teva

2018-01710*
2018-01711
2018-01712

Eli Lilly and Company
v.
Teva Pharmaceuticals International GmbH

Sterne Kessler

January 8, 2020

(* - unless otherwise indicated, all citations to papers refer to IPR2018-01710)

A POSA would not have had a reason to treat migraine with anti-CGRP antibodies with a reasonable expectation of success

A POSA would not have extended Olesen's small-molecule receptor "CGRP antagonists" to anti-CGRP ligand antibodies

- Olesen: The **CGRP antagonist BIBN 4096 BS** was effective in treating acute attacks of migraine. EX1025, Abstract
- Dr. Ferrari: "A POSA reviewing Olesen would not have drawn a conclusion that clinical trials using BIBN4096BS would translate broadly to all 'CGRP antagonism' being effective in treating migraine." EX2268, ¶98; EX1040, 182; EX2265, 60-62; POR, 12-13, Surreply, 6

Tan's full-length antibody did not achieve immunoblockade

- "**only the Fab' fragment** was found to be an effective tool for blockade " in rats. EX1022, 570; POR, 39; EX2265, ¶51.

Active research of anti-CGRP antibodies stopped with Tan

- In the decade between Tan and Teva's invention, multiple companies developed small-molecule, short half-life, receptor antagonists. POR 8-9, EX2268, ¶52; EX2014, Abstract; EX2071, Abstract; EX2009, 617; EX2003, 910; EX2009, 617; EX2012, 769; EX2015; EX2016.

A POSA would not have reasonably expected an anti-CGRP antibody to successfully treat migraine POR, 3-4, 8, 19-20, 35-36, 38-42, 45-47; Surreply, 17-25; EX2265, ¶¶60-68, 88-90, 134; EX1022, 565-566, 571, Abstract; EX2268, ¶¶25-38, 42, 56-57, 75, 88-90; EX1096, 567; EX2161, 6; EX2335, 1; EX2306; EX2291, 4; EX2296, 1452; EX2222, Abstract; EX2310, 5881; EX2223, 2; EX2306, 789.

Teva's invention led to breakthrough migraine therapy POR, 7, 32, 56-59; Surreply, 27-29

Lilly admits that Emgality® satisfied a long-felt, unmet need:

- "[A] Lilly co-authored publication acknowledged that humanized anti-CGRP antibodies were a '[s]afe, effective and well tolerated treatment for the prevention of migraine' that satisfied this 'enormous unmet medical need.'" POR, 59, EX2161, 890; EX2262, ¶40
  - "LY2951742 was effective and generally well tolerated for the preventive treatment of migraine in patients with frequent attacks." EX2161, 890
  - "Safe, effective, and well tolerated treatment for the prevention of migraine represents an enormous unmet medical need." EX2161, 890

The Industry praised the claimed methods of treatment:

- "an enormous step forward" EX2172, 1-2; POR, 56-58; EX2260, ¶54
- "a game changer" EX2179, 4; POR, 56-58; EX2262, ¶56
- a "breakthrough in migraine" EX2174 ,707; POR, 56-58; EX2262, ¶53

Lilly's expert, Dr. Charles, also praised the claimed methods of treatment as:

- "radical concept" EX2053, 23; POR, 7, 32; EX2262, ¶61
- "very exciting and compelling" EX2182, 207; POR, 56; EX2262, ¶61
- "absolutely life-changing" EX2186, 4; POR, 56; EX2262, ¶61
- "spectacular" EX2186, 4-5; POR, 56; EX2262, ¶61

Skepticism surrounded development of anti-CGRP antibodies for treating migraine POR, 61-62; Surreply, 28

Inventor Jaume Pons:

- "Key Opinion Leaders ("KOL") frequently expressed **skepticism** that an antibody like fremanezumab would be able to **treat migraine** because it could not cross the BBB. EX2331, ¶6
- "Pfizer expressed the same **concerns** over fremanezumab's ability to **treat migraine** due to its inability to enter the CNS." EX2331, ¶7
- "After Pfizer acquired Rinat, work on RN307 [fremanezumab] was halted for several years because Pfizer **did not think** that the molecule would **treat migraine**." EX2331, ¶8
- "Several of the [venture capital firms] expressed **skepticism** that **treatment of migraine** was possible with a drug that could not enter the CNS." EX2331, ¶11

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