Filed: October 1, 2018

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. IPR2018-01711
Patent No. 9,884,907

PETITION FOR *INTER PARTES* REVIEW

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GLOSSARY

ADCC	Antibody-dependent cellular cytotoxicity
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	*Inter partes* review
Italicized text	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
Teva or Patent Owner	Teva Pharmaceuticals International GmbH
USPTO or Office	U.S. Patent and Trademark Office
’907 patent	U.S. Patent No. 9,884,907

I. Introduction

Teva's '907 patent broadly claims using humanized monoclonal anti-CGRP antagonist IgG antibodies that bind to human CGRP for treating headache, including migraine. The claims recite features common to all therapeutic IgG antibodies (e.g., heavy chains with three complementarity determining regions ("CDRs") and four framework regions ("FRs")) and a binding specificity for human CGRP possessed by many prior art antibodies. The concept of using an anti-CGRP antagonist antibody for treating migraine 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.

Anti-CGRP antagonist antibodies that specifically bound to CGRP were also well known in the art. These monoclonal antibodies were shown to block the biological effects of the CGRP pathway *in vivo*. For example, Tan demonstrated that its anti-CGRP antagonist IgG 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 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 '907 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 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 '907 patent would have been obvious over Olesen, Tan, and Queen. Lilly therefore requests *inter partes* review of claims 1-18 of the '907 patent.

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

A. Grounds for Standing

Petitioner certifies that the '907 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. 1216, 4-6 (listing priority chain and declining to designate as a transition application); Ex. 1001, 1:9-30, title page, item (60).)[1]

B. Identification of Challenge

Lilly respectfully requests review under 35 U.S.C. § 311 of claims 1-18 of the '907 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.

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

[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.

III. The ’907 Patent and Its Provisional Application

The ’907 patent is entitled “Methods for Treating Headache Using Antagonist Antibodies Directed Against Calcitonin Gene-Related Peptide.” (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 ’907 patent discloses a single humanized antagonist antibody (G1) and its purported derivatives. (*E.g., id.*, Abstract, Example 4.) The ’907 patent does not include any clinical or other human data.

The ’907 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. 1016 ¶88.)

The provisional application, like the ’907 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. 1016 ¶¶94-95.)

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

Claim 1, the only independent claim, recites:

> A method for treating headache in an individual, comprising:
>
> administering to the individual an effective amount of a humanized monoclonal anti-Calcitonin Gene-Related Peptide (CGRP) antagonist antibody, comprising:
>
> two human IgG heavy chains, each heavy chain comprising three complementarity determining regions (CDRs) and four framework regions, wherein portions of the two heavy chains together form an Fc region; and
>
> two light chains, each light chain comprising three CDRs and four framework regions;
>
> wherein the CDRs impart to the antibody specific binding to a CGRP consisting of amino acid residues 1 to 37 of SEQ ID NO:15 or SEQ ID NO: 43.

(Ex. 1001, claim 1.) The recited Sequence IDs 15 and 43 correspond to human αCGRP and βCGRP, respectively. (Ex. 1016 ¶91; Ex. 1001, cols. 53-54 (Table 4).)

The recited "heavy chain" and "light chain" limitations are *generic* to IgG antibodies and do not provide meaningful structure that correlates with specific binding to CGRP for treating headache. (Ex. 1017 ¶¶61-62.)

Dependent claims 2-18 are addressed in Section VIII below.

B. Patent Owner Admissions in the Specification

The '907 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 '907 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, 2:20-24.) The '907 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.*, 2:32-40.)

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

The '907 patent states that "[a]nti-CGRP antagonist antibodies are known in the art," including those described by Tan. (*Id.*, 26:28-32 (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 '907 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, 28:10-14, 32:4-8 ("Anti-CGRP antagonist antibodies and polypeptides derived from antibodies can be identified or characterized using methods *known in the art* . . . ."); 28:15-16 ("General techniques for production of human and mouse antibodies are *known in the art* and are described herein.").)

The '907 patent states that preparing humanized and human antibodies from non-human antibodies, such as murine antibodies, was "known" and "conventional." (*Id.*, 28:10-16, 32:4-8, 32:51-52, 36:24-25; *see also id*., cols. 28-30; Ex. 1017 ¶66.) According to the '907 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, 29:27-36 (citing Queen (Ex. 1023) and other prior art patents); Ex. 1017 ¶67.)

The ’907 patent acknowledges that humanized anti-CGRP antagonist antibodies “are designed to minimize unwanted immunological response toward rodent anti-human antibody molecules.” (Ex. 1001, 29:54-59.)

C. Prosecution of the ’907 Patent

During prosecution, the Office rejected the pending claims based on obviousness-type double patenting over related U.S. Patent Nos. 8,586,045; 8,734,802; 9,328,168; and 9,365,648. (Ex. 1220, 3-5.)

Teva did not substantively dispute these rejections but instead filed terminal disclaimers. (Ex. 1221, 6-7; Ex. 1222.)

IV. Background and Asserted Prior Art

A. CGRP Structure and Its Isoforms

By 2005, the neuropeptide CGRP had been identified and extensively studied. (Ex. 1016 ¶¶17-24.) Human CGRP is expressed in two closely related isoforms, αCGRP and βCGRP, both 37 amino acids in length. (*Id*. ¶17; Ex. 1032, 275; Ex. 1096, 534.) Human αCGRP and βCGRP differ by only three amino acids. (Ex. 1016 ¶17; 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. 1016 ¶17; Ex. 1032, 275; Ex. 1096, 534.) CGRP shows significant sequence identity across species: human αCGRP and βCGRP differ from their rat counterparts by only four and three variations, respectively. (Ex. 1016 ¶17; Ex. 1033, 93-94; Ex. 1096, 534.) Whereas human βCGRP is predominantly expressed in the enteric nervous system and pituitary gland, αCGRP was known to be expressed in sensory neurons, suggesting that αCGRP had an important role in migraine. (Ex. 1016 ¶22; Ex. 1031, 317.)

CGRP has powerful vasodilatory effects that, by 2005, had been directly linked to various human diseases, including migraine. (Ex. 1016 ¶¶27-39, 120; 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, 567-70.)

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. 1016 ¶¶51-62.) This is known as "immunoblockade." (Ex. 1022, 566; Ex. 1016 ¶51.) 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 their "inherent advantages of defined specificity, known affinity, reproducibility, and unlimited availability." (Ex. 1016 ¶¶51, 62; Ex. 1022, 572.)

B. Migraine and CGRP

Migraine is a chronic, and often debilitating disease. (Ex. 1016 ¶25; 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. 1016 ¶28; Ex. 1035, 290.) This results in pain and further nerve activation. (Ex. 1016 ¶¶26, 28; 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. 1016 ¶¶29, 36.) 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. 1016 ¶¶30, 36.)

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. 1016 ¶¶27, 39.) Indeed, as discussed in § IV.F.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 αCGRP, 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; *see* Ex. 1017 ¶¶28-30.) Anti-CGRP antagonist antibodies had been prepared against both human and rat αCGRP. (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. IgG Antibodies

The anti-CGRP antagonist antibodies of the prior art were IgG antibodies. (Ex. 1022, 566; Ex. 1033, 93; Ex. 1055, 89.) As of 2005, IgG was the preferred immunoglobulin class for all therapeutic antibodies, regardless of target antigen. (Ex. 1016 ¶65; Ex. 1062, 43; Ex. 1017 ¶22.) The structure of an IgG antibody is shown in the simplified depiction below (Figure 1). It possesses two heavy chains and two light chains. (Ex. 1016 ¶66; Ex. 1017 ¶16; Ex. 1058, 95, 100.)

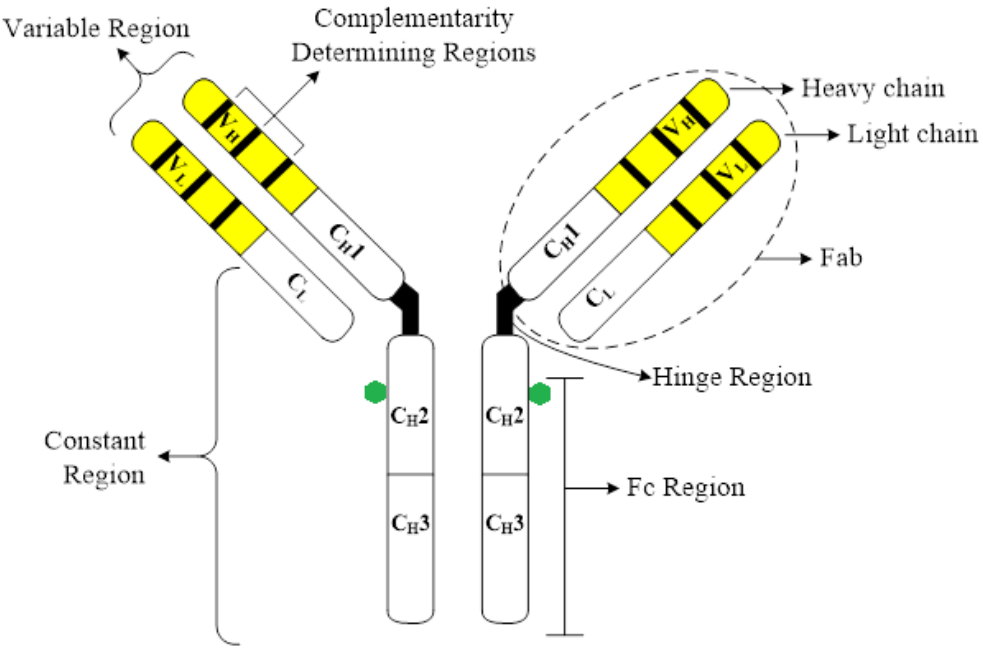

Figure 1: Exemplary IgG Antibody Structure

(Ex. 1058, 95, 101; Ex. 1059, 143.)

The heavy and light chains each contain three complementarity determining regions (CDRs), which are primarily responsible for antigen binding. (Ex. 1016 ¶68; Ex. 1017 ¶19; Ex. 1058, 100-01.) In both the heavy and light chains, the three CDRs

are interspersed between four regions called framework regions (FRs) that support the CDRs. (Ex. 1016 ¶69; Ex. 1017 ¶19; Ex. 1058, 100-01.) In Figure 1, the CDRs are depicted as black lines traversing the FRs shown in yellow. (Ex. 1016 ¶¶68-69; Ex. 1017 ¶19; Ex. 1058, 100-01.)

The remainder of an IgG antibody (shown in white in Figure 1) is referred to as the constant region. (Ex. 1016 ¶70; Ex. 1017 ¶20; Ex. 1058, 96.) Portions of the two heavy chains of an IgG antibody together form an Fc region. (Ex. 1016 ¶70; Ex. 1017 ¶20; Ex. 1058, 96.) The constant region may interact with the immune system, invoking cellular responses, including cell destruction. Such responses are known as "effector functions." (Ex. 1016 ¶70; Ex. 1017 ¶¶20, 24-25; Ex. 1058, 96.)

E. 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. 1017 ¶¶31-34; Ex. 1023, 1:44-57.) Consequently, researchers developed therapeutic antibodies that were more "human." (Ex. 1017 ¶¶35-37; *see also id.* ¶¶38-54.)

One prominent method was to humanize antibodies by grafting CDRs from a non-human antibody into a human IgG antibody scaffold. (Ex. 1017 ¶40.) 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.* ¶41; Ex. 1101, 522; Ex. 1075, 10029; Ex. 1023, 2:61-3:32.) By 2005, antibody humanization was considered a "clinically well-validated technology." (Ex. 1017 ¶42; 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. 1017 ¶¶22, 94.)

F. 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. 1016 ¶¶75-76.)

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. (*Id.*, 1106; Ex. 1016 ¶33.)

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. 1016 ¶33.) 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. 1016 ¶33.)

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. 1016 ¶34.) 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. 1016 ¶34.) 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. 1016 ¶35.)

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. 1016 ¶77.) 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. 1016 ¶77.)

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. 1016 ¶¶78-79.) A Fab' fragment consists primarily of a portion of the antibody's variable domain. (Ex. 1017 ¶17; 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 αCGRP. (Ex. 1022, 566-67; Ex. 1016 ¶56.) Both antibodies successfully did so. (Ex. 1022, 568-69; Ex. 1016 ¶56.)

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 '907 patent to support its claims. (Ex. 1052, 772-73; Ex. 1022, 567; Ex. 1019, Examples 3 and 5; Ex. 1001, 32:41-44, Examples 3 and 5; Ex. 1016 ¶¶57, 94-95.) The Fab' fragment effectively blocked increased

skin blood flow, i.e., vasodilation, after stimulation of the saphenous nerve. (Ex. 1022, 569; Ex. 1016 ¶59.) Under similar conditions, the full-length antibody did not appear to block increased skin blood flow. (Ex. 1022, 569; Ex. 1016 ¶59.) 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. 1016 ¶59; *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. 1016 ¶60.) 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. 1016 ¶60.) In contrast, Tan recommended the Fab' fragment for acute immunoblockade of the CGRP pathway. (Ex. 1022, 572; Ex. 1016 ¶60.)

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. 1016 ¶62.)

3. Queen

Queen issued on January 30, 2001. (Ex. 1016 ¶80.) 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. 1016 ¶81; Ex. 1017 ¶48.) 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. 1016 ¶81; Ex. 1017 ¶48.)

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. 1016 ¶83; Ex. 1017 ¶¶49-52.) 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. 1016 ¶83.) This translates into dissociation values (K_D) on the order of 10 nM to 0.1 nM, or less. (Ex. 1016 ¶83; Ex. 1017 ¶53.)

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. 1017 ¶53; 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 '907 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. 1016 ¶¶84-86.) A POSA with respect to the aspects of the '907 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. 1017 ¶¶71-73.)

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. "treating"

Under a proper construction, the phrase "treating" headache in claim 1 must be at least as broad as the express definition 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 definition does not require a clinical response.

The '907 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, 18:4-5); *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. 1016 ¶110.) 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"). Notably, the '907 patent does not contain any examples demonstrating any clinical response in human patients.

Thus, the term "treating" does not require a clinical response.

B. "effective amount"

The term "effective amount" should be construed as (1) including, at least via the doctrine of claim differentiation, doses of an anti-CGRP antagonist antibody that are less than 3 μg/kg, and (2) not requiring a clinical response. (Ex. 1016 ¶¶111-112).

Independent claim 1 recites "an effective amount." Claim 7, which depends from claim 1, recites a dose of "at least 3 μg/kg." Under this claim structure, "effective amount" must encompass a broader dose range than "at least 3 μg/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 cannons 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, claim 1 *must* encompass doses *lower* than 3 μg/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, 19:3-35 ("an effective amount" includes decreasing one or more "biochemical, histological and/or behavioral" symptoms), 32:34-41 (identifying stimulation of cAMP as a "targeted biological activit[y]"); Ex. 1016 ¶112.)

Furthermore, as Dr. Charles explains, a POSA would have understood that the specifically claimed antibody doses of 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. 1016 ¶113; 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. "specific binding"

Independent claim 1 recites that the CDRs impart "specific binding to" human αCGRP or βCGRP. As used in the '907 patent, the term "specific binding" includes antibodies that may bind to more than one isoform of CGRP, e.g., the α and β

isoforms of human and/or rat CGRP, and does not preclude binding to another peptide, such as amylin. (Ex. 1016 ¶114; Ex. 1017 ¶76.) Nor does it require any special degree of binding to one CGRP isoform compared to another. (Ex. 1017 ¶77.)

The '907 patent states as follows: "an antibody (or moiety or epitope) that specifically or preferentially binds to a first target *may or may not* specifically or preferentially bind to a second target." (Ex. 1001, 16:33-36.) Thus, under the '907 patent's definition, a binding preference for a first target or a second target is not required. (Ex. 1016 ¶114; Ex. 1017 ¶¶76-77.) The patent confirms that "specific binding" is not limited to "exclusive binding." (Ex. 1001, 16:36-39.)

VII. Claim 1 Is Obvious over Olesen, Tan, and Queen

Each and every element of claim 1 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. 1016 ¶76.) 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. 1016 ¶79.) 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. 1016

¶79.) 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 1 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. (*See 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 the Humanized Monoclonal Anti-CGRP Antagonist Antibody of Claim 1

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. 1016 ¶¶32-37, 76-77, 117.) Its successful results provided a concrete impetus to pursue CGRP antagonism—specifically with anti-CGRP antagonist antibodies—to treat migraine. (Ex. 1025, 1104, 1108-09; Ex. 1016 ¶¶117, 120-121.)

Olesen expressly extends its results beyond the small molecule CGRP-receptor inhibitor it tested to CGRP antagonists generally. (Ex. 1016 ¶117.) 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. 1016 ¶117.) 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. 1016 ¶117.) Consequently, a POSA reading Olesen would have extended its teachings to other CGRP antagonists. (Ex. 1016 ¶¶115-121.)

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., $CGRP_{8-37}$ 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 '907 patent itself reflects this prior art understanding, stating that CGRP "has a causative role in migraine." (Ex. 1001, 2:27-31.)

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. 1016 ¶63.) 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. 1016 ¶¶123-125.) 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. 1016 ¶¶136-138.) 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*. ¶136; *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. (Ex. 1016 ¶138.) 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). (*Id*.) 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. (*Id*. ¶121.) Thus, a POSA would have been motivated to target CGRP for treating 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 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. 1016 ¶123.) Sveinsson also acknowledges that antibodies against CGRP have been described in the art. (Ex. 1026, 7:19-24; Ex. 1016 ¶123.)

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. 1016 ¶124.) 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. 1016 ¶124.) Indeed, by 2005, "CGRP antagonism" had been confirmed as a "therapeutic principle" for the treatment of migraine. (Ex. 1029, 119; Ex. 1030, 129; Ex. 1016 ¶124.)

Salmon, as another example, disclosed that αCGRP is involved in modulating neurogenic inflammatory pain, a trigger for migraine. (Ex. 1027, [0002]-[0003]; Ex.

1031, 325; Ex. 1016 ¶125.) Salmon discloses methods for ameliorating pain caused by neurogenic inflammation by inhibiting the CGRP-pathway. (Ex. 1027, [0012].) It identifies anti-αCGRP antagonist antibodies for use in such methods. (Ex. 1027, [0039]; *see also id.*, claim 8; Ex. 1016 ¶125.)

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. 1017 ¶¶84-87; Ex. 1016 ¶126.) 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. 1017 ¶¶84-87; Ex. 1016 ¶126.) 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 provisional application and the '907 patent to support claims to migraine. (Ex. 1022, 569-70; Ex. 1001, Examples 3 and 5; Ex. 1016 ¶94; *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 treating chronic migraine. (Ex. 1016 ¶133.) BIBN4096BS has a relatively short half-life of approximately 2.5 *hours*, and thus is

cleared from the system rapidly. (Ex. 1042, 652; Ex. 1016 ¶132.) In contrast, humanized monoclonal antibodies remain in the body for *weeks* or even months following a single administration. (Ex. 1016 ¶134; 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 $CGRP_{8-37}$, a peptide fragment of CGRP, "proved ineffective in migraine treatment" due to "its low potency and *short half-life*." (Ex. 1031, 323; Ex. 1016 ¶132.) 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. 1016 ¶135.) Monoclonal antibodies generally exhibited fewer off-target side effects and lower toxicity than small molecule drugs. (Ex. 1057, 1348; Ex. 1017 ¶56.) This was important because liver toxicity was often a significant concern for existing migraine treatments. (Ex. 1016 ¶135; Ex. 1250, 4, 22.) In contrast, antibodies were known to be processed in various other organs, reducing the risk of liver toxicity. (Ex. 1016 ¶135; 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. 1017 ¶56.) 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. 1016 ¶¶136-137; 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, 702-03 ("The present study strongly suggests that the clinically effective migraine drug BIBN4096BS (Olesen *et al.* 2004) does not cross the BBB.").) 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. 1016 ¶159.)

Accordingly, a POSA would have been motivated to treat migraine with anti-CGRP antagonist antibodies with their benefits of longer half-lives, lower toxicity, and enhanced specificity and affinity. (Ex. 1016 ¶¶131-140; Ex. 1017 ¶¶83-88, 55-58.)

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

A POSA intending to use an anti-CGRP antagonist antibody to 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. 1016 ¶¶127-130; Ex. 1017 ¶¶89, 94; *see also id.* ¶¶42-45.) 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. 1017 ¶¶22, 89.)

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. 1017 ¶¶89-92; Ex. 1016 ¶128.) 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. 1016 ¶129.) Immunogenic responses could also cause serum sickness and other harmful effects, especially after repeated administration. (Ex. 1023, 1:51-57; Ex. 1017 ¶¶31-34, 90; Ex. 1016 ¶129.) Thus, by 2005, humanized IgG antibodies were preferred for clinical use. (Ex. 1017 ¶¶22, 89-96.)

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. 1016 ¶¶129-130.) 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. 1017 ¶¶89-90; 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 IgG anti-CGRP antagonist antibody that specifically binds to human CGRP for treating migraine in a human patient. (Ex. 1016 ¶145.); *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 1 is broadly directed to an "approach" for treating headaches, including migraine, without requiring a clinical response. (*Supra* §§ VI.A-B; Ex. 1016 ¶¶109-110.) The term "effective amount" recited in claim 1 similarly does not require a clinical response, and it encompasses exceedingly low doses. (*Supra* § VI.B; Ex. 1016 ¶¶111-113.) 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 1 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 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 treat migraine in humans.

1. A POSA Would Have Reasonably Expected that a Humanized Anti-CGRP Antagonist Antibody of Claim 1 Would Successfully 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. 1016 ¶147.) 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. 1016 ¶147.)

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. 1016 ¶148; *supra* §§ IV.F.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; Ex. 1016 ¶148; *supra* §§ IV.F.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 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. 1016 ¶¶148-149.)

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 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. 1016 ¶150.) 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. 1016 ¶150.) 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 '907 patent. (Ex. 1022, 569-72; Ex. 1016 ¶¶94-95, 152.) Under the conditions tested, Tan's anti-CGRP antagonist Fab' fragment demonstrated similar activity to

a known CGRP-receptor antagonist, $CGRP_{8-37}$. (Ex. 1022, 569-70.) These results established that an anti-CGRP antagonistic antibody or a receptor inhibitor produces similar *in vivo* effects. (Ex. 1016 ¶¶61, 154.)

Accordingly, a POSA would have reasonably expected that a humanized anti-CGRP antagonist antibody would successfully 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. 1016 ¶156.)

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

A POSA would have had a reasonable expectation of success of making a humanized anti-CGRP antagonist IgG antibody that specifically binds to human

[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. 1016 ¶¶157-160; 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.").)

CGRP for treating migraine.

The first step in making a humanized anti-CGRP antagonist antibody that binds to human CGRP would have been to make a murine monoclonal anti-CGRP antagonist antibody that binds to human CGRP. (Ex. 1017 ¶42.) Such antibodies, and techniques for making them, are extensively described in the prior art. (Ex. 1021, 704; Ex. 1001, 28:10-16; *supra* § IV.E.) As a result, a POSA would have reasonably expected to succeed in making a murine anti-CGRP antagonist antibody that specifically bound *human* CGRP like those reported in Tan, Wong, Andrew, and elsewhere. (Ex. 1017 ¶¶99-103; Ex. 1021, 706, 709; Ex. 1022, 572; Ex. 1055, 88, 90, 93.) The '907 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, 28:10-11; *see also* 28:11-14 ("[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. 1016 ¶162; Ex. 1017 ¶104.) Queen, for example, discloses humanization techniques that were known as the "gold standard" for

producing humanized antibodies. (Ex. 1016 ¶162; Ex. 1017 ¶¶48, 105; *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. 1017 ¶105; Ex. 1023, Abstract, 2:28-34.) Humanized antibodies made with a human IgG scaffold contain the following features (and thus a POSA would have reasonably expected that humanized anti-CGRP antagonist IgG antibodies would have them):

- Two human IgG heavy chains. (Ex. 1058, 95, 100.)
- Each heavy chain comprising three CDRs and four framework regions. (*Id.*, 100-01.)
- Portions of the two heavy chains together forming an Fc region. (*Id.*, 96.)
- Two light chains. (*Id.*, 95, 100.)
- Each light chain comprising three CDRs and four framework regions. (*Id.*, 100-01.)

(Ex. 1016 ¶163; Ex. 1017 ¶¶106-107; *see supra* § IV.D.)

Because Queen teaches humanization techniques that maintain an antibody's binding specificity after CDR grafting, a POSA would have reasonably expected that

the CDRs grafted from a donor antibody to a human IgG antibody scaffold would impart the same or similar binding affinity and specificity as the donor murine antibody. (Ex. 1023, 2:61-3:32, 3:33-41; Ex. 1017 ¶107.) Thus, a POSA would have expected the CDRs of the resulting humanized antibody to impart specific binding to human CGRP (i.e., SEQ ID NO: 15 and/or SEQ ID NO: 43), just like the monoclonal anti-CGRP antagonist antibodies of the prior art. (Ex. 1017 ¶107; Ex. 1021, 707, 709; Ex. 1022, 572; Ex. 1033, 97, 102; Ex. 1055, 90.)

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 provisional 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 '907 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.E.) Thus, the prior art provides a reasonable expectation of success in making a humanized anti-CGRP antagonist IgG antibody that specifically binds to human CGRP that would be effective for 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 '907 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).)

Contrary to Teva's assertions, Tan fully supports the obviousness of treating patients with a full-length anti-CGRP antagonist antibody. (Ex. 1016 ¶¶141-144; Ex. 1017 ¶¶97-98.) 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. (*Id*., 569, 571; Ex. 1016 ¶59; Ex. 1017 ¶98.)

Tan also made specific recommendations for improving the *in vivo* efficacy of full-length anti-CGRP antagonist antibodies. (Ex. 1022, 571; Ex. 1016 ¶¶142-

143; Ex. 1017 ¶98.) 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. 1016 ¶143.) 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**
"In Tan, only the Fab' fragment (and NOT the full antibody) 'was found to be	"With repeated administration IgG should eventually distribute into

an effective tool for blockade' in the hind paw . . . ." (Ex. 1136, 4 (quoting Ex. 1022, 570).)	interstitial space and achieve the sufficiently high concentrations required for immunoblockade." (Ex. 1022, 571.)
"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).)	"Given an adequate incubation period in a tissue bath, Mab C4.19 IgG *clearly diffuses into the synaptic cleft* since it was effective at blocking CGRP released from primary afferent nerves by capsaicin *in vitro*." (Ex. 1022, 571.)
"In Tan . . . 'the most likely barrier to effective immunoblockade with IgG *in vivo* is a transport limitation due to poor capillary permeability." (Ex. 1136, 4 (quoting Ex. 1022, 570-71).)	"The slow distribution of whole IgG to the site of immunoblockade could be overcome by . . . *chronic administration of IgG* . . . . With *repeated administration* IgG should eventually distribute into interstitial space and achieve the sufficiently high concentrations required for immunoblockade." (Ex. 1022, 571.)

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 when stimulated by αCGRP, 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. 1016 ¶143.) 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. 1016 ¶143.) 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. 1016 ¶144.)

Tellingly, the '907 patent merely followed Tan's guidance. When testing full-length anti-CGRP antagonist antibodies in the rat saphenous nerve model used in Tan, the '907 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. (*Id*. ¶¶96-105; *see also id.* ¶¶106-108; Ex. 1001, Examples 3 and 5.) For example, the '907 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. 1016 ¶¶96-98; 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. 1016 ¶¶96-98, 100-102; Ex. 1001, 56:52-56; 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 treating migraine. (Ex. 1016 ¶¶141-144.)

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

The subject matter of claim 1 as a whole would have been obvious to a POSA. (*See supra* §§ VII.A-C; Ex. 1016 ¶¶11-15, 165-167, 193; Ex. 1017 ¶¶12-15, 79-82, 129-130.) By 2005, Olesen's breakthrough results had confirmed the clinical viability of targeting and blocking the CGRP pathway for 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 IgG antibody that specifically binds human CGRP for use in treating migraine, which would possess the "generic" heavy—and light—chain features recited in Teva's claims. A POSA also would have had a reasonable expectation of success because anti-CGRP antagonist antibodies that specifically bind human CGRP had been made previously using known techniques, and because humanization, as the '907 patent acknowledges, was routine by November 2005.

(Ex. 1016 ¶¶11-15, 165-167, 193; Ex. 1017 ¶¶12-15, 79-82, 129-130.) By applying routine humanization processes such as those disclosed in Queen, a POSA would have expected the resulting antibodies to be suitable for administration in humans. (Ex. 1023, 3:55-59.)

Consequently, claim 1 encompasses nothing more than the routine use of known antagonist antibodies, consistent with their established function, for the known use of treating migraine. This is not inventive. *KSR*, 550 U.S. at 401.

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

Claims 2-18 depend directly or indirectly from claim 1 and also include limitations previously described in the prior art. For the reasons provided above in § VII, and for the additional following reasons, the asserted art would have rendered obvious claims 2-18.

A. Claim 2

Claim 2 depends directly from claim 1 and recites that the "antibody is formulated with a pharmaceutically acceptable carrier, excipient, or stabilizer." The prior art had already described such compositions. (Ex. 1016 ¶169; Ex. 1017 ¶110.) For instance, Tan's antibody preparations contained PBS (phosphate buffered saline), one of the pharmaceutically acceptable carriers expressly identified in the '907 patent. (Ex. 1001, 19:59-63; 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 '907 patent indicates that pharmaceutical formulations, including pharmaceutically acceptable excipients, of antibodies were well known. (Ex. 1001, 19:59-20:3, 21: 29-32, 22:3-13.)

Claim 2 is therefore obvious. (Ex. 1016 ¶169; Ex. 1017 ¶¶109-111.)

B. Claims 3 and 4

Claims 3 and 4 recite certain routes of administration, including intravenous and subcutaneous administration. Olesen administered its CGRP antagonists for treatment of migraine via intravenous administration. (Ex. 1023, 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 '907 patent acknowledges that intravenous and subcutaneous administration were known in the art. (Ex. 1001, 21:39-47.)

Thus, a POSA would have been motivated to administer a humanized anti-CGRP antagonist antibody intravenously or subcutaneously for treating migraine, and would have had a reasonable expectation of success. Claims 3 and 4 are therefore obvious. (Ex. 1016 ¶¶170-172; Ex. 1017 ¶113.)

C. Claims 5 and 6

Claims 5 and 6 specifically encompass treating migraine. These claims are obvious for the reasons explained above. (*See supra* § VII.)

D. Claim 7

Claim 7 directly depends from claims 1 and recites a dose of "at least 3 μg/kg." Tan administered its anti-CGRP antagonist antibodies within this range. (Ex. 1016 ¶175.) 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 ~71 μg/kg, significantly more than the 3 μg/kg floor recited in claim 7. Moreover, as of Teva's earliest filing date, every FDA-approved antibody therapy recommended doses of greater than 3 μg/kg. (Ex. 1016 ¶176.) Claim 7 is obvious. (*Id*. ¶¶174-176.)

E. Claims 8, 11, and 15

Claims 8, 11, and 15 depend directly from claim 1 and recite that the anti-CGRP antagonist antibody have IgG_1, IgG_2, or IgG_4 constant regions, respectively. These claims would have been obvious. (*Id*. ¶177; Ex. 1017 ¶114.)

A POSA would have been motivated to treat migraine with a humanized anti-CGRP antagonist antibody that has a human IgG_1, IgG_2, or IgG_4 heavy chain

constant region, and would have had a reasonable expectation of success. (Ex. 1016 ¶¶177-181; Ex. 1017 ¶¶114-119.) The IgG class of antibodies has only four subclasses, designated as IgG_1, IgG_2, IgG_3, and IgG_4, which presents a very limited number of options. (Ex. 1016 ¶178; Ex. 1017 ¶¶23, 115; Ex. 1058, 95; Ex. 1063, 68.) The differences among these subtypes lie in their constant regions, which can affect the effector functions of the antibody. (Ex. 1017 ¶23; *see* Ex. 1063, 68.) The '907 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, 12:64-65, 41:11-33 ("the constant region is modified as described" in prior art references); Ex. 1017 ¶68.)

Queen describes humanizing antibodies using constant regions from any of the IgG subclasses. (Ex. 1023, 11:4-20; Ex. 1017 ¶115.) It was well known that when humanizing an IgG 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. 1017 ¶44.)

A POSA would have had a motivation and a reasonable expectation of successfully using a human IgG_1 constant region to treat migraine, as recited in claim 8, because the IgG_1 subclass is the most prevalent IgG subclass in human serum. (Ex. 1059, 142; Ex. 1017 ¶116; Ex. 1016 ¶180.) As of 2005, it was also the most

common subclass of FDA-approved therapeutic humanized antibodies. (Ex. 1056, 1075; Ex. 1017 ¶116; Ex. 1016 ¶180.)

A POSA also would have been motivated to use a human IgG_2 (claim 11) or IgG_4 (claim 15) constant region to treat migraine with a reasonable expectation of success. (Ex. 1017 ¶¶117-118; Ex. 1016 ¶¶178-179.) The IgG_2 and IgG_4 subclasses were 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."); Ex. 1017 ¶118 (discussing examples where developers selected the IgG4 subclass for FDA-approved antibodies); Ex. 1103, 1; Ex. 1104, 3; Ex. 1105, 2375.) Specifically, the IgG_2 and IgG_4 subclasses were known to have relatively weak effector functions, which was viewed as desirable for treating migraine. (Ex. 1016 ¶178; Ex. 1017 ¶117; Ex. 1065, 1357-58.) The IgG_2 and IgG_4 subclasses were also known to have longer half-lives, which would also be desirable for treating migraine. (*See* Ex. 1106, 240 (the IgG_4 isotype was selected for Mylotarg® "because it is the least likely to participate in immune-mediated mechanisms such as complement fixation and antibody-dependent cellular cytotoxicity (ADCC) and because it has the longest circulating half-life of all isotypes").)

As explained above, as of 2005, it would have been routine to generate the claimed humanized anti-CGRP antagonist antibodies of claims 8, 11, and 15. (*Supra* §§ IV.C-E, VII.B.) These claims are also obvious.

F. Claims 9, 12, 13, and 16

Claims 9, 12, and 16 depend from claims 8, 11, and 15, respectively, and recite that the CDRs of the anti-CGRP antagonist antibody "impart to the antibody specific binding to a fragment of the CGRP comprising amino acid residues 8 to 37 of [human αCGRP]." Claim 13 depends from claim 11 and recites that the CDRs "impart to the antibody specific binding to a fragment of the CGRP comprising amino acid residues 33 to 37 of [human αCGRP]." The additional limitations of these claims merely recite well-known properties of anti-CGRP antagonist antibodies, and thus would have been obvious.

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. 1016 ¶183; Ex. 1017 ¶121.) 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, 26:28-32, 51:48-55; Figure 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 regions recited in claims 9, 12, 13, and 16. (Ex. 1016 ¶183; Ex. 1017 ¶121.)

In addition, before 2005, it was known that the C-terminal region of CGRP was responsible for receptor binding. (Ex. 1034, 117; Ex. 1016 ¶183; Ex. 1017 ¶122; 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 treat migraine, a POSA would have been motivated to make and use a humanized anti-CGRP antagonist antibody that binds to the claimed fragments or epitopes within the C-terminal region because such antibodies would have been expected to disrupt the interaction between CGRP and its receptors. (Ex. 1016 ¶183; Ex. 1017 ¶¶121-123; 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. 1016 ¶¶183-184; Ex. 1017 ¶¶121-123; Ex. 1048, 258; Ex. 1033, 99, 102.) Claims 9, 12, 13, and 16 are therefore obvious. (Ex. 1016 ¶185; Ex. 1017 ¶123.)

G. Claims 10, 14, and 17

Claims 10, 14, and 17 depend from claims 8, 11, and 15, respectively, and recite that the "CDRs of the humanized monoclonal antibody are derived from mouse, rat, or rabbit CDRs." These claims are also obvious.

The anti-CGRP antagonist antibodies of Tan 1995 were derived from mice. (Ex. 1021, 704; Ex. 1016 ¶187; Ex. 1022, 566; Ex. 1017 ¶125.) Queen describes humanizing non-human monoclonal antibodies (e.g., mouse or rat) by grafting the CDR amino acid sequences from donor mouse or rat antibodies (such as Tan's) into a human IgG scaffold. (Ex. 1023, 2:61-2:65, 12:1-4; Ex. 1016 ¶187; Ex. 1017 ¶125.) And Queen discloses that its humanization techniques maintain the original binding attributes of the non-human antibodies. (Ex. 1023, 3:33-41; Ex. 1016 ¶187; Ex. 1017 ¶¶48-54, 125.) By following Queen's humanization processes, a POSA therefore would have expected to make and use humanized IgG_1, IgG_2, or IgG_4 antibodies with CDRs derived from the mouse CDRs of the donor murine antibodies. (*See supra* § VII; Ex. 1016 ¶¶186-187; Ex. 1017 ¶125.)

H. Claim 18

Claim 18 depends from claim 15 and recites a constant region that "comprises a mutation in an oligosaccharide attachment amino acid residue that is part of an N-glycosylation recognition sequence in the constant region."

An IgG antibody may be modified with oligosaccharides, referred to as "glycosylation." (Ex. 1059, 142-43; Ex. 1064, 27; Ex. 1017 ¶21.) For example, the constant region has a conserved asparagine residue (Asn297), which can serve as a bonding site for a range of oligosaccharides. (Ex. 1064, 27; Ex. 1017 ¶21.) Because the nitrogen of the amide group of asparagine can form a covalent link with an oligosaccharide, such modification is generally referred to as "N-glycosylation." (Ex. 1017 ¶21.) The N-glycosylation of an IgG antibody is depicted with green hexagons in Figure 1 above.

A POSA would have been motivated to mutate an oligosaccharide attachment amino acid residue in the constant region of an IgG_4 anti-CGRP antagonist antibody to reduce the effector functions of the antibody. (*Id*. ¶¶127-128; Ex. 1016 ¶190.) Removing an oligosaccharide attachment point was known to significantly reduce effector functions that may negatively impact the therapeutic effect of an antibody. (Ex. 1017 ¶¶27, 127-128; Ex. 1016 ¶190; Ex. 1064, 27-28; Ex. 1067, 2595.) Thus, by 2005, mutating the oligosaccharide attachment amino acid and replacing it with an amino acid that lacks the basic nitrogen of asparagine was a well-recognized

strategy for making antibodies that lack their natural effector functions to treat diseases such as migraine. (Ex. 1017 ¶¶27, 44; Ex. 1066, 734.)

A POSA also would have reasonably expected to make and use an antibody with an IgG_4 constant region that includes a mutation in an oligosaccharide attachment amino acid, as this was routine. (Ex. 1017 ¶¶127-128; Ex. 1016 ¶191.) Indeed, the prior art had already demonstrated that oligosaccharide attachment residues could be successfully mutated. (Ex. 1067, 2595.) The '907 patent admits that various ways to make aglycosylated constant regions were known in the art. (Ex. 1001, 41:19-33 (citing prior art references published in 1989 and 1998).)

Accordingly, a POSA would have been motivated to make an anti-CGRP antagonist antibody falling within the scope of claim 18 to treat migraine with a reasonable expectation of success. (Ex. 1016 ¶¶188-192; Ex. 1017 ¶¶127-128.)

IX. 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 treating any type of headache with humanized monoclonal anti-CGRP antagonist IgG antibodies that specifically bind to human CGRP. Despite this breadth, the '907 patent discloses just one specific humanized anti-CGRP antagonist antibody and its highly homologous derivatives. (*E.g.*, Ex. 1001, Abstract, Example 4.)

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. 1016 ¶¶141-145.)

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 that specifically bound to both forms of human CGRP and antagonized its activity *in vivo*. (Ex. 1127, 13, Example 5.) Lilly further described the use of humanized antibodies with framework and constant regions encoded by human IgG genes. (*Id*., 19-23.) Lilly also specifically disclosed the use of humanized anti-CGRP antagonist antibodies to treat and prevent migraine.[3]

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

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 treating headache.

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.

X. 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. The Examiner did not cite Olesen, Tan, or Queen in any Office Action, which is unsurprising given that Teva listed these references in Information Disclosure Statements containing over 450 references. (Exs. 1217-1219.) 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.

XI. 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. 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 '907 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. Lilly filed a petition for *inter partes* review against U.S. Patent No. 8,586,045 on September 28, 2018, and the petition is pending before the Board as IPR2018-01710. Lilly has also co-filed a petition for *inter partes* review against U.S. Patent No. 9,884,908.

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.

XII. 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.

XIII. 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: October 1, 2018 By: /William B. Raich/
William B. Raich (Reg. No. 54,386)

CERTIFICATION OF COMPLIANCE

The undersigned hereby certifies that the foregoing Petition contains 12,998 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 October 1, 2018, a copy of the foregoing **Petition for *Inter Parties* 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. 9,884,907:

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. 9,884,907:

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Date: October 1, 2018

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