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 IPR2018-01710 (Patent No. 8,586,045)
Case IPR2018-01711 (Patent No. 9,884,907)
Case IPR2018-01712 (Patent No. 9,884,908)[1]

PETITIONER'S REPLY TO PATENT OWNER'S PRELIMINARY RESPONSE

[1] Lilly was authorized to file this Reply pursuant to the Board's email sent on January 16, 2019. The word-for-word identical paper is filed in each proceeding identified in the caption, pursuant to the Board's previous order. For convenience, citations refer to papers filed in IPR2018-01710 involving Teva's Patent No. 8,586,045. Emphases are added unless otherwise noted. Lilly does not acquiesce to any of Teva's arguments not specifically addressed herein.

I. Introduction

Teva's § 325(d) arguments are unavailing. First, none of Lilly's asserted references—Olesen, Tan or Queen—was used to reject any claims of the '045, '907, or '908 method-of-treatment patents during prosecution. Second, the asserted references are not cumulative of the Frobert and Pisenga references used to reject *composition* claims. Indeed, Lilly's asserted references and expert testimony[2] establish an explicit motivation to make humanized anti-CGRP antagonist antibodies to treat migraine, which Teva argues was missing during prosecution. Third, Lilly specifically addressed how Teva's one-sided arguments regarding Tan were incorrect. Thus, the *Becton* factors strongly favor institution.

II. Lilly's Asserted References Were Not Used to Reject Any Claims

During prosecution of the '045, '907, and '908 patents, the Examiner did not make any art-based rejections. Ex. 2034, 459-73; Ex. 2044, 172-78; Ex. 2045, 185-92. In fact, Olesen and its key teaching that blocking the CGRP pathway effectively treated migraine in human patients was *not even of record* in the '045 patent. POPR, 16. Because the Office did not consider Olesen, much less in a

[2] Teva's reliance on *Invidior*, *Argentum*, *Dorco*, *Hologic*, *Siemens*, and *Telebrands* (POPR, 28) is misplaced because those cases did not involve new, noncumulative references and disclosures in addition to undisputed expert testimony.

combination with Tan and Queen, a § 325(d) denial is not warranted.

III. Lilly's Asserted References Are Not Cumulative

Olesen is not cumulative of any purported consideration by the Examiner of the specification's limited disclosures about BIBN4096BS. *See* POPR, 17. Olesen itself was never cited, and BIBN4096BS itself is referred to in the Background section only once. Ex. 1001, 2:14-18. Moreover, Lilly's use of Olesen is not restricted to "its [alleged] teaching that a small molecule CGRP-receptor antagonist BIBN4096BS *could* be used to treat migraine," as Teva incorrectly contends. POPR, 16-17. Instead, Lilly and its unrebutted evidence[3] demonstrates that Olesen's proof-of-concept study (1) "established that blocking the *CGRP pathway* reduced the incidence of migraine;" (2) "demonstrates that CGRP itself—and *not only its receptors*—was also a therapeutic target;" and (3) "confirmed the reasonable expectation that a *CGRP antagonist* could be successfully used to reduce incidence of or treat migraine." *E.g.*, Pet., 25-26, 38 (emphases added); *see also id.*, 1, 15.

Teva's reliance on Example 6 is also misplaced. Example 6 merely compares

[3] Teva did not respond to Lilly's background references except to incorrectly argue that the Board should ignore them. POPR, 33-34; *Genzyme Therapeutic Prods. Ltd. P'ship v. Biomarin Pharm. Inc.*, 825 F.3d 1360, 1369 (Fed. Cir. 2016) (the Board should consider references illustrating the state of the art under § 103).

the effects of BIBN4096BS and a *murine*—not humanized—monoclonal anti-CGRP antibody in an *in vivo* animal model. Ex. 1001, 68:64-67, 69:25-27; *see also id.*, 10:62-11:7. Olesen, by contrast, demonstrates that blocking the CGRP pathway *had already been shown to effectively treat migraine in humans*. Teva's brief discussion of Example 6 in response to an enablement rejection (Ex. 2034, 497) did not inform the Examiner of Olesen's successful treatment of migraine in humans.

Further, Teva's § 325(d) position relies heavily on a rejection over Frobert and Pisegna made during prosecution of each of the '794 and '649 *composition* patents. *E.g.*, POPR, 18-19, 22, 24-25. But Teva fails to explain how that one art-based rejection is applicable to method of treatment claims that the Office and Teva treated as separately patentable. Ex. 2033, 391-97, 403-09; Ex. 2034, 331-32; Ex. 2044, 172-78; Ex. 2045, 185-92; *Vizio, Inc. v. Nichia Corp.*, IPR2017-00551, Paper 9 at 8 (PTAB July 7, 2017) (rejecting § 325(d) argument where there was "no evidence that the Examiner considered[] [the prior art] *in the context of the claims of the [challenged] patent*"). Thus, prosecution of Teva's *composition* patents poses no basis for a § 325(d) denial here.

Even if Teva's arguments are considered, however, Olesen is not cumulative of Pisegna or Frobert. Frobert relates to an immunoassay for measuring biological levels of CGRP. Ex. 1032, 275. Pisegna focuses on isolating the CGRP receptor itself, and its antibody disclosure is limited to rat antibodies that were not tested in

any way. Ex. 1134, ¶ [0002], Example 1. Neither reference discloses successful treatment of migraine in humans with a CGRP antagonizing agent.

Nor is Tan cumulative of Frobert and Pisegna.[4] Teva attempts to cabin Lilly's reliance on Tan to its disclosure of murine anti-CGRP antibodies. POPR, 19. But as Lilly and its experts have established, Tan discloses that anti-CGRP antagonist antibodies (1) effectively block the CGRP pathway *in vivo*, (2) were known alternatives to CGRP receptor antagonists (such as $CGRP_{8-37}$ or Olesen's BIBN4096BS) for blocking the CGRP pathway *in vivo*, and (3) "clearly diffuse[] into the synaptic cleft," i.e., the site of action that Teva alleges is necessary for *in vivo* effectiveness. Pet. 24, 26-27, 43-48; Ex. 1014, ¶¶ 111, 118. Neither Frobert nor Pisegna contains these disclosures. Nor do they describe Tan's guidance to use higher doses and longer distribution times of antibodies to reach the site of action, which Teva followed in its specification. Pet., 43-48; Ex. 1014, ¶¶ 88-100.

Instead, Olesen's disclosure that blocking the CGRP pathway is effective for treating migraine—along with Tan's disclosure that anti-CGRP antagonist antibodies are a known "alternative" or "complementary" technique to using CGRP-receptor antagonists—establish a motivation to humanize an anti-CGRP antibody

[4] Contrary to Teva's assertion, the '045 patent was allowed *before* the Examiner received any Tan arguments from Teva. Ex. 2034, 519-24; Ex. 2005, 179-84.

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