s LY2951742. The article states that “Safe, effective and well

¹⁰⁵ X. Ning et al., *Long-Term Impact of Fremanezumab on Response Rates, Acute Headache Medication Use, and Disability in Patients With Chronic Migraine: Results of a 1-Year Study*, P1.015. This exhibit appears to be a poster-format presentation, with a marking indicating that it was presented at The American Academy of Neurology 71st Annual Meeting Philadelphia, Pennsylvania, USA May 4–10, 2019 (Ex. 2175). Several of the authors are identified as associated with Teva.

¹⁰⁶ P. McAllister et al., *Long-Term Safety of Fremanezumab: Results of a 1-Year Study*, P2.015. This exhibit appears to be a poster-format presentation, with a marking indicating that it was presented at The American Academy of Neurology 71st Annual Meeting Philadelphia, Pennsylvania, USA May 4–10, 2019 (Ex. 2176). Several of the authors are identified as associated with Teva.

¹⁰⁷ J. Brandes et al., *Long-Term Impact of Fremanezumab on Response Rates, Acute Headache Medication Use, and Disability in Patients With Episodic Migraine: Results of a 1-Year Study*, P1.005. This exhibit appears to be a poster-format presentation, with a marking indicating that it was presented at The American Academy of Neurology 71st Annual Meeting Philadelphia, Pennsylvania, USA May 4–10, 2019 (Ex. 2177). Several of the authors are identified as associated with Teva.

¹⁰⁸ David W. Dodick et al., *Safety and efficacy of LY2951742, a monoclonal antibody to calcitonin gene-related peptide, for the prevention of migraine: a phase 2, randomized, double-blind, placebo-controlled study*, 13 LANCET NEUROL. 885–92 (2014) (Ex. 2161).

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tolerated treatment for the prevention of migraine represents an enormous unmet medical need” and “[a]ntibody treatment seems to be a particularly attractive option.” *Id.* at 890.

Exhibit 2167 relates the story of the superresponder who was migraine free after four injections of Teva’s drug and how 15% of patients in clinical trials were getting complete relief. *Id.* at 119.

Analysis

Patent Owner argues that “a long-felt need for a safe, effective, well-tolerated, disease-specific prophylactic treatment for migraine was met for the first time by Teva’s pioneering humanized anti-CGRP antagonist antibodies.” PO Resp. 55 (citing Ex. 2237 ¶ 25). Patent Owner advances evidence of the lost work days of employees from migraine, and that its antibodies met the need for a disease-specific treatment for migraine prevention. *Id.* at 55–56. Patent Owner also refers to a statement in a report about Petitioner’s Emgality® antibody (LY2951742) that “[s]afe, effective, and well tolerated treatment for the prevention of migraine represents an enormous unmet medical need.” Ex. 2161, 890 (cited at PO Resp. 52); see Ex. 2237 ¶ 37.

Petitioner argues that “Teva’s position confirms the strong motivation to make a humanized anti-CGRP antagonist antibody,” and that “[t]he sheer prevalence of migraine and its economic cost . . . would have *driven* a POSA to develop such an antibody.” Reply 27. Patent Owner replies that “Lilly conflates its motivation arguments with long-felt need, ultimately ignoring the latter,” thus failing to rebut Patent Owner’s “strong evidence” of satisfaction of a long-felt, unmet need. Sur-reply 26.

As discussed above, Patent Owner has not established a nexus based on a presumption, i.e., based on a tie between the challenged claims and the Ajovy® or Emgality® antibodies. For similar reasons as for praise, Patent Owner has not established a direct showing of nexus between the claimed invention and the proffered evidence of a long-felt need for the antibody treatments.¹⁰⁹

(c) Unexpected Results

Factual Findings

Patent Owner relies on certain testimony and documentary evidence for showing unexpected results for the claimed antibodies. See PO Resp. 56–58. We have reviewed the evidence relied on by Patent Owner and make the following factual findings.

Dr. Rapoport opines that the claimed antibodies have the surprising ability to treat medication-overuse headache (MOH). Ex. 2237 ¶¶ 65–69. According to Dr. Rapoport, MOH is defined as a headache occurring on 15 or more days per month in a patient with a pre-existing primary headache and developing as a consequence of regular overuse of acute or symptomatic headache medication. *Id.* ¶ 65. Dr. Rapoport opines that there was no study linking CGRP to MOH. We credit the testimony of Dr. Rapoport, based on his clinical experience, inasmuch as it may apply to the clinical products. Further, one study of fremanezumab compared to placebo disclosed a

¹⁰⁹ We also observe that none of the challenged claims specifically recite any of the features of a “safe, effective, well-tolerated, disease-specific prophylactic treatment for migraine” to which the asserted evidence of long-felt need is directed.

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reduction in medication overuse in patients treated with fremanezumab.
Ex. 2195¹¹⁰, 1.

Analysis

Patent Owner argues that “[s]tudies have confirmed that Ajovy® reduces incidences of MOH, a phenomenon nothing in the prior art suggested. PO Resp. 54 (citing Ex. 2195, 1 (“Treatment with fremanezumab may help reduce medication overuse and the number of days of acute medication use in individuals with chronic migraine.”)). Petitioner argues that Patent Owner’s arguments regarding MOH lack nexus because they are attributed solely to the Ajovy® product, and that they show nothing different than Dr. Rapoport’s “prior-art study with a different CGRP-blocking preventative migraine therapy [triptans] in medication-overusing migraineurs.” Reply 25–26. Patent Owner argues in reply that “Lilly overlooked Dr. Rapoport’s testimony that the decrease in medication overuse “probably didn’t have anything to do with Naratriptan” and that preventive use of naratriptan is “certainly not a standard treatment today” because the study was performed “on an experimental basis, in a very unsafe situation.” Sur-reply 26 (citing Ex. 1304, 69:16–70:9). On this record, we cannot give weight to Dr. Rapoport’s testimony regarding decrease in MOH because Dr. Rapoport has not provided a comparison in his testimony to the closest prior art, as required for a comparison to show unexpected results for the claimed invention, such as a comparison with a triptan. *See Bristol-Myers Squibb Co. v. Teva Pharm. USA, Inc.*, 752 F.3d 967, 977 (Fed. Cir. 2014) (“To be particularly probative, evidence of unexpected results must

¹¹⁰ Florence Chaverneff, *Fremanezumab May Help Reduce Medication Overuse in Chronic Migraine* (July 1, 2018) (Ex. 2195).

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establish that there is a difference between the results obtained and those of the closest prior art, and that the difference would not have been expected by one of ordinary skill in the art at the time of the invention”); *In re Klosak*, 455 F.2d 1077, 1080 (CCPA 1972) (unexpected results are based on comparison to closest prior art). To the extent that Patent Owner’s Sur-reply points to deposition testimony by Dr. Rapoport that the decrease in medication “probably didn’t have anything to do with Naratriptan,” we find that this testimony is too thin a reed to support a finding of unexpected results by a preponderance of the evidence, with respect to the closest prior art. In this regard, we find that Dr. Rapoport’s testimony does not provide support for the statement that Naratriptan probably did not have anything to do with decrease in medication overuse. *See* Ex. 1304, 69:16–70:9.

Patent Owner also argues that the claimed antibodies demonstrate better efficacy and safety than that predicted by Tan and Wimalawansa. PO Resp. 57–58. Petitioner argues that Patent Owner’s unexpected results arguments are “predicated on an exaggerated and incorrect ‘inherent threat of severe side effects.’” Reply 25.

Patent Owner asserts that Wimalawansa recognizes that systemic vasoconstriction and severe consequences to the cerebrovascular and cardiovascular systems are significant risks, and we agree that Wimalawansa did express certain safety concerns. Ex. 1096, 543, 597. If safety in administration to humans is the asserted unexpected result, it does not appear that Tan or Wimalawansa would be the closest prior art, given that neither provide a safety study. In contrast, Olesen provides safety information related to blocking the CGRP pathway, which Patent Owner asserts gave rise to the “concern in the field.” PO Resp. 57. In particular,

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Olesen showed no serious adverse events with BIBN (a receptor antagonist), although Olesen stated that it could not assess cardiovascular safety. Ex. 1025, 1104, 1109. We do not assess the actual safety of the monoclonal antibody products, but if anything, Olesen demonstrated that CGRP antagonists could be administered to patients. We discuss the issue of safety further above with respect to motivation to combine. *See supra* Section II.D.2.b)(2).

Patent Owner argues that Tan 1995's murine anti-CGRP monoclonal antibody C4.19 increased baseline MAP at doses that failed to have any effect in the rat. PO Resp. 53. We agree with Patent Owner that the full length antibody products Ajovy® and Emgality® may have shown increased efficacy compared with Tan. *See* Ex. 1022, 569; Ex. 2232 ¶ 50; Ex. 2191, 118:12–119:1; Ex. 2214 ¶ 78–81. In any event, as above, we do not find the antibody products to be co-extensive with the claimed invention. As discussed above, Patent Owner has not shown a nexus between the challenged claims and Ajovy® or Emgality® antibodies. Nor has Patent Owner shown a direct nexus between any unexpected results and the claimed invention (as opposed to unclaimed features of the Ajovy® or Emgality® antibodies).

(d) Industry Skepticism

Patent Owner argues that humanized anti-CGRP antibodies faced industry skepticism because of safety concerns of cardiovascular risks, i.e., it was known that CGRP was a potent vasodilating substance and because the antibodies had longer half-lives, which would present difficulty in reversing any side effects. PO Resp. 54–55 (citing Ex. 2162, 447; Ex. 2189, 3; Ex. 2214 ¶¶ 46, 82–83; Ex. 2180, 27; Ex. 2226 ¶ 48). Patent Owner argues

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that “[a]s of 2005, CGRP was understood as the most potent vasodilating substance and that its blockade raised “concerns with possible cardiovascular risks such as medication-induced hypertension and inhibition of cardio-protective mechanisms during ischemia.” *Id.* at 58 (citing Ex. 2162, 447; Ex. 2189, 3; Ex. 2214 ¶¶ 82–83). Patent Owner further argues that this “skepticism was compounded” because the side-effects from an anti-CGRP antibody “could not be quickly reversed due to its relatively long half-life.” *Id.* Petitioner argues that Patent Owner’s arguments regarding side-effects are exaggerated and incorrect. Reply 25.

The evidence cited by Patent Owner reflects the fact that any so-called concerns were potential or theoretical concerns that merely raised the possibility of adverse side effects. *See, e.g.*, Ex. 2180, 7 (“a theoretical risk exists that CGRP blockade could hinder vasodilation”); Ex. 2189, 3 (“the possibility that inhibition of CGRP could affect a range of systems . . . Inhibition of CGRP has the potential to inhibit vasodilation”). Such evidence is in stark contrast to other test data that existed in 2005 relating to the blockade or binding of CGRP receptors or the CGRP ligand. *See supra* Section II.D.2.b)(2).

In any event, Patent Owner’s arguments relate to the administration of an anti-CGRP antibody, the particularly Ajovy® and Emgality® antibodies, to humans. For similar reasons as for the category of praise, Patent Owner has not established a nexus between the claimed invention and the objective indicia.

(e) *Commercial Success*

Factual Findings

Patent Owner relies on certain testimony and documentary evidence for showing commercial success for the claimed antibodies. *See* PO Resp. 59–60. We have reviewed the evidence relied on by Patent Owner and make the following factual findings.

Investment analysts at Leerink Transformation Partners (“Leerink”) have forecasted that the migraine antibody market will break the blockbuster barrier by 2025 and that the entire class of drugs will be worth \$4.5 billion by 2022, and \$6.9 billion by 2025. Ex. 2085,¹¹¹ 2–3. Patent Owner asserts that Leerink predicted that by 2025, the Ajovy® product will generate \$1.24 billion, while the Emgality® product will earn \$1.59 billion. *Id.* JPMorgan forecasted that Ajovy® and Emgality® products will each reap more than \$1 billion in annual sales by 2023. Ex. 2153,¹¹² 2. An Evercore ISI analyst has estimated that the market size for CGRP drugs have the potential to reach the range of \$8 to \$10 billion, with over 7 million patients treated. Ex. 2170,¹¹³ 1–2.

Analysis

Patent Owner argues “commercial success” based on market forecasts for Ajovy® and Emgality® antibodies, as well as for the market “potential”

¹¹¹ E. Sagonowsky, *Amgen’s quick Aimovig launch boosts blockbuster hopes for Lilly, Teva and Alder: analyst*, FIERCE PHARMA, fiercepharma.com (Aug. 20, 2018) (Ex. 2085).

¹¹² A. Weintraub, *Teva abandons Ajovy's cluster headache ambitions, clearing a path for Lilly to forge a new market*, FIERCE PHARMA, fiercepharma.com (Apr. 24, 2019) (Ex. 2153).

¹¹³ Emma Court, *New migraine drugs have promise — and a \$8,500 price tag*, MARKETWATCH, marketwatch.com (June 9, 2017) (Ex. 2170).

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for those antibodies, in addition to the Aimovig® product and Alder’s eptinezumab. PO Resp. 59. Patent Owner also argues that “there is a presumption” that the commercial success of Ajovy® and Emgality® antibodies have nexus to the challenged claims because they “are embodiments of the claimed invention,” and that “any commercial success attributable to Alder’s product also has nexus to the challenged claims due to Alder’s decision to license Teva’s patents.” *Id.* at 59–60.

Petitioner argues that “Teva cites no evidence of any commercial sales of Ajovy® or Emgality®,” but rather “cites forecasts of potential future sales, failing to establish any evidence of meaningful market share in the anti-migraine drug market.” Reply 26. Patent Owner replies that “Lilly willfully ignores multiple financial analysts whose independent research concluded that Ajovy® and Emgality® will achieve significant commercial success.” Sur-reply 27.

Patent Owner’s asserted evidence of commercial success is based on forecasts, predictions, and potential sales or market size rather than any *actual* sales or market share. *See In re Applied Materials, Inc.*, 692 F.3d 1289, 1300 (Fed. Cir. 2012) (“An important component of the commercial success inquiry in the present case is determining whether Applied had a significant market share.”); *see also In re Huang*, 100 F.3d 135, 140 (Fed. Cir. 1996) (“This court has noted in the past that evidence related solely to the number of units sold provides a very weak showing of commercial success, if any.”). Patent Owner provides no support for the contention that mere forecasts, predictions, and potential sales or market size constitute persuasive evidence of commercial success.

To the extent that the proffered evidence of commercial success may be understood as *praise* of the Ajovy® or Emgality® antibodies by the investment analysts, we find above that Patent Owner is not entitled to a presumption of nexus based on the Ajovy® or Emgality® antibodies, and further find in the alternative that any such presumption has been rebutted by Petitioner. *See supra*. Nor has Patent Owner made a showing of a nexus between the claims and the objective indicia (as opposed to unclaimed features of Ajovy® or Emgality® antibodies). In particular, Patent Owner has not explained how the objective indicia is attributable to the claimed invention. At most, we would give little weight to praise based on Ajovy® or Emgality® antibodies.

(f) *Licensing*

Patent Owner cites the AlderBio License (Ex. 2257¹¹⁴) as evidence of nonobviousness that “has nexus to the challenged claims because the challenged patent is part of the license” (citing Ex. 2241 ¶ 19). *See* PO Resp. 60–61. Patent Owner states that the license includes the right to commercialize AlderBio’s humanized anti-CGRP antibody eptinexumab for migraine treatment in exchange for AlderBio withdrawing its appeal before the European Patent Office and paying licensing and royalty fees. *Id.* (citing Ex. 2243 ¶¶ 15–18; Ex. 2257, 1, 4, 8–9¹¹⁵, 20–29, 31; Ex. 2255, 1–2;

¹¹⁴ We granted Patent Owner’s Motion to Seal with respect to Exhibit 2257. *See* Paper 48. The record contains both a confidential version and a public, redacted version of Exhibit 2257. Citations herein are to the public version of the document. We do not rely on any of the redacted information for purposes of this Final Written Decision.

¹¹⁵ The specific details of the royalty fees are redacted from pages 8–9 of the public version Exhibit 2257. However, we do not rely on those details for purposes of this Final Written Decision.

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Ex. 2260, 1). Patent Owner also states that AlderBio acknowledged that the “patents were valid and enforceable” and that “[a]bsent the license agreement, AlderBio would otherwise infringe the challenged patent, precluding it from marketing eptinezumab following FDA approval.” *Id.* at 57 (citing Ex. 2243 ¶¶ 19; Ex. 2257, 5, 29; Ex. 2255, 2; Ex. 2260, 1).

Petitioner argues that the AlderBio License was designed to settle a European litigation, and “includes 188 licensed patents from many different patent families” and “would remain in force and Teva’s licensee would continue to owe royalties on the remaining 187 patents even if the ’211 patent is cancelled, demonstrating Teva’s failure to prove nexus.” See Reply 26–27. Petitioner also argues that Patent Owner “apportions no particular value to the ’211 patent” as between the 188 licensed patents (*id.* at 26), to which Patent Owner replies that “an apportionment is not necessary here because the licensed patents are all related and necessary for the licensee to produce a product,” citing Dr. Stoner’s testimony (Sur-reply 26 (citing Ex. 2243 ¶ 19)).

The court has explained that “without a showing of nexus, ‘the mere existence of ... licenses is insufficient’” *In re Antor Media Corp.*, 689 F.3d 1282, 1293 (Fed. Cir. 2012) (citations omitted). “[T]he relevant inquiry is whether there is a nexus between the patent and the licensing activity itself, such that the factfinder can infer that the licensing ‘arose out of recognition and acceptance of the subject matter claimed’ in the patent.” *S. Alabama Med. Sci. Found. v. Gnosis S.p.A.*, 808 F.3d 823, 827 (Fed. Cir. 2015) (citations omitted). Thus, Patent Owner would have to show a nexus between the challenged patents and the licensing activity.

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The “whereas” clause of the license agreement and definition section indicate that the purpose of the license is to settle opposition proceedings before the European Patent Office relating to EP1957106 and to grant a license to AlderBio to develop the Alder Product, i.e., eptinezumab, also referred to as ALD403, as described in U.S. 9,745,373, or any other of Alder’s antibodies, or fragments. *See* Ex. 2257, 1 (preamble; §§ 1.2, 1.3). Patent Owner granted Alder a covenant not to sue as part of the license agreement with respect to the Alder Product (*id.* § 2.8), and granted a license in the patents in Schedule 1.14, including the challenged patents (*id.* §§ 1.14, 3.1(a), Schedule 1.14). Thus, to make a direct showing of nexus (i.e., not based on a presumption of nexus), Patent Owner would have to explain how the challenged claims relate to eptinezumab (Aimovig®) or another Alder Product, aside from being one of the patents included in the license.

Based on our review of the Patent Owner response, we determine that Patent Owner has not explained such a relationship, other than that the challenged patents are included in the license. This is insufficient. *See Antor Media*, 689 F.3d at 1293.

Nor does Patent Owner show that any of the challenged patents cover the Alder Product by a comparison of the Aimovig® product to the claims. Rather, Dr. Stoner opines that AlderBio would not have taken a license of the challenged patents if it did not infringe. *See* Ex. 2243 ¶¶ 21–22, 24–25; *see also* PO Resp. 60–61 (citing Ex. 2243 ¶¶ 20, 22, 24–25; Ex. 2255, 2; Ex. 2260, 1). The license itself includes an “admission” that the Alder products would infringe (Ex. 2257, 5), although it is unclear that Alder would not have licensed but for infringement, i.e., whether this admission constitutes more than the mere taking of a license under *Antor Media*.

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We have considered Dr. Stoner’s testimony, and the fairly standard validity, enforceability, and infringement clauses of the AlderBio License, and do not find that Patent Owner has made an adequate showing that the AlderBio License was the result of the challenged claims. *See Merck & Cie v. Gnosis S.p.A.*, 808 F.3d 829, 838 (Fed. Cir. 2015) (concluding that the Board’s finding that the evidence of licensing should not be afforded much weight was reasonable where the license agreement covered several patents and “[i]t is . . . difficult to determine the extent to which the licensing agreement was a result of the novel features in the [challenged patent], as opposed to the other patents involved.”).

On this record, we find that the challenged patents were only three of 188 patents included in the AlderBio License as part of a settlement of litigation, and that all of those licensed patents are necessary for the licensee to manufacture its product. The fact that the challenged patents are only three of 188 licensed patents, and all licensed patents are necessary to the marketing activities of the licensee, minimizes any nexus between the challenged claims and the AlderBio License. Moreover, the lack of specific apportionment evidence regarding any of the challenged patents, or any evidence that the AlderBio License was entered into out of respect for the challenged patents, further minimizes any nexus.

Nevertheless, even if there is some degree of nexus due to the fact that the challenged patents are in some way related to the settled European litigation, as evidenced by their inclusion in the settlement, we would give any objective indicia of nonobviousness less weight to the extent that the challenged patents may be broader than the Aimovig® product.

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(g) Summary of Objective Indicia of Nonobviousness

Based on the foregoing reasons, we accord Patent Owner's objective indicia of nonobviousness little or no weight.

We do not reach Petitioner's arguments as to objective indicia of obviousness (simultaneous invention) (*see* Pet. 62–67) because we have already found that a person of ordinary skill would have combined the references based on the showing in Petitioner's case in chief.

e) Summary as to Obviousness of the Independent 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 weighed the objective indicia of nonobviousness and find that Patent Owner has failed to establish nexus to the challenged claims, and that the objective indicia is otherwise relatively weak as compared to the evidence of obviousness. After doing so, we conclude that Petitioner has satisfied its burden of demonstrating, by a preponderance of the evidence, that claim 1 of each of the challenged patents would have been obvious over the combination of Tan, Wimalawansa, and Queen (and Doods in the case of the '881 patent). On balance, we determine that the explicit teachings in the prior art, including the motivation to

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humanize anti-CGRP antibodies for therapeutic purposes as taught or suggested by Wimalawansa outweigh any objective indicia of nonobviousness. *See* Ex. 1096; *see also* Ex. 1026, Ex. 1027, and Ex. 1028.

3. Dependent Claims

a) The '211 Patent

Petitioner sets forth arguments and evidence to show, with respect to each of claims 2–15 of the '211 patent, that the limitations are disclosed or suggested by the prior art, that a person of ordinary skill in the art would have had a reason to combine the teachings of the prior art to achieve the claimed invention, and that a person of ordinary skill in the art would have had a reasonable expectation of success in doing so. *See* Pet. 50–60. Patent Owner does not challenge Petitioner's evidence and arguments regarding claims 2–15 separately from independent claim 1. Patent Owner also argues that all of the challenged claims have a presumption of nexus for purposes of objective indicia of obviousness. PO Resp. 52 (citing Ex. 2237 ¶¶ 22–24; Ex. 2226 ¶ 114; Ex. 2243 ¶¶ 19, 23, 24, 26).

(1) Claim 2

Claim 2 depends from claim 1, and further recites “wherein the binding affinity is about 1 nM or less, about 500 pM or less, or about 100 pM or less as measured by surface plasmon resonance at 37° C.” Ex. 1001, 103:46–48. The further recitation contains a Markush group because of the connecting term “or,” such that the claim may be met by a binding affinity of 1 nM or less. Our discussion above with respect to independent claim 1 explains that a person of ordinary skill in the art would have had the motivation and reasonable expectation of success to raise antibodies with an affinity of 10 nM or 1 nM, based on the range of affinities

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normally found in antibodies, because that was the common practice for therapeutic antibodies, and in order to optimize affinity. For example, Dr. Vasserot avers that muomonab-CD3 had a K_D of 0.83 nM. Ex. 1013 ¶ 69 (citing Ex. 1078¹¹⁶, 3618). Accordingly, that discussion applies with equal force to dependent claim 2, as to independent claim 1. Accordingly, we determine that dependent claim 2 would have been obvious over Tan, Wimalawansa, and Queen.

(2) Claims 3, 7, and 12

Claims 3, 7, and 12 depend from claim 1, and further recite that the anti-CGRP antibody has an IgG₁, IgG₂, or IgG₄ constant region, respectively. Ex. 1001, 103:49–50, 104:32–33, 104:49–50. Petitioner asserts that Queen describes using constant regions from any of the IgG subclasses. Pet. 54 (citing Ex. 1023, 11:4–20). Petitioner further argues that a person of ordinary skill would have been motivated to use the IgG₁ subclass because it was the most common in FDA-approved humanized antibodies (citing Ex. 1012 ¶ 168; Ex. 1013 ¶ 138; Ex. 1056, 1075; Ex. 1059, 142), and would also have been motivated, in the alternative, to use the IgG₂ or IgG₄ constant region because each was known to have desirable properties, e.g., weak effector functions and longer half-lives (citing, e.g., Ex. 1013 ¶¶ 139–140; Ex. 1106, 240). *Id.* at 54–55. We adopt Petitioner’s undisputed assertions as factual findings. *See NuVasive*, 841 F.3d at 974.

¹¹⁶ M. Cole et al., *Human IgG2 Variants of Chimeric Anti-CD3 Are Nonmitogenic to T Cells*, 159 J. IMMUNOLOGY 3613–3621 (1997) (Ex. 1078).

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Petitioner further argues that there were a limited number of options to choose from, i.e., 4 receptor subtypes. *Id.* at 53. We conclude that it would have been obvious to a person of ordinary skill to further modify the antibody of claim 1 to use any of IgG₁, i.e., because it was accepted as common in therapeutic antibodies, or in the alternative IgG₂ or IgG₄ in order to weaken undesirable effector functions. Accordingly, we determine that dependent claims 3, 7, and 12 would have been obvious over Tan, Wimalawansa, and Queen.

(3) *Claims 4, 8, 9, and 13*

Claims 4, 8, and 13 depend from claims 3, 7, and 12, respectively, and recite that the CDRs of the anti-CGRP antagonist antibody “impart to the antibody specific binding to a fragment of the CGRP comprising amino acid residues 8 to 37 of SEQ ID NO:15.” Ex. 1001, 103:51–53, 104:34–36, 104:50–52. Claim 9 depends from claim 7 and recites that the CDRs “impart to the antibody specific binding to a fragment of the CGRP comprising amino acid residues 33 to 37 of SEQ ID NO:15.” *Id.* at 104:37–39. It is undisputed that SEQ ID NO:15 is human α -CGRP. *See supra*, independent claim 1.

Petitioner asserts that Tan refers to the anti-CGRP antagonist antibodies of Louis, which were known to target the C-terminus of CGRP, i.e., that bound amino acids 28–37. Pet. 56 (citing Ex. 1022, 573 (citing Ex. 1048¹¹⁷); Ex. 1048, 258). Petitioner asserts that Wong also described a commercially available anti-CGRP antagonist antibody, #4901, which was

¹¹⁷ S.M. 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*, 102 NEUROSCIENCE LETTERS 257–260 (1989).

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known to bind to a C-terminal portion of CGRP, i.e., amino acids 28–37. *Id.* (citing Ex. 1033, 104; Ex. 1012 ¶ 171; Ex. 1013 ¶ 143). Petitioner asserts that Andrew also reported anti-CGRP antagonist antibodies that bound to the C-terminal region of CGRP. *Id.* (citing Ex. 1055, 91). Petitioner asserts that a person of ordinary skill in the art would have been motivated to make an anti-CGRP antagonist antibody that bound to fragments comprising amino acids 8–37 or 33–37 of CGRP, and would have had a reasonable expectation of success, because such antibodies were both known in the prior art and known to be active *in vivo*. *Id.* at 56–57 (citing Ex. 1012 ¶¶ 171–172; Ex. 1013 ¶ 145; Ex. 1033, 99, 102; Ex. 1055, 88). We adopt Petitioner’s undisputed assertions as factual findings. *See NuVasive*, 841 F.3d at 974.

Further, we find that Andrew discloses an antibody that bound residues 26–37 of human α -CGRP. Ex. 1055, 90 (Table III). Wong states that it produced an antibody that was C-terminal specific for rat α -CGRP. Ex. 1033, 104. Dr. Vasserot opines that a person of ordinary skill, following routine immunization techniques, would have reasonably expected to obtain an antibody that binds to the C-terminal portion of α CGRP, including fragments comprising amino acid residues 8 to 37 and amino acid residues 33 to 37. Ex. 1013 ¶ 143.

We conclude that a person of ordinary skill would have further modified the antibodies of 3, 7, and 12 to target the C-terminus of human α -CGRP, as further recited in claims 4, 8, 9, and 13, in order to effectively block the binding of CGRP to its receptor. Accordingly, we determine that claims 4, 8, 9, and 13 would have been obvious over Tan, Wimalwansa, and Queen.

(4) Claims 5, 10, and 14

Claims 5, 10, and 14 respectively depend from claims 3, 7, and 12, and further recite that the “CDRs of the humanized monoclonal antibody are derived from mouse, rat, or rabbit CDRs.” Ex. 1001, 103:54–56, 104:40–42, 104:53–55. The further recitation is a Markush group because of the connecting term “or,” and can therefore be met by CDRs derived from any of the animals.

Petitioner asserts that Queen describes humanizing non-human monoclonal antibodies (e.g., mouse or rat) by grafting the CDR amino acid sequences from donor mouse or rat antibodies (such as Tan’s) into a human IgG scaffold. Pet. 58 (citing Ex. 1023, 2:61–65, 12:1–4; Ex. 1012 ¶ 175; Ex. 1013 ¶ 147). We adopt Petitioner’s undisputed assertions as factual findings. See *NuVasive*, 841 F.3d at 974. We conclude that a person of ordinary skill would have sought to use CDR amino acid sequences from a mouse or rat in the process when creating a humanized antibody, as taught by Queen, because the original antibodies would have been raised using animal models, as taught by Tan and Andrew and as discussed above with respect to independent claim 1. Accordingly, we determine that claims 5, 10, and 14 would have been obvious over Tan, Wimalwansa, and Queen.

(5) Claims 6, 11, and 15

Claims 6, 11, and 15 respectively depend from claims 3, 7, and 12, respectively, and further recite “wherein a constant region of at least one IgG heavy chain comprises a mutation in an oligosaccharide attachment amino acid residue that is part of an N-glycosylation recognition sequence in the constant region.” Ex. 1001, 103:56–61, 104:43–48, 104:56–61. Petitioner asserts that prior art had already demonstrated that oligosaccharide

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attachment residues could be successfully mutated, and argues that a person of ordinary skill would have done so because it was known to avoid effector functions, which negatively impact therapy. Pet. 59–60 (citing Ex. 1067, 2595; Ex. 1076, 1632; Ex. 1013 ¶¶ 28, 149–150; Ex. 1012 ¶ 178; Ex. 1064, 27–28). We adopt Petitioner’s undisputed assertions as factual findings. *See NuVasive*, 841 F.3d at 974. We conclude that a person of ordinary skill would have mutated an oligosaccharide attachment, as recited, in order to reduce the effector function of the therapeutic antibodies. Accordingly, we determine that claims 6, 11, and 15 would have been obvious over Tan, Wimalwansa, and Queen.

b) The ’649 patent

Petitioner sets forth arguments and evidence to show, with respect to each of claims 2–9 of the ’649 patent, that the limitations are disclosed or suggested by the prior art, that a person of ordinary skill in the art would have had a reason to combine the teachings of the prior art to achieve the claimed invention, and that a person of ordinary skill in the art would have had a reasonable expectation of success in doing so. 1427 IPR Pet. 51–60. Patent Owner does not challenge Petitioner’s evidence and arguments regarding claims 2–9 separately from independent claim 1. The discussion of the parties’ respective arguments regarding the ’211 patent also apply to the ’649 patent. *See supra* Section II.D.3.a).

(1) Claims 2 and 3

Claim 2 depends from claim 1, and further recites “wherein the anti-CGRP antagonist antibody binds a C-terminal fragment having amino acids 25–37 of CGRP.” 1427 IPR Ex. 1001, 101:42–45. Petitioner argues that a person of ordinary skill would have been motivated to prepare a

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humanized anti-CGRP antagonist antibody that binds to the C-terminal region of CGRP, including those fragments recited in claim 2 because it was known that this region was critical for binding to the CGRP receptor. 1427 IPR Pet. 54 (citing Ex. 1427 IPR 1002 ¶ 156; Ex. 1034, 118, 121–22; Ex. 1048, 259; Ex. 1033, 104; 1427 IPR Ex. 1003 ¶ 123). Patent Owner does not dispute Petitioner’s argument. We find that Exhibit 1048 discloses an antibody that binds to a radiolabeled CGRP fragment with amino acids 28–37. *See* Ex. 1048, 257. We conclude that claim 2 would have been obvious over Tan, Wimalawansa, and Queen for the reasons stated by Dr. Charles and Dr. Vasserot, i.e., because these regions were critical to prevent binding the receptor. *See* 1427 IPR 1002 ¶¶ 155–156; Ex. 1427 IPR 1003 ¶¶ 122–123.

Claim 3 depends from claim 2, and further recites that “the anti-CGRP antagonist antibody binds a C-terminal epitope within amino acids 25–37 of CGRP.” 1427 IPR Ex. 1001, 101:45–48. We determine that claim 3 would have been obvious over Tan, Wimalawansa, and Queen, for similar reasons as for claim 2.

(2) Claim 4

Claim 4 depends from claim 3, and further recites and recites that the anti-CGRP antagonist antibody is an IgG, IgM, IgE, IgA, or IgD molecule or derived therefrom. 1427 IPR Ex. 1001, 101:49–51. The further recitation is a Markush group because of the connecting term “or,” and can therefore be met by any of the classes of antibody, including IgG. We determine that claim 4 of the ’649 patent would have been obvious over Tan, Wimalawansa, and Queen, for similar reasons as for claims 3, 7, and 12 of

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the '211 patent. *See* 1427 IPR Ex. 1002 ¶ 158; 1427 IPR Ex. 1003 ¶¶ 22, 126; *supra* Section II.D.3.a)(2).

(3) Claim 5

Claim 5 depends from claim 1 and further recites “wherein said antibody comprises an Fc region.” 1427 IPR Ex. 1001, 102:37–38. Petitioner asserts that full-length antibodies possess an Fc region as part of their heavy chain constant regions. 1427 IPR Pet. 56 (citing Ex. 1058, 95; Ex. 1023, 11:21–27; 1427 IPR Ex. 1003 ¶ 20). This is undisputed. We determine that claim 5 of the '649 patent would have been obvious over Tan, Wimalawansa, and Queen, for similar reasons as for independent claim 1 of the '211 patent.

(4) Claim 6

Claim 6 further depends from claim 5 and further recites “wherein said Fc region comprises an impaired effector function.” 1427 IPR Ex. 1001, 102:39–41. We determine that claim 6 of the '649 patent would have been obvious over Tan, Wimalawansa, and Queen, for similar reasons as for independent claims 6, 11, and 15 of the '211 patent. *See* 1427 IPR Ex. 1003 ¶ 133; *supra* Section II.D.3.a)(5).

(5) Claim 7

Claim 7 depends from claim 1 and further recites “wherein said antibody is a humanized antibody.” 1427 IPR Ex. 1001, 102:42–43. We determine that claim 7 of the '649 patent would have been obvious over Tan, Wimalawansa, and Queen, for similar reasons as for independent 1 of the '211 patent.

(6) *Claim 8*

Claim 8 depends from claim 1 and recites a “pharmaceutical composition comprising the antibody according to claim 1 and a pharmaceutically acceptable excipient.” 1427 IPR Ex. 1001, 102:44–46. Petitioner asserts that Tan’s antibody preparations contained PBS (phosphate buffered saline), one of the pharmaceutically acceptable carriers expressly identified in the ’649 patent. 1427 IPR Pet. 59 (citing 1427 IPR Ex. 1001, 19:37–38; Ex. 1022, 568). Petitioner also asserts that Queen expressly teaches that humanized antibodies can be formulated into pharmaceutical compositions including pharmaceutically-acceptable excipients. *Id.* (citing Ex. 1023, 24:29–51). We adopt Petitioner’s undisputed assertions as factual findings. *See NuVasive*, 841 F.3d at 974.

Petitioner argues that a person of ordinary skill would have been motivated to make a preparation with a pharmaceutical composition and pharmaceutically acceptable excipient and would have done so with a reasonable expectation of success. 1427 IPR Pet. 59. Because pharmaceutically acceptable excipients were known, we conclude that a person of ordinary skill would have been able to make the recited composition with a reasonable expectation of success. *Intelligent Bio-Sys.*, 821 F.3d at 1367 (reasonable expectation of success is determined with respect to the scope of the claims); *see also Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007) (“The evidence would convince a reasonable finder of fact that the skilled artisan would have had that reasonable expectation of success that an acid addition salt of besylate would form and would work for its intended purpose”). Based on our review of the evidence, we determine that it was within the skill of the art to provide a

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pharmaceutically-acceptable excipient, as recited, and that a person of ordinary skill would have been motivated to do so to administer the composition to humans. *See also* Ex. 1028, 5:40–50 (Example 2) (disclosing an ointment).

Patent Owner does not argue claim 8 separately from claim 1, but argues that the safety concerns are particularly relevant to claim 8. 1427 IPR PO Resp. 22 n.6. However, we have addressed the safety concerns with respect to claim 1 of the '211 patent and do not find that they would have outweighed the motivation to use humanized antibodies in view of the express teachings and suggestions in the art. *See supra* Section II.D.2.b)(2).

Accordingly, we determine that claim 8 of the '649 patent would have been obvious over Tan, Wimalawansa, and Queen.

(7) *Claim 9*

Claim 9 depends from claim 1 and recites “the anti-CGRP antagonist antibody of claim 1, wherein the antibody is formulated for systemic administration.” 1427 IPR Ex. 1001, 102:47–49. Petitioner asserts that the antibody preparations of Tan 1995 were formulated with PBS and were administered intravenously, which is a form of systemic administration. 1427 IPR Pet. 59 (citing Ex. 1022, 567). Petitioner asserts that Queen states that humanized antibodies can be formulated for human administration, including for systemic administration, which includes subcutaneous and intravenous administration. *Id.* at 59–60 (citing Ex. 1023, 24:29–51). We adopt Petitioner’s undisputed assertions as factual findings. *See NuVasive*, 841 F.3d at 974.

Patent Owner does not argue claim 9 separately from claim 1, but argues that the safety concerns are particularly relevant to claim 8. 1427

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IPR PO Resp. 22 n.6. However, we have addressed the safety concerns with respect to claim 1 of the '211 patent and do not find that they would have outweighed the motivation to use humanized antibodies in view of the express teachings and suggestions in the art. *See supra* Section II.D.2.b)(2).

We determine that claim 9 would have been obvious over Tan, Wimalawansa, and Queen, based on the teachings of Tan and Queen and for similar reasons as for claim 1.

c) The '881 patent

Petitioner sets forth arguments and evidence to show, with respect to each of claims 2–6 and 14–19 of the '881 patent, that the limitations are disclosed or suggested by the prior art, that a person of ordinary skill in the art would have had a reason to combine the teachings of the prior art to achieve the claimed invention, and that a person of ordinary skill in the art would have had a reasonable expectation of success in doing so. 1424 IPR Pet. 52–63. Patent Owner does not challenge Petitioner's evidence and arguments regarding claims 2–6 and 14–19 separately from independent claim 1. The discussion of the parties' respective arguments regarding the '211 patent also apply to the '881 patent. *See supra* Section II.D.3.a).

(1) Claim 2

Claim 2 depends from claim 1, and further recites further recite “wherein the anti-CGRP antagonist antibody binds the C-terminal fragment having amino acids 25-37 of human α -CGRP.” 1424 IPR Ex. 1001, 99:18–21. Although “the C-terminal fragment” has no literal antecedent basis, we treat for purposes of this discussion that it refers to a C-terminal portion of the CGRP. *See Energizer Holdings, Inc. v. Int’l Trade Comm’n*, 435 F.3d 1366, 1370–71 (Fed. Cir. 2006) (construing the antecedent basis of “said

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zinc anode” to refer to the antecedent anode gel). We determine that claim 2 of the ’881 patent would have been obvious over Tan, Wimalawansa, Queen, and Doods, for similar reasons as for claims 4, 8, 9, and 13 of the ’211 patent. *See* 1424 IPR Ex. 1006 ¶¶ 168–169; 1424 IPR Ex. 1007 ¶¶ 120–121.

(2) Claim 3

Claim 3 depends from claim 1, and further recites “wherein the anti-CGRP antagonist antibody binds a C-terminal epitope within amino acids 25-37 of human α -CGRP.” 1424 IPR Ex. 1001, 99:22–24. We determine that claim 3 would have been obvious over Tan, Wimalawansa, Queen, and Doods, for similar reasons as for claim 2. *See* 1424 IPR Ex. 1006 ¶¶ 165–167; 1424 IPR Ex. 1007 ¶¶ 117.

(3) Claims 4 and 5

Claim 4 depends from claim 3 and recites “wherein the anti-CGRP antagonist antibody binds the C-terminal fragment having amino acids 33-37 of human α -CGRP.” 1424 IPR Ex. 1001, 99:25–28. Claim 5 depends from claim 4 and further recites wherein the anti-CGRP antagonist antibody binds a C-terminal epitope within amino acids 33-37 of human α -CGRP.” *Id.* at 99:29–31. We determine that claims 4 and 5 of the ’881 patent would have been obvious over Tan, Wimalawansa, Queen, and Doods, for similar reasons as for independent claim 1 of the ’881 patent and claim 9 of the ’211 patent. *See* 1424 IPR Ex. 1006 ¶¶ 165–167, 169; 1424 IPR Ex. 1007 ¶¶ 117–121.

(4) Claim 6

Claim 6 further depends from claim 1 and further recites “wherein the anti-CGRP antagonist antibody binds the C-terminal fragment having amino

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acids G33 and/or F37 of human α -CGRP.” 1424 IPR Ex. 1001, 99:32–35. We determine that claim 6 of the ’881 patent would have been obvious over Tan, Wimalawansa, Queen, and Doods, for similar reasons as for dependent claims 4 and 5. In particular, the G33 and F37 residues are highly conserved. *See* 1424 IPR Ex. 1006 ¶ 169.

(5) Claim 14

Claim 14 depends from claim 1 and further recites “wherein the anti-CGRP antagonist antibody comprises a heavy chain constant region derived from a human IgG2 constant region.” 1424 IPR Ex. 1001, 100:32–35. We determine that claim 14 of the ’881 patent would have been obvious over Tan, Wimalawansa, Queen, and Doods, for similar reasons as for independent 1 of the ’881 patent and claim 12 of the ’211 patent. *See* 1424 IPR Ex. 1006 ¶¶ 170–173; 1424 IPR Ex. 1007 ¶¶ 122–125.

(6) Claim 15

Claim 15 depends from claim 1 and further recites an anti-CGRP antagonist antibody that comprises an Fc region. 1424 IPR Ex. 1001, 100:37–38. We determine that claim 15 of the ’881 patent would have been obvious over Tan, Wimalawansa, Queen, and Doods, for similar reasons as for independent claim 1 of the ’881 patent and claim 5 of the ’649 patent. *See* 1424 IPR Ex. 1007 ¶ 20; *supra* Sections II.D.2.a)(3).

(7) Claim 16

Claim 16 further depends from claim 15 and further recites “wherein the Fe region comprises an impaired effector function.” 1424 IPR Ex. 1001, 100:39–41. We determine that claim 16 of the ’881 patent would have been obvious over Tan, Wimalawansa, Queen, and Doods, for similar reasons as

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for independent claim 1 of the '881 patent and claim 6 of the '649 patent. *See* 1424 IPR Ex. 1006 ¶¶ 174–177.

(8) Claim 17

Claim 17 depends from claim 1 and further recites “wherein the antibody is a humanized antibody.” 1424 IPR Ex. 1001, 100:42–43. We determine that claim 17 of the '881 patent would have been obvious over Tan, Wimalawansa, Queen, and Doods, for similar reasons as for independent claim 1 of the '881 patent and claim 7 of the '649 patent. *See* 1424 IPR Ex. 1006 ¶ 178; 1424 IPR Ex. 1007 ¶ 134.

(9) Claim 18

Claim 18 depends from claim 1 and further recites a “pharmaceutical composition comprising the antibody according of claim 1 and a pharmaceutically acceptable excipient.” 1424 IPR Ex. 1001, 100:44–46.

Patent Owner does not argue claim 18 separately from claim 1, but argues that the safety concerns are particularly relevant to claim 18. 1424 IPR PO Resp. 21 n.6. However, we have addressed the safety concerns with respect to claim 1 of the '211 patent and do not find that they would have outweighed the motivation to use humanized antibodies in view of the express teachings and suggestions in the art. *See supra* Section II.D.2.b)(2).

We determine that claim 18 of the '881 patent would have been obvious over Tan, Wimalawansa, Queen, and Doods, for similar reasons as for independent claim 1 of the '881 patent and claim 8 of the '649 patent. *See* 1424 IPR Ex. 1006 ¶ 179; 1424 IPR Ex. 1007 ¶ 135–136.

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(10) *Claim 19*

Claim 19 depends from claim 1, and further recites “wherein the anti-CGRP antagonist antibody is formulated for systemic administration.” 1424 IPR Ex. 1001, 100:47–49.

Patent Owner does not argue claim 19 separately from claim 1, but argues that the safety concerns are particularly relevant to claim 19. 1424 IPR PO Resp. 21 n.6. However, we have addressed the safety concerns with respect to claim 1 of the ’211 patent and do not find that they would have outweighed the motivation to use humanized antibodies in view of the express teachings and suggestions in the art. *See supra* Section II.D.2.b)(2).

We determine that claim 19 of the ’881 patent would have been obvious over Tan, Wimalawansa, Queen, and Doods, for similar reasons as for independent claim 1 of the ’881 patent and claim 9 of the ’649 patent. *See* 1424 IPR Ex. 1006 ¶¶ 180–181; 1424 IPR Ex. 1007 ¶¶ 137–138.

d) *Summary of Dependent Claims*

For the foregoing reasons, we find that Petitioner has established by a preponderance of the evidence that each of the limitations of the challenged dependent claims are taught or suggested by the prior art, that a person of ordinary skill in the art would have had a reason to combine the teachings of the prior art to achieved the challenged claims, that outweighs any alleged reasons not to combine, and would have had a reasonable expectation of success in doing so. We further find that, in view of the little or no weight we accord to Patent Owner’s objective indicia of obviousness, the evidence of obviousness outweighs the objective indicia of nonobviousness.

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.

Because we do not rely on the Tan Thesis, we dismiss the motion as to Exhibit 1287 as *moot*.

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

Patent Owner moves to exclude portions of the following deposition testimony: Ex. 1301, 36:16–39:11, 27:25–28:6, 73:22–75:20, 115:9–116:21, 154:24–156:21; Ex. 1302, 45:20–46:19, 81:9–82:2, 179:14–180:19; Ex. 25:11–17, 38:22–39:10, 49:1–20, 54:12–23, 69:10–16, 70:13–75:11, 102:9–106:19, 108:25–133:7, 160:2–9, 193:3–10; Ex. 1304, 59:23–71:17, 82:17–134:18, 90:10–15, 91:6–10, 142:1–8, 143:6–23, 145:23–146:3. Mot. Excl. 7–12. Petitioner opposes. Opp. Excl. 3–13.

Patent Owner variously argues that the questions were in improper form, not relevant, vague, mischaracterizing the witnesses' prior testimony, call for a legal conclusion, lack clarity, or contained compound questions. Mot. Excl. 7–12. We consider Patent Owner's arguments in this regard to

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go to issues of weight rather than admissibility, and we deny this aspect 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 understand 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.

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 he declared himself qualified to testify. *See* Ex. 2214 ¶ 4; *see also* Ex. 1303, 16:25–30:4 (discussing experience with sumatriptan); Opp. Excl. 7. We deny this aspect of the motion.

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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. Exc. 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. 2214 ¶ 38; Opp. Excl. 10. We deny this aspect of the motion.

Patent Owner argues that 52 pages of deposition testimony (Ex. 1303, 82:17–134:18), should be excluded, *inter alia*, as beyond the scope of direct testimony. Mot. Excl. 11. Because Patent Owner does not point more specifically to the objectionable material, we deny this aspect of the motion for lack of specific argument.

Patent Owner seeks to exclude discussion of the meaning of “antibody serum” (Ex. 1303, 69:10–16). Mot. Excl. 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 the meaning of “a pharmacokinetic study” (Ex. 1304, 145:23–146:3) as beyond the scope of

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Dr. Rapoport's testimony on secondary considerations. Mot. Excl. 12. We agree with Patent Owner that the questions regarding "a pharmacokinetic study" were beyond the scope of Dr. Rapoport's testimony on objective indicia. Accordingly, we grant 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. 11. 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. 2237 ¶¶ 65–69; Opp. Excl. 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. 10. 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 1110, 1247, 1261, 1262, 1264, 1267–1279, 1281, 1286, 1293, 1296, 1311, 1313, 1314, 1316, and 1317)*

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 1110, 1247, 1261, 1262, 1264, 1267–1279, 1281, 1286, 1293, 1296, 1311, 1313, 1314, 1316, and 1317. Mot. Excl. 12–13. We deny this aspect of the motion. Where, as here, the

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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 1012, 1013, 1327, and 1328*

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 26–27, 60–67, 90, and 160 in Exhibit 1012, paragraphs 74–75, 132, and 135 in Exhibit 1013, and paragraphs 1–14 in Exhibit 1327. 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 3, 9, 11, 19–20; Exhibits 1082, 1240, 1287, 1309; paragraphs 15–34, 38, 51, 52, 54, 60, 69 of Exhibit 1327; and paragraphs 17, 31, 74, and 77 of Exhibit 1328. Mot. Strike 1–2 (citing 37 C.F.R. § 42.22(a)(2); 37 C.F.R. § 42.23; Trial Practice Guide at 40; *Henny Penny*, 938 F.3d at 1324; *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). Mot. Strike 2–3. For similar reasons for the motion to exclude the exhibit itself, we dismiss the motion to strike these portions of the Reply Brief as *moot*, i.e., because we do not rely on the Tan Thesis in our Decision.

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Second, Patent Owner seeks to strike the portions of Dr. Balthasar's declaration relating to Tan's full-length antibody (Ex. 1327 ¶¶ 15–34) and the portions of the Reply based thereon (Reply 19–20). 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. 2273), and also the opportunity to submit a Sur-reply (Paper 51). 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.

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Third, Patent Owner seeks to strike portions of the Reply (page 9) and related exhibits (Exhibits 1082, 1240, 1309) that discuss aptamers as presenting a new theory that should have been presented in the petition. Mot. Strike 4–5. Petitioner argues that the arguments and evidence on aptamers was responsive to Patent Owner’s arguments that a person of ordinary skill would have had safety concerns associated with directly antagonizing CGRP, particularly for compounds with a long half-life. Opp. Strike 3 (citing PO Resp. 21–30; Ex. 2232 ¶¶ 73–82; Ex. 2212 ¶¶ 12, 27–70). We agree with Petitioner that the line of argument on aptamers is responsive to Patent Owner’s arguments that a person of ordinary skill would have had concerns about CGRP antagonists with longer half-lives. See PO Resp. 21–30. This evidence was not being introduced to supply a limitation but rather to buttress previously presented arguments about motivation to combine. See *Chamberlain Grp.*, 944 F.3d at 925. Accordingly, we deny this aspect of the motion, for similar reasons as for the Balthasar testimony.

IV. CONCLUSION¹¹⁸

For the foregoing reasons, we conclude that Petitioner has established by a preponderance of evidence that claims 1–6 and 14–19 of the ’881 patent

¹¹⁸ Should Patent Owner wish to pursue amendment of the challenged claims in a reissue or reexamination proceeding subsequent to the issuance of this decision, we draw Patent Owner’s attention to the April 2019 *Notice Regarding Options for Amendments by Patent Owner Through Reissue or Reexamination During a Pending AIA Trial Proceeding*. See 84 Fed. Reg. 16,654 (Apr. 22, 2019). If Patent Owner chooses to file a reissue application or a request for reexamination of the challenged patent, we remind Patent Owner of its continuing obligation to notify the Board of any such related matters in updated mandatory notices. See 37 C.F.R. § 42.8(a)(3), (b)(2).

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are unpatentable, that claims 1–15 of the '211 patent are unpatentable, and that claims 1–9 of the '649 patent are unpatentable.

In summary:

IPR2018-01424 U.S. Patent No. 9,346,881 B2				
Claims	35 U.S.C. §	Reference(s)/Basis	Claims Shown Unpatentable	Claims Not shown Unpatentable
1–6, 14–19	103(a)	Tan, Wimalawansa, Queen, Doods	1–6, 14–19	
Overall Outcome			1–6, 14–19	

IPR2018-01426 U.S. Patent No. 9,890,211 B2				
Claims	35 U.S.C. §	Reference(s)/Basis	Claims Shown Unpatentable	Claims Not shown Unpatentable
1–15	103(a)	Tan, Wimalawansa, Queen	1–15	
Overall Outcome			1–15	

IPR2018-01427 U.S. Patent No. 8,597,649 B2				
Claims	35 U.S.C. §	Reference(s)/Basis	Claims Shown Unpatentable	Claims Not shown Unpatentable
1–9	103(a)	Tan, Wimalawansa, Queen	1–9	
Overall Outcome			1–9	

V. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that Petitioner has proved by a preponderance of the evidence that claims 1–6 and 14–19 of U.S. Patent No. 9,346,881 B2 are unpatentable;

FURTHER ORDERED that Petitioner has proved by a preponderance of the evidence that claims 1–15 of U.S. Patent No. 9,890,211 B2 are unpatentable;

FURTHER ORDERED that Petitioner has proved by a preponderance of the evidence that claims 1–9 of U.S. Patent No. 8,597,649 B2 are unpatentable;

FURTHER ORDERED that, pursuant to 35 U.S.C. § 328(b), upon expiration of the time for appeal of this Decision, or the termination of any such appeal, certificates shall issue canceling (1) 1–6 and 14–19 of U.S. Patent No. 9,346,881 B2, (2) 1–15 of U.S. Patent No. 9,890,211 B2, and (3) 1–9 of U.S. Patent No. 8,597,649 B2;

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 to certain arguments and dismissed as to other arguments, as discussed herein (*see* Section III.B.);

FURTHER ORDERED that Patent Owner’s Motion to Exclude is granted as to questions regarding “a pharmacokinetic study,” denied as to certain arguments, and dismissed as to other arguments, as discussed herein (*see* Section III.A.); and

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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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