

Filed on behalf of: Eli Lilly and Company

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

ELI LILLY AND COMPANY
Petitioner

v.

TEVA PHARMACEUTICALS INTERNATIONAL GMBH
Patent Owner

Case No. IPR2018-01710
Patent No. 8,586,045

PETITION FOR *INTER PARTES* REVIEW

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GLOSSARY

AIA	America Invents Act
BRI	Broadest reasonable interpretation
CDR	Complementarity-determining region
CGRP	Calcitonin gene-related peptide
Fab	Fragment antigen binding
FDA	U.S. Food and Drug Administration
IPR	<i>Inter partes</i> review
<i>Italicized text</i>	Emphasis added unless otherwise indicated
Lilly or petitioner	Eli Lilly & Company
MAb	Monoclonal antibody
POSA	Person of ordinary skill in the art
provisional application	U.S. Provisional App. No. 60/736,623
RIA	Radioimmunoassay
SPR	Surface plasmon resonance
Teva or Patent Owner	Teva Pharmaceuticals International GmbH
USPTO or Office	U.S. Patent and Trademark Office
'045 patent	U.S. Patent No. 8,586,045

I. Introduction

Teva's '045 patent broadly claims using *any* human or humanized monoclonal anti-CGRP antagonist antibody for reducing incidence of or treating any vasomotor symptom, including migraine. The concept of using an anti-CGRP antagonist antibody for these purposes was disclosed in the prior art. The challenged claims are obvious.

By the time Teva filed its first application in November 2005, the CGRP pathway was a clinically validated target for treating migraine. A published, double-blind, placebo-controlled clinical trial by Olesen firmly established that blocking the CGRP pathway resulted in migraine relief in human patients. Olesen was not before the USPTO during examination of the '045 patent.

Anti-CGRP antagonist antibodies that bound to and blocked the biological effects of CGRP were also well known in the art. These monoclonal antibodies were shown to block the CGRP pathway *in vivo*. For example, Tan demonstrated that its anti-CGRP antagonist antibodies effectively blocked CGRP in the very same *in vivo* animal model that Teva used in its provisional application to support its original claims to preventing and treating migraine. Thus, it was unsurprising that the prior art had expressly recommended using *humanized* monoclonal anti-CGRP antagonist antibodies to treat human diseases linked to CGRP, including migraine.

As Teva's '045 patent admits, humanization was a well-established and routine procedure by the time Teva filed its application. Researchers had long understood that humanized antibodies advantageously avoided immunogenic reactions caused by administering murine antibodies to humans. By 2005, half of the FDA-approved antibodies were humanized antibodies, and most antibodies in phase 2 and 3 clinical trials were humanized. Queen, which was also not submitted to the USPTO, represented the "gold standard" of humanization. As a result, humanization does not and cannot provide any patentable weight to the challenged claims.

As explained below and in the Expert Declarations of Dr. Andrew Charles, a neurologist and long-time CGRP researcher who specializes in the treatment of migraine, and Dr. Alain Vasserot, an antibody engineer with expertise in antibody humanization, the challenged claims of the '045 patent would have been obvious over Olesen, Tan, and Queen. Lilly therefore requests *inter partes* review of claims 1, 3, 4, 8-17, 19, 20, and 24-31 of the '045 patent.

II. Requirements for *Inter Partes* Review Under 37 C.F.R. § 42.104

A. Grounds for Standing

Petitioner certifies that the '045 patent is available for IPR based on Teva's assertions to the Office that it is entitled to claim priority to a pre-AIA effective filing

date of November 14, 2005, and that Petitioner is not barred or estopped from requesting review on the ground identified. (Ex. 1206, 3; Ex. 1207, 5-6 (listing priority chain and declining to designate as a transition application); Ex. 1001, 1:7-14, title page, item (60).)¹

B. Identification of Challenge

Lilly respectfully requests review under 35 U.S.C. § 311 of claims 1, 3, 4, 8-17, 19, 20, and 24-31 of the '045 patent. Lilly requests that the Board find these claims unpatentable as obvious under 35 U.S.C. § 103(a) in view of the following combination of references:

Reference 1: Olesen, J. et al., *New Engl. J. Med.* 350:1104-1110 (2004) (“Olesen”) (Ex. 1025), published on March 11, 2004.

Reference 2: Tan, K.K.C. et al., *Clin. Sci.* 89:565-573 (1995) (“Tan”) (Ex. 1022), published on December 1, 1995.

Reference 3: U.S. Patent No. 6,180,370 (“Queen”) (Ex. 1023) issued on January 30, 2001.

¹ Citations refer to the original page numbering of each exhibit except for references that do not have any pagination in their original form. Citations to such references refer to the stamped-on page numbers.

Olesen, Tan, and Queen are each prior art under 35 U.S.C. § 102(b).

III. The '045 Patent and Its Provisional Application

The '045 patent is entitled “Methods of Using Anti-CGRP Antagonist Antibodies.” (Ex. 1001, title page, item (54).) It states that the alleged invention relates to “methods for preventing or treating CGRP associated disorders such as vasomotor symptoms, including headaches (e.g., migraine, cluster headache, and tension headache) and hot flushes, by administering an anti-CGRP antagonist antibody.” (Ex. 1001, Abstract.) The '045 patent discloses a single humanized antagonist antibody (G1) and its purported derivatives. (*E.g., id.*, Abstract, Example 4.) The '045 patent does not include any clinical or other human data.

The '045 patent belongs to a family of fifteen patents and applications, all of which purport to claim priority to U.S. Provisional Application No. 60/736,623, filed on November 14, 2005. (Ex. 1014 ¶80.) The provisional application, like the '045 patent, identifies only one humanized anti-CGRP antagonist antibody, G1, as well as its variants with minor sequence differences. (*E.g., Ex. 1019, Example 4; Ex. 1001, Abstract, Example 4.*) The only *in vivo* data disclosed in the provisional application was generated using a well-known assay—the rat saphenous nerve assay—used in the prior art for the specific purpose of evaluating anti-CGRP

antagonist antibodies. (*Compare* Ex. 1019, [0244] (citing Ex. 1052), *with* Ex. 1022, 572 (citing Ex. 1052 as reference 9); Ex. 1014 ¶¶86-87.)

When filing its PCT application a year later, Teva only added additional animal study results, not clinical data, to the disclosure of its provisional application. (Ex. 1020, 66-68 (adding Examples 6-8).)

A. The Challenged Claims

Independent claim 17 recites “[a] method of reducing incidence of or treating headache in a human, comprising administering to the human an effective amount of an anti-CGRP antagonist antibody, wherein said anti-CGRP antagonist antibody is a human monoclonal antibody or a humanized monoclonal antibody.” (Ex. 1001, claim 17; Ex. 1014 ¶82; Ex. 1015 ¶69.)

Independent claim 1, the only other independent claim, is even broader. Rather than specifying “headache,” it encompasses *any* vasomotor symptom. (Ex. 1001, claim 1; Ex. 1014 ¶83; Ex. 1015 ¶70.) It is also directed to any “individual” (all mammals such as rats, Ex. 1001 at 19:4-7) rather than specifying a “human.” (Ex. 1001, claim 1; Ex. 1014 ¶83; Ex. 1015 ¶70.)

The challenged dependent claims further require:

- reducing incidence of or treating a subset of vasomotor symptoms or headache, including migraine (claims 3, 9, 19, and 24);

- a binding affinity of 50 nM or less as measured by surface plasmon resonance at 37 °C (claims 4 and 20);
- a human individual (claim 8);
- binding to a particular fragment or epitope (claims 10 and 25);
- an Fc region with an impaired effector function (claims 11 and 26);
- various routes of administration (claims 12 and 27);
- a heavy chain constant region derived from a human IgG₂ constant region (claims 13 and 28);
- a formulation (claims 14 and 29);
- a humanized monoclonal antibody (claims 15 and 30); and
- a dose of at least about 3 µg/kg (claims 16 and 31).

(Ex. 1001, claims 3, 4, 8-16, 19, 20, and 24-31; Ex. 1015 ¶71.)

B. Patent Owner Admissions in the Specification

The '045 patent discloses that many of the claimed limitations were known in the art. “Admissions in the specification regarding the prior art are binding on the patentee for the purposes of a later inquiry into obviousness.” *PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 491 F.3d 1342, 1362 (Fed. Cir. 2007).

1. CGRP and Its Role in Migraine Was Known

The '045 patent acknowledges that “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.” (Ex. 1001, 2:3-7.) The '045 patent further acknowledges that “[p]ossible CGRP involvement in migraine has been the basis for the development and testing of a number of compounds” that block the CGRP pathway. (*Id.*, 2:14-23.)

2. Anti-CGRP Antagonist Antibodies and Methods of Making Them, Including Humanization Techniques, Were Known

The '045 patent states that “[a]nti-CGRP antagonist antibodies are known in the art,” including those described by Tan. (*Id.*, 25:59-63 (citing Tan (Ex. 1022)).) It confirms that anti-CGRP antibodies were commercially available, such as antibody #4901 from Sigma Aldrich. (*Id.*; Ex. 1051, 350.) The '045 patent also expressly discloses that the claimed anti-CGRP antagonistic antibodies may be made using prior art methods:

The anti-CGRP antagonist antibodies may be made by any method known in the art. The route and schedule of immunization of the host animal are generally in keeping with *established and conventional techniques* for antibody stimulation and production, as further described herein.

(Ex. 1001, 27:41-45, 31:27-31 (“Anti-CGRP antagonist antibodies and polypeptides derived from antibodies can be identified or characterized using methods *known in the art . . .*”); 27:45-47 (“General techniques for production of human and mouse antibodies are *known in the art* and are described herein.”).)

The ’045 patent states that preparing humanized and human antibodies from non-human antibodies, such as murine antibodies, was “known” and “conventional.” (*Id.*, 27:41-47, 31:27-31, 32:7-8, 35:46-47; *see also id.*, cols. 28-30; Ex. 1015 ¶72.) According to the ’045 patent, the prior art taught methods to humanize a monoclonal antibody:

(1) determining the nucleotide and predicted amino acid sequence of the starting antibody light and heavy variable domains[;] (2) designing the humanized antibody, i.e., deciding which antibody framework region to use during the humanizing process[;] (3) the actual humanizing methodologies/techniques[;] and (4) the transfection and expression of the humanized antibody.

(Ex. 1001, 28:55-64 (citing Queen (Ex. 1023) and other prior art patents); Ex. 1015 ¶73.)

The ’045 patent acknowledges that humanized anti-CGRP antagonist antibodies “are designed to minimize unwanted immunological response toward rodent anti-human antibody molecules.” (Ex. 1001, 29:15-20.)

C. Prosecution of the '045 Patent

During prosecution, the Office did not raise any art-based rejections against the pending claims. But certain key documents, including Olesen (Ex. 1025) and Queen (Ex. 1023), had not been submitted.

The Office rejected the pending claims as lacking enablement. (Ex. 1213, 4-5.) In response, Teva argued that the enablement requirement was met because, *inter alia*, four murine anti-CGRP antibodies (including Antibody #4901, commercially available at the time of filing) inhibited skin vasodilation in a rat saphenous nerve model and other models. (Ex. 1143, 10; Ex. 1001, 25:59-63; Ex. 1051, 350.) Teva also admitted that *skin vasodilation*, like migraine, is a *vasomotor symptom*. (Ex. 1143, 10; Ex. 1001, 3:37-45.)

IV. Background and Asserted Prior Art

A. CGRP Structure and Its Isoforms

By 2005, the neuropeptide CGRP had been identified and extensively studied. (Ex. 1014 ¶¶16-23.) Human CGRP is expressed in two closely related isoforms, α CGRP and β CGRP, both 37 amino acids in length. (*Id.* ¶16; Ex. 1032, 275; Ex. 1096, 534.) Human α CGRP and β CGRP differ by only three amino acids. (Ex. 1014 ¶16; Ex. 1032, 275; Ex. 1096, 534.) Rat CGRP is also expressed in α and β isoforms, and they differ by only one amino acid. (Ex. 1014 ¶16; Ex. 1032, 275; Ex. 1096, 534.) CGRP shows significant sequence identity across species: human

α CGRP and β CGRP differ from their rat counterparts by only four and three variations, respectively. (Ex. 1014 ¶16; Ex. 1033, 93-94; Ex. 1096, 534.) Whereas human β CGRP is predominantly expressed in the enteric nervous system and pituitary gland, α CGRP was known to be expressed in sensory neurons, suggesting that α CGRP had an important role in migraine. (Ex. 1014 ¶21; Ex. 1031, 317.)

CGRP has powerful vasodilatory effects that, by 2005, had been directly linked to various human diseases, including migraine. (Ex. 1014 ¶¶26-38, 112; Ex. 1026, 7:5-12, 7:19-24, 10:25-30; Ex. 1027, [0002]-[0003]; Ex. 1025, 1105; Ex. 1040, 182-83; Ex. 1096, 533, 567-570.)

Researchers had also investigated the biological functions of CGRP by using monoclonal antibodies that bound to CGRP and prevented it from binding to its receptors. (Ex. 1014 ¶¶50-61.) This is known as “immunoblockade.” (Ex. 1022, 566; Ex. 1014 ¶50.) By 2005, immunoblockade with monoclonal anti-CGRP antibodies was shown to inhibit the effects of CGRP *in vivo* and was recognized as an alternative to blocking CGRP with receptor antagonists because of its “inherent advantages of defined specificity, known affinity, reproducibility, and unlimited availability.” (Ex. 1014 ¶¶50, 61; Ex. 1022, 572.)

B. Migraine and CGRP

Migraine is a chronic, and often debilitating disease. (Ex. 1014 ¶24; Ex. 1040, 176.) During migraine attacks, changes in nerve activity in the trigeminal region of the head, which lies outside the blood brain barrier (“BBB”), lead to a painful, reflexive vasodilatation of cranial blood vessels. (Ex. 1031, 322; Ex. 1089, 258.)

Well before Teva filed its provisional application, CGRP had been identified as a key substance involved in provoking migraine. Upon stimulation, the trigeminal nerve releases CGRP in an antidromic manner (i.e., in the opposite direction of the normal nerve fiber conduction). (Ex. 1014 ¶27; Ex. 1035, 290.) This results in pain and further nerve activation. (Ex. 1014 ¶¶25, 27; Ex. 1035, 290.)

By the early 2000s, it was understood that: (1) levels of CGRP—but not other neuropeptides—are significantly elevated in migraine patients compared to those without migraine; (2) plasma CGRP concentrations and migraine headache strongly correlate; (3) baseline CGRP levels are considerably higher during migraine; and (4) the changes in plasma CGRP levels during migraine attacks significantly correlate with headache intensity. (Ex. 1043, 185; Ex. 1044, 48; Ex. 1045, 467; Ex. 1040, 182-83; Ex. 1014 ¶¶28, 35.) Further, administering CGRP to migraine patients induced not only an immediate headache, but also a delayed headache bearing most of the characteristics of migraine. (Ex. 1047, 56, 59; Ex. 1014 ¶¶29, 35.)

These clinical findings and observations led to the consensus that CGRP played a causative role in migraine, making it an attractive target for treatment of migraine. (*See* Ex. 1031, 316; Ex. 1040, 182; Ex. 1041, 1073; Ex. 1014 ¶¶26, 38.) Indeed, as discussed in § IV.E.1 below, the prior art had even shown that migraine could be treated—in human patients—by blocking the CGRP pathway.

C. Anti-CGRP Antagonist Antibodies Were Well Known in the Art and Had Been Disclosed for Therapeutic Use in Humans

By 2005, several publications had described anti-CGRP antagonist antibodies and methods of making them. (Ex. 1021; Ex. 1022; Ex. 1032; Ex. 1033; Ex. 1055.) These well-established prior art methods generally involved immunizing mice with α CGRP, collecting serum, screening for antibodies that exhibit anti-CGRP activity, culturing hybridoma cells, and producing the monoclonal antibodies in bulk. (*See, e.g.*, Ex. 1033, 95-96; Ex. 1021, 704; Ex. 1015 ¶¶27-29.) Anti-CGRP antagonist antibodies had been prepared against both human and rat α CGRP. (Ex. 1021, 704; Ex. 1033, 95-96, 102; Ex. 1055, 88.)

The prior art specifically identified anti-CGRP antagonist antibodies, including humanized antibodies, to treat human diseases such as migraine. (*See infra* §§ VII.A.1-2.)

D. Humanization of Antibodies

Before Teva filed its provisional application, researchers understood that administering non-human antibodies to human patients resulted in immunogenicity that could eliminate the therapeutic effects of an antibody drug, or worse, cause harmful effects in patients. (Ex. 1015 ¶¶30-33; Ex. 1023, 1:44-57.) Consequently, researchers developed therapeutic antibodies that were more “human.” (Ex. 1015 ¶¶34-36; *see also id.* ¶¶37-53.)

One prominent method was to humanize antibodies by grafting CDRs from a non-human antibody into a human IgG antibody scaffold. (Ex. 1015 ¶39.) This technique was first introduced nearly twenty years before Teva’s earliest filing date, and was thereafter refined by the work of Queen and others. (*Id.* ¶40; Ex. 1101, 522; Ex. 1075, 10029; Ex. 1023, 2:61-3:32.) By 2005, antibody humanization was considered a “clinically well-validated technology.” (Ex. 1015 ¶41; Ex. 1073, 120; Ex. 1056, 1077.) Moreover, the FDA had approved many humanized antibodies, and most monoclonal antibodies in phase 2 and phase 3 trials were humanized. (Ex. 1056, 1077; Ex. 1073, 120.) IgG antibodies were the preferred scaffold for humanized antibodies. (Ex. 1015 ¶¶21, 98.)

E. The Asserted Prior Art

1. Olesen

Olesen, a 2004 publication in *The New England Journal of Medicine*, reported that blocking the CGRP pathway in human patients effectively treated migraine. (Ex. 1014 ¶¶67-68.)

Olesen confirms that by 2004, researchers understood that CGRP played an important role in initiating and mediating migraine attacks, making the CGRP pathway a prime target for treating migraine in the clinic. (Ex. 1025, 1105.) Olesen attributes these extensive pre-clinical findings as the basis for its clinical study in human patients to evaluate the efficacy of BIBN4096BS, a known CGRP-receptor antagonist, that had been shown to “potently block[] the effect of CGRP.” (*Id.*)

Patients in the Olesen study experiencing acute migraine attacks received an intravenous infusion of either BIBN4096BS or placebo. (Ex. 1025, 1106; Ex. 1014 ¶32.) The primary study endpoint was a reduction of severe or moderate headache at baseline to mild or no headache at two hours after dosing. (Ex. 1025, 1106; Ex. 1014 ¶32.) Secondary endpoints included the rates of response at different time points after administration; the rates of sustained response over a 24-hour period; the relief of other migraine-associated symptoms; side effects; and clinical laboratory values. (Ex. 1025, 1106-07; Ex. 1014 ¶32.)

Two hours after treatment with BIBN4096BS, 66% of patients exhibited a positive response compared to only 27% of patients on placebo. (Ex. 1025, 1107-08; Ex. 1014 ¶33.) BIBN4096BS was also superior to placebo for the tested secondary endpoints. For example, the rate of migraine recurrence was only 20% of patients for the BIBN4096BS groups, whereas the rate was 46% for those receiving placebo. (Ex. 1025, 1108; Ex. 1014 ¶33.) Based on these results, Olesen concluded that BIBN4096BS was effective in treating migraine attacks up to six hours after onset. (Ex. 1025, 1108.) Although BIBN4096BS was a CGRP-receptor antagonist, Olesen announced that “proof-of-concept was thus established” for treatment more generally—blocking the CGRP pathway with a CGRP *antagonist*. (*Id.*, 1108-09; Ex. 1014 ¶34.)

In a symposium held shortly after the publication of Olesen, the authors further emphasized the general applicability of the study, concluding that their study “establishes a totally novel principle in the acute treatment of migraine: CGRP antagonism.” (Ex. 1029, 119; *see also* Ex. 1030, 129 (“[T]hese data demonstrate the validity of the CGRP concept paving a novel way in migraine pain treatment.”); Ex. 1014 ¶69.) Olesen conclusively demonstrated that migraine was treated in the clinic by blocking the CGRP pathway, thereby validating CGRP as a viable clinical target for migraine. (Ex. 1014 ¶69.)

2. Tan

Tan reports on the *in vivo* activity of anti-CGRP antibodies, including the murine monoclonal antibody MAb C4.19 and its Fab' fragment, in a 1995 publication. (Ex. 1022, 566; Ex. 1014 ¶¶70-71.) A Fab' fragment consists primarily of a portion of the antibody's variable domain. (Ex. 1015 ¶16; Ex. 1063, 60-61.)

Tan conducted two types of experiments with the MAb C4.19 full-length antibody and its Fab' fragment. Tan first analyzed whether these antibodies could inhibit the *in vivo* hypotensive effect of exogenously administered α CGRP. (Ex. 1022, 566-67; Ex. 1014 ¶55.) Both antibodies successfully did so. (Ex. 1022, 568-69; Ex. 1014 ¶55.)

Tan next analyzed these antibodies using the well-known rat saphenous nerve model that evaluates CGRP-induced skin blood flow—the same assay Teva relied on in its provisional application and the '045 patent to support its claims. (Ex. 1052, 772-73; Ex. 1022, 567; Ex. 1019, Examples 3 and 5; Ex. 1001, 31:64-67, Examples 3 and 5; Ex. 1014 ¶¶56, 86-87.) The Fab' fragment effectively blocked increased skin blood flow, i.e., vasodilation, after stimulation of the saphenous nerve. (Ex. 1022, 569; Ex. 1014 ¶58.) Under similar conditions, the full-length antibody did not appear to block increased skin blood flow. (Ex. 1022, 569; Ex. 1014 ¶58.) But with a longer period between treatment and nerve stimulation and a higher dose,

a 16% block in increased blood flow was observed. (Ex. 1022, 569; Ex. 1014 ¶58; *see also infra* § VII.C.) In view of these results, Tan recommended increasing the dose and/or allowing for a longer duration of time to allow full-length antibodies to reach the site of action. (Ex. 1022, 571; Ex. 1014 ¶59.) Tan recognized that “[w]ith repeated administration, IgG [i.e., full-length antibody] should . . . achieve the sufficiently high concentrations required for immunoblockade.” (Ex. 1022, 571; Ex. 1014 ¶59.) In contrast, Tan recommended the Fab’ fragment for acute immunoblockade of the CGRP pathway. (Ex. 1022, 572; Ex. 1014 ¶59.)

Tan further reinforced the advantages of using anti-CGRP antagonistic antibodies to target CGRP directly: “[t]he present investigations have been performed with an MAb with inherent advantages of defined specificity, known affinity, reproducibility and unlimited availability.” (Ex. 1022, 572; Ex. 1014 ¶61.)

3. Queen

Queen issued on January 30, 2001. (Ex. 1014 ¶72.) 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.” (Ex. 1023, Abstract, 1:22-23; Ex. 1014 ¶73; Ex. 1015 ¶47.) Queen states that its technologies are useful for “treating substantially any disease

susceptible to monoclonal antibody-based therapy.” (Ex. 1023, 19:6-8, 1:19-21; Ex. 1014 ¶73; Ex. 1015 ¶47.)

Queen describes methods to humanize a non-human antibody by incorporating the CDRs from the non-human donor antibody, e.g., a murine antibody, into a homologous human immunoglobulin sequence, such as an IgG antibody. (Ex. 1023, 2:61-3:32, 11:4-20; Ex. 1014 ¶75; Ex. 1015 ¶¶48-51.) In addition, to maintain efficacy, Queen describes making additional optional substitutions into the human framework regions from corresponding positions on the non-human donor antibody. (Ex. 1023, 2:66-3:7, 3:33-41.) The humanized antibodies of Queen have binding affinities (K_A) of at least about $10^8 M^{-1}$, preferably $10^9 M^{-1}$ to $10^{10} M^{-1}$, or stronger. (*Id.*, 10:60-63; Ex. 1014 ¶75.) This translates into dissociation values (K_D) on the order of 10 nM to 0.1 nM, or less. (Ex. 1014 ¶75; Ex. 1015 ¶52, 59.)

Queen’s technology is specifically designed to reduce or eliminate the immunogenic effect of non-human sequences while retaining the original binding affinity of the donor non-human antibody. (Ex. 1015 ¶52; Ex. 1023, 3:33-41.)

V. Person of Ordinary Skill in the Art

For the purposes of this proceeding, a POSA with respect to the aspects of the ’045 patent pertaining to using anti-CGRP antibodies would have generally

possessed a Ph.D. in a relevant field (e.g., neurobiology, neurology, pharmacology) or an M.D. with a residency in a relevant field (e.g., neurology), with several years of experience studying CGRP or treating patients with migraine. (Ex. 1014 ¶¶76-78.) A POSA with respect to the aspects of the '045 patent pertaining to designing and optimizing anti-CGRP antibodies would have generally possessed a Ph.D. in immunology, molecular biology, or pharmacology with several years of post-doctoral research experience focused on antibody engineering and/or antibody pharmacology. (Ex. 1015 ¶¶77-79.)

VI. Claim Construction

A claim in an unexpired patent subject to *inter partes* review “shall be given its broadest reasonable construction in light of the specification of the patent in which it appears.” 37 C.F.R. § 42.100(b). The Office is currently considering changing its rules to adopt the same standard “that would be used to construe [a] claim in a civil action” under *Phillips* and applying this standard to all pending IPR proceedings. Notice of Proposed Rulemaking at 13-14, 22 (May 3, 2018).

Solely for purposes of this proceeding, Lilly provides the following constructions under either the BRI or *Phillips* standards.

A. “reducing incidence of or treating”

Under a proper construction, the phrase “reducing incidence of or treating” at least one vasomotor symptom (claim 1) or headache (claim 17) must be at least as broad as the express definitions in the specification. *In re Am. Acad. of Sci. Tech Ctr.*, 367 F.3d 1359, 1364 (Fed. Cir. 2004); *Phillips v. AWH Corp.*, 415 F.3d 1303, 1321 (Fed. Cir. 2005) (en banc) (“Usually, [the specification] is dispositive; it is the single best guide to the meaning of a disputed term.”). The express definitions do not require a clinical response.

The '045 patent expressly defines “treatment” as “an *approach* for obtaining a beneficial or desired clinical result”—it does not require *achieving* any particular result. (Ex. 1001, 17:37-38); *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996) (a patentee acts as her lexicographer when defining terms in the specification). Thus, “treating” merely refers to an *approach* for a particular outcome without requiring a clinical response. (Ex. 1014 ¶102.) Courts, including the PTAB, have similarly construed “treating” or “treatment” as not requiring a clinical response. *See, e.g., Novartis Pharm. Corp. v. Actavis, Inc.*, No. 12-cv-366, 2013 WL 6142747, at *11 (D. Del. Nov. 21, 2013) (construing “treating” as merely an “*attempt* to cause a therapeutic improvement,” relying on “the term’s use in the patent”); *Coherus Biosciences Inc. v. AbbVie Biotechnology Ltd.*, IPR2016-00172,

Paper 9 at 9 (PTAB May 17, 2016) (concluding that “treat” or “treating” refer to the management and care of a patient, and “do[] not require a particular level of efficacy”).

Similarly, the '045 patent expressly defines “reducing incidence of” to encompass merely “*administering* the anti-CGRP antagonist antibody based on a reasonable expectation that such administration *may likely* cause such a reduction in incidence”—it does not require achieving any particular “reduction.” (Ex. 1001, 17:61-65.) Here again, Teva’s language in the specification describes an approach, rather than requiring any clinical effect. (Ex. 1014 ¶103); *Vitronics*, 90 F.3d at 1582. Notably, the '045 patent does not contain any examples demonstrating any clinical response in human patients.

Thus, the phrase “reducing incidence of or treating” does not require a clinical response.

B. “effective amount”

The term “effective amount” recited in independent claims 1 and 17 should be construed as (1) including, at least via the doctrine of claim differentiation, doses of an anti-CGRP antagonist antibody that are less than 3 µg/kg, and (2) not requiring a clinical response. (Ex. 1014 ¶104).

Independent claims 1 and 17 recite “an effective amount.” Claims 16 and 31, which depend from claims 1 and 17, respectively, recite a dose of “at least about 3 $\mu\text{g}/\text{kg}$.” Under this claim structure, “effective amount” must encompass a broader dose range than “at least 3 $\mu\text{g}/\text{kg}$.” *Alcon Research Ltd. v. Apotex Inc.*, 687 F.3d 1362, 1367-68 (Fed. Cir. 2012). In the directly analogous *Alcon* decision, the independent claims recited a “therapeutically effective amount” without specifying a numerical value for that term, while the dependent claims limited the dose to specific numeric ranges. The Federal Circuit concluded that, under well-established canons of claim construction, the particularly recited dose ranges *had to be* a “therapeutically effective amount,” and as a corollary the generic term “therapeutically effective amount” had to be broader than those specifically recited ranges. *Id.* Consequently, claims 1 and 17 *must* encompass doses *lower* than 3 $\mu\text{g}/\text{kg}$.

“Effective amount” should not be construed to require a clinical response. *See, e.g., Novartis*, 2013 WL 6142747, at *10 (“[W]hile the claims require administering a dose of the claimed compound that is a ‘therapeutically effective amount[,]’ such a requirement does not qualify the method of ‘treating’ or otherwise requiring that ‘treating’ cause a specific *outcome*.”) (emphasis in original). Indeed, the patent states that the term “effective amount” encompasses amounts that produce

merely biochemical or histochemical effects, such as stimulation of cAMP. (Ex. 1001, 18:38-19:3 (“an effective amount” includes decreasing one or more “biochemical, histological and/or behavioral” symptoms), 31:57-64 (identifying stimulation of cAMP as a “targeted biological activit[y]”); Ex. 1014 ¶104.)

Furthermore, as Dr. Charles explains, a POSA would have understood that the specifically claimed antibody doses of about 3 µg/kg would be too low to generate a clinical response because such doses were orders of magnitude lower than typical antibody doses. (Ex. 1014 ¶105; Ex. 1252, 26 (recommending a 1,000-fold greater antibody dose of 3 mg/kg); Ex. 1022, 567 (administering doses approximately 1,000-fold greater than 3 µg/kg).)

C. “anti-CGRP antagonist antibody” and “humanized monoclonal antibody”

Under a proper construction, “anti-CGRP antagonist antibody” and “humanized monoclonal antibody” must at least encompass Teva’s express definitions of these terms in the ’045 patent. The 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).” (Ex. 1001, 12:18-20, 26:9-22; Ex. 1014 ¶106; Ex. 1015 ¶81.) The 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)" (Ex. 1001, 12:61-65; Ex. 1014 ¶106; Ex. 1015 ¶82.) Further, the patent states that "[f]or the purpose of the present invention, it will be explicitly understood that the term 'anti-CGRP antagonist antibody' encompasses all the previously identified terms, titles, and functional states and characteristics" (Ex. 1001, 14:4-12; Ex. 1014 ¶106; Ex. 1015 ¶81.) Antibody fragments therefore fall within the scope of these terms. (Ex. 1014 ¶106; Ex. 1015 ¶80.)

VII. Claim 17 Is Obvious over Olesen, Tan, and Queen

Each and every element of claim 17 is disclosed or suggested by the prior art. (*Supra* §§ III.B, IV; *infra* §§ VII.A-C.) Olesen's clinical study demonstrated that blocking the CGRP pathway effectively treats migraine in human patients. (Ex. 1025, 1108-09; Ex. 1014 ¶68.) Anti-CGRP antagonist antibodies had already been proven to block the CGRP pathway and were proposed to treat migraine, and thus were an obvious choice after Olesen's study due to their specificity, affinity, and demonstrated *in vivo* activity. (Ex. 1096, 567-70; Ex. 1022, 572; Ex. 1014 ¶71.) Tan had described murine anti-CGRP antagonist antibodies, including a full-length antibody, that blocked the effects of CGRP *in vivo*. (Ex. 1022, 567-71; Ex. 1014 ¶71.) Queen disclosed humanized antibodies and methods of making them, and

explained that humanized antibodies minimize potential immunogenic responses, rendering them suitable for administration to humans. (*See generally* Ex. 1023.)

Thus, all of the elements of claim 17 are disclosed or suggested in the prior art. Indeed, Teva has admitted that (1) elevated CGRP levels were linked to migraine; (2) Tan describes anti-CGRP antagonist antibodies; (3) anti-CGRP antagonist antibodies may be generated by known, standard techniques; and (4) humanization techniques were well known and conventional. (Ex. 1001, 2:3-31, 25:59-63, 27:41-47, 28:55-29:28, 35:46-47; *see also id.*, cols. 28-30; *supra* §§ III.B.1-2.)

As explained below, the prior art provides motivation to combine the asserted prior art to arrive at Teva's claimed method and a reasonable expectation of success.

A. A POSA Would Have Been Motivated to Treat Migraine With a Humanized Monoclonal Anti-CGRP Antagonist Antibody

1. The Prior Art Would Have Motivated a POSA to Use a CGRP Antagonist to Treat Migraine

Olesen's published clinical trial validated the CGRP pathway as a therapeutic target for treating migraine, and established that blocking the CGRP pathway reduced the incidence of migraine. (Ex. 1025, 1104, 1108-09; Ex. 1014 ¶¶31-36, 68-69, 109.) Its successful results provided a concrete impetus to pursue CGRP

antagonism—specifically with anti-CGRP antagonist antibodies—to reduce incidence of or treat migraine. (Ex. 1025, 1104, 1108-09; Ex. 1014 ¶¶109, 112-113.)

Olesen expressly extends its results beyond the small molecule CGRP-receptor inhibitor it tested to CGRP antagonists generally. (Ex. 1014 ¶109.) For example, Olesen identifies CGRP *antagonists*, without limitation, as agents to treat migraine. (Ex. 1025, 1105 (“We therefore hypothesized that *CGRP antagonists* might be effective in the treatment of acute migraine.”), 1109 (reporting proof-of-concept for CGRP antagonism); Ex. 1014 ¶109.) The Olesen investigators also broadly reported that “CGRP antagonism [w]as a new therapeutic principle” for treating migraine. (Ex. 1029, 119 (S26); *see also* Ex. 1024, 422 (“[W]e expect that *CGRP antagonists* will be effective anti-migraine drugs.”); Ex. 1014 ¶109.) Consequently, a POSA reading Olesen would have extended its teachings to other CGRP antagonists. (Ex. 1014 ¶¶107-113.)

Other prior art supports Olesen’s broad teachings regarding anti-CGRP antagonists and demonstrates that CGRP itself—and not only its receptors—was also a therapeutic target at the time. Tan, which demonstrated the effectiveness of anti-CGRP antibodies in the rat saphenous nerve model (the same model used by Teva to support claims to migraine), referred to immunoblockade with anti-CGRP antagonist antibodies as “an alternative” strategy to blocking CGRP with CGRP

receptor antagonists (i.e., CGRP₈₋₃₇ or BIBN4096BS). (Ex. 1022, 566, 571; Ex. 1019, Examples 3 and 5; *infra* § VII.C.) Another reference states that antagonism of CGRP can be achieved “either at the receptor level using specific CGRP antagonists, or by neutralizing endogenous [CGRP] peptide with a specific antibody.” (Ex. 1033, 95.) A 2005 review article reported that “inhibition of CGRP *or* antagonism of CGRP receptors could be a viable therapeutic target for the pharmacological treatment of migraine.” (Ex. 1040, 182.) The '045 patent itself reflects this prior art understanding, stating that CGRP “has a causative role in migraine.” (Ex. 1001, 2:3-31.)

Multiple prior art publications focused on inhibiting CGRP rather than the receptor. For example, researchers investigating methods for treating migraine studied compounds called aptamers that bound to CGRP and interrupted receptor binding. (Ex. 1082, 1; Ex. 1240, 923; Ex. 1014 ¶¶62.) Several prior art patent publications also specifically referenced anti-CGRP antagonist antibodies for treating migraine and neurogenic pain. (Ex. 1026, 7:5-24, 10:25-30; Ex. 1027, [0002]-[0003], [0039], claim 8; Ex. 1028, Abstract, 1:16-21, 2:7-10, 2:66-67, 3:21-22, Example 2, granted claim 2; Ex. 1014 ¶¶115-117.) For example, Wimalawansa identified *humanized* anti-CGRP antagonist antibodies for treating migraine, among

other human diseases. (Ex. 1096, 567, 570 (“The role of CGRP antagonists and humanized monoclonal antibodies *should be explored*. . .”).)

Furthermore, a POSA in 2005 would have known that targeting the ligand—CGRP—as opposed to one of its receptors, had several therapeutic advantages. (Ex. 1014 ¶¶128-130.) First, a POSA would have known that small molecule receptor antagonists are often not sufficiently specific for a given receptor target, which leads to off-target effects from non-specific binding. (*Id.* ¶128; *see also* Ex. 1022, 572 (monoclonal antibodies have the “inherent advantage[] of defined specificity”).) Second, by 2005, the art recognized that at least two CGRP receptors may exist but had not yet identified which one was implicated in migraine. (*See* Ex. 1099, 235-37.) Thus, a POSA would have been motivated to target CGRP to fully block the pathway by preventing CGRP from binding to its receptors. Third, blocking receptors has consequences beyond simply blocking the targeted biological process. For example, the body may respond by upregulating receptor concentrations (i.e., producing more receptors). (Ex. 1014 ¶130.) This can result in tolerance to the administered drug. (*Id.*)

Thus, the prior art explicitly identified CGRP *itself* as a therapeutic target for treating various conditions including migraine, and Olesen confirmed that blocking the CGRP pathway would work in the clinic. (Ex. 1014 ¶113.) Thus, a POSA would

have been motivated to target CGRP for treating and reducing incidence of migraine.

(*Id.*)

2. A POSA Would Have Been Motivated to Use an Anti-CGRP Antagonist Antibody to Treat Migraine

A POSA would have been motivated to use anti-CGRP antagonist *antibodies* to reduce incidence of or treat migraine. The prior art had already identified anti-CGRP antagonist antibodies as suitable options for treating migraine. (Ex. 1096, 567, 569-70; *supra* § VII.A.1.)

Sveinsson, for example, discloses using anti-CGRP antagonist antibodies to treat migraine in human patients. (Ex. 1026, 7:5-12, 7:19-24, 10:25-30; Ex. 1014 ¶115.) Sveinsson also acknowledges that antibodies against CGRP have been described in the art. (Ex. 1026, 7:19-24; Ex. 1014 ¶115.)

Wimalawansa specifically identified humanized anti-CGRP antagonist antibodies for use in treating several diseases, including neurogenic inflammation and migraine. (Ex. 1096, 567-68, 570 (“The role of CGRP antagonists and humanized monoclonal antibodies *should be explored. . .*”); Ex. 1014 ¶116.) While, as of 1996, Wimalawansa appreciated the need for further studies before initiating human clinical trials, that work had occurred by 2005. (*See supra* § VII.A.1; *see also* Ex. 1047, 59 (“The outcome of the present study is very clear. CGRP caused headache in virtually all migraine sufferers . . .”), 60 (“This finding

greatly increases the likelihood that a CGRP antagonist may be effective in the treatment of migraine attacks.”); Ex. 1014 ¶116.) Indeed, by 2005, “CGRP antagonism” had been confirmed as a “therapeutic principle” for the treatment of migraine. (Ex. 1029, 119; Ex. 1030, 129; Ex. 1014 ¶116.)

Salmon, as another example, disclosed that α CGRP is involved in modulating neurogenic inflammatory pain, a trigger for migraine. (Ex. 1027, [0002]-[0003]; Ex. 1031, 325; Ex. 1014 ¶117.) Salmon discloses methods for ameliorating pain caused by neurogenic inflammation by inhibiting the CGRP-pathway. (Ex. 1027, [0012].) It identifies anti- α CGRP antagonist antibodies for use in such methods. (*Id.*, [0039]; *see also id.*, claim 8; Ex. 1014 ¶117.)

Multiple murine anti-CGRP antagonist monoclonal antibodies had already been developed and characterized, and were also available commercially. (Ex. 1021, 706-08; Ex. 1022, 568-70; Ex. 1033, 98-102; Ex. 1051, 350; Ex. 1055, 90-93; Ex. 1015 ¶¶88-91; Ex. 1014 ¶118.) These antibodies had been shown to bind to and block the biological activity of CGRP in both *in vitro* and *in vivo* assays. (Ex. 1021, 706-08; Ex. 1022, 568-70; Ex. 1033, 98-102; Ex. 1055, 90-93; Ex. 1015 ¶¶88-91; Ex. 1014 ¶118.) For example, Tan demonstrated that anti-CGRP antagonist antibodies inhibited CGRP activity *in vivo* in the rat saphenous nerve model—the same model used in Teva’s priority application and the ’045 patent to support claims

to migraine. (Ex. 1022, 569-70; Ex. 1001, Examples 3 and 5; Ex. 1014 ¶86; *infra* § VII.C.)

There were also several known advantages of antibodies compared to small molecule drugs like Olesen's BIBN4096BS compound. Because migraine is a chronic condition in many patients, a POSA would have been motivated to use a longer acting drug, particularly for reducing incidence of migraine and treating chronic migraine. (Ex. 1014 ¶125.) BIBN4096BS has a relatively short half-life of approximately 2.5 *hours*, and thus is cleared from the system rapidly. (Ex. 1042, 652; Ex. 1014 ¶124.) In contrast, humanized monoclonal antibodies remain in the body for *weeks* or even months following a single administration. (Ex. 1014 ¶126; Ex. 1070, 18.) By 2005, numerous humanized antibodies with long half-lives had been approved by the FDA for treating chronic diseases. (Ex. 1253, 938, 2955, 1338, 1359, 1966.)

The prior art expressly recognized the downside of treating migraine patients with CGRP inhibitors having a short half-life. For example, researchers reported that CGRP₈₋₃₇, a peptide fragment of CGRP, "proved ineffective in migraine treatment" due to "its low potency and *short half-life*." (Ex. 1031, 323; Ex. 1014 ¶124.) Consequently, a POSA would have embraced the use of an anti-CGRP

antagonist antibody, which would have been expected to have a high affinity and relatively long half-life.

A POSA also would have chosen antibodies to avoid the known side effects of existing small-molecule migraine drugs. (Ex. 1014 ¶127.) Monoclonal antibodies generally exhibited fewer off-target side effects and lower toxicity than small molecule drugs. (Ex. 1057, 1348; Ex. 1015 ¶55.) This was important because liver toxicity was often a significant concern for existing migraine treatments. (Ex. 1014 ¶127; Ex. 1250, 4, 22.) In contrast, antibodies were known to be processed in various other organs, reducing the risk of liver toxicity. (Ex. 1014 ¶127; Ex. 1247, 3969.)

Antibodies also would have been particularly appealing because they were viewed as “perfect tools” for disrupting ligand-receptor interactions, such as inhibiting CGRP from binding with its receptors. (Ex. 1057, 1348-49; Ex. 1015 ¶55.) Multiple FDA-approved antibodies had already demonstrated their ability to interact with and bind to their target antigens with exquisite specificity, as had already been shown for the anti-CGRP antagonist antibodies of the prior art. (Ex. 1014 ¶¶128-129; Ex. 1056, 1075; Ex. 1022, 572; Ex. 1033, 102.) Moreover, it was known that anti-migraine drugs did not need to cross the BBB to effectively treat migraine. For example, Olesen’s BIBN4096BS compound did not cross the BBB. (Ex. 1090, 702-703.) Similarly, other migraine drugs were

known to be effective despite poor penetration of the BBB. (Ex. 1241, Abstract, 454-55; Ex. 1242, Abstract; Ex. 1243, 591-92; Ex. 1244, 286; Ex. 1014 ¶151.) Accordingly, a POSA would have been motivated to reduce incidence of and treat migraine with anti-CGRP antagonist antibodies with their benefits of longer half-lives, lower toxicity, and enhanced specificity and affinity. (Ex. 1014 ¶¶123-132; Ex. 1015 ¶¶87-92, 54-57.)

3. A POSA Would Have Been Motivated to Use a *Humanized Monoclonal Anti-CGRP Antagonist Antibody for Treating Migraine*

A POSA intending to use an anti-CGRP antagonist antibody to reduce incidence of or treat migraine in human patients would have been motivated to use a humanized IgG antibody. By 2005, humanized antibodies, specifically those of the IgG class, were a “clinically well-validated technology.” (Ex. 1073, 120; *see* Ex. 1014 ¶¶119-122; Ex. 1015 ¶¶93, 98; *see also id.* ¶¶41-44.) By then, half of the eighteen FDA-approved antibodies were humanized IgG antibodies, and most antibodies in phase 2 and 3 clinical trials were humanized. (Ex. 1056, 1075, 1077; Ex. 1015 ¶¶21, 93.)

In addition to the many benefits of antibody therapeutics (e.g., longer half-lives, greater stability, and flexible utility), the prior art had embraced *humanized* antibodies for treating human patients to reduce immunogenicity. (Ex. 1023, 1:44-

47; *see also* Ex. 1056, 1074, 1075 (Table 1); Ex. 1015 ¶¶93-96; Ex. 1014 ¶120.) As Queen explains, such immunogenic responses “can be quite strong, essentially eliminating the antibody’s therapeutic utility after initial treatment.” (Ex. 1023, 1:44-50; Ex. 1014 ¶121.) Immunogenic responses could also cause serum sickness and other harmful effects, especially after repeated administration. (Ex. 1023, 1:51-57; Ex. 1015 ¶¶30-33, 94; Ex. 1014 ¶121.) Thus, by 2005, humanized IgG antibodies were preferred for clinical use. (Ex. 1015 ¶¶21, 93-100.)

A POSA would have been specifically motivated to humanize an anti-CGRP antagonist antibody because migraine is a chronic condition requiring repeated administration of the therapeutic agent. (Ex. 1014 ¶¶121-122.) Because repeat administration is associated with unwanted immunogenic responses, a POSA would have been motivated to make a humanized anti-CGRP antagonist antibody to minimize the risk of immunogenicity. (*Id.*; Ex. 1015 ¶¶93-94; Ex. 1023, 1:44-57; 1:19-21 (disclosing humanized antibodies as therapeutic agents for “treating substantially any disease susceptible to monoclonal antibody-based therapy”).) A POSA would have been motivated to make a full-length antibody because full-length antibodies have longer half-lives and greater stability than antibody fragments. (Ex. 1056, 1074, 1075 (Table 1); Ex. 1070, 18.) Indeed, the vast majority of antibodies

approved by the FDA and being tested in 2005 were full-length antibodies. (Ex. 1056, 1075.)

Consequently, a POSA—with her ordinary creativity—would have been motivated to combine and follow the disclosures of Olesen, Tan, and Queen to obtain a humanized anti-CGRP antagonist antibody for reducing incidence of or treating migraine in a human patient. (Ex. 1014 ¶137.); *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 419 (2007) (“If the claim extends to what is obvious, it is invalid under § 103.”).

B. The Prior Art Provided a Reasonable Expectation of Success

Claim 17 is broadly directed to an “approach” for reducing incidence of or treating headaches, including migraine, without requiring a clinical response. (*Supra* §§ VI.A-B; Ex. 1014 ¶¶101-103.) The term “effective amount” recited in claim 17 similarly does not require any clinical response, and it encompasses exceedingly low doses. (*Supra* § VI.B; Ex. 1014 ¶¶104-105.) The burden of establishing a reasonable expectation of success is therefore low, and is met for all of the reasons explained below. *Allergan, Inc. v. Sandoz Inc.*, 726 F.3d 1286, 1292 (Fed. Cir. 2013) (a POSA need only have a reasonable expectation of success of developing the claimed invention, not an embodiment exhibiting additional, unrequired features); *Allergan, Inc. v. Apotex Inc.*, 754 F.3d 952, 962-63 (Fed. Cir.

2014) (the challenger did not have an “exacting burden” of proving a reasonable expectation given the breadth of the claims).

Even if the Board construes claim 17 to require a clinical response (notwithstanding the express definitions in the specification), a POSA would have reasonably expected a humanized anti-CGRP antagonist antibody to reduce incidence of or treat migraine in humans. Indeed, the prior art had established that anti-CGRP antagonist antibodies block the CGRP pathway, and that blocking the CGRP pathway treated migraine in humans. (Ex. 1025, 1108-09; Ex. 1022, 569, 571; Ex. 1033, 102.) The prior art also broadly recognized that CGRP antagonism was a therapeutic principle for migraine treatment. (*See, e.g.*, Ex. 1024, 422 (“we expect that CGRP antagonists *will be effective* anti-migraine drugs”); Ex. 1047, 60 (“This finding greatly increases the likelihood that a CGRP antagonist may be effective in the treatment of migraine attacks.”).) Thus, a POSA would have reasonably expected that a humanized monoclonal anti-CGRP antagonist antibody would successfully reduce the incidence of or treat migraine in humans.

1. A POSA Would Have Reasonably Expected that a Humanized Anti-CGRP Antagonist Antibody Would Successfully Reduce Incidence of or Treat Migraine

a) Blocking the CGRP Pathway Had Been Clinically Proven to Treat Migraine

Before 2005, researchers understood that anti-CGRP drugs would treat migraine based on the strong evidence that CGRP plays a causative role in migraine. (Ex. 1014 ¶139.) In the early 2000s, researchers recognized that CGRP had been implicated in the pathogenesis of migraine headache and thus “inhibition of the CGRP-induced vasodilation could be expected to attenuate migraine symptoms.” (Ex. 1024, 420, 422; Ex. 1022, 569-70; Ex. 1052, 773-74.) Based on “several lines of evidence indicat[ing] that CGRP might be a key factor in the initiation of migraine headache,” researchers reported that “*we expect that CGRP antagonists will be effective anti-migraine drugs.*” (Ex. 1024, 422.) Likewise, after demonstrating that CGRP causes migraine, researchers in 2002 emphasized that “[t]his finding greatly increases the likelihood that a CGRP antagonist may be effective in the treatment of migraine attacks.” (Ex. 1047, 60; Ex. 1014 ¶139.)

In 2004, Olesen’s double-blind, placebo-controlled Phase II study provided clinical proof-of-concept that blocking the CGRP pathway treats migraine, further validating the reasonable expectation of success in the art. (Ex. 1025, 1108-09; Ex. 1014 ¶140; *supra* §§ IV.E.1, VII.A.1.) Olesen reported that 66% of patients

exhibited a response two hours after treatment with BIBN4096BS compared to only 27% of patients on placebo, and that BIBN4096BS also met all secondary endpoints. (Ex. 1025, 1107-08; *supra* §§ IV.E.1, VII.A.1.) CGRP antagonism was thus broadly recognized as a “therapeutic principle” in migraine treatment. (Ex. 1025, Abstract.) Accordingly, Olesen’s clinical study confirmed the reasonable expectation that a CGRP antagonist could be successfully used to reduce incidence of or treat migraine. (*Id.*, 1108-09; Ex. 1040, 182-83 (characterizing Olesen’s study as an “important breakthrough” and reporting that “inhibition of CGRP *or* antagonism of CGRP receptors” may be “a viable therapeutic target for treating migraine”); Ex. 1014 ¶¶140-141.)

b) Immunoblockade with Anti-CGRP Antagonist Antibodies Had Been Confirmed *In Vivo*, and Was a Known “Alternative” Technique for Blocking the CGRP Pathway

A POSA would have reasonably expected to reduce incidence of or treat migraine with an anti-CGRP antagonist antibody. Tan expressly compared its anti-CGRP antagonist antibody (MAb C4.19) to a CGRP-receptor antagonist and reported that immunoblockade with an anti-CGRP antagonist antibody was “an alternative” strategy to using CGRP-receptor antagonists such as BIBN4096BS. (Ex. 1022, 566, 571 (“Immunoblockade should be regarded as a technique that is complementary to the use of receptor antagonists.”).)

Indeed, Tan successfully demonstrated the effectiveness of its anti-CGRP antagonist antibody at blocking the CGRP pathway *in vivo*. (Ex. 1014 ¶142.) In a first *in vivo* experiment, Tan confirmed that both MAb C4.19 and its Fab' fragment blocked the biological activity of CGRP in a blood pressure assay in rats. (Ex. 1022, 568-69, 571; Ex. 1014 ¶142.) In a second *in vivo* experiment, Tan reported that MAb C4.19 and its Fab' fragment inhibited the biological activity of CGRP in the rat saphenous nerve model—i.e., an animal model of neurogenic inflammation that had been linked to migraine pain, and the same model used in Examples 3 and 5 of the '045 patent. (Ex. 1022, 569-72; Ex. 1014 ¶¶86-87, 144.) Under the conditions tested, Tan's anti-CGRP antagonist Fab' fragment demonstrated similar activity to a known CGRP-receptor antagonist, CGRP₈₋₃₇. (Ex. 1022, 569-70.) These results established that an anti-CGRP antagonistic antibody or a receptor inhibitor produces similar *in vivo* effects. (Ex. 1014 ¶¶60, 146.)

Accordingly, a POSA would have reasonably expected that a humanized anti-CGRP antagonist antibody would successfully reduce incidence of or treat migraine, regardless of whether the Board determines that the claims require a clinical

response.² (*See* Ex. 1025, 1104, 1108 (reporting that a CGRP antagonist confirmed to block the biological effects of CGRP was clinically effective in treating migraine); Ex. 1029, 119 (“CGRP antagonism” is a “therapeutic principle” for treating migraine); Ex. 1014 ¶148.)

2. A POSA Would Have Had a Reasonable Expectation of Success in Making a Humanized Anti-CGRP Antagonist Antibody for Therapeutic Use in Humans

A POSA would have had a reasonable expectation of success of making a humanized anti-CGRP antagonist antibody for reducing or treating migraine in a human.

The first step in making a humanized anti-CGRP antagonist antibody that binds to human α CGRP would have been to make a murine monoclonal anti-CGRP antagonist antibody that binds to human CGRP. (Ex. 1015 ¶41.) Such antibodies, and techniques for making them, are extensively described in the prior art. (Ex. 1021, 704; Ex. 1001, 27:41-47; *supra* § IV.D.) As a result, a POSA would have

² As discussed in § VII.A.2, a POSA also would have known that an anti-migraine drug did not need to cross the BBB to treat migraine. (Ex. 1014 ¶¶149-152; Ex. 1090, 702-03 (“The present study strongly suggests that the clinically effective migraine drug BIBN4096BS (Olesen *et al.* 2004) does not cross the BBB.”).)

reasonably expected to succeed in making a murine anti-CGRP antagonist antibody that bound *human* CGRP like those reported in Tan, Wong, Andrew, and elsewhere. (Ex. 1015 ¶¶103-107; Ex. 1021, 706; Ex. 1055, 88, 90, 93.) The '045 patent acknowledges the routine nature of generating anti-CGRP antagonist antibodies, stating that they “may be made by *any method known in the art.*” (Ex. 1001, 27:41-42; *see also* 27:42-45 (“[t]he route and schedule of immunization of the host animal are generally in keeping with *established and conventional techniques* for antibody stimulation and production . . .”).)

A POSA also would have had a reasonable expectation of success in humanizing that antibody. By 2005, conventional humanization techniques were routinely used that preserved the specificity and binding affinity of the donor antibody. (Ex. 1023, 2:28-34; Ex. 1014 ¶154; Ex. 1015 ¶108.) Queen, for example, discloses humanization techniques that were known as the “gold standard” for producing humanized antibodies. (Ex. 1014 ¶154; Ex. 1015 ¶¶47, 109; *see generally* Ex. 1023.) Following Queen’s teachings, a POSA 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. (Ex. 1015 ¶109; Ex. 1023, Abstract, 2:28-34.)

The '045 patent admits that technology for making humanized antibodies with desired specificity and binding affinity was “known” and “conventional.” (Ex. 1001, 27:41-47, cols. 28-30; 37:39-43 (confirming that anti-CGRP antagonist antibodies may be mutated “to obtain an antibody with the desired binding affinity to CGRP,” and stating that such mutation processes are “routine practice[s] in the art and need not be described in detail”).) These admissions further confirm that a POSA would have had a reasonable expectation of successfully producing a humanized antibody for reducing incidence of or treating migraine in a human.

In a highly analogous case, a district court upheld a jury’s conclusion that a POSA would have had a reasonable expectation to make the claimed human antibody from a known mouse antibody in a patent filed in 1999—six years before Teva’s priority application. *Abbott GmbH & Co., KG v. Centocor Ortho Biotech, Inc.*, 971 F. Supp. 2d 171, 185-86 (D. Mass. 2013). Central to the court’s analysis was the fact that the art taught mouse antibodies, and that the tools to prepare human antibodies were available. *Id.* at 182-83. The result here should be no different, particularly because the '045 patent admits that anti-CGRP antagonist antibodies were known and methods to prepare humanized and/or human versions were well-established. (*Supra* §§ III.B.2, IV.C, IV.D.) Thus, the prior art provides a

reasonable expectation of success in making a humanized anti-CGRP antagonist antibody that would be effective for reducing incidence of and treating migraine.

C. The Prior Art Did Not Teach Away from Using a Humanized Anti-CGRP Antagonist Antibody, as Teva Incorrectly Argued During Prosecution

During prosecution of one of the applications related to the '045 patent, Teva incorrectly argued that Tan evidenced that “one skilled in the art prior to Applicant’s disclosure would have had no reasonable expectation that a humanized antibody would have such a therapeutic application,” asserting that “only the Fab’ fragment (and NOT the full antibody) ‘was found to be an effective tool for blockade.’” (Ex. 1136, 4 (citing Ex. 1022, 570).)

As an initial matter, Teva’s argument *supports* the obviousness of any challenged claim that *encompasses* Fab’ fragments. (*Supra* § VI.C.) This includes at least claims 1, 3, 4, 8-10, 12, 14-17, 19, 20, 24, 25, 27, and 29-31. (*Supra* § III.A.)

Contrary to Teva’s assertions, Tan fully supports the obviousness of reducing incidence of or treating patients with a full-length anti-CGRP antagonist antibody. (Ex. 1014 ¶¶133-136; Ex. 1015 ¶¶101-102.) Tan states that it had “clearly demonstrated the ability of MAb C4.19 IgG [i.e., the full-length antibody] and its Fab’ fragment to block the hypotensive effects” of CGRP *in vivo*. (Ex. 1022, 571.) Moreover, while the Fab’ fragment outperformed the full-length antibody in the rat

saphenous nerve model under the conditions tested (which involved a single administration, short distribution times, and low doses), Tan expressly discloses that the full-length antibody achieved a response when the dose and experimental time were increased. (Ex. 1022, 569, 571; Ex. 1014 ¶¶58; Ex. 1015 ¶¶102.)

Tan also made specific recommendations for improving the *in vivo* efficacy of full-length anti-CGRP antagonist antibodies. (Ex. 1022, 571; Ex. 1014 ¶¶134-135; Ex. 1015 ¶¶102.) In particular, Tan states that slow distribution to the site of immunoblockade could be overcome by (1) increasing the dose, (2) chronic administration, and/or (3) active immunization. (Ex. 1022, 571.) Tan further states that “[w]ith repeated administration,” full-length IgG should achieve sufficiently high concentrations for immunoblockade. (*Id.*; Ex. 1014 ¶¶135.) Thus, Tan does not teach away because it does not “criticize, discredit, or otherwise discourage investigation into” using a full-length, humanized anti-CGRP antagonist antibody. *In re Mouttet*, 686 F.3d 1322, 1334 (Fed. Cir. 2012). Instead, it affirmatively demonstrates *in vivo* activity—activity linked in the prior art to migraine (*see, e.g.*, Ex. 1047, 59 (“CGRP caused headache in virtually all migraine sufferers”))—and provides specific recommendations for achieving immunoblockade of the CGRP pathway with a full-length anti-CGRP antagonistic antibody.

Teva’s erroneous teaching-away argument during prosecution thus omits more than half the story. While Teva selectively quotes portions of Tan that appear to support its contention, it fails to acknowledge Tan’s express guidance as to how the *in vivo* efficacy of full-length antibodies could be improved:

Teva’s Argument	Disclosures of Tan Ignored by Teva
<p>“In Tan, only the Fab’ fragment (and NOT the full antibody) ‘was found to be an effective tool for blockade’ in the hind paw” (Ex. 1136, 4 (quoting Ex. 1022, 570).)</p>	<p>“With repeated administration IgG should eventually distribute into interstitial space and achieve the sufficiently high concentrations required for immunoblockade.” (Ex. 1022, 571.)</p>
<p>“Tan provides that ‘distribution of the antibody to the synaptic cleft is a prerequisite for the immunoblockade of endogenous CGRP.’” (Ex. 1136, 4 (quoting Ex. 1022, 571).)</p>	<p>“Given an adequate incubation period in a tissue bath, Mab C4.19 IgG <i>clearly diffuses into the synaptic cleft</i> since it was effective at blocking CGRP released from primary afferent nerves by capsaicin <i>in vitro</i>.” (Ex. 1022, 571.)</p>
<p>“In Tan . . . ‘the most likely barrier to effective immunoblockade with IgG <i>in vivo</i> is a transport limitation due to poor capillary permeability.’” (Ex. 1136, 4 (quoting Ex. 1022, 570-71).)</p>	<p>“The slow distribution of whole IgG to the site of immunoblockade could be overcome by . . . <i>chronic administration of IgG</i> With <i>repeated administration</i> IgG should eventually</p>

	distribute into interstitial space and achieve the sufficiently high concentrations required for immunoblockade.” (Ex. 1022, 571.)
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Teva’s argument disregarded fundamental antibody pharmacokinetics that were well understood when the provisional application was filed. Tan reports that, in the rat saphenous nerve model, the full-length antibody produced a 16% reduction in increased blood flow stimulated by α CGRP, which was less than the reduction produced by the Fab’ fragment. (Ex. 1022, 569, 571.) Tan explains that its results were “consistent with reported antibody distribution characteristics,” in which large full-length antibody molecules take a longer time to distribute than their relatively smaller Fab’ fragments, particularly within the short time frames tested. (*Id.*; see Ex. 1014 ¶135.) Thus, Tan taught that the full-length antibody would be *expected to work* under different conditions, and specifically instructed that “[w]ith repeated administration, IgG [i.e., the full-length antibody] should eventually distribute into interstitial space and achieve the sufficiently high concentrations required for immunoblockade” of CGRP. (Ex. 1022, 571; Ex. 1014 ¶135.) Tan further reinforces that similar strategies had already been successfully employed by other researchers. (Ex. 1022, 571 (citing Ex. 1048).) Accordingly, Tan does not, as Teva asserted,

discourage a POSA from further exploring a full-length humanized anti-CGRP antagonist antibody—Tan, in fact, urges a POSA to use one. (Ex. 1014 ¶136.)

Tellingly, the '045 patent merely followed Tan's guidance. When testing full-length anti-CGRP antagonist antibodies in the rat saphenous nerve model used in Tan, the '045 patent reports using *higher doses* of full-length anti-CGRP antagonist antibodies and allowing *more time* for the antibody to distribute to the interstitial space before nerve stimulation. (Ex. 1014 ¶¶88-97; *see also id.* ¶¶98-100; Ex. 1001, Examples 3 and 5.) For example, the '045 patent discloses administering antibody up to *72 hours* before nerve stimulation in the rat saphenous nerve model, whereas the longest period tested in Tan was only *two hours*. (Ex. 1014 ¶¶88-90; Ex. 1001, Examples 3 and 5; Ex. 1022, 569.) Teva also administered doses of up to 25 mg/kg, higher than the approximately 3-12 mg/kg doses administered in Tan. (Ex. 1014 ¶¶88-90, 92-94; Ex. 1001, 55:61-66; Ex. 1022, 569.)

Following the teachings of Tan, Teva reported that full-length anti-CGRP antagonist antibodies, including those known in the prior art, effectively reduced CGRP-mediated skin vasodilation. (Ex. 1001, Examples 3 and 5.) The only *in vivo* data disclosed in Teva's provisional application to support a claim directed to treating and preventing migraine with anti-CGRP antagonist antibodies came from the *same* rat saphenous nerve model used in Tan. (Ex. 1019, Examples 3 and 5,

[0244] (citing 1052); Ex. 1022, 572 (citing Ex. 1052).) The fact that Teva followed the express guidance of the prior art cannot constitute inventive activity. *KSR*, 550 U.S. at 425 (finding invention obvious because it “follow[ed]” the prior art, and rejecting patent owner’s teaching-away argument).

Finally, Teva’s incorrect teaching-away argument also overlooked the disclosures of Wimalawansa, Sveinsson, and Salmon, each of which published after Tan and expressly stated that anti-CGRP antagonist antibodies should be used to treat humans for migraine, neurogenic inflammation, and pain relief. (*Supra* § VII.A.1.) These disclosures further confirm that Tan did not teach away from using anti-CGRP antagonist antibodies for therapeutic purposes. *In re Mouttet*, 686 F.3d at 1334. Instead, these references reinforce the value of a full-length anti-CGRP antagonist antibody for reducing incidence of and treating migraine. (Ex. 1014 ¶¶133-136.)

D. The Claimed Methods for Treating Migraine Would Have Been Obvious

The subject matter of claim 17 as a whole would have been obvious to a POSA. (*See supra* § VII.A-C; Ex. 1014 ¶¶11-14, 157-159, 190; Ex. 1015 ¶¶12-14, 83-86, 139-140.) By 2005, Olesen’s breakthrough results had confirmed the clinical viability of targeting and blocking the CGRP pathway for reducing incidence of or treating migraine. The prior art was replete with examples of anti-CGRP antagonist

antibodies that were known to bind to and inhibit CGRP's biological effects, including in animal models for neurogenic inflammation linked to migraine. The prior art had also identified anti-CGRP antagonist antibodies, including humanized antibodies, for treatment of migraine. A POSA therefore would have been motivated to prepare a humanized anti-CGRP antagonist antibody to reduce incidence of or treat migraine in humans, and would have done so with a reasonable expectation of success. By applying routine humanization processes such as those disclosed in Queen, a POSA would have expected the resulting antibodies to be suitable for administration for humans. (Ex. 1023, 3:55-59.) Consequently, claim 17 encompasses nothing more than the routine use of known antagonist antibodies, consistent with their established function, for the known use of treating or reducing incidence of migraine. This is not inventive. *KSR*, 550 U.S. at 401.

VIII. The Prior Art Likewise Demonstrates the Obviousness of Claim 1

Claim 1, the only other independent claim, is broader than claim 17. It is directed to any vasomotor symptom (rather than specifically to headache) and any individual (rather than just humans). (Ex. 1001, 99:2-7, 100:3-7; Ex. 1014 ¶83.) Teva defined vasomotor symptoms to include migraine. (Ex. 1001, 19:51 (“vasomotor symptom” includes “headache (such as migraine)”); Ex. 1014 ¶156.) Because claim 1 encompasses claim 17, claim 1 would have been obvious for all of

the reasons discussed above. (Ex. 1014 ¶¶11-14, 156-159, 190; Ex. 1015 ¶¶12-14, 83-86, 139-140.)

The prior art renders claim 1 obvious for additional reasons. For example, a POSA would have been motivated to use an anti-CGRP antagonist antibody, including a humanized antibody, to reduce incidence of or treat skin vasodilation, which Teva admitted was a vasomotor symptom, and is an underlying cause of hot flush. (Ex. 1143, 10; Ex. 1245, 1:18-23; Ex. 1001, 19:51.) Tan established that murine monoclonal anti-CGRP antagonist antibodies reduced incidence of skin vasodilation in rats. (Ex. 1022, 569; *supra* §§ IV.E.3, VII.C.) Others had demonstrated similar effects using an anti-CGRP antagonist in a marmoset model of hot flush. (Ex. 1245, 1:18-23, 9:32-66.) A POSA thus would have been motivated to make and use a humanized anti-CGRP antagonist antibody to reduce skin vasodilation and hot flush. A POSA would have reasonably expected to succeed, at least because Tan previously disclosed reducing incidence of skin vasodilation in an individual with a monoclonal anti-CGRP antagonist antibody. (Ex. 1014 ¶¶56-58.) Thus, for these additional reasons, claim 1 is obvious over the asserted art.

IX. The Challenged Dependent Claims Would Have Been Obvious Over Olesen, Tan, and Queen

Claims 1 and 17 are the only independent claims in the '045 patent. The remaining challenged claims depend from either claim 1 or claim 17. For all of the

reasons provided above in §§ VII-VIII, and for the additional following reasons, the asserted art would have rendered obvious claims 3, 4, 8-16, 19, 20, and 24-31.

A. Claims 3, 9, 19, and 24

Claims 3, 9, 19, and 24 specifically encompass reducing incidence of or treating migraine. These claims are obvious for the reasons explained above. (*Supra* §§ VII-VIII.)

B. Claims 4 and 20

Claims 4 and 20 depend from claims 1 and 17, respectively, and recite an anti-CGRP antagonist antibody that “has a binding affinity (K_D) to human α -CGRP of 50 nM or less as measured by surface plasmon resonance at 37 °C.”

A POSA would have been motivated to make and use an anti-CGRP antibody that binds to human α CGRP with the recited affinity, and would have done so with a reasonable expectation of success. By 2005, antibodies with lower K_D values (i.e., tighter antigen binding) were known to be associated with increased biological potency (Ex. 1088, 350; Ex. 1023, 2:12-27; Ex. 1015 ¶113), and the prior art demonstrated a clear preference for antibodies with stronger binding affinities. For example, all of the FDA-approved antibodies indicated for human therapeutic use before 2005 had binding affinities of less than 50 nM (in the range of 32 nM to 0.08 nM (i.e., 80 pM)). (Ex. 1014 ¶163; Ex. 1015 ¶¶67-68; Ex. 1088, 350.)

Moreover, numerous anti-CGRP antagonist antibodies bound α CGRP with affinities less than 50 nM. For example, Andrew generated antibodies against *human* CGRP with binding affinities ranging from 40 nM to 4 nM. (Ex. 1055, 89, 92; Ex. 1014 ¶164; Ex. 1015 ¶115.) Similarly, as measured by RIA, Tan's anti-CGRP antagonist antibodies had K_D values of 1.9 and 2.5 nM to rat α and β CGRP. (Ex. 1021, 705, 707.) Dr. Vasserot explains that SPR values generally correspond with those measured using RIA. (Ex. 1015 ¶118; *see, e.g.*, Ex. 1086, 117.) Tan's studies would have reinforced a POSA's motivation to obtain a humanized anti-CGRP antagonist antibody with an affinity to human α CGRP of less than 50 nM since antibodies within that range had already been shown to have anti-CGRP antagonist activity both *in vitro* and *in vivo*. (Ex. 1014 ¶164; Ex. 1015 ¶113.)

Queen's methods are designed to obtain humanized antibodies that have binding affinities on the order of 10 nM or less. (Ex. 1023, 10:62-63; Ex. 1015 ¶116.) A POSA would have further known that, using routine technology, modifications could be made to the CDRs or framework regions to maintain or improve binding affinity. (Ex. 1015 ¶¶52-53, 116-117; Ex. 1023, 3:33-41; Ex. 1068, 351-55.) Notably, the '045 patent admits that "[m]odification of polypeptides is routine practice," including methods to obtain a desired binding affinity. (Ex. 1001

at 37:39-43 (“[amino acid sequence] may be mutated to obtain an antibody with the desired binding affinity to CGRP”); Ex. 1015 ¶74.)

A POSA would have screened for such antibodies using SPR. (Ex. 1014 ¶166; Ex. 1015 ¶118.) SPR was the preferred screening method because it was easy to use, commercially available, and reliable. (Ex. 1084, 141, 148-49; Ex. 1015 ¶¶65, 118.) By 2005, SPR had also been highlighted as particularly appropriate for identifying “agonists/antagonists that, e.g., compete with each other or with other possible ligands to the CGRP-receptors.” (Ex. 1134, [0162].) Indeed, SPR was understood as “the standard method for measuring the affinity of antigen-antibody interactions.” (Ex. 1084, Abstract; Ex. 1015 ¶¶65, 118.) The ’045 patent admits that “[m]ethods for determining binding affinity are well-known in the art,” and specifically lists SPR as a suitable, known method. (Ex. 1001, 41:22-34; *see also id.*, 27:3-40 (stating that SPR may be used to obtain binding affinity); Ex. 1015 ¶74.)

Evaluating binding affinity at 37 °C would have been routine. As of 2005, binding affinities were typically evaluated at human body temperature (37 °C), particularly for antibodies intended for therapeutic use. (Ex. 1014 ¶166; Ex. 1015 ¶66; Ex. 1087, Abstract, 333.) A POSA would have conducted SPR at human body temperature because the art recognized that binding affinities obtained at physiological temperatures more accurately reflect the binding affinity of the

antibody in the *human* body. (Ex. 1014 ¶166; Ex. 1015 ¶¶66, 119; Ex. 1087, Abstract, 333.) Claims 4 and 20 are therefore obvious. (Ex. 1014 ¶167; Ex. 1015 ¶120.)

C. Claim 8

Claim 8 recites a method according to claim 1, wherein the individual is a human. This claim is obvious for the reasons discussed in §§ VII-VIII above.

D. Claims 10 and 25

Claims 10 and 25 depend from claims 1 and 17, respectively, and recite methods wherein the anti-CGRP antagonist antibody “binds the C-terminal fragment having amino acids 25-37 of CGRP or a C-terminal epitope within amino acids 25-37 of CGRP.”

A POSA would have been motivated to make and use an anti-CGRP antibody that binds to the claimed C-terminal region of human CGRP, and would have done so with a reasonable expectation of success. By 2005, many of the prior art anti-CGRP antagonist antibodies were known to bind to the C-terminal region of CGRP. (Ex. 1048, 258; Ex. 1033, 99, 102, 104; Ex. 1014 ¶170; Ex. 1015 ¶122.) Tan, for example, refers to the anti-CGRP antagonist antibodies of Louis, which were known to target the C-terminus of CGRP and blocked CGRP *in vivo*. (Ex. 1022, 573 (citing Ex. 1048); *see* Ex. 1048, 258 (reporting binding to a CGRP fragment of amino acids

28-37).) Wong also described a commercially available anti-CGRP antagonist antibody, #4901, which was known to bind to a C-terminal portion of CGRP (amino acids 28-37). (Ex. 1033, 104.) Teva's patent confirms this. (Ex. 1001, 25:59-63, 50:48-52; Fig. 1.) Andrew and colleagues also reported anti-CGRP antagonist antibodies that bound to the C-terminal region of CGRP. (Ex. 1055, 90-91.) Thus, the prior art described biologically active anti-CGRP antagonist antibodies that bound to epitopes within the C-terminal region recited in claims 10 and 25. (Ex. 1014 ¶170; Ex. 1015 ¶122.)

In addition, before 2005, it was known that the C-terminal region of CGRP was responsible for receptor binding. (Ex. 1034, 117; Ex. 1014 ¶170; Ex. 1015 ¶123; Ex. 1061, 196.) Specifically, researchers identified amino acids Thr³⁰, Val³², Gly³³, and Phe³⁷ as the "most sensitive" to change and, consequently, the most likely involved in receptor binding. (Ex. 1034, 118, 121-22.)

Thus, to reduce incidence of or treat migraine, a POSA would have been motivated to make and use a humanized anti-CGRP antagonist antibody that binds to the claimed fragment or epitopes within the C-terminal region, including specifically in the region recited in claims 10 and 25, because such antibodies would have been expected to disrupt the interaction between CGRP and its receptors. (Ex. 1014 ¶170; Ex. 1015 ¶¶122-124; Ex. 1048, 258; Ex. 1033, 99, 102.) A POSA

would have had a reasonable expectation of success for the reasons discussed above (*see supra* § VII.B), and because the prior art had already reported anti-CGRP antagonist antibodies that bound to the C-terminal region and blocked CGRP *in vivo*. (Ex. 1014 ¶¶170, 171; Ex. 1015 ¶¶122-124; Ex. 1048, 258; Ex. 1033, 99, 102.) Claims 10 and 25 are therefore also obvious. (Ex. 1014 ¶172; Ex. 1015 ¶124.)

E. Claims 11 and 26

Claims 11 and 26 depend from claims 1 and 17, respectively, and recite an anti-CGRP antagonist antibody that “comprises an Fc region with an impaired effector function.” The ’045 patent acknowledges that antibodies with Fc regions, including modified Fc regions, were known. (Ex. 1001, 40:7-61; *see also id.*, 43:63-67.)

A POSA would have been motivated to make a full-length antibody with an impaired effector function for reducing incidence of or treating migraine, and would have done so with a reasonable expectation of success. Antibodies with impaired effector functions were well known in the prior art. (Ex. 1015 ¶126.) Queen states that monoclonal antibody technology allowed for the development of “essentially unlimited quantities of uniform antibodies capable of binding to a predetermined antigenic site and having *various immunological effector functions*.” (Ex. 1023, 1:28-32.) A POSA also would have known how to modify a human constant region

to reduce or eliminate its effector functions. (Ex. 1066, 734; Ex. 1014 ¶175; Ex. 1015 ¶126.) When targeting a soluble ligand, such as CGRP, a POSA would have sought to reduce or eliminate the effector functions to lower the risk of side effects. (Ex. 1015 ¶127; Ex. 1062, 43.)

As discussed above in §§ VII-VIII, a POSA also would have had a reasonable expectation of success. (Ex. 1014 ¶176; Ex. 1015 ¶128.) Specifically, as described above, a POSA would have been able to follow known methods to prepare a humanized anti-CGRP antagonist antibody, including an antibody that comprises an Fc region with an impaired effector function, and would have reasonably expected such antibodies to reduce incidence of or treat migraine. (§ VII.B.1-3.) The '045 patent admits that it would have been routine to generate an antibody with an impaired effector function. (Ex. 1001, 40:16-40; *see also id.*, 43:63-67; Ex. 1062, 43; Ex. 1015 ¶75.) Thus, claims 11 and 26 would have been obvious. (Ex. 1014 ¶177; Ex. 1015 ¶¶126-128.)

F. Claims 12 and 27

Claims 12 and 27 recite certain routes of administration, including intravenous and subcutaneous administration. Olesen administered its CGRP antagonists for treatment of migraine via intravenous administration. (Ex. 1025, 1106.) Tan likewise administered its anti-CGRP antagonist antibodies intravenously.

(Ex. 1022, 567.) Queen specifically discloses that its humanized antibodies are “particularly useful for parenteral administration,” including by intravenous and subcutaneous administration. (Ex. 1023, 24:28-34.) The ’045 patent acknowledges that intravenous and subcutaneous administration were known in the art. (Ex. 1001, 21:8-15; Ex. 1015 ¶76.)

Thus, a POSA would have been motivated to administer a humanized anti-CGRP antagonist antibody intravenously or subcutaneously for reducing incidence of or treating migraine, and would have had a reasonable expectation of success. Claims 12 and 27 are thus obvious. (Ex. 1014 ¶180; Ex. 1015 ¶130.)

G. Claims 13 and 28

Claims 13 and 28 depend from claims 1 and 17, respectively, and recite an anti-CGRP antagonist antibody that comprises a heavy chain constant region derived from a human IgG₂ constant region.

A POSA would have been motivated to reduce incidence of or treat migraine with a humanized anti-CGRP antagonist antibody that comprises a heavy chain constant region derived from a human IgG₂ constant region, and would have had a reasonable expectation of success. (Ex. 1014 ¶¶181-184; Ex. 1015 ¶¶131-134.) The IgG class of antibodies has only four subclasses, designated as IgG₁, IgG₂, IgG₃, and IgG₄. (Ex. 1014 ¶182; Ex. 1015 ¶¶22, 132; Ex. 1058, 95; Ex. 1063, 68.). The

differences among these subtypes lie in their constant regions, with different constant regions having different effector functions. (Ex. 1015 ¶22; *see* Ex. 1063, 68.) The '045 patent admits that these constant regions, including mutated derivatives, were well known in the art: “The subunit structures and three-dimensional configurations of different classes of immunoglobulins are well known.” (Ex. 1001, 12:35-37; 40:23-44 (“the constant region is modified as described” in prior art references); Ex. 1015 ¶75.)

Queen describes humanizing antibodies using constant regions from any of the IgG subclasses. (Ex. 1023, 11:4-20; Ex. 1015 ¶132.) It was well known that when humanizing a murine antibody, a POSA would have been able to select from among the IgG subclasses to choose the most suitable subclass for the intended purpose of the humanized antibody. (*See* Ex. 1062, 43; Ex. 1015 ¶43.)

The IgG₂ subclass was well known to have desirable properties for therapeutic applications involving the inhibition of soluble ligand-receptor binding. (Ex. 1062, 43 (“[I]f the antibody were required simply to activate or block a receptor, then human IgG₂ or IgG₄ would probably be more appropriate.”).) Specifically, the IgG₂ subclass was known to have relatively weak effector functions, which was viewed as desirable for treating migraine. (Ex. 1014 ¶182; Ex. 1015 ¶133; Ex. 1065, 1357-58.)

As explained above, as of 2005, it would have been routine to generate the claimed humanized anti-CGRP antagonist antibody comprising a heavy chain constant region derived from a human IgG₂ constant region. (*Supra* §§ IV.D, IV.E.3, VII.B.2.) Claims 13 and 28 are also obvious. (Ex. 1014 ¶184; Ex. 1015 ¶134.)

H. Claims 14 and 29

Claims 14 and 29 depend from claims 1 and 17, respectively, and recite that the “anti-CGRP antagonist antibody is formulated with a pharmaceutically acceptable carrier, excipient, and/or stabilizer.” The prior art had already described such compositions. (Ex. 1014 ¶185; Ex. 1015 ¶136.) For instance, Tan’s antibody preparations contained PBS (phosphate buffered saline), one of the pharmaceutically acceptable carriers expressly identified in the ’045 patent. (Ex. 1001, 19:28-32; Ex. 1022, 568.) Moreover, Queen expressly teaches that humanized antibodies can be formulated into pharmaceutical compositions, including with pharmaceutically-acceptable excipients. (Ex. 1023, 24:29-51.) The ’045 patent indicates that pharmaceutical formulations, including pharmaceutically acceptable excipients, of antibodies were well known. (Ex. 1001, 19:24-39, 20:63-21:1, 21:34-49; Ex. 1015 ¶176.) Claims 14 and 29 are also obvious. (Ex. 1014 ¶185; Ex. 1015 ¶137.)

I. Claims 15 and 30

Claims 15 and 30 depend from claims 1 and 17, respectively, and recite a humanized monoclonal antibody. These claims are obvious for the reasons provided in §§ VII-VIII above.

J. Claims 16 and 31

Claims 16 and 31 depend from claims 1 and 17, respectively, and recite a dose of “at least about 3 $\mu\text{g}/\text{kg}$.” Tan administered its anti-CGRP antagonist antibodies within this range. (Ex. 1014 ¶188.) Queen also describes doses of humanized antibodies falling within this range, stating that its humanized antibodies can be administered in an amount of about 1 mg to about 200 mg per dose, with dosages of from 5 mg to 25 mg being more commonly used. (Ex. 1023, 25:14-19.) For a 70 kg adult, a 5 mg dose equates to $\sim 71 \mu\text{g}/\text{kg}$, significantly more than the 3 $\mu\text{g}/\text{kg}$ floor recited in claims 16 and 31. Moreover, as of Teva’s earliest filing date, every FDA-approved antibody therapy recommended doses of greater than at least about 3 $\mu\text{g}/\text{kg}$. (Ex. 1014 ¶189; *see, e.g.*, Ex. 1252, 26.) Claims 16 and 31 are obvious. (Ex. 1014 ¶189.)

X. There Is No Objective Evidence of Nonobviousness

A. Teva Cannot Establish Nexus to the Full Scope of the Challenged Claims

The challenged claims are directed *broadly* to methods of reducing incidence of or treating vasomotor symptoms or headache with *any* human monoclonal or humanized monoclonal anti-CGRP antagonist antibody. The challenged claims do not recite specific antibody structures or sequences, but instead are directed to antibodies having the *functional property* of antagonizing CGRP. Despite this breadth, the '045 patent discloses just one specific humanized anti-CGRP antagonist antibody and its highly homologous derivatives. (*E.g.*, Ex. 1001, Abstract, Example 4.) The challenged claims also encompass any type of headache and any type of vasomotor symptom.

Teva's limited disclosure cannot support the expansive scope of the challenged claims. *AbbVie Deutschland GmbH v. Janssen Biotech, Inc.*, 759 F.3d 1285, 1301 (Fed. Cir. 2014) (finding that description of a family of closely related and structurally similar antibodies derived from a single antibody was insufficient to demonstrate possession of the full scope of the claims directed to genus of functionally defined antibodies). Thus, Teva cannot establish the requisite nexus with the claimed subject matter to argue any meaningful unexpected results or other secondary indicia. *See Apotex*, 754 F.3d at 962, 965 (reversing district court

conclusion of nonobviousness for failure to consider the full scope of the claims, including in its analysis of secondary considerations).

B. There Are No Unexpected Results

For the reasons presented above, Teva cannot establish any unexpected results for such broad claims over the prior art where, as here, the prior art (1) showed that blocking the CGRP pathway was clinically effective to treat migraine; (2) anti-CGRP antagonist antibodies that showed *in vivo* efficacy were known; and (3) the prior art provided express guidance to further optimize *in vivo* performance of full-length antibodies, which Teva itself followed. (*Supra* §§ IV, VII, VIII; Ex. 1014 ¶¶133-137.)

C. Lilly’s and Others’ Near-Simultaneous Development Preclude a Holding of Nonobviousness

In this case, the near-simultaneous development of humanized anti-CGRP antibodies to treat migraine by others serves as objective evidence of *obviousness*. *Ecolochem, Inc. v. S. Cal. Edison Co.*, 227 F.3d 1361, 1376 (Fed. Cir. 2000); *George M. Martin Co. v. All. Mach. Sys. Int’l LLC*, 618 F.3d 1294, 1305 (Fed. Cir. 2010) (“Independently made, simultaneous inventions, made ‘within a comparatively short space of time,’ are persuasive evidence that the claimed apparatus ‘was the product only of ordinary mechanical or engineering skill.’”). Within less than two months of Teva’s filing, Lilly filed a provisional application directed to “Treatment of

Migraine with Anti-CGRP Antibodies” describing specific monoclonal antibodies and Fab’ fragments that bound to CGRP and antagonized its activity *in vivo*. (Ex. 1127, 13, Example 5.) Lilly specifically disclosed the use of humanized anti-CGRP antagonist antibodies to treat and prevent migraine.³

Lilly and Teva were not alone in filing patent applications directed to using anti-CGRP antagonist antibodies for treating headache. In August 2005, researchers associated with Stanford University, as well as with Trigemina, Inc. and HealthPartners Research & Education, also filed a provisional application directed to therapeutic treatments for humans using an anti-CGRP antagonist antibody. (Ex. 1128, [0021], [0108].) That application discloses, for example, “treating an individual for trigeminal nerve associated pain comprising administering an effective amount of an analgesic agent,” and in “some examples the analgesic is an antibody directed against calcitonin gene-related peptide (CGRP).” (*Id.*, [0021].) Thus, no less than three different entities—Teva, Lilly, and Stanford—had nearly simultaneously filed U.S. patent applications directed to using monoclonal anti-CGRP antagonist antibodies for reducing incidence of and treating headache.

³ Lilly *never* pursued its claims in any jurisdiction, instead allowing the application to go abandoned.

On similar facts, the Federal Circuit agreed that a machine made a year after the earliest reduction to practice of the invention constituted near-simultaneous invention. *Martin*, 618 F.3d at 1305-06. Thus, the independent and near simultaneous development of the subject matter of the challenged claims by others provides additional evidence of their obviousness.

XI. The Evidence Submitted in this Petition Was Not Previously Considered by the Office

The evidence identified in this Petition was either not before the Examiner or not fully considered during prosecution. Teva did not submit Olesen or Queen to the USPTO during examination of the '045 patent. (Exs. 1208-1212.) Moreover, the Examiner did not cite *any* of the asserted references in any Office Action. In addition, the Examiner did not have benefit of Dr. Charles's and Dr. Vasserot's declarations, which explain what a POSA would have understood from the asserted references as of Teva's earliest filing date. This Petition also highlights factual and legal flaws in Teva's arguments presented during prosecution of related applications, including its erroneous teaching-away arguments.

Accordingly, Lilly submits that any argument for noninstitution under § 325(d) is misplaced, and respectfully requests that the Board institute trial on the sole ground presented in this Petition.

XII. Mandatory Notices Under 37 C.F.R. § 42.8

A. Real Parties-in-Interest

Eli Lilly and Company is the real party-in-interest.

B. Related Matters

Teva filed a declaratory judgment action on October 24, 2017, in the U.S. District Court for the District of Massachusetts, seeking a declaration that Lilly's investigational drug galcanezumab will infringe U.S. Patent Nos. 8,586,045; 8,597,649; 9,266,951; 9,340,614; and 9,346,881. Teva filed an amended complaint in this first action on January 16, 2018. On February 6, 2018, Teva filed another declaratory action, seeking a declaration that Lilly's product will infringe U.S. Patent Nos. 9,884,907 and 9,884,908. A week later, Teva amended its complaint in the second-filed action to incorporate two more patents: U.S. Patent Nos. 9,890,210 and 9,890,211.

On September 27, 2018, the court dismissed Teva's Amended Complaints in both declaratory judgment actions. Later that day, Teva filed a third action for patent infringement for the same patents. The patents in the litigations purport to claim priority to the same U.S. provisional application as the '045 patent. Two applications based on the same provisional application are also pending before the USPTO: 15/883,218 and 15/956,580.

On August 8, 2018, Lilly filed petitions for *inter partes* review against U.S. Patent Nos. 9,340,614; 9,266,951; 9,346,881; 9,890,210; 9,890,211; and 8,597,649. These petitions are pending before the Board as IPR2018-01422; IPR2018-01423; IPR2018-01424; IPR2018-01425; IPR2018-01426; and IPR2018-01427, respectively.

C. Lead and Backup Counsel

Lead Counsel	Backup Counsel
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D. Service Information

Please send all correspondence to lead counsel at the address shown above.

Petitioner consents to service by e-mail at the e-mail addresses identified in the table above.

XIII. Payment of Fees

The required fees are submitted herewith in accordance with 37 C.F.R. §§ 42.103(a) and 42.15(a). If any additional fees are due during this proceeding, the Office is authorized to charge such fees to Deposit Account No. 06-0916.

XIV. Conclusion

Lilly respectfully requests that the Board grant this Petition for *Inter Partes* Review, institute trial, and find all challenged claims unpatentable.

Respectfully submitted,

Date: September 28, 2018

By: /William B. Raich/
William B. Raich (Reg. No. 54,386)

CERTIFICATION OF COMPLIANCE

The undersigned hereby certifies that the foregoing Petition contains 13,497 words, excluding those portions identified in 37 C.F.R. § 42.24(a), as measured by the word-processing system used to prepare this paper.

By: /William B. Raich/
William B. Raich (Reg. No. 54,386)

CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. §§ 42.6(e) and 42.105(a), the undersigned certifies that on September 28, 2018, a copy of the foregoing **Petition for *Inter Partes* Review** was served by Priority Mail Express on the correspondence address of record indicated in the Patent Office's public PAIR system for U.S. Patent No. 8,586,045:

FISH & RICHARDSON P.C. (BO)
P.O. Box 1022
Minneapolis, MN 55440-1022

A courtesy copy of the foregoing was also served by FedEx on the attorney for assignee Teva Pharmaceuticals International GmbH indicated in the Patent Office's public PAIR system for U.S. Patent No. 8,586,045:

Todd E. Garcia, Ph.D.
FISH & RICHARDSON P.C.
One Marina Park Drive
Boston, MA 02210-1878

Date: September 28, 2018

By: /William Esper/
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