UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

TEVA PHARMACEUTICALS INTERNATIONAL GMBH and TEVA PHARMACEUTICALS USA, INC.,	*	
Plaintiffs,	*	Civil Action No. 18-cv-12029-ADB
v.	*	
ELI LILLY AND COMPANY,	*	
Defendant.	*	

MEMORANDUM & ORDER ON CROSS-MOTIONS FOR SUMMARY JUDGMENT

Plaintiffs Teva Pharmaceuticals International GmbH and Teva Pharmaceuticals USA, Inc. (collectively, "Teva") and Defendant Eli Lilly and Company ("Lilly"), competing pharmaceutical companies, have both developed antibodies capable of treating headache disorders associated with calcitonin gene-related peptide ("CGRP"). In the instant case, Teva alleges that Lilly has infringed three of its patents[1] (the "Patents-in-Suit"), seeks a declaration that Lilly is judicially estopped from raising arguments that conflict with arguments it made in prior *inter partes* review ("IPR") proceedings, and argues that Teva does not have unclean hands or engage in inequitable conduct. Lilly, in turn, seeks declarations that its product, Emgality®, also known as Galcanezumab, does not infringe the patents, willfully or otherwise, and that the asserted patents are invalid under 35 U.S.C. § 112.

[1] U.S. Patent Nos. 8,586,045 (the "'045 patent"); 9,884,907 (the "'907 patent"); and 9,884,908 (the "'908 patent").

I. FACTUAL BACKGROUND

After weeding through the more than 1,296 pages of asserted facts and responses, the following facts are undisputed except where otherwise noted.

A. Migraine, Headache Disorders & CGRP

"Migraine is a common chronic, recurrent neurological disorder that affects greater than 10% of adults globally and approximately 39 million individuals in the United States." [ECF No. 400 ¶ 106 (citation omitted)].[2] It is among the more than 200 classifications of headache disorders listed by the International Classification of Headache Disorders, 2nd edition. [Id. ¶ 110].

CGRP is a neuropeptide that, as of 2005–2006,[3] was understood to be involved in head pain in a variety of contexts, including migraine headaches. [ECF No. 400 ¶¶ 114, P47]. At that time, CGRP had been the subject of thousands of peer-reviewed articles, [id. ¶ P46], and drugs affecting the CGRP pathway were used to treat migraine and other forms of headaches, [id. ¶ P48]. CGRP has four functional regions: (1) the N-terminal end; (2) the mid-region; (3) a hinge-like region; and (4) the C-terminal end. [Id. ¶ 113].

B. Antibodies

An antibody, or immunoglobin, is a specialized protein molecule that recognizes and binds to a target molecule known as an antigen. [ECF No. 400 ¶ 26]. "The main function of

[2] The Court draws the facts primarily from the parties' Reply Statements of Material Facts, [ECF Nos. 387 (Unclean Hands), 389 (Judicial Estoppel), 395 (Willful Infringement), 400 (Written Description), 406 (Non Infringement), and 411 (Lack of Enablement)], which contain both parties' positions on the material facts, and the documents referenced therein. The Court further notes that citations to specific paragraphs are inclusive of the response to said paragraph.

[3] The Court looks to scientific knowledge as of 2005 to 2006 because the Patents-in-Suit claim priority to Provisional Application No. 60/736,623, which was filed on November 14, 2005, and to Application No. 12/093,638, which was filed on November 2, 2006. [ECF No. 411 ¶ 142].

antibodies is to bind to antigens and neutralize them or to mark them for destruction." [Id. ¶ 48]. The portion of an antigen that is bound by an antibody is called an epitope. [Id. ¶ 27]. Antibodies themselves are made up of amino acids that are connected to each other in linear chains, often referred to as amino acid sequences. [Id. ¶ 29].

Typical full-length antibodies have four chains of amino acids: two identical heavy chains and two identical light chains. [ECF No. 400 ¶¶ 30, 32]. Each heavy chain and each light chain has a variable domain and each variable domain has three complementarity determining regions ("CDRs"). [Id. ¶¶ 31–33]. Thus, a typical full-length antibody has six unique CDRs and two unique variable domains. See [id. ¶¶ 32–33, 68, P35, P104]. The CDRs, which combine to form the variable domains, form the primary binding interface between the antibody and the epitope of the antigen, [id. ¶ 37], with the amino acid sequence of each of the CDRs causing the variable domains to adopt unique three-dimensional structures, [ECF No. 406 ¶¶ 17–18]. The amino acid sequence of the variable region differs for each antibody, [ECF No. 400 ¶ 34], and contains approximately 220 amino acid residues, [id. ¶ 35].

The number of possible permutations of antibodies is extraordinarily broad. See [ECF No. 400 ¶ 59]. The claims in the Patents-in-Suit, however, do not claim every antibody that could possibly be generated, rather they claim "a specific subset of anti-CGRP antibodies that antagonize CGRP function." [Id. ¶ 66 (quoting ECF No. 296-64 ¶ 206)]. Lilly argues that this subset of antibodies would nonetheless be extraordinarily hard to identify because "[a]s of 2005–2006 it was not possible to predict an antibody's function based on its amino acid sequence." [Id. ¶ 72]. Teva disputes this, arguing that, by that time, "it was well known that antibodies have common amino acid sequences that contribute in known ways to known functions, including antibodies generally and antibodies within particular known classes." [Id.].

C. Development of Antibodies for Therapeutics

To be safe and effective as a treatment for any type of headache disorder, an antibody must share certain general characteristics with naturally occurring human antibodies. See [ECF No. 400 ¶¶ 93–94]. If it does not, the antibody may be recognized by the body as foreign and become the target of a potentially dangerous immune response, resulting in the elimination of the antibody, a loss of therapeutic efficacy, and possibly serious allergic reactions. [Id. ¶ 93].

As of 2005–2006, one of the processes used to develop new therapeutic antibodies involved the use of murine (*i.e.*, mouse) antibodies. [ECF No. 400 ¶ 91]. These murine antibodies were generated by injecting mice with an antigen of interest, which caused the mouse to produce a type of white blood cell, referred to as B cells, that, in turn, produced a large variety of antibodies to protect against what the mouse's immune system perceived as a foreign antigen. See [id. ¶¶ 91–92]. Scientists then could isolate a B cell, fuse it to a cancer cell to form a hybrid cell known as a hybridoma, which then produced antibodies having an identical amino acid sequence (*i.e.*, "monoclonal" antibodies). [Id. ¶ 92]. An antibody produced in this way is not human, however, and to avoid human immune systems rejecting the foreign antibody, it was necessary to use genetic engineering to "humanize" the murine antibodies. [Id. ¶¶ 93–94]. This process involved replacing portions of the genes encoding the murine antibody with portions that encode a human antibody. [Id. ¶ 94]. As of 2005–2006, humanization of murine antibodies was sufficiently established to be considered "conventional" and "routine," but the parties dispute how labor intensive and time consuming the process was. See [id. ¶¶ 95–98, P8, P54, P64–66].

D. Key Antibody Attributes

To be effective in treating headache disorders caused by CGRP, an antibody produced by the methods previously described must possess several characteristics. Among the most important is its "affinity" for the target antigen, which refers to how strongly the antibody

attaches to the target. [ECF No. 400 ¶ 42]. One measure of affinity is the dissociation constant of the antibody-antigen interaction, or "K_D" value. See [id. ¶ 189]. A related property is an antibody's "neutralizing" capability, meaning its ability to inhibit the biological activities of the antigen to which it binds. [Id.]. A high affinity is integral to an antibody's neutralizing capability, otherwise the antibody will not effectively inhibit the target antigen (*e.g.*, CGRP). See [id. ¶ P67].[4]

E. The Asserted Patents and Specifications

Teva asserts twenty claims from three patents: the '045, '907, and '908 patents. See [ECF No. 400 ¶ 1; ECF No. 298 at 6]. The patents each claim the use of human or humanized anti-CGRP antagonist antibodies[5] to treat vasomotor symptoms, such as headaches. [ECF No. 400 ¶ 185–86]. The '045 patent is titled "Methods of Using Anti-CGRP Antagonist Antibodies," and the '907, and '908 patents share the title "Methods for Treating Headache Using Antagonist Antibodies Directed Against Calcitonin Gene-Related Peptide." [ECF No. 387 ¶¶ 1, 3, 5]. Named inventors for all three patents include, among others, Joerg Zeller, Kristian T. Poulsen, Yasmina Noubia Abdiche, and Jaume Pons. [Id. ¶¶ 2, 4, 6]. Each of the Patents-in-Suit claim priority to Provisional Patent Application No. 60/736,623, which was filed on November 14, 2005, and to Application No. 12/093,638, which was filed on November 2, 2006, [ECF No. 400 ¶ 183], and later published on May 18, 2007 as International Publication Number WO 2007/054809 (the "'809 application"), [ECF No. 395 ¶ P2].

[4] Teva objects to Paragraph P67, [ECF No. 400 ¶ P67], but does not dispute that antibodies that bind to the C-terminal, mid-, or N-terminal regions of CGRP can all antagonize CGRP if they exhibit high enough binding affinity and block CGRP's interaction with the CGRP receptor.
[5] The Court has construed the term "anti-CGRP antagonist antibody" as "an antibody that is able to bind to CGRP and inhibit CGRP biological activity and/or downstream pathway(s) mediated by CGRP signaling." [ECF No. 101 at 11].

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