UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE PATENT TRIAL AND APPEAL BOARD

ELI LILLY AND COMPANY
v.
TEVA PHARMACEUTICALS INTERNATIONAL GMBH

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

ELI LILLY TRIAL DEMONSTRATIVES

January 8, 2020

Demonstrative Exhibits – Not Evidence

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

The Breadth of Teva's Claims

The '045 Patent:

We claim:

1. A method for reducing incidence of or treating at least one vasomotor symptom in an individual, comprising administering to the individual an effective amount of an anti-CGRP antagonist antibody, wherein said anti-CGRP antagonist antibody is a human monoclonal antibody or a humanized monoclonal antibody.

Ex. 1001 ('045 Patent), 99:1-7

The '908 Patent:

We claim:

1. 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:

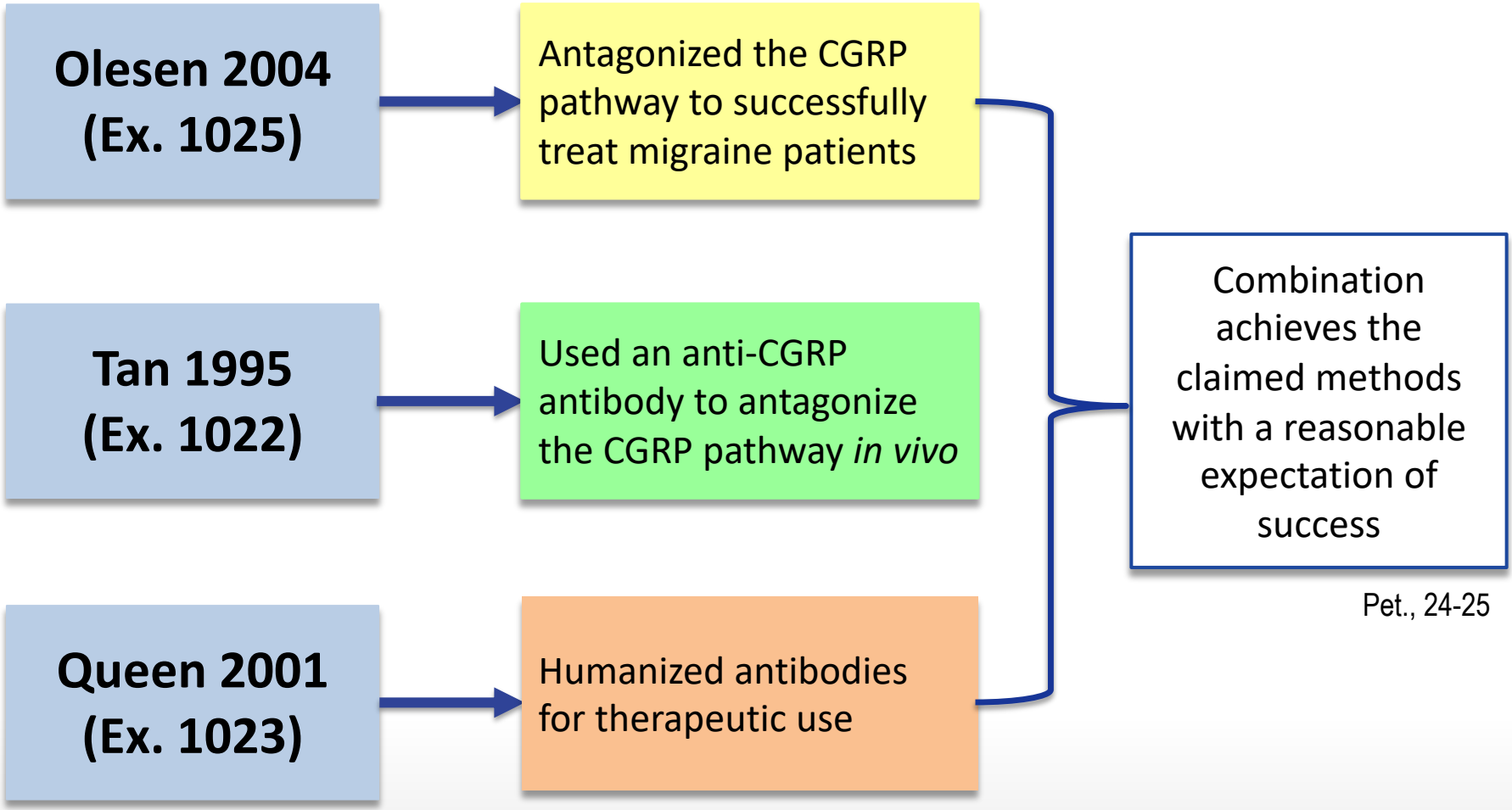
two human IgG heavy chains, each heavy chain comprising three complementarity determining regions (CDRs) and four framework regions, wherein portions of the two heavy chains together form an Fc region; and

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, and wherein the antibody binds to the CGRP with a binding affinity (K_D) of about 10 nM or less as measured by surface plasmon resonance at 37° C.

Ex. 1001 ('908 Patent), 99:54-67, 100:54-58

The Combination of Olesen, Tan 1995, and Queen Renders Teva's Claims Obvious



Pet., 24-25

A POSA in 2005 Expected CGRP Antagonists to Treat Migraine

Doods (Ex. 1024):

"Since several lines of evidence indicate that CGRP might be a key factor in the initiation of migraine headache, we expect that CGRP antagonists will be effective anti-migraine drugs."

Ex. 1024, 422; Ex. 1014, ¶139; Pet., 37

Lassen 2002 (Ex. 1047):

- "CGRP caused headache in virtually all migraine sufferers, whereas placebo did not."
- "This finding greatly increases the likelihood that a CGRP antagonist may be effective in the treatment of migraine attacks."

Ex. 1047, 59, 60; Ex. 1014, ¶¶29, 139; Pet., 11, 37

Wimalawansa (Ex. 1096):

- "Evidence is accumulating that inappropriate release of CGRP is a potential causative factor in several diseases, including migraine"
- "The role of CGRP antagonists and humanized monoclonal antibodies should be explored"

Ex. 1096, 567, 570; Ex. 1014, ¶116; Pet., 29

A POSA in 2005 Expected CGRP Antagonists to Treat Migraine

Olesen (Ex. 1025):

- Multicenter, double-blind, randomized clinical trial of BIBN4096BS
- 126 patients with migraine
- Intravenous administration
- "Proof of concept was thus established."
- Conclusion: "The CGRP antagonist BIBN 4096 BS was effective in treating acute attacks of migraine."

Ex. 1025, 1104, 1108-1109; Ex. 1014, ¶¶31-34; Pet., 25-26

Arndt 2004 (Ex. 1030):

Olesen's data "demonstrate the validity of the CGRP concept paving a novel way in migraine pain treatment."

Ex. 1030, 129; Ex. 1014, ¶¶69, 116; Pet., 15, 30

Dr. Charles:

Olesen's study "encouraged the development of additional agents to treat migraine by blocking the CGRP pathway."

Ex. 1014, ¶109; Pet., 25-26

A POSA in 2005 Expected CGRP Antagonists to Treat Migraine

Dr. Ferrari in 2005:

- "Olesen and colleagues evaluated the effectiveness of the CGRP-antagonist BIBN4096BS for acute migraine treatment….There were no serious adverse events"
- "CGRP antagonists … seem promising, new antimigraine drugs without vascular side effects."

Ex. 1290, 657; Ex. 1338, ¶89; Reply, 5, 12

Dr. Ferrari in 2007:

Olesen's study "firmly establish[ed] blockade of the CGRP pathway as a novel and important new emerging treatment principle for acute migraine."

Ex. 1332, 443; Ex. 1338, ¶29; Reply, 5

Dr. Rapoport in 2005:

Olesen's study "suggests that antagonising the effect of CGRP may provide acute relief of migraine headache. Preventive drugs might be developed on the same principle."

Ex. 1297, S119; Ex. 1338, ¶29; Reply, 5

Well-Known Advantages of Humanized Antibodies for Chronic Treatment

Long Half-Lives to Treat Chronic Migraine Conditions

Ex. 1041, 1073; Ex. 1014, ¶¶124-126; Ex. 1015, ¶55; Pet., 31; Reply, 14

Lower Toxicity and Fewer Side-Effects Compared to Small Molecules

Ex. 1014, ¶127; Ex. 1015, ¶55; Ex. 1337, ¶¶77-79; Pet., 32; Reply, 18

High Affinity and Specificity – "Perfect Tool" for "Disrupting Ligand-Receptor Interactions"

Ex. 1014, ¶132; Ex. 1015, ¶55; Ex. 1266, 521; Pet., 32, 33; Reply, 20

Reduced Immunogenicity in Human Patients

Ex. 1023, 1:44-47; Ex. 1015, ¶¶93-96; Ex. 1014, ¶120; Pet., 33-34

Humanized IgG Antibodies Were a "Clinically Well-Validated Technology"

Ex. 1073, 120; Ex. 1014, ¶119; Ex. 1015, ¶¶41, 93, 98; Pet., 33

Long Half-Life Desired for Chronic Migraine Treatment

Dr. Charles:

- **Episodic Nature of Migraine**: Motivated a POSA "to target long-term approaches for migraine treatment, i.e., a POSA would have looked for drugs that persist in the body long enough to reduce incidence of future migraine attacks."
- **Duration of Attack**: "Because a migraine attack can last anywhere between 4 hours and 3 days, a POSA would have been motivated to look for other drugs that persist in the body for longer periods of time."

Ex. 1014, ¶¶124-126; Pet., 31

Dr. Vasserot:

- **Less-Frequent Administration:** "Full-length antibodies for chronic treatment are desirable because they have longer half-lives and as such would require fewer administrations."
- **Widely Adopted Drug Format:** "[B]y 2005, the discovery and development of therapeutic antibodies had outpaced small molecule drug discovery and development."

Ex. 1015, ¶¶55, 99; Pet., 32, 34

Teva's Experts:

- **Dr. Ferrari**: "short plasma half-life" was a "[m]ain disadvantage" of sumatriptan
- **Dr. Rapoport**: advocated daily triptan administration for a full year
- **Dr. Tomlinson**: long half-life of antibodies provides a "favorable pharmacokinetic profile"

Ex. 1281, S76; Ex. 1294, Abstract; Ex. 1266, 521; Ex. 1338, ¶¶ 18-19; Reply, 14

Teva Admitted CGRP's Involvement in Migraine

Teva Argument:

CGRP not a "biomarker"

Teva Patents:

350:1073-1075, 2004. The serum levels of CGRP in the external jugular vein are elevated in patients during migraine headache. Goadsby et al., Ann. Neurol. 28:183-7, 1990. Intrave-

Ex. 1001 ('045 Patent), 2:7-9; Reply, 6

Possible CGRP involvement in migraine has been the basis for the development and testing of a number of compounds that inhibit release of CGRP (e.g., sumatriptan), antagonize at the CGRP receptor (e.g., dipeptide derivative BIBN4096BS (Boerhringer Ingelheim); CGRP (8-37)), or interact with one or more of receptor-associated proteins, such as, receptor activity membrane protein (RAMP) or receptor component protein (RCP), both of which affect binding of CGRP to its receptors. Brain, S. et al., Trends in Pharmacological Sci-

Ex. 1001 ('045 Patent), 2:14-23; Pet., 7

Spare Receptor Theory and Ligand Cross-Binding Did Not Deter Researchers

Teva Arguments:

Spare Receptor

Sheykhzade 2004 (Ex. 2065):

"In our study, approximately 27% of all receptors must be occupied by CGRP to elicit a half-maximal response (EC_{50}), indicating the presence of a relatively small CGRP1-receptor reserve pool in the human subcutaneous arteries."

Dr. Charles: Ex. 2065, 1071; Ex. 1337, ¶46; Reply, 18-19

"[T]here is no indication that it would be necessary to 'sequester 99,999 ligands' out of 100,000 (i.e., 99.999% of all CGRP molecules) to prevent anti-CGRP antagonist antibodies from eliciting a full clinical response. Rather, clinical evidence indicated that merely normalizing CGRP levels can successfully treat migraine."

Cross-Binding

Dr. Charles: Ex. 1338, ¶117; Ex. 1044, Abstract; Reply, 18-19

- "[C]ross-binding of CGRP to these other receptors was understood to be poor before November 2005."
- "The anti-CGRP ligand aptamers had been shown to inhibit neurogenic blood flow increases in the rat cranial dura (Ex. 1240, 923) just as BIBN4096BS did in Doods (Ex. 1024, 422)."

Ex. 1338, ¶¶121-124; Ex. 2059, Table 1; Ex. 1240, 923; Reply, 19

Extensive Prior-Art Evidence Demonstrates Treatment of Migraine Through Peripheral CGRP Antagonism

Teva Argument: Blood-Brain Barrier

Triptans:

Dr. Ferrari: "Important pharmacological actions of sumatriptan are (i) poor penetration of the blood-brain barrier suggesting a peripheral point of action"

Ex. 1281, S73; Ex. 1338, ¶18; Reply, 9

Aptamers:

Healy: "None of the aptamer conjugates or compositions showed a propensity to traverse the blood/brain barrier."

Ex. 1310, 2244; Ex. 1338, ¶24; Reply, 9

BIBN4096BS:

- **Peterson 2004:** "The present study strongly suggest that the clinically effective migraine drug BIBN4096BS (Olesen et al., 2004) does not cross the BBB." (Ex. 1090, 703)
- **Peterson 2005**: BIBN "prevents or treats headache predominantly in an extracerebral manner." (Ex. 1333, 211)
- **Edvinsson 2005**: BIBN "does not appear to pass the blood-brain barrier freely" (Ex. 2215, 75)
- **Arulmani 2004:** BIBN "does not seem to penetrate the blood-brain barrier" (Ex. 1031, 326)
- **Dr. Foord's testimony**: "it would be unlikely" that BIBN crosses the BBB (Ex. 1343, 76:12-77:8)
- **Storer**: Peripherally administered BIBN "resulted in a dose-dependent inhibition of" trigeminocervical nucleus activity (Ex. 2307, 1175-1176)
- **Fischer**: "Blockade of CGRP receptors, possibly at central and peripheral sites, may therefore be an effective way to decrease nociceptive transmission." (Ex. 2310, Abstract)

- *cf.* **Levy**: "These findings . . . support a central site of action for the role of CGRP in promoting migraine, as well as the antimigraine effect of CGRP antagonism." (Ex. 2298, 704)

Ex. 1338, ¶¶ 36-53; Reply, 7-10; Pet., 32-33

Development of Anti-CGRP Antibodies

1993	Wong	Teaching "specific blocking of endogenous CGRP either at the receptor level using specific CGRP antagonists, or by neutralizing endogenous peptide with a specific antibody." (Ex. 1033, 95)
1994	Tan Thesis	"There seems to be no reason why anti-peptide MAbs should not be investigated as therapeutic agents" for "migraine" (Ex. 1287, 247)
1995	Tan 1995	"Immunoblockade" as "an alternative strategy" or "complementary" to the use of receptor antagonists. (Ex. 1022, 566, 571)
1996	Wimalawansa	"The role of CGRP antagonists and humanized monoclonal antibodies should be explored" (Ex. 1096, 567, 570)
2002	Salmon	Compositions can include anti-CGRP "monoclonal antibodies for the modulation of" "neurogenic inflammatory pain" (Ex. 1027, [0039])
2002	'438 patent	Disclosing and claiming "anti-CGRP antibodies" for therapeutic use (Ex. 1028, claim 2)
2004	Sveinsson	Disclosing and claiming "anti-CGRP antibodies" for therapeutic use (Ex. 1026, claim 2)
2004	**Olesen**	**"Proof of Concept was thus established"** (Ex. 1025, 1109)
2005	Arulmozhi	"[I]nhibition of CGRP or antagonism of CGRP receptors could be a viable therapeutic target for the pharmacological treatment of migraine." (Ex. 1040, 182)

Ex. 1014, ¶¶111, 116-117; Pet., 26- 27; Reply, 6, 15

Teva's Concerns Did Not Deter Development of Anti-CGRP Aptamers

Teva Arguments:

- Blood-Brain Barrier
- Safety Concerns
- Spare Receptor
- Cross-Binding

Pendergrast (Ex. 1309):

"[A]ptamers can be thought of as nucleic acid analogs to antibodies."

Ex. 1309, Abstract; Ex. 1338, ¶24; Ex. 1337, ¶¶ 57, 60; Reply, 13

Healy (Ex. 1310):

"None of the aptamer conjugates or compositions showed a propensity to traverse the blood/brain barrier."

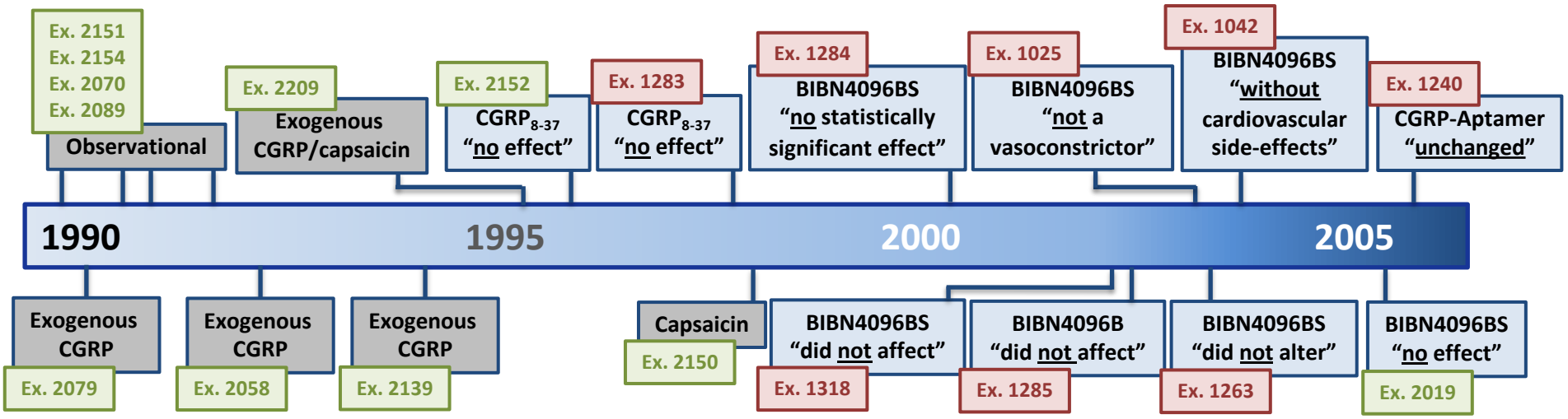
Ex. 1310, 2244; Ex. 1338, ¶24; Reply, 9

Messlinger (Ex. 1240):

- Tested "a new high-affinity CGRP-binding RNA-Spiegelmer, which is a biostable aptamer"
- Efficacy: "Neurogenic blood flow increases in the meninges are reduced by binding of the released CGRP to the Spiegelmer"
- Safety: "Basal blood flow and systemic arterial pressure were unchanged."
- "The Spiegelmer may open a new therapeutic strategy in diseases that are linked to excessive CGRP release such as migraine and other primary headaches."

Ex. 1240, 923; Ex. 1014, ¶62; Pet., 27

Teva's Purported Safety Concerns Were Resolved by November 2005



Dr. Charles:

"There were multiple studies in humans that indicate that, in fact, it was safe to therapeutically target CGRP, and animals also."

Ex. 2338, 40:11-20

Lilly Exhibit

Teva Exhibit

Ex. 1338, ¶¶67-87; Reply, 16-18

Anti-CGRP Antibodies Did Not Raise Safety Concerns

Tan 1995 (Ex. 1022):

MAP gradually recovered within "10 to 15 min" for full-length IgG and Fab' fragment

Ex. 1022, 568; Ex. 1338, ¶¶91-93; Ex. 1337, ¶¶62-66; Reply, 14

Tan's contemporaneous statements:

"There seems to be no reason why anti-peptide MAbs or their fragments should not be investigated as therapeutic agents."

Ex. 1287, 247; Reply, 6, 15

Wong (Ex. 1033):

"The monoclonal antibody had no significant effect on MAP and heart rate (n=6)."

Ex. 1033, 101; Ex. 1338, ¶92; Ex. 1337, ¶¶68-70; Reply, 15

Andrew (Ex. 1055):

"Although the immunized rats had high levels of circulating antibodies to rat CGRP, they did not show any signs of physical or behavioral abnormality."

Ex. 1055, 93; Ex. 1338, ¶98; Ex. 1337, ¶71; Reply, 15

Teva's Patents Do Not Identify or Solve the Problems Teva Raises in this Litigation

***Alcon Research, Ltd. v. Apotex Inc.*, 687 F.3d 1362, 1369 (Fed. Cir. 2012)** (affirming obviousness where purported safety concerns were not addressed in the invalidated patent)

Reply, 4

Teva Arguments:

Safety Concerns | Spare Receptor | Cross-Binding | Blood-Brain Barrier

Dr. Ferrari:

- "There is no text mentioning data from safety studies."
- "The patents do not disclose studies in humans."

Ex. 1303, 56:4-11; Reply, 3

Dr. Foord:

Teva's patent examples "will never satisfy concerns about safety and efficacy."

Ex. 1300, 174:5-11; Reply, 3

Dr. Ferrari:

Teva's patent examples are "not aimed at studying the blood-brain barrier."

Ex. 1345, 61:5-65:2; Reply, 4

Tan 1995 (Ex. 1022): Immunoblockade of CGRP Was Effective *In Vivo*

Tan 1995 (Ex. 1022):

Block hypotensive effect:
"This study has clearly demonstrated the ability of MAb C4.19 IgG and its Fab' fragment to block hypotensive effects of exogenous rat αCGRP *in vivo*.

Rat saphenous nerve effect:
"Further nerve stimulation performed at 2 h after 3 mg/rat MAb produced an AUC which was slightly smaller compared with baseline stimulation, but not by more than 16% (n=2)."

Provided Guidance:

- "The data of Covell et al. suggest that much larger doses and longer distribution times are required for successful immunoblockade with IgG."
- "The slow distribution of whole IgG to the site of immunoblockade could be overcome by the alternative strategies of active immunization with CGRP or 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, 569-571; Pet., 45-46; Reply, 10-11

Dr. Charles:

"A POSA would have been motivated to follow Tan's recommendations because they are consistent with how a POSA would have wanted to reduce incidence of or chronically treat migraine, i.e., with therapeutic agents having high specificity and long half-lives."

Ex. 1014, ¶136; Pet., 46-47

Teva's Synaptic Cleft Size Arguments Are Meritless

Wrong Synaptic Cleft Size:

- **Teva relies on a 20 nm cleft in CNS tissues (Ex. 2280, 333)**
- **Cleft size in tissues relevant to migraine: 100 to several hundred nm (Ex. 1349, 275-277)**

Ex. 2265, ¶90; POR, 37; Ex. 1337, ¶38; Reply, 11

Wrong Antibody Type and Antibody Size:

- **Teva relies on an IgE antibody having 15 nm in its longest direction (Ex. 2281, 1967)**
- **Size of IgG antibodies: ~8-10 nm (Ex. 1347, 7184)**

Ex. 2265, ¶90; POR, 37; Ex. 1337, ¶37; Reply, 11

Ignored Mobility & Three-Dimensional Nature of Antibodies

- **Dr. Balthasar: an antibody may be "rotated or folded such that it has a profile significantly narrower than 15 nm wide" (Ex. 1337, ¶36)**
- **Even IgE antibodies are only 5 nm in profile (Ex. 2281, 1967)**

Ex. 2265, ¶90; POR, 37; Reply, 11

Tan Demonstrates Access to Synaptic Cleft

- **MAb IgG C4.19 "reached equilibrium in the synaptic cleft after 45 min[utes]" (Ex. 1021, 709)**
- **Vas deferens tissues have 20 nm synaptic cleft size (Ex. 1348, 5)**

Ex. 1337, ¶38; Reply, 10-11

Dr. Foord's Admission:

Q: [Y]ou're not an expert in the dynamics of an antibody and how they behave in the synaptic cleft?

A: That is correct.

Ex. 1343, 70:4-9; Reply, 11

Tan Teaches that Anti-CGRP Antibodies Were Expected to Access the Synaptic Cleft

Tan 1995 (Ex. 1022):

antibody distribution characteristics. Covell et al. [14] showed that the time to reach steady-state interstitial to plasma concentration ratio in the carcass (including muscle and skin) was 14 times more rapid for Fab' fragments than for whole IgG.

Ex. 1022, 571; Ex. 1337, ¶29; Reply, 10

Covell (Ex. 1247):

Table 3 *Steady-state interstitial:plasma antibody concentrations (I:P) and time to reach steady state (T_{ss}, min)*

	Whole		$F(ab')_2$		Fab'	
Organ	*I:P*[a]	T_{ss}[b]	*I:P*	T_{ss}	*I:P*	T_{ss}
Gut	0.54	19.2	0.53	21.3	0.80	8.9
Liver	0.97	0.7	0.95	1.1	0.96	1.3
Spleen	0.87	1.0	0.89	0.8	0.97	0.3
Kidney	0.66	2.6	0.63	3.4	0.96	0.1
Carcass	0.18	251.0	0.21	265.2	0.86	17.7
Lung	0.68	0.8	0.69	0.7	0.83	0.6

[a] Calculated by model simulation.
[b] Calculated as $T_{ss} = (V_p + V_i)/PS$.

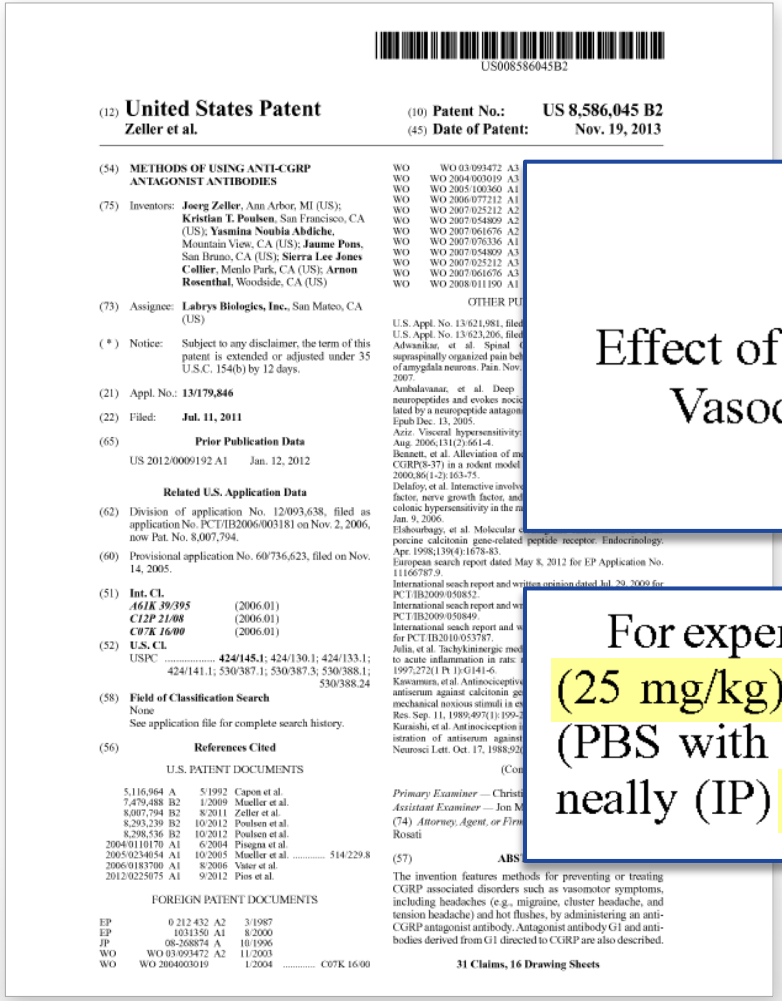
Ex. 1247, 3972; Ex. 1337, ¶28; Reply, 10

Dr. Balthasar:

"Consistent with Covell's data," "[a] POSA would have readily appreciated that permitting a longer time for distribution, as well as higher doses or chronic administration, was appropriate just as Tan 1995 repeatedly recommended"

Ex. 1337, ¶¶27-29; Reply, 10

Teva Followed Tan's Express Guidance



US008586045B2

(12) **United States Patent**
Zeller et al.

(10) **Patent No.: US 8,586,045 B2**
(45) **Date of Patent: Nov. 19, 2013**

(54) **METHODS OF USING ANTI-CGRP ANTAGONIST ANTIBODIES**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 12 days.

(21) Appl. No.: **13/179,846**

(22) Filed: **Jul. 11, 2011**

(65) **Prior Publication Data**

US 2012/0009192 A1 Jan. 12, 2012

Related U.S. Application Data

(62) Division of application No. 12/093,638, filed as application No. PCT/IB2006/003181 on Nov. 2, 2006, now Pat. No. 8,007,794.

(60) Provisional application No. 60/736,623, filed on Nov. 14, 2005.

(51) **Int. Cl.**
A61K 39/395 (2006.01)
C12P 21/08 (2006.01)
C07K 16/00 (2006.01)

(52) **U.S. Cl.**
USPC **424/145.1**; 424/130.1; 424/133.1; 424/141.1; 530/387.1; 530/387.3; 530/388.1; 530/388.24

(58) **Field of Classification Search**
None
See application file for complete search history.

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Assistant Examiner — Jon M
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(57) **ABS**

The invention features 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. Antagonist antibody G1 and antibodies derived from G1 directed to CGRP are also described.

31 Claims, 16 Drawing Sheets

Example 3

Effect of Anti-CGRP Antagonist Antibodies on Skin Vasodilatation Induced by Stimulation of Rat Saphenous Nerve

For experiments shown in FIGS. **2**A and **2**B, antibody 4901 (25 mg/kg), antibody 7D11 (25 mg/kg), or vehicle control (PBS with 0.01% Tween 20) was administered intraperitoneally (IP) 72 hours before the electrical pulse stimulation.

Ex. 1001, 55:61-64; Ex. 1014, ¶¶88-95; Pet., 47-48; Reply, 11

Teva's Secondary Considerations Are Not Commensurate with the Scope of the Challenged Claims

Headache Types	250	Ex. 1304, 74:17-75:12; Ex. 1001, 20:25-40; Pet., 62; Reply, 21-22
Sequence Mutations	20^{220}	Ex. 1301, 92:8-10; Ex. 2217, 8-9; Reply, 22
Binding Affinity	2 pM-250 nM • '045 patent claims 4 & 20 (50 nM or less) • '908 patent (about 10 nM or less)	Ex. 1301, 102:1-103:15, 104:7-19; Ex. 1001, 5:35-46; Reply, 23
Antibody Format (e.g., fragments) ('045 patent)	Fab, Fab', F(ab')2 , Fv, single chain (ScFv), fusion proteins	Ex. 1301, 27:25-28:6; Ex. 1001, 12:61-65; Pet., 23-24; Reply, 23
Antibody Class ('045 patent)	IgA, IgD, IgE, IgG, IgM	Ex. 1301, 37:16-39:11; Ex. 1001, 12:29-37; Reply, 23

***In re Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011)** ("Evidence of secondary considerations must be reasonably commensurate with the scope of the claims.").

Reply, 23

Teva Failed to Rebut Evidence Showing Lack of Nexus

***Allergan, Inc. v. Apotex Inc.*, 754 F.3d 952, 963 (Fed. Cir. 2014)**

- "Neither the district court nor appellees explain the nexus between [secondary consideration evidence] and the broad scope of '029 patent's claimed invention."
- "The district court needed to have found that other embodiments falling within the claim will behave in the 'same manner' as compounds with C1-amide groups, in order to establish that evidence of [secondary considerations] 'is commensurate with the scope of the claims.'"

Reply, 23

Dr. Tomlinson's testimony:

- Selected mutations were made to fremanezumab "[t]o increase binding affinity" and "to prevent antibody dependent cell cytotoxicity, ADCC, and complemental dependent cytotoxicity, CDC." (Ex. 1301, 115:9-116:21; Ex. 2217, 8-9; Reply, 22)
- Fremanezumab and galcanezumab "do not cover or represent the full range of affinities" (Ex. 1301, 104:7-19; Reply, 23)
- "I think it's pretty clear that an unformatted antibody fragment is not going to be effective as a human therapeutic against that target." (Ex. 1301, 134:14-25; Reply, 23)

Teva Failed to Rebut Evidence Showing Lack of Nexus

***In re Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011)** ("Where the offered secondary consideration actually results from something other than what is both claimed and novel in the claim, there is no nexus to the merits of the claimed invention.")

Reply, 23

Dr. Rapoport's cross-examination:

Q: … So it's your opinion that the antibodies that you have indicated met a long-felt need is based on their characteristic that they block the CGRP pathway, correct?

A: Correct.

Ex. 1304, 142:1-8; Reply, 23-24

Teva Failed to Establish A Presumption of Nexus

***Fox Factory, Inc. v. SRAM, LLC*, 2019 WL 6884530 (Fed. Cir. Dec. 18, 2019)**

- "[N]exus can only be presumed where the evidence of secondary considerations is tied to a specific product that 'is the invention disclosed and claimed.'" (*id.* at *8)
- "We reject SRAM's attempt to reduce the coextensiveness requirement to an inquiry into whether the patent claims broadly cover the product that is the subject of the evidence of secondary considerations." (*id.* at *8)
- "[W]hen the thing that is commercially successful is not coextensive with the patented invention … the patentee is not entitled to a presumption of nexus." (*id.* at *5)
- "[B]ecause there are one or more features not claimed by the [] patent that materially impact the functionality of the [commercial] products," "nexus may not be presumed." (*id.* at *7)

Teva Failed to Establish A Presumption of Nexus

Fox Factory	The instant case
Rejected changing the coextensiveness requirement to an inquiry into whether the patent claims broadly "cover" the product.	Teva: "Ajovy® and Emgality® are covered by the claims." (Sur-reply, 27; POR, 55-56) Dr. Tomlinson: claims "cover administration of at least one of" Ajovy® and Emgality®. (Ex. 2271, ¶127)
No presumed nexus when the product has one unclaimed feature that "materially impacts" functionality (>80% gap filling)	Sequence and Mutations: 20[220] • Ajovy® and Emgality® have optimized amino acid sequences with specific mutations to modify their functionalities (Reply, 22) • Ajovy®: targeted mutations at residues 99, 100, 330, 331 (Ex. 2217, 8-9; Ex. 2216, 17 (Emgality® mutations) • Teva does not dispute in sur-reply
Additional unclaimed features that materially impact functionality further demonstrate no entitlement to presumption of nexus: —tooth tips —hook features —mud clearing features	Binding affinity: • Tomlinson: Low pM affinities of Ajovy® and Emgality® do not cover or represent the full range of affinities claimed. (Ex. 1301, 104:7-19 ("They're just two antibodies within that range."); Reply, 23) Antibody fragments: • Tomlinson: "an unformatted antibody fragment is not going to be effective as a human therapeutic" (Ex. 1301, 134:14-25; Reply, 23) Antibody class (IgG_3, IgA, IgM, IgD, IgE): • Tomlinson: could not identify any marketed drug within these classes (Ex. 1301, 111:7-115:1; 34:9-35:1, Reply, 23; Reply ('908 patent), 23) Indication: • Rapoport: there are 250 different types of headache (Ex. 1304, 74:17-75:12; Reply, 21-22)

Teva's Evidence of Industry Acclaim Is Deficient

Teva's arguments:

First, Lilly's expert, Dr. Charles, has himself praised the humanized anti-CGRP antagonist antibodies used in the claimed methods—repeatedly—as:

- "very exciting and compelling;"
- "unlike what we've seen with other therapies;"
- "absolutely life-changing;"
- having the "possibility to transform our clinical approach to migraine and cluster headache;" and
- "spectacular."

EX2182, 207; EX2186, 4; EX2052, 1; EX2262, ¶¶61-62.

POR, 56

- "First up will likely be erenumab (Aimovig)".
- "[A]t least one prophylactic GGRP-antagonizing small molecule (and several others for acute treatment) might not be far behind."
- "'These are really the first therapies, ever, that have been designed based on a specific laboratory understanding of the mechanisms of migraine,' says Andrew Charles…'That, to me, very exciting and compelling.'"

Ex. 2182, 207; Ex. 1338, ¶131; Reply, 24-25

- "In fact, the [FDA] this May approved ereunumab-aooe, the first drug based on monoclonal antibodies to prevent migraine."
- "'A smaller percentage have shown complete remission, which is unlike what we've seen with other therapies.'"

Ex. 2053, 26; Ex. 1338, ¶131; Reply, 24-25

- "'[T]hese therapies have the possibility to transform our clinical approach to migraine and cluster headache,' said Charles, from the University of California, Los Angeles."
- "Charles noted having treated approximately 500 patients with erenumab (Aimovig), following its approval in May 2018. He said that response to erenumab were consistent or often better than reported in clinical trials, with a majority of patients responding."

Ex. 2052, 1; Ex. 1338, ¶131; Reply, 24-25

Teva's Evidence of Industry Acclaim Is Deficient

UCLA U Magazine (Ex. 2053):

- "Researchers have found that serum concentrations of CGRP become elevated during migraine attack, and they normalize when the attack resolves. Infusion of CGRP in patient volunteers provokes migraine attacks that are very similar to those that occur spontaneously. Small molecule drugs binding to the CGRP receptor were able to abort migraine attacks."
- "It was this body of evidence that led researchers to suspect that by blocking CGRP receptors, or targeting the neuropeptides itself, a migraine attack could be prevented. According to results from late-stage clinical trials of erenumab-aoo and other anti-CGRP antibodies, the researchers were right."

"'The notion that would be using antibodies for treating migraine is really quite a radical concept,' … 'This is a very different approach because, in contrast to other treatments that we've used in the past, which often have been developed for other reasons and we've borrowed them as migraine treatments, this has been developed based on our understanding of the chemistry of migraine and what is going on during a migraine attack.'"

Ex. 2053, 23; Ex. 1338, ¶¶ 131, 135; Reply, 24-25, 27

Teva Failed to Establish Unexpected Results or Industry Skepticism

Teva Arguments:

Medication Overuse Headache

Industry Skepticism

Dr. Rapoport in 2003:

"[S]ome of the patients stopped overusing acute care medication during the [naratriptan] study"

Ex. 1294, 487; *see also* Ex. 1295, Table 1; Ex. 1338, ¶¶ 137-143; Reply, 25-26

Dr. Pons:

Q: So Pfizer conducted five Phase I trials with fremanezumab from 2009 to 2012, correct?

A: Yes.

Ex. 1346, 42:22-43:2; Reply, 26

"Labrys was created specifically to move forward on RN307": "$31 million in series A financing"

Ex. 2331, ¶13; Reply, 26

Pfizer "decided that migraine was not an area it wanted to pursue."

Ex. 2167, 118-119 (quoting Dr. Pons); Reply, 26

Teva's Purported Evidence of Licensing, Long-Felt Need, and Commercial Success Do Not Support Patentability

Teva Arguments:

Dr. Stoner:

Licensing

Q: [I]f all of the challenged claims were canceled, Alder Bio would still owe the same considerations to Teva for the same reason, that they had admitted infringement of all of the 179 additional patents, correct?

A: That appears to be a reasonable interpretation of this paragraph

Ex. 1302, 179:14-180:19; Reply, 26-27

Dr. Charles:

Long-felt but Unmet Need

"The fact that researchers have been working on the CGRP pathway more than 25-30 years is consistent with my previous testimony that (1) it was well known that the CGRP pathway is important in migraine pathophysiology (Ex. 1014, ¶¶26-38, 107-113), and (2) the prior art would have motivated a POSA to use a humanized anti-CGRP antagonist antibody for treating or reducing incidence of migraine (*id.*, ¶¶107-137)."

Ex. 1338, ¶135; Reply, 27

Commercial Success

NO evidence of any commercial sales

Reply, 26

Teva's Affinity Claims Were Obvious

Dr. Tomlinson in 2004:

"An ideal drug would have the following qualities: it would have very high affinity and exquisite specificity for its target"

Ex. 1266, 521; Ex. 1337, ¶87; Reply, 20

Tan 1994 (Ex. 1021):

"The dissociation constants (Kd) of MAb C4.19 for rat αCGRP and βCGRP were very similar (1.9 and 2.5 nM respectively)."

Ex. 1021, 707; Ex. 1015, ¶113; Pet., 52

Dr. Vasserot:

Andrew's antibodies "against human αCGRP were already shown to have affinities of about 4 nM to 40 nM. (Ex. 1055, 92)"

Ex. 1015, ¶115; Pet., 52

Teva's Argument:

"The art teaches a disconnect between binding and activity. … [T]he anti-CGRP antibody MAb R1.50 'clearly showed the greatest [binding] activity' among the tested antibodies to rat αCGRP, yet it 'blocked rat αCGRP poorly.'"

Sur-reply, 24-25

Tan 1994 (Ex. 1021):

"The use of RIA and a receptor binding assay as biochemical screens was generally successful in predicting blocking MAbs. An interesting exception was MAb R1.50"

Ex. 1021, 707; Ex. 1337, ¶81; Reply, 19-20

Teva's Claims Do Not Require A Clinical Response

Claim Terms:

We claim:

1. 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:

Ex. 1001('907 patent), 103:20-35

We claim:

1. A method for reducing incidence of or treating at least one vasomotor symptom in an individual, comprising administering to the individual an effective amount of an anti-CGRP antagonist antibody, wherein said anti-CGRP antagonist antibody is a human monoclonal antibody or a humanized monoclonal antibody.

Ex. 1001('045 patent), 99:1-7

Teva Patents:

As used herein, "treatment" is an approach for obtaining beneficial or desired clinical results. For purposes of this

Ex. 1001, 17:37-38; Ex. 1014, ¶102; Pet., 20

"method of reducing incidence of headache in an individual" reflects administering the anti-CGRP antagonist antibody based on a reasonable expectation that such administration may likely cause such a reduction in incidence in that particular individual.

Ex. 1001, 17:61-65; Ex. 1014, ¶103; Pet., 21

***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").

Pet., 20

Teva's Claims Do Not Require A Clinical Response

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Ex. 1001('045 patent), 99:1-7

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1. 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:

Ex. 1001('907 patent), 103:20-35

16. The method of claim **1**, wherein the dose of said anti-CGRP antagonist antibody is at least about 3 μg/kg.

Ex. 1001 ('045 patent), 100:1-2

Teva Patents:

As used herein, an "effective dosage" or "effective amount" of drug, compound, or pharmaceutical composition is an amount sufficient to effect beneficial or desired results.

notypes presenting during development of the disease. For therapeutic use, beneficial or desired results include clinical results such as reducing pain intensity, duration, or frequency of headache attack, and decreasing one or more symptoms resulting from headache (biochemical, histological and/or behavioral), including its complications and intermediate

Ex. 1001 , 18:38-57; Ex. 1338, ¶¶7-8; Pet., 22-23; Reply, 2-3

Dr. Foord:

An effect in a cAMP assay "and the effective dose within an individual human for treatment are enormously apart."

Ex. 1343, 33:24-34:6; Reply, 2-3

Dr. Charles:

"A POSA would view doses as low as about 3 μg/kg to be exceedingly low and likely to be insufficient to generate a clinical response, let alone any response."

Ex. 1014, ¶105; Pet., 22-23

Detailed Analysis

Novartis v. West-Ward Is Inapposite

Novartis v. West-Ward	The instant case
Patent claimed using a specific compound (everolimus), defined by chemical structure, to inhibit tumor growth.	Teva's patents broadly cover using any humanized anti-CGRP antagonist antibody, with no structural limitations, for the aspirational goal of treating migraine.
No Phase II data existed for everolimus or any other mTOR inhibitor.	Olesen published a Phase II clinical trial, establishing that blocking the CGRP pathway effectively treats migraine.
The claimed disease resisted all treatment modalities.	Multiple effective CGRP-pathway inhibitors were known to treat migraine, including sumatriptan and BIBN.
No prior art disclosure that everolimus would be effective in treating the claimed disease.	The prior art disclosed: "we expect that CGRP antagonists will be effective anti-migraine drugs."

Reply, 20-21

Known Anti-CGRP Pathway Antagonists Were Reported to Be Safe and Effective

Triptans: FDA-approved anti-migraine drugs advocated for daily administration

Ex. 1282, 1521; Ex. 1294, Abstract; Ex. 1338, ¶¶19, 93; Reply, 13

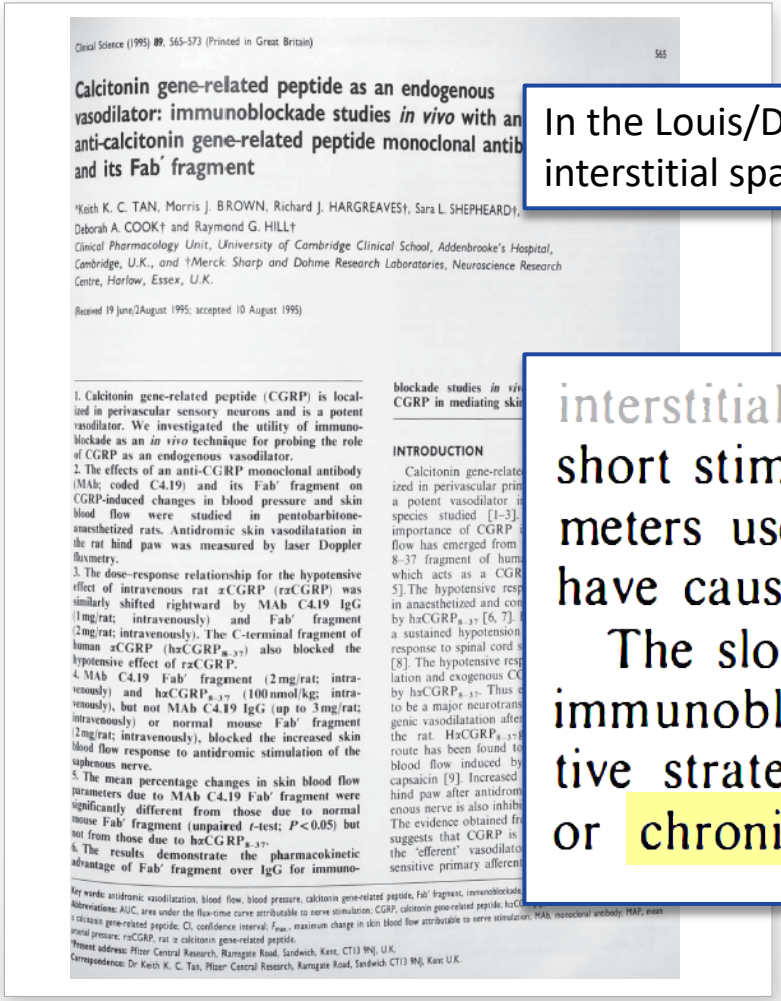
BIBN4096BS: "caused only minor adverse events and had no constrictor effect"

Ex. 1025 (Olesen), 1108; Ex. 1338, ¶82; Reply, 12

CGRP-binding "biostable aptamer": "Basal blood flow and systemic arterial pressure were unchanged"; "a new therapeutic strategy in diseases … such as migraine"

Ex. 1240, 923; Ex. 1082, Abstract, 2; Ex. 1338, ¶80; Reply, 13

Tan 1995 Offers Express Guidance to Improve Immunoblockade



Clinical Science (1995) 89, 565–573 (Printed in Great Britain) 565

Calcitonin gene-related peptide as an endogenous vasodilator: immunoblockade studies *in vivo* with an anti-calcitonin gene-related peptide monoclonal antib and its Fab′ fragment

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(Received 19 June/2August 1995; accepted 10 August 1995)

1. Calcitonin gene-related peptide (CGRP) is localized in perivascular sensory neurons and is a potent vasodilator. We investigated the utility of immunoblockade as an *in vivo* technique for probing the role of CGRP as an endogenous vasodilator.
2. The effects of an anti-CGRP monoclonal antibody (MAb; coded C4.19) and its Fab′ fragment on CGRP-induced changes in blood pressure and skin blood flow were studied in pentobarbitone-anaesthetized rats. Antidromic skin vasodilatation in the rat hind paw was measured by laser Doppler fluxmetry.
3. The dose–response relationship for the hypotensive effect of intravenous rat αCGRP (rαCGRP) was similarly shifted rightward by MAb C4.19 IgG (1 mg/rat; intravenously) and Fab′ fragment (2 mg/rat; intravenously). The C-terminal fragment of human αCGRP (hαCGRP$_{8-37}$) also blocked the hypotensive effect of rαCGRP.
4. MAb C4.19 Fab′ fragment (2 mg/rat; intravenously) and hαCGRP$_{8-37}$ (100 nmol/kg; intravenously), but not MAb C4.19 IgG (up to 3 mg/rat; intravenously) or normal mouse Fab′ fragment (2 mg/rat; intravenously), blocked the increased skin blood flow response to antidromic stimulation of the saphenous nerve.
5. The mean percentage changes in skin blood flow parameters due to MAb C4.19 Fab′ fragment were significantly different from those due to normal mouse Fab′ fragment (unpaired *t*-test; $P < 0.05$) but not from those due to hαCGRP$_{8-37}$.
6. The results demonstrate the pharmacokinetic advantage of Fab′ fragment over IgG for immuno-blockade studies *in vi* CGRP in mediating ski

INTRODUCTION

Calcitonin gene-relate ized in perivascular prin a potent vasodilator i species studied [1–3]. importance of CGRP. flow has emerged from 8–37 fragment of huma which acts as a CGR 5]. The hypotensive resp in anaesthetized and con by hαCGRP$_{8-37}$ [6, 7]. a sustained hypotension response to spinal cord s [8]. The hypotensive resp lation and exogenous CG by hαCGRP$_{8-37}$. Thus to be a major neurotrans genic vasodilatation after the rat. HαCGRP$_{8-37}$ route has been found to blood flow induced by capsaicin [9]. Increased hind paw after antidrom enous nerve is also inhibi The evidence obtained fr suggests that CGRP is the 'efferent' vasodilato sensitive primary afferent

Key words: antidromic vasodilatation, blood flow, blood pressure, calcitonin gene-related peptide, Fab′ fragment, immunoblockade.

Abbreviations: AUC, area under the flux-time curve attributable to nerve stimulation; CGRP, calcitonin gene-related peptide; hαCGRP, human α calcitonin gene-related peptide; CI, confidence interval; F_{max}, maximum change in skin blood flow attributable to nerve stimulation; MAb, monoclonal antibody; MAP, mean arterial pressure; rαCGRP, rat α calcitonin gene-related peptide.

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Teva's arguments:

In the Louis/Dockray experiments, "the antibodies 'leaked' into the interstitial space due to 'plasma extravasation.'"

Sur-reply, 18-19

Tan 1995 (Ex. 2022):

interstitial space by plasma extravasation [13]. The short stimulation period and mild stimulation parameters used in the present investigation would not have caused plasma extravasation [9].

The slow distribution of whole IgG to the site of immunoblockade could be overcome by the alternative strategies of active immunization with CGRP or chronic administration of IgG. Responses to

Ex. 1022, 571; Ex. 1337, ¶¶15-39; Reply, 10

Absolute Risk of Stroke and Myocardial Ischemia in Migraine Patients Was Very Low

Bousser (Ex. 2157):

The "absolute risk of stroke in young women with migraine is low: 18 per 100,000 per year."

Ex. 2157, 535; Ex. 1338, ¶108; Reply, 18

Dr. Ferrari:

Q: Well, for the percentage of patients that experience migraine without aura, as of 2005 there was no known association between migraine without aura and ischemic stroke, correct?

A: In 2005 there was no known association.

Ex. 1303, 193:3-10; Reply, 18

Dr. Charles:

"Clinicians' experience with triptans led to the understanding that (1) the absolute risk of suffering from clinical ischemia is low among migraine patients, and (2) a drug that could potentially worsen ischemic episodes can be used safely with little or no adverse events when patients are appropriately selected."

"At most, the risk that a drug could worse ischemic episodes would have amounted to a warning or contraindication, similar to those that already existed for triptans and ergots."

Ex. 1338, ¶113; Reply, 18

Prior Art Clinical Evidence Undermines Teva's Hypothetical Application of the "Spare Receptor Theory"

The Trigeminovascular System and Migraine: Studies Characterizing Cerebrovascular and Neuropeptide Changes Seen in Humans and Cats

evaluation of sumatriptan for the treatment of acute migraine. **In 7 of 8 patients responding to subcutaneous sumatriptan administration, elevated CGRP levels (60 ± 8 pmol/liter) were normalized, with the headache being relieved (40 ± 8 pmol/liter).** These data characterize some aspects of the cerebrovascular physiology of the trigeminovascular

jugular vein peptide levels determined prior to and after administration of either sumatriptan or dihydroergotamine. Stimulation of the trigeminal ganglion led to a frequency-dependent increase in cerebral blood flow, with a mean maximum of 43 ± 9% at a stimulus frequency of 20 per second. There was a marked reduction in these responses by some 50% after administration of either sumatriptan or dihydroergotamine. Trigeminal ganglion stimulation at a frequency of 5 per second also led to a release into the cranial circulation of calcitonin gene–related peptide (CGRP), with the level rising from 67 ± 3 to 82 ± 5 pmol/liter on the side of stimulation. These increases were also markedly antagonized by both sumatriptan and dihydroergotamine. Human studies were conducted as part of the overall evaluation of sumatriptan for the treatment of acute migraine. In 7 of 8 patients responding to subcutaneous sumatriptan administration, elevated CGRP levels (60 ± 8 pmol/liter) were normalized, with the headache being relieved (40 ± 8 pmol/liter). These data characterize some aspects of the cerebrovascular physiology of the trigeminovascular system and demonstrate important interactions between this system and the effective antimigraine agents sumatriptan and dihydroergotamine and that such interactions can be represented in animal models.

Goadsby PJ, Edvinsson L. The trigeminovascular system and migraine: studies characterizing cerebrovascular and neuropeptide changes seen in humans and cats. Ann Neurol 1993;33:48–56

There is little doubt from a clinical standpoint that the trigeminal system is intimately involved in the expression of migraine [1]. The connections of the trigeminal system with the cranial vessels [2] have led to the concept of the trigeminovascular system [3]. This system consists of the cranial vessels and their trigeminal innervation, implying a functional network that may have a role both in normal physiology and in disease. Many aspects of this relationship remain uncharacterized and new effective migraine treatments provide a challenge to existing ideas and an impetus to further study.

Stimulation of the trigeminal ganglion (VG) leads to both direct (antidromic) and indirect (orthodromic) changes in cerebral blood flow. Activation of the ganglion increases blood flow via a reflex (trigeminovascular reflex) that traverses the brainstem, with its efferent path being through the seventh cranial nerve [4]. The seventh cranial nerve is the main parasympathetic outflow for the cerebral arteries. It can increase blood flow independent of metabolic needs [5] through classic autonomic ganglia, the sphenopalatine and otic ganglia [6], via a nicotinic receptor [7]. The transmitter for both the extracerebral [8] and the cerebral [9] parts of the effect is likely to be vasoactive intestinal peptide (VIP). Indeed, sphenopalatine ganglion stimulation alone can also increase cerebral blood flow again without any effect on cerebral metabolism [10, 11]. More specifically, the terminal distribution of these fibers through the ethmoidal nerve can also be activated to increase cerebral blood flow [12].

The trigeminal system can also increase blood flow via antidromic activation and release of vasoactive substances. Both substance P (SP) [13, 14] and calcitonin gene–related peptide (CGRP) [15, 16] can be found

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Received Apr 7, 1992, and in revised form Jul 16. Accepted for publication Jul 17, 1992.

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Ex. 1044, Abstract; Ex. 1338, ¶116; Reply, 18-19

Dr. Charles's testimony:

116. The clinical evidence contradicts Dr. Foord's assertion. As of 2005, it was widely known that migraine was linked to *elevated* or *inappropriate* levels of CGRP, and that as CGRP levels normalized migraine headache subsided. (Ex. 1043, Abstract; Ex. 1044, Abstract; *see also* Ex. 1047, 59 (administering exogenous CGRP "caused migraine in virtually all migraine sufferers"); Ex. 1096, 567 ("inappropriate release of CGRP is a potential causative factor in several diseases, including migraine"); *supra* §V; Ex. 1014, ¶¶26-38.)

Ex. 1338, ¶116; Reply, 18-19

Dr. Charles (Olesen)

Teva's assertion:

Dr. Charles ignored Olesen's warning against relying on its BIBN4096BS study for cardiovascular safety: "our data base was too small for us to assess cardiovascular safety." EX1025, 1109; POR, 29; EX2268, ¶50; EX1338, ¶83. Dr.

Sur-reply, 13

Dr. Charles's testimony:

83. Despite Olesen's express recognition of BIBN4096BS's favorable safety profile, Dr. Ferrari asserts that little can be gleaned from it because Olesen's data base was purportedly too small. (Ex. 2268, ¶50.) A POSA, however, would have considered this study as part of the growing body of work (e.g., additional animal and clinical studies), establishing that the CGRP-pathway could be antagonized without the vasoconstrictive properties of triptans. As a result, a POSA would have viewed Olesen's study—and his comments about BIBN4096BS's lack of vasoconstrictive effects—as a further indication that blocking the CGRP pathway was expected to be both safe and effective in humans.

Ex. 1338, ¶83; Reply, 12

Dr. Ferrari's statements in 2005:

release of CGRP [22–24]. Therefore, CGRP antagonists may be effective in the treatment of acute migraine. Olesen and colleagues evaluated the effectiveness of the CGRP-antagonist BIBN4096BS for acute migraine treatment [56]. In a double-

cebo. There were no serious adverse events and the most frequent side effect was paresthesia. Although further trials are necessary in order to confirm this result and to compare the effectiveness of CGRP antagonists with the triptans, they seem promising, new antimigraine drugs without vascular side effects.

Ex. 1290, 657; Ex. 1338, ¶89; Reply, 12

Dr. Charles (Triptans)

Teva's assertion:

Despite mechanism-of-action and pharmacokinetic differences, Dr. Charles analogizes antibody-induced BP increases to similar increases observed with triptans, arguing (without explanation) that such transient changes were not of concern. EX1338, ¶93. His analogy fails to explain the basis for equating the two classes of molecules.

Sur-reply, 14

Dr. Charles's testimony:

researchers developed additional, triptans with longer half-lives. For example, frovatriptan had a relatively longer half-life of about 26 hours. (Ex. 1293, S125-26.) These longer-acting triptans were intended to reduce recurrence of migraine, but were also considered as potential preventive therapies. (*Id.*) For instance, frovatriptan and naratriptan were considered as short-term preventive therapies (daily dosing for about a week) for menstrual migraine. (*Id.*, S127.) Naratriptan was also administered daily up to 1 year as a preventative treatment for chronic migraine with no serious adverse events. (*See* Ex. 1294, Abstract; Ex. 1295, Abstract.)

Ex. 1338, ¶19; Reply, 14

Dr. Charles (CGRP-Binding Aptamer)

Teva's assertion:

Abstract; EX2338, 114:6-115:5. Aptamers have characteristics that are similar to *small-molecules* and are not antibody "analogs." EX1309, Abstract; Reply 13.

Sur-reply, 14-15

Pendergrast (Ex. 1309):

In the simplest view, aptamers can be thought of as nucleic acid analogs to antibodies. They are able to bind specifically to proteins, and, in many cases, that binding leads to a modulation of protein activity. New aptamers are rapidly generated through

Ex. 1309, Abstract; Reply, 13

Dr. Charles's testimony:

¶¶62-63.) Indeed, they were known as "nucleic analogs to antibodies" due to their specificity, biological activity, favorable safety profile, and potential long *in vivo* half-lives ranging from hours to days. (Ex. 1309, Abstract.) Moreover, just like

Ex. 1338, ¶24; Reply, 13

Dr. Balthasar's testimony:

aptamers were recognized as having the benefit of "a long in vivo half life" and had been analogized to antibodies. Ex. 1309, 224 ("aptamers can be thought of as nucleic analogs to antibodies"). Indeed, stabilized aptamers were disclosed as having longer half-lives, potentially requiring only weekly or biweekly dosing. *Id.*

Ex. 1337, ¶57; Reply, 13

Dr. Charles (Purported Safety Concerns)

Teva's assertion:

EX2144, 1665; EX2268, ¶108; EX2338, 65:12-68:6; EX2342, 2901. Any increase in the incidence or severity of TIAs would have been a serious concern. Dr. Charles offered no rebuttal to Dr. Ferrari's testimony that CGRP inhibition would worsen common ischemic episodes in migraineurs. Dr. Charles' only argument is

Sur-reply, 16

Dr. Charles's testimony:

detail below, Dr. Ferrari primarily relies on outdated studies that did not reflect the consequences of antagonizing naturally-present CGRP, i.e., endogenous CGRP. By 2005, these older studies had been superseded by numerous animal and clinical studies demonstrating that blocking the endogenous CGRP pathway does *not* increase blood pressure and does *not* worsen ischemic episodes. (*E.g.*, Exs. 1283, 1284, 1285, 1318, 1263, 1240, 1025, 1042, 2019.) Based on these subsequent

Ex. 1338, ¶68; Reply, 16-17

Dr. Charles (Purported Safety Concerns)

Teva's assertion:

30:25, 35:1-36:21; EX2340, 53-54; EX2341, 246. Lilly's EX1284 demonstrates this: CGRP reduced infarct size in an ischemia rat model by up to 89%, while BIBN4096BS blocked "[t]he *cardioprotective effect* of CGRP," concluding: "CGRP is a very potent myocardial protective substance." EX1284, 591-593, Figure 3; EX2338, 21:17-22:4. Lilly's papers omitted this unfavorable information, and its expert refused to even acknowledge it as "germane" on cross. EX2338, 20:1-21:3. Lilly's refusal to consider CGRP's vasoprotective role dooms its

Sur-reply, 9

Dr. Charles's testimony:

significant effect on the infarct size").) Moreover, consistent with studies administering exogenous CGRP that Dr. Ferrari relies upon (*see, e.g.*, Exs. 2058, 2079, 2139), CGRP's cardioprotective effect was observed only when exogenous CGRP (about 10-fold excess over endogenous CGRP) was administered, suggesting that "[o]nly high plasma levels [of] CGRP may cause cardioprotection." (Ex. 1284, 593.)

Ex. 1338, ¶77; Reply, 16-17

Dr. Charles (Cross-Reactivity)

Teva's assertion:

concerns in the Petition. Reply, 19; POR, 21. On Reply, Dr. Charles belatedly testified—without explanation or support—that "hypothetical and unsupported concerns about ligand-receptor cross-binding would not have deterred development of a humanized anti-CGRP antagonist antibody." EX1338, ¶120;

Sur-reply, 7-8

Dr. Charles's testimony:

121. Moreover, cross-binding of CGRP to these other receptors was understood to be poor before November 2005. Dr. Foord includes in his declaration a table from the Geppetti reference that illustrates that CGRP is a secondary or worse binding ligand to each of the calcitonin, amylin, and adrenomedullin receptors:

	Calcitonin	Amylin (AMY)	CGRP	Adrenomedullin (AM)
Composition	*CALCR*	AMY-1: *CALCR+RAMP1* AMY-2: *CALCR+RAMP2* AMY-3: *CALCR+RAMP3*	*CALCRL+RAMP1*	AM-1: *CALCRL+RAMP2* AM-2: *CALCRL+RAMP3*
Transduction pathway	G_s/G_q	G_s	G_s/G_q	G_s
Selective agonists	Human CT	AMY	α-CGRP	AM
Selective antagonists	–	–	BIBN4096BS (+++) SB-273779 (+)	$AM_{22\text{-}52}$
Potency	Salmon CT≥human CT≥AMY, CGRP>AM	Salmon CT≥AMY≥ CGRP>human CT>AM	CGRP>AM≥ AMY≥salmon CT	AM-1: AM>>CGRP> AMY>salmon CT AM-2: AM≥CGRP> AMY>salmon CT

(Ex. 2059, Table 1 (highlighting added); Ex. 2265, ¶37.) In addition, Geppetti

1026-1028, 1096.) Likewise, aptamers were designed to bind to the CGRP ligand "for the specific interruption of disease-related protein-protein interactions." (Ex. 1082, 1.) The anti-CGRP ligand aptamers had been shown to inhibit neurogenic blood flow increases in the rat cranial dura (Ex. 1240, 923) just as BIBN4096BS did in Doods (Ex. 1024, 422).

Ex. 1338, ¶¶121, 123; Reply, 19

Dr. Charles (Blood-Brain Barrier)

Teva's assertion:

EX2161, 6; EX2336, 80:19-81:7. In 2019, Dr. Charles himself was "still debating over central versus peripheral site of action of anti-CGRP antibodies." EX2336, 34:12-16; EX2335, 1. Therefore, Lilly is wrong: the field has not settled on the peripheral site of action of anti-migraine drugs by 2005. Thus, a POSA would not

Sur-reply, 22

Dr. Charles's testimony:

Q: Still unresolved.

A: I would say the preponderance of evidence indicates that a peripheral action of the CGRP monoclonal antibody is the reason for its efficacy.

Ex. 2336, 34:21-35:3

A: As of 2005, … the preponderance of evidence would indicate that therapies targeting CGRP were acting peripherally, so to that extent, my opinion or statement regarding the peripheral site of action was the same then as it was in 2019.

Ex. 2336, 125:6-13

Teva's Experts – Dr. Ferrari (Olesen)

Dr. Ferrari's testimony:

migraine, and reported that it "was effective" in doing so. EX1025, 1104. Olesen reported an overall rate of adverse events of 25%, and that "no serious adverse events" were observed. EX1025, 1104. However, Olesen also cautioned that their study did not assess whether BIBN4096BS has any negative effects on the cardiovascular system or "vasoconstrictor properties" because "[its] data base was too small for us to assess cardiovascular safety," and therefore Olesen could not conclude whether BIBN4096BS was different from the triptans in that regard.

Ex. 2268, ¶50

Dr. Ferrari's statements in 2005:

effective in the treatment of acute migraine. Olesen and colleagues evaluated the effectiveness of the CGRP-antagonist BIBN4096BS for acute migraine treatment [56]. In a double-blind, randomized, controlled trial, patients received different doses of BIBN4096BS intravenously over 10 min. The primary end point was a response reduction of severe or moderate headache at baseline to mild or no headache at 2 h. The 2.5 mg group had a response rate, that was significantly superior to placebo. There were no serious adverse events and the most frequent side effect was paresthesia. Although further trials are necessary in order to confirm this result and to compare the effectiveness of CGRP antagonists with the triptans, they seem promising, new antimigraine drugs without vascular side effects.

Ex. 1290, 657; Ex. 1338, ¶89; Reply, 5, 12

Teva's Experts – Dr. Ferrari (CGRP as Biomarker)

Dr. Ferrari's testimony:

60. In view of Tvedskov's results and conclusions and other relevant references, a POSA would have had doubts about CGRP's status as a biomarker of migraine by November 14, 2005, and would not have concluded that CGRP inhibition was an established and validated therapeutic target for migraine.

Ex. 2268, ¶60

Dr. Ferrari's statements in 2007:

Human evidence that CGRP is elevated in the headache phase of migraine, both spontaneous (Gallai et al., 1995; Goadsby et al., 1990), and triggered attacks (Juhasz et al., 2003), although not in less severe attacks (Tvedskov et al., 2005), cluster headache (Fanciullacci et al., 1995; Goadsby & Edvinsson, 1994) and chronic paroxysmal hemicrania (Goadsby & Edvinsson, 1996). These data

Ex. 1332, 443; Ex. 1338, ¶27; Reply, 6

Teva patents:

350:1073-1075, 2004. The serum levels of CGRP in the external jugular vein are elevated in patients during migraine headache. Goadsby et al., Ann. Neurol. 28:183-7, 1990. Intrave-

Ex. 1001 ('045 Patent), 2:7-9; Reply, 6

Teva's Experts – Dr. Rapoport (Olesen)

Dr. Charles's testimony:

receiving placebo experienced recurrence. (Ex. 1025, 1108.) In view of these clinical results on reducing migraine recurrence, Olesen established that blocking the CGRP pathway was equally viable as a therapy for both preventing migraine and for treating acute migraine headache.

Ex. 1014, ¶33; Pet., 15

Dr. Rapoport's statements in 2005:

CGRP is one of several neuropeptides found within the sensory terminals of the trigeminal nerve. Recent data suggests that antagonising the effect of CGRP may provide acute relief of migraine headache [47] Preventive drugs might be developed on the same principle.

47. Olesen J, Diener HC, Husstedt IW, Goadsby PJ, Hall D, Meier U, Pollentier S, Lesko LM; BIBN 4096 BS Clinical Proof of Concept Study Group (2004) Calcitonin gene-related peptide receptor antagonist BIBN 4096 BS for the acute treatment of migraine [see comment]. N Engl J Med 350:1104–1110

Ex. 1297, S119; Ex. 1338, ¶29; Reply, 5, 12

Teva's Experts – Dr. Rapoport (MOH)

Dr. Rapoport's testimony:

73. Before 2005, nothing in the art would have suggested that prescribing an additional preventive migraine treatment to a patient who suffers from chronic migraine and MOH would have reduced medication overuse. Nor were there any studies showing that CGRP was linked to MOH. This effect is especially surprising

Ex. 2262, ¶73

Dr. Rapoport's statements in 2003:

Naratriptan in the Preventive Treatment of Refractory Chronic Migraine: A Review of 27 Cases

Alan M. Rapoport, MD; Marcelo E. Bigal, MD, PhD; Michel Volcy, MD; Fred D. Sheftell, MD; Michele Feleppa, MD; Stewart J. Tepper, MD

Ex. 1294; Ex. 1338, ¶¶138-139; Reply, 25-26

ment. Fourth, some of the patients stopped overusing acute care medication during the study, and at least a

Ex. 1294, 487; Ex. 1338, ¶¶138-139; Reply, 25-26

Teva's Experts – Dr. Foord

Dr. Foord's Admissions:

Q: Are you an antibody expert?

A: I am not.

Ex. 1343, 67:12-13; Reply, 11

Q: [Y]ou're not an expert in the dynamics of an antibody and how they behave in the synaptic cleft?

A: That is correct.

Ex. 1343, 70:4-9; Reply, 11

A: Immunology was one of those subjects that I never liked. I have a grasp, but it's tenuous.

Ex. 1300, 33:8-11; Reply, 14

Motions

Exhibit 1287 and Related Sections of Lilly's Reply

Dr. Ferrari's testimony:

147. Moreover, the testing of BIBN4096BS is reflective of the fact that, to the extent that a POSA would have been interested in targeting CGRP-related activity before November 14, 2005, that interest would have directed that POSA to CGRP *receptor* antagonism with a small molecule therapeutic. I am not aware of any discussion of pursuing anti-CGRP antibodies as a therapeutic in that time frame, either in the literature or in my personal conversations with experts in the field. For example, I was in frequent contact with researchers at Merck (including authors of Tan 1995) during the pre-2005 time frame while they pursued small molecule therapeutics that targeted the CGRP receptor, and I do not recall them ever discussing the possibility of targeting CGRP, much less targeting CGRP with an antibody for clinical use in human patients—despite the direct involvement of Merck researchers in the Tan 1995 study. Therapeutic antibodies were a new

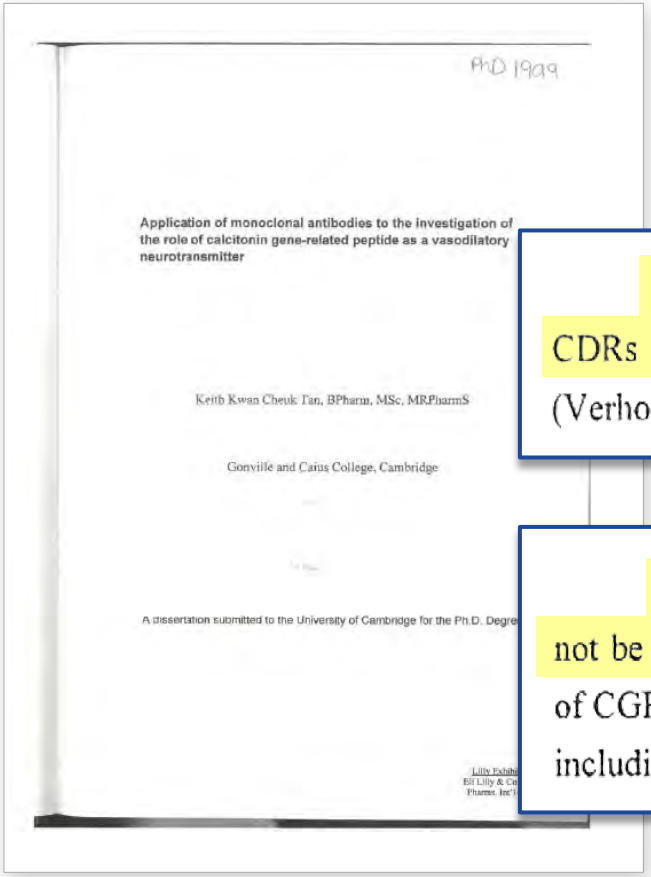
Ex. 2268, ¶147; POR, 4, 6

Lilly's reply:

Teva incorrectly attempts to undermine Tan's disclosures by characterizing Tan as a "basic research paper" and citing Dr. Ferrari's purported personal knowledge of its authors. Ex. 2268 ¶147; POR, 4. But in describing his own work, Dr. Tan wrote in 1994 that there was "no reason" why *humanized* anti-CGRP monoclonal antibodies should not be developed and used as "therapeutic agents" for migraine and other diseases. Ex. 1287, 247.

Reply, 15; Opp. Mot. Strike, 2-3

Exhibit 1287



PhD 1999

Application of monoclonal antibodies to the investigation of the role of calcitonin gene-related peptide as a vasodilatory neurotransmitter

Keith Kwan Cheuk Tan, BPharm, MSc, MRPharmS

Gonville and Caius College, Cambridge

A dissertation submitted to the University of Cambridge for the Ph.D. Degre

Tan thesis (Ex. 1287):

Mouse MAbs such as MAb C4.19 may be humanized by transplanting the CDRs from mouse MAbs on to human antibody variable region frameworks (Verhoeyen *et al.*, 1988). In such "classical" antibody engineering, hybridomas of

There seems to be no reason why anti-peptide MAbs or their fragments should not be investigated as therapeutic agents. The review of the pathophysiological roles of CGRP in Chapter 1 have suggested several therapeutic targets for CGRP blockade, including inflammation and migraine. Conversely, CGRP itself may be beneficial in

Ex. 1287, 247; Reply, 6, 15; Opp. Mot. Strike, 2-3

Ex. 1287 and Related Sections of Lilly's Reply

Teva's Assertion:

premised entirely on misreading cited references. For example, Dr. Charles states that Tan "provides guidance to a POSA on how to use full-length antibodies" and that "a POSA would have been motivated to follow Tan's recommendations because they are consistent with how a POSA would have wanted to reduce incidence of or chronically treat migraine …." EX1014, ¶¶134, 136. These are unsupported mischaracterizations: Tan has nothing to do with humans or treatment of *any* conditions whatsoever, as Lilly's experts admit. EX2191, 122:16-123:15; EX2192, 154:21-156:9. It is a basic research paper, which unambiguously reported that full-length anti-CGRP antibodies *failed* to show immunoblockade in a rat saphenous nerve assay. EX2265, ¶¶15, 56, 84-85; EX2271, ¶¶10-11, 75, 90-91, 95; EX2268, ¶¶137-138.

POR, 4

Lilly's reply:

treating migraine. Exs. 1021, 1022; Pet., 16-17. Although Teva argues Tan is a basic research paper having "nothing to do with humans or treatment" (POR, 4), Dr. Tan contemporaneously wrote that there is "no reason" why *humanized* anti-CGRP antagonist antibodies should not be developed and used for treating migraine. Ex. 1287, 247; *see also* Ex. 1096, 567, 570 (contemporaneously disclosing humanized anti-CGRP antagonist antibodies for treating migraine).

Reply, 6; Opp. Mot. Strike, 2-3

Teva incorrectly attempts to undermine Tan's disclosures by characterizing Tan as a "basic research paper" and citing Dr. Ferrari's purported personal knowledge of its authors. Ex. 2268 ¶147; POR, 4. But in describing his own work, Dr. Tan wrote in 1994 that there was "no reason" why *humanized* anti-CGRP monoclonal antibodies should not be developed and used as "therapeutic agents" for migraine and other diseases. Ex. 1287, 247.

Reply, 15; Opp. Mot. Strike, 2-3

Ex. 1287 Is Admissible

Tan 1994 (Ex. 1021):

MAb C4.19 to diffuse into the synaptic cleft. The results of the time-course experiment suggested that the concentration of the antibody had reached equilibrium in the synaptic cleft after 45 min since incubation with MAb C4.19 for 90 min did not enhance blockade of the capsaicin response.

Ex. 1021, 709; Opp. Mot. Excl., 1-2

Tan Thesis (Ex. 1287):

the synaptic cleft. The results of the time-course experiment suggested that the concentration of the antibody had reached equilibrium in the synaptic cleft after 45 minutes since incubation with MAb C4.19 for 90 minutes did not enhance blockade of the capsaicin response.

Ex. 1287, 196; Opp. Mot. Excl., 1-2

Ex. 1287 Is Admissible

Tan 1995 (Ex. 1022):

allowed for antibody distribution. The data of Covell et al. [14] suggest that much larger doses and longer distribution times are required for successful immunoblockade with IgG. In this

Ex. 1022, 571; Opp. Mot. Excl., 1-2

The slow distribution of whole IgG to the site of immunoblockade could be overcome by the alternative strategies of active immunization with CGRP or chronic administration of IgG. Responses to

Ex. 1022, 571; Opp. Mot. Excl., 1-2

With repeated administration, IgG should eventually distribute into interstitial space and achieve the sufficiently high concentrations required for immunoblockade. A limited example is found in an

Ex. 1022, 571; Opp. Mot. Excl., 1-2

Tan Thesis (Ex. 1287):

and doubling the time allowed for antibody distribution. The data of Covell *et al.*(1986) suggest that much larger doses and longer distribution time are required for successful immunoblockade with IgG. In this respect, it is interesting to note that

Ex. 1287, 222; Opp. Mot. Excl., 1-2

The slow distribution of whole IgG to the site of immunoblockade could be overcome by the alternative strategies of active immunization with CGRP or chronic administration of IgG. Responses to stimuli that potentially release endogenous CGRP

Ex. 1287, 223; Opp. Mot. Excl., 1-2

With repeated administration, IgG should eventually distribute into interstitial space and achieve sufficiently high concentrations required for immunoblockade. A

Ex. 1287, 223; Opp. Mot. Excl., 1-2

Exhibit 1287 Is Admissible

Carney's declaration:

14. The title page of the Tan Thesis includes the following University of Cambridge Library stamp.

As discussed above, upon receiving a published book or report, it is standard library practice to stamp a book with the library name and then shelve the book or report within a matter of a few days or weeks.

15. Attached as Exhibit C is a true and correct copy of the current Cambridge University Library ("CUL") catalogue entry for the Tan Thesis, which I accessed at http://idiscover.lib.cam.ac.uk/permalink/f/t9gok8/44CAM_ALMA21429648480003606 on August 27, 2019. As indicated in the CUL catalogue, the entry was created in 1994 and the Tan Thesis was approved on July 29, 1994.

16. Attached as Exhibit D to this declaration is a true and correct copy of the MARC record from the Cambridge University Library Catalog for its copy of Tan Thesis, which I downloaded from http://idiscover.lib.cam.ac.uk/primo-explore/sourceRecord?vid=44CAM_PROD&docId=44CAM_ALMA21429648480003606 on August 27, 2019.

17. The MARC record for the Tan Thesis, includes a number of fields. The date field 008 lists the first six characters "020506" in "YYMMDD" format, indicating that the MARC record for the Tan Thesis was created on May 6, 2002. This means, at the latest, the Tan Thesis was catalogued by the Cambridge University Library on May 6, 2002. The first six characters are also followed by the code "s" in character position 06 and "1994" in character positions 07-10. As discussed above, this indicates that the Tan Thesis was produced in 1994.

Ex. 1307, ¶¶14-17; Opposition to Motion to Exclude, 3