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

ELI LILLY AND COMPANY v.

TEVA PHARMACEUTICALS INTERNATIONAL GMBH

Case IPR2018-01422 (Patent No. 9,340,614)

Case IPR2018-01423 (Patent No. 9,266,951)

Case IPR2018-01424 (Patent No. 9,346,881)

Case IPR2018-01425 (Patent No. 9,890,210)

Case IPR2018-01426 (Patent No. 9,890,211)

Case IPR2018-01427 (Patent No. 8,597,649)*

ELI LILLY TRIAL DEMONSTRATIVES

November 22, 2019

Demonstrative Exhibits - Not Evidence



Eli Lilly Trial Demonstratives

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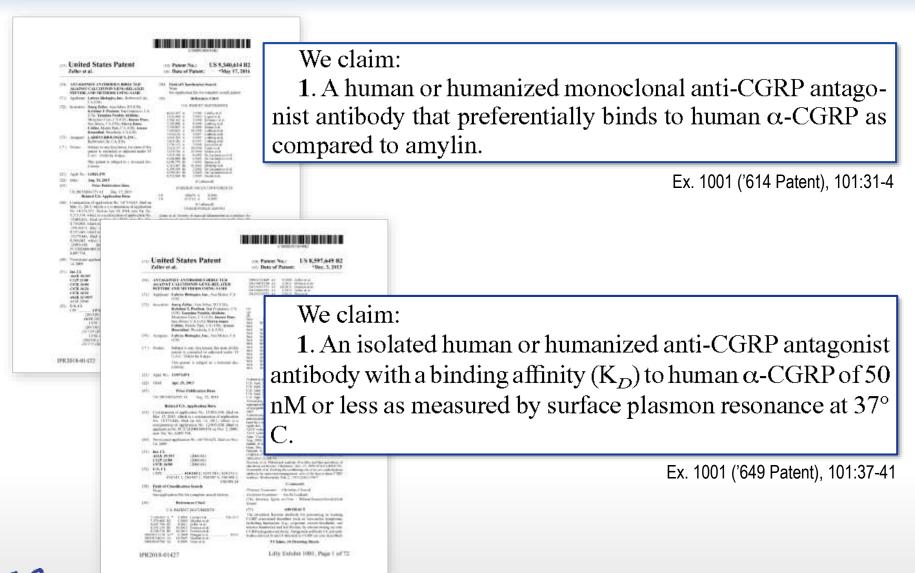


Summary of Case

- Teva's patents broadly claim any humanized anti-CGRP antagonist antibody with known or routinely achievable features
- Tan 1995 describes an anti-CGRP antagonist antibody effective in vivo and provides guidance to improve immunoblockade
- Wimalawansa expressly teaches that humanized anti-CGRP antibodies "should be explored" to treat human diseases
- The prior art is replete with reports providing additional motivation to make a humanized anti-CGRP antagonist antibody
- Teva conceded it was routine to make a humanized antibody
- Neither Tan 1995 nor Teva's purported safety concerns teach away from the claimed subject matter
- Teva's purported secondary considerations lack nexus and are insufficient to overcome obviousness



The Breadth of Teva's Claims



Tan 1995 (Ex. 1022) Shows MAb C4.19 Was Effective In Vivo

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

**Each K. C. TAN, Morris J. BROWN, Richard J. HANGREAVER, Sars L. SHEMEARDS, Second A. COOK! and Raymond G. HELL?

Direct Phonocology Unit, University of Combridge Consol School, Addenbrook's Hospital, Canbridge, U.K., and 1 Marcia Sharp and Dahme Research Entermines, Neuroscitory Research

Served (Friend August 1990) accepted 1th August 1990)

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6 The results demonstrate the pharmacokinetic situating of Full Seagment over IgG for immereblockade studies in vivo and sup CGRP in mediating skin variedilate

INTRODUCTION

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This study has clearly demonstrated the ability of MAb C4.19 IgG and its Fab' fragment to block the hypotensive effects of exogenous raCGRP in vivo.

Ex. 1022, 570; Ex. 1008, ¶71; Pet., 17

to CGRP. MAb C4.19 does not cross-react with rat amylin in vitro but the potential of MAb C4.19 to

Ex. 1022, 572; Ex. 1009, ¶76; Pet., 31

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Tan 1995 (Ex. 1022) Shows MAb C4.19 Was Effective In Vivo

Sand Street (1995) 88, 365-577 (French in Great Street)

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

Rich K. C. TAN, Morris J. BROWN, Richard J. HANGREAVESY, Sara L. SHEPHEARDS, Second A. COOK? and Raymond G. HELL?

Direct Phornacology Unit, University of Combridge Control School, Addedmisle's Haspital, Carbridge, U.K., and 1 Marvin Sharp, and Dahme Research Cabonitaires, Neurocologic Research Comp. Herbow, Essex, U.K.

Stored (FriedDague 1992 accepted 15 August 1995)

1. Calcitonia gene-related poptide (CGRP) is localind in perviscolar sensory neutrons and is a potent unificate. We irrestigated the utility of internatliciate as an exist technique for probing the role of CGRP as an enforcement vascolitation.

3. The effects of an anti-CCRP manochonal antibody SAA: code CA19: and its Fab fragment on CRP-induced changes in blood present and skin fool flow more studied in periodicibitonmuthetined ran. Audithoritis skin ranofflantation in fir to kind pain was measured by laser Doppler funnity.

3. The done-response relationship for the hypotensise flow of intravenous rat of GHP (ref GRP) was smilet; shilled rightward by Male CA19 [gG legical intravenous); The Cartesiand Fourier Legical intravenous); The Cartesiand Fourier of luma a CGRP (Int GRP_{d-N}) also blacked the shinting effect of proCGRP.

5.5ch C4.19 Fab fragment (2 mg/m); intramody, and hot G8R₂ or 100 models; intrasonably, but no MAI C4.19 [e] (up to 3 mg/m; intercondy) or natural mouse Fab fragment "agrant, invariously), looked the increased white intelligence of the companion of the companion of the spheres, nearest.

 The sman percentage changes in skin blood flow municipes due to: MAh C4.19 Fah fragment mete spillemely different from those due to cornal more fah fragment (uspected r-test; P < 0.05) but no line those due to heCGRP_{n, 1}.

6 De results demonstrate the pharmacokinetic situatige of Fab' fragment over IgG for immereMockade studies in vive and sa CGRP in mediating skin vasodila

INTRODUCTION

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MAb C4.19 IgG at 1 mg/rat given 60 min before nerve stimulation did not block the skin blood flow response to antidromic nerve stimulation (n=2; Fig. 5a). Increasing the dose to 3 mg/rat did not produce a significant difference in F_{max} or AUC (P=0.83; n=4) after 60 min (Fig. 5a). Further nerve stimulation performed at 2h after 3 mg/rat MAb produced an AUC which was slightly smaller compared with baseline stimulation, but not by more than 16% (n=2).

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Committee Prior Legge Surgert, Ranges Stat. Society. Cor., 2717 Mg. CA. 18. September Dr. Kom N. C. Ser, New County Species, Surgers Stat. Society (71) Mg. Cor. 18.

Ex. 1022, 569; Ex. 1008, ¶57; Pet., 17-18; Reply, 20



Tan 1995 (Ex. 1022) Provided Guidance to Improve Immunoblockade

hard bleast (1995), 88, 163-577 (French in Great Britany)

Calcitonin gene-related peptide as an endogenous asodilator: immunoblockade studies in vivo with an anti-calcitonin gene-related peptide monoclonal antibody and its Fab fragment

Wart K. C. TAN, Morris J. BROWN, Richard J. HANGREAVESY, Sara L. SHEPHEARDS. Secret A COOK! and Raymond G. HELL!

Direct Phonoscology Unit, University of Combridge Clinical School, Addenbriole's Hospital, Controlpe, U.K., and †Maryk Sharp and Dahme Research Laboratories, Neuroscience Research Sens Horlow, Estex, U.K.

Stored (Friendlague 1990, accepted 10 August 1990).

I Calcitonia gene-related poptide (CGRP) in localind is perivascular sumony neurons and is a potent uniflator. We investigated the utility of immunolickade as an in vivo technique for probing the role of CGRP as an endogenous vasodilator.

I The officers of an anti-CCRP monoclosul antibody MAS coded C4.19; and its Fab' fragment on CERP-induced changes in blood pressure and skin loof flow were studied in pentoharbitumemurbetted rats. Antidromic skin rasodilatation in for my hind pare was measured by laser Dopplet

3. The dese-response relationship for the hypotensive effect of intravenous rat oCGRP (coCGRP) was solarly shifted rightward by MAE C419 IgG linging intravenessly) and Fab' fragment Ingust intravenuesly). The C-terminal fragment of terms aCGRP (haCGRPairs) also blocked the intotenine effect of rat GRP.

6 MAb C4.19 Fab' fragment (2 mg/rat; iteramody) and hacGRP_{a,y}, (100 omilikg intra-mody), but not MAb C4.19 IgG top to Jungitati Starreously) or normal mouse Fab fragment Engrat; intravenously), blocked the increased skin find flow response to accidromic stimulation of the

3. The mean percentage changes in skin blood flow persenters due to MAh C419 Fah' fragment note spallenely different from those due to scental some Fab' fragment (unpaired f-nest; P < 0.0% but ne from those due to hat GRP

The results demonstrate the pharmacokinetic sharings of Fab' fragment over IgG for immere-

Mockade studies in vive and s CGRP in mediating skin varietil

INTRODUCTION

Calcitosia gene-related peptid used in persyancials primary after a potent vasofilator in man species studied [1-3]. Some reportunit of CGRP is the flow has emerged from studies w 8-37 fragment of human aCG which sets as a CGRP mag 52 The hypotenion impense to in appendictional and companie by InCGRPs, p. (8, 7). Exagens a systemed hypotrasion that reresponse to spinal cord strendal [8]. The hypotimise responses to lation and evopourum CGRP are: by hoCGRPs at Their endogene to be a major neurotransmitter of genic casesbirtation after spenic the rat HeCGRP_{s, 2}-poon 59 route has been found to inhelic blood flow induced by intrade cognition [9] Increased skin bloom hind pea ofter antidrorse stemi enous serve is also inhibited by to The evidence obspired from the a suggests that CGRP is an impo the 'efferted' tanoniamy fund sensitive primary afferred recorns

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

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

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

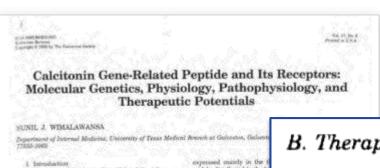
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Ex. 1022, 571; Ex. 1008, ¶122; Ex. 1305, ¶¶24-29; Pet., 39-42; Reply, 20



Wimalawansa (Ex. 1096): Humanized Anti-CGRP Antagonist **Antibodies "Should Be Explored"**



II. Discovery of Calcitonics Gove-Related Peptide III. Molecular Genetics and Structure of the CT/CGRF, Amylin, and Adrenomedulin Genes

A. Adrenomedullin B. America

C. Calciumo

IV. Distribution and Lecalization A. Distribution of S-CCRP

B. Distribution of CGRP exceptors V. Ago-Related Changes of CGRP and Circadian Rhythm

VI. Structure-Activity

VII. Secondary and Tertiary Structures of CCRP

VIII. CGEP Receptors A. CGRP receptor binding

 CGRP receptor subtypes: C. Isslation, closing, sequencing, and characterizing

OK. Puptide Measurements

XI. Bale of Matte Oxide and Other Second Messengers in CCRP-Mediated Actions XII. Biological Actions of CCRF

XIII. Therapostic Potentials

A. Therapeutic potentials of CGRF and its agontats B. Therapeutic potentials of CCRP antagoraris

XIV. Corclusions and Future Prospects

1. Latroduction

THE calcitosis (CT) and calcitosis gard-related popular (CGBP) are derived from the CV (CGBP) (CGRP) are derived from the CT / CGRP gene, which is localized in chroscoonse 11. Alternative splitting of the pri-mary ENA transcript leads to the translation of CGRF and CT peptides in a timus-specific manner. This alternative the sue-specific processing of primary mRNA from the a-CT/ CGRP gone in nits generates two distinct poptides, CT and CGRP (1, 2). CGRP is a 37-amout and neutripopule evpressed predominantly in the nervous system and CT is

Addition typin represent the Control Malacine and Distortionings, MisCrash, EECF, Denoises of Control Malacine and Pharmackeg, Unionality for Team Indian Practice of Galeston, M. Unionently Dedecard, S.OK, Malaci Research Suiten, Galeston, Teas 7005-5085.

widely distributed in the b emnus towodilatory profic rived from the C cells of fi potent peptide inhibitor et during periods of "talci isancy, and lactation (3).

In 1961, Copp and col bence of the calcium fown atructure were determ Similar to CGRP and an hormone consisting of X secreted by the parafoll (6, 7), which are of neut nomity of CT produc Kulchitrky (K) ords in t

small cell caccinoma of the lung, both of which secrete C (16, 11). Therefore, even after total thyrodectomy, the complete absence of CT from the circulation is unlikely, and minute amounts of CT in the circulation may be sufficient to counteract the bone-resorbing effects of other horspores such as PTH (125-

Amelin, a 37-amino acid re Incated to chromosome 17 chromonome 11 during acid homology with CGR pencreas. Its involvene abeten in thought to be b pascress, leading to it ce of this popule family is a acid vasuactive poptide Histor (19-21). Not only d amine sciel horselegg w profile in the cardiovasco

albeit less petent (12, 12 Previous CGRP-relate or more of those areas; it

activity of CGRP, mulic Several expellent reviews cover cardiovascular hemodynamics (27, 28) and circuit applications of CGRP (29) have been published. There is a growing

B. Therapeutic potentials of CGRP antagonists

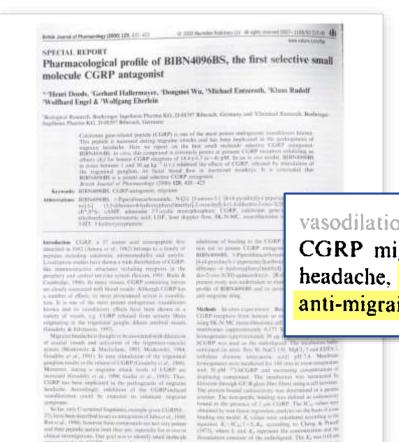
Evidence is accumulating that inappropriate release of CGRP is a potential causative factor in several diseases, including migraine, inflammation, and cardiogenic shock associated with sepsis. These postulations were derived after

Ex. 1096, 567; 1008, ¶74; Pet., 19

disease. The role of CGRP antagonists and humanized monoclonal antibodies should be explored with respect to control of pain and inflammation, type II diabetes, and in conditions with intractable hypotension, such as septic shock syndrome.

Ex. 1096, 570; 1008, ¶74; Pet., 19; Reply, 2.

Doods (Ex. 1024): Motivation to Make an Anti-CGRP Antagonist Antibody



and 0.12 are for the barrier and on CORP tempor of discretized by saturation bridge experiment with \$7.

Apparation of SHINGPORD was dearwood to memorial the formation of cyclic AMP in SK-N-MC with For colle AMP (addressed TS-cyclic recovering their) merconated to

SK-holdC salls were recobased with CEGEF game or in Re-

vasodilation. 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. Much remains to be investigated to

Ex. 1024, 422; Ex. 1008, ¶113; Pet., 26



arragement for the CGRP people and in our three reasons has

Our high throughput screening led to the investment of departure into congruends that should must hav recommend

one of CHIRP in regarded beautiful.

Market for communities.

Description in the backets on the same

Salmon (Ex. 1027) Disclosed Anti-CGRP Antagonist Antibodies for Therapeutic Use



- (19) United States
- (12) Patent Application Publication (10) Pub. No.: US 2002/0162125 A1 Salmon et al. (43) Pub. Date: Oct. 31, 2002
- (\$4) METHODS AND COMPOSITIONS FOR THE MODULATION OF NEUROGENIC INFLAMMATORY PAIN AND PHYSICAL OPIATE WITHDRAWAL
- (70) Investor: Anne-Marie Salmon, Paris (FR); Susumu Sekine, Kusagawa (IP), Marine Picclette, Gelferd, CT (US); Joan-Pierre Changawa, Paris (FR)

Correspondence Address: Finangon Handarwan Familiare Garrett & Bunner Salte 749 1300 I Street, N.W. Washington, DC 24005 (US)

- (21) Appl. No.: 16091,327
 - Bristed U.S. Application Data
- (60) Provisional application No. 60/273,349, filed on Mar. 6, 2001.

Publication Classification

- (57) ABSTRACT

A method of secreting five a compound that is an entigenist of coloritonia gene related peptide (or GRP) is precised. The method comprises expessing a metant norse to a compound. The method comprises expessing a metant norse to a compound to a remain research to the compound of the method response of the control of the control of the control of the control of the precise at the control of the precise at the control of the precise of excellent produces of the method recompound to a widely resource. The response of GRP and A difference in response compand to a widely resource is indicative of the compound functioning selecting to a their coffeed active; it as prefutured embodisment, the disruption comprises the inserting of an appropriate discontinuously in section of the compound functional to the compound functional to the compound functional of the compound of the compound functional of the function of the compound functional of the compound functional of the compound functional of the compound function o

[0039] Described herein are compounds, including pharmaceutical compositions, which can be utilized for the amelioration of neurogenic inflammatory pain and/or physical opiate withdrawal. More specifically, said compounds are antagonists of calcitonin gene related peptide (αCGRP). Such compounds can include, but are not limited to, small peptides, small organic molecules, antisense, and triple helix molecules. Compositions can include polyclonal and/or monoclonal antibodies for the modulation of such pain and/or withdrawal symptoms.

Ex. 1027, ¶[0039]; Ex. 1008, ¶110; Pet., 25

- 6. A compound, which is an antagonist of α CGRP, identified by the method of any one of claims 1 to 5.
- 7. The compound of claim 6, which is a peptide, small organic molecule, antisense molecule, or a triple helix molecule.
- 8. The compound of claim 6, which is a monoclonal antibody.



Ex. 1027, claim 8; Ex. 1008, ¶110; Pet., 25; Reply, 12

Sveinsson (Ex. 1026) Disclosed Anti-CGRP Antagonist Antibodies for Therapeutic Use



CLAIMS

- A method of treating, remedying or preventing psoriasis in a subject comprising administering. to the subject a therapeutically effective dose of at least one CGRP antagonist compound in a pharmaceutically acceptable formulation.
- The method according to claim 1, wherein the at least one CGRP antagonist compound is selected from the group consisting of 4-sulfinyl benzamide compounds, 3,4-dinitrobenzamide compounds, benzamidazolinyl piperadine compounds, anti-CGRP antibodies, CGRP derivatives including the peptide CGRP 8-37, tryptase active polypeptide, and the compound BIBN4096BS, and compund stabilising tryptase, including heparin.
- 6. The use of a CGRP antagonist compound for the manufacture of a medicament for treating, preventing or remedying psoriasis in a subject.
- 7. The use according to claim 6, wherein the compound is selected from the group comprising 4sulfinyl benzamide compounds, 3,4-dinitrobenzamide compounds, benzamidazolinyl piperadine compounds, anti-CGRP antibodies, CGRP derivatives including CGRP 8-37, tryptase, tryptase stabilizing compounds including heparin, and the compound BIBN4096BS.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Ex. 1026, claims 2 and 7; Ex. 1008, ¶109; Pet., 24-25; Reply, 12

The '438 Patent (Ex. 1028) Disclosed Anti-CGRP Antagonist **Antibodies for Therapeutic Use**



(12) United States Patent De Lacharriere et al.

- (10) Patent No.: US 6,344,438 B1 (45) Date of Patent: Feb. 5, 2002
- (54) THERAPEUTIC/COSMETIC COMPOSITIONS COMPRISING CORP ANTAGONISTS FOR TREATING THE EYES OR EYELIDS
- (25) Inventors: Offivier De Lacharriere, Paris; Lionel Bruton, Versailles, both of (FR)
- (73) Assignor: Societe POreal S.A., Paris (FR)
- Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.
- (21) Appl. No.: 09/589,117
- (22) Filed: Jun. 8, 2000

Related U.S. Application Data

- Foreign Application Princity Data Mar. 28, 1995 (FR)
- (52) U.S. CL ...
- References Cited
- POREIGN PATENT DOCUMENTS

93/21901 11/1993

OTRER PUBLICATIONS

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pp. 738-742, Hughes et al.

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British Journal of Pharmacology, vol. 130, No. 772-776, Escott et al. British Journal of Pharmacology, vol. 164, No. 3

Primary Examiner-Zohnih Fay 4) Attorney, Agenc, or Firm-Burns, Donne Mathis, L.L.P.

ABSTRACT

Ocular audior rainebral pruritus audior ocular a bral pain and/or ocular and/or palpebral dynamiing a mammalian, notably human patient, are the treated by administering to such patient a thera-

cosmetically effective amount of at least one CGR antigonist, advantageously in combinatory immirrare with at least one antagonist of a neuropoptide other than CGRP, o.g., a substance P antagonist, and/or at least one inflammation mediator antagonist; the subject compositions are also well suited for making up and/or curing for human even cyclashes and/or cyclids, especially sensitive eyes and eye-

19 Claims, No Drawings

A major object of the present invention is the administration of one or more CGRP antagonists to a mammalian, notably human patient, for treating the disease states indicated above.

Ex. 1028, 2:7-10; Pet., 25

CGRP 8-37 and anti-CGRP antibodies are suitable CGRP antagonists according to the invention.

Ex. 1028, 3:21-22; Ex. 1008, ¶111; Pet., 25



Motivation to Make a Humanized Antibody

Dr. Ferrari's cross-examination:

- Q: Hypothetically speaking, as an expert in the field, if a reference stated that an anti-CGRP antagonist antibody was to be administered to a human to treat a chronic human disease, would that have been understood as a reference to a humanized antibody?
- A: I think that, and, again, I'm not an antibody expert, but by 2005 it was well-known that you would significantly reduce the risk of immunological side effects to an antibody by humanizing it. So developing an antibody at that time without including humanization would not mean would not be useful to use in patients.

Ex. 1303, 49:1-20; Reply, 3

Dr. Tomlinson's cross-examination:

- Q: As of 2005, by the time that an antibody in drug development reached a Phase 1 clinical study for dosing in humans, it would likely be a human or humanized antibody, correct?
- A: In 2005, yes.
- Q: And then as of 2005 in a clinical trial program, it would not have been acceptable for a person of ordinary skill to have administered a murine antibody to a human for chronic use without first humanizing it, correct?
- A: I would say that was quite very unlikely.



Ex. 1301, 211:2-15; Reply, 3

Lassen 2002 (Ex. 1047): Motivation to Make an Anti-CGRP Antagonist Antibody

Calcitorin personated peptide (CCRP) has been detected in increase contral juguiar sentua blood during migraine situades. However, it is until this is secondary in reignance or whether CCRP any cause heartache, it is crosseer attaly, the effect of harran oCCRP (2 ug/min) or placeto leveraging for 20 aims new studied in 12 pointers suffering from migraine Hondacke intensity was sensed on a scale from 40 july in present the contract of the cont

push bandsche score was 1.0 in the boCGBP group vs. 0 in the placebo go During the following 10 h all patients experienced headaches often has patient after placebo (P = 0.000). The median monumal headache score we and 0 other placebo (P = 0.000). In these patients after boCGBP, that is no placebo, the designed headache fulfilled the IRS criteris for singuine will introvirous administration of locCGBP remain headache and migrains are one unity suggests that the intronse in CGGBP observed during sportaneous registrates are given by they a creative seets. (CGCMB attents, attents, headach, pagings).

Lamin LH, Strautin B, DK-2520 Gerteffe, Densurk-Tel. +45:38650542, fee: +45:39650042, e-mail Th lanser@eladfort.sk Received 28 February 2001. accepted 5 Newsider 2001 The outcome of the present study is very clear. CGRP caused headache in virtually all migraine sufferers, whereas placebo did not. The headache occurred during

Ex. 1047, 59; Ex. 1008, ¶113; Pet., 26

Introduction

Calcitonin gene-related peptide (CGBP) immunimentary libors originating in the trigeminal ganglion innervate cranial cerebral blood vessels (3). In animals, attanulation of these sensory nerve fibres has been shown to cause artifeenic release of CGRP with subsequent vasodilatotion of the cerebral vasculature (7). CGRP is also one of the mediators of neurogenic inflammation. This phonomenon has been implicated in the perhapenesis of migraine headache in an impressive range of previous enadies (5): CGRP levels are increased in the blood from the extental jugular vein but not in cubital venous blood. during migraine attacks (ii). The 5HT₁₈₋₀₃ receptor agentat, nametromes, which aborts migraine attacks, normalism CGRP levels (5). Whether this arphabic CGRP retuse plays a role in the pathophysiology of migrater. or only represents a consequence of the migroine attack. is unknown. In province studies where CGRP was minisod into oce-migraineurs, a feeling of fulfness in the head but an handache was reported (6, 7). To efucidate the role of CCSP in migraine we therefore decided to study whether intravenous CGRP infusion in migratus.

sufferers causes more beedache or migraine than placebo using a double blind, crossover dissign.

Material

Twelve volunteers (11 females, 1 mail 395 years, reges the range 31-47 years, trees the range 51-48 kg), all suffering from epice serfector area according to the clerk to broattained Headsheb Society (8), it healthy, veree included. The perfector has negative staticles per morth and so reignate year customers included. Patients had be not beneather the perfect of terminophy headshelp per month.

The subjects were told not to have heads and they were bold not to use medication; or consumer coffee, tex, alcohol or tobecco for 12 h before the study. They were not allowed to toke a triptern for 2h to or repetamine for 4h before the study. Evclusive criteria were use of any kind of daily medication, including prophylatric beadshot between plot availables great contaceptives; programmy or invast-feeding, exceptive use all analysis or a doubtle actions scentify or provisionity.

CGRP in migraine. This finding greatly increases the likelihood that a CGRP antagonist may be effective in the treatment of migraine attacks. Several drugs that in

Ex. 1047, 60; Ex. 1008, ¶113; Pet., 26

© Blackwell Science Ltd Cophrisiph, 2002, 25, 74-65



Olesen (Ex. 1025): Motivation to Make an Anti-CGRP **Antagonist Antibody**

THE STEW WHEN LAND SOURS AND ASSESSED. ORIGINAL ARTICLE Calcitonin Gene-Related Peptide R Antagonist BIBN 4096 BS for the Treatment of Migraine

Jes Olesen, M.D., Hans-Christoph Diener, M.D., Ingo W. Hus Peter J. Goadsby, M.D., David Hall, Ph.D., Ulrich Meier Stephane Pollentier, M.D., and Lynna M. Lesko, M. for the BIBN 4096 BS Clinical Proof of Concept Study 5

ABSTRACT

vasodilation.7 Cranial CGRP levels are elevated in patients with migraine, and an infusion of CGRP can trigger a migraine attack.9 We therefore hypothesized that CGRP antagonists might be effective in the treatment of acute migraine.

BS than after the infusion of placebo. The robust-

ness of this primary conclusion was confirmed by

the similarly positive results we found for all the

secondary end points with the use of descriptive

methods. Proof of concept was thus established.

Ex. 1025, 1105; Pet., 10-11

Calcitoring gene-related poptide (CGRP) may have a causative role in a for hypothesized that a CGRP-receptor antagoniat might be effective of migraine attacks.

Experiuges, Deniruli (LOL) the Depart ment of Housebeg, University of Exces.

isses, Gormany (H.-CDL); the Department Neumings University Hospital, Müncie sermany D.WHC); the Invitigate of Nasara

gs London (P.J.G.); Bushinger Ingelheim

Pharmaendican, Inderfield, Corn. (ILIK., L.M.); and Bodynger Ingelletin Phar-

these apprint requests to Or. Obser at the

rup, Copenhagen, Denmark, or et jeel 🕸 14 Engl | May 2004;250 (164-15)

In an international, multicenter, double-blind, randomined clinical BS, a highly specific and potent nonpeptide CGRP-receptor antago with migraine received one of the following: placebo or 0.25, 0.5, 1 of SIBN 4096 BS introvenously over a period of 10 minutes. A group Intensity of Coperhages, Department of tive treatment-assignment design was used to minimize the number than the property of Coperhages (Section 1997).

The 2.5-mg dose was selected, with a response rate of 66 percent. 27 percent for placebo (P=0.001). The BIBN 4096 BS group as a who rate of 60 percent. Significant superiority over placebo was also obs to most secondary end points: the pain-free rate at 2 hours; the rat sponse over a period of 24 hours; the rate of recurrence of headache names, photophobis, phonophobis, and functional capacity; and ingful relief. An effect was apparent after 30 minutes and increased hours. The overall rate of adverse events was 25 percent after the 2.5-m and 20 percent for the BIBN 4096 B5 group as a whole, as compared placebo. The most frequent side effect was puresthesia. There were no

Ex. 1025, 1108-1109; Ex. 1008, ¶¶41-44, 113; Pet., 10-11, 24, 26

The CGRP antagonist RIBN 4096 ES was effective in treating acute attacks of sugniture

CONCLUSIONS

The CGRP antagonist BIBN 4096 BS was effective in treating acute attacks of migraine.



Ex. 1025, 1104; Ex. 1008, ¶¶41-44, 113; Pet., 10-11, 24, 26

Targeting CGRP and Its Receptor Were Alternatives



Available online at www.sciencedirect.com



Vascular Planesarology 43 (2005) 176-187



Migraine: Current concepts and emerging therapies

D.K. Arulmozhi ^{a,b,a}, A. Veeranjaneyulu ^a, S.L. Bodhankar ^b

"New Countred Entity Research, Sights Revision First, 1955p. Numbs, Solds Mohr, Princ 417 Od.; Mahamahira, Josh "Department of Physical Origin; Bharath Vilgingradis, Perinc College of Physicals, Name 431 Od.; Mahamahira, Joshu Washington, 2018, April 1965; worked to revised from 17 Jans 1965; sciented 15 Adv. 2065

Abstract

Migatine is a recurrent inequestating source-occular disorder destructural by antacks of disbilitating point associated with photospholis, phosopholis, assume and verorities, Migatine affects a substantial function of reveal population and in a majer cause, disability in the work place. Though the pathophysiology of migratine is still succlear three neight theories proposed with agent to the mechanisms of arganism or security of the control of some forestend standardisation, neurological finite production of which causes the succlear depression and triggatine) and managenic dural inflammation (release of inflammatory nitrospeptides). The another confirmation got the publicagement of migratine in bound on it is a conversation elisability districts. The drags used in the tourisms of substantial elisability of the publicagement of migratine in bounded or min in prevention. The base decade has witnessed the advent of Susmitterian and the "trigitation closured behavior, Self-21, recopers assignment to the context of the context of

Xovenic Migrins; CHD; Sentrals; Inipas

1. Introduction

Migraine is a chronie, often debilitating disease that affects 12% of the general population. This episodic benish disorder is characterized by unilateral throbbing headache lasting from 4 h to 3 days. Associated synaptoms include tausier vomining and sensitivity to light, somel and head movements (Silbersein, 2006). A working definition of sugariate in beniga recorning headache andice neurological dysfunction usually attended by pain-free interhules and often provoked by stereotyped stimuli. Migraine is more common in females, with a benefitary predisposition

 $1502\!-\!1991.5$ - see frost swater to 2005 Published by Election Inc. this 20.16 to $J_{\rm C}(vg)$, $2005\!-\!67.001$

towards attacks and the cranial circulatory phenomenon appears to be secondary to a primary central nervous system disorder.

The Henduche Clansifictional Hapdache Society (and diagnostic criteria for Henduche Society, 2004), and 'classical migraine' It without sum' and 'triggain operational celetia have easily ache entities in a reliable it

Migraine apparently a ricen, cultures and gengr suggest that 18% of won from migraine and those of for Disease Control report

Dr. Rapoport's statements in 2018:

1.2 Why Block CGRP or Its Receptor?

Based on all this information, it was considered that blocking CGRP or its receptor might treat an acute migraine attack or prevent migraine from occurring. The first studies were performed on short-acting, small molecule, CGRP receptor antagonists. All the acute care

Ex. 2169, 915; Ex. 1306, ¶86; Opp. Mot. Excl., 12

Arulmozhi 2005:

Hence, inhibition of CGRP or antagonism of CGRP receptors could be a viable therapeutic target for the pharmacological treatment of migraine (Edvinsson, 2004).

Ex. 1040, 182; Ex. 1008, ¶116; Pet., 27; Reply, 9



^{*} Corresponding nuther, Department of Planemacology, New Charaked Early Research, Lopic Research Park, Village Numbe, Bulsk Medals, Park 411 SHJ, Mahamahm, India, Tol. 196 20:2552 (106); Soc. 993 20:2512 (200). E-mail authors: add. binolyphine.com/ (U.K. Andronath).

Targeting CGRP and Its Receptor Were Alternatives

Immunoneutra Calcitonin Ge

G. J. DOCKHAY # B A. K. BANDY MRC Resease Doporty United

Understanding the physiotogical penals, in limit in part, on the suppression Typically, this is achieved size in the substantial maker connections, by

on nine fact trust ions. The user is compte observed populates of the approximation proposation of over. It is provide the population of the field approximation is governmental. in vivo. Typically, this is achieved using antagonists that occupy the same receptor sites as the substance under consideration. In the case of peptide and protein messengers, however, the development of antagonists of suitable affinity for work in vivo has frequently presented a formidable, although not insurmountable, problem. The use of antibodies to neutralize endogenous regulatory peptides offers a simple alternative strategy. It is generally straightforward to raise antibodies to

Calcitorin gene-related peptide as an endogenous suscilator: immunobiockade studies in vivo with an uti-calcitonin gene-related peptide monoclonal antibody and its Fab fragment

Sun E. C. TANK Planck J. BACORN, Biolout J. HARDERYED, Tacs L. SHOMENEZH, South R. COCKY and Represent C. HOLLY

and Removable Dr. Dremote of Gordonia Dremot School, Albertania's Happin. Service, 118 , and 1984-19. Story and Dalone Research Johnson, Storyana

Enclosure: D5

Monoclonal Antibody to Rat α-CGRP: Production, Characterization, and In Vivo Immunoneutralization Activity

H.C. WONG, * V. TACHÉ, * K.C.K., * LLOYD: * N. YANG, * C. STERNING, * P. HOLZER, * and J.R. WALSH* * Control of the Walsh * Annual Control of the Walsh

ABSTRACT

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ne LORE so

Ex. 1049, Abstract; Reply, 20

The aim of the present study was to investigate immunoblockade as an alternative strategy for probing the role of CGRP as a vasodilator in vivo.

Immunoblockade should be regarded as a technique that is complementary to the use of receptor antagonists. A comparison of the two approaches

Ex. 1022, 566, 571; Ex. 1008, ¶114; Ex. 1305, ¶37; Reply, 9

Elucidation of the physiological relevance of the pharmacological actions of CGRP requires specific blocking of endogenous CGRP either at the receptor level using specific CGRP antagonists (10,11), or by neutralizing endogenous peptide with a specific antibody (12-15). There is evidence for the existence of various CGRP receptor subtypes (10, 16) for

at the mount more gaugest which produce of gasolic tensory fibers by arche captured injection

Ex. 1033, 95; Ex. 1305, ¶37; Reply, 9



Teva's Patents Do Not Address Safety



Alcon Research Ltd. v. Apotex Inc., 687 F.3d 1362, 1369 (Fed. Cir. 2012)

"Although Alcon argues that Kamei would not give a skilled artisan an expectation of success because it does not teach that olopatadine is safe for the human eye, we find this contention to be without merit. While it is true that [the prior art] does not expressly disclose that olopatadine would be safe for use in human eyes, neither does the '805 patent. The patent is not based on testing in humans; instead it reports only in vitro tests."

Reply, 4-5

Dr. Ferrari's cross-examination:

- Q: [Y]ou would agree that the '614 patent does not disclose any safety studies at all, correct?
- A: There is no text mentioning data from safety studies.
- Q: Teva's patents do not disclose any studies in humans at all, correct?
- A: The patents do not disclose studies in humans.

•••

- Q: ...And you would agree with me Teva's patents do not mention cardiovascular effects resulting from anti-CGRP antagonist antibodies, correct?
- A: The same answer, yes.



Ex. 1303, 56:4-57:19; Reply, 4

Teva's Patents Do Not Address Safety

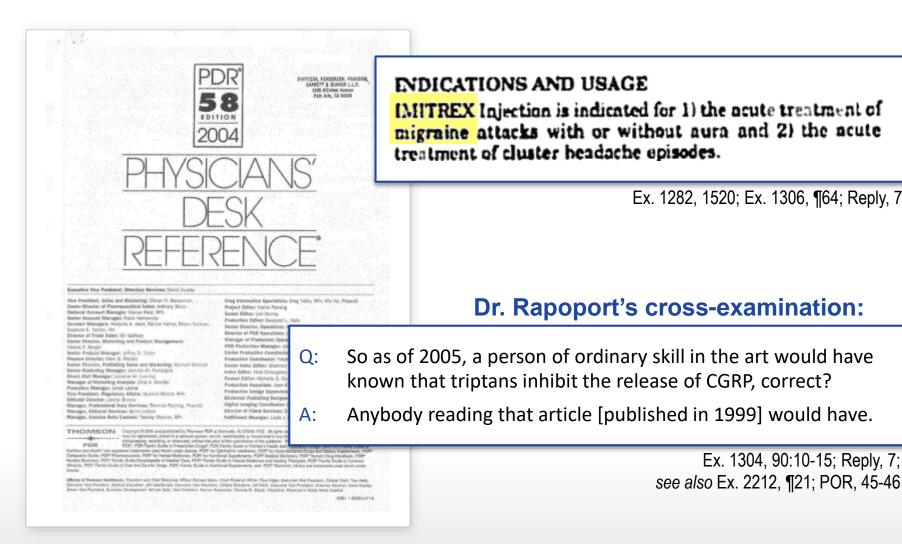
Dr. Foord's cross-examination:

- Q: [W]ould a description of a successful use, whether a statistically significant efficacy was shown of an anti-CGRP antibody in a rat saphenous nerve assay, have adequately resolved the concerns you identify in your declaration about safety and efficacy?
- A: No.
- Q: Would the description of the successful use of anti-CGRP antibodies in the rat closed cranial window assay have adequately resolved the concerns you identified about safety and efficacy?
- A: No. These are preclinical animal experiments that will never satisfy concerns about safety and efficacy, until that agent goes into man.

Ex. 1300, 173:20-174:11; Reply, 4



Sumatriptan, FDA-Approved for Treating Migraine, Was Understood to Inhibit CGRP Release





Prior Art Clinical Studies Disclosed the Vascular Safety of CGRP Antagonism (Ex. 1025)

THE REW EMILLAND DUTCHAL SHEEDING ORIGINAL ARTICLE Calcitonin Gene-Related Peptide Re-Antagonist BIBN 4096 BS for the A Treatment of Migraine

> Jes Glesen, M.D., Hans-Christoph Diener, M.D., Ingo W. Huss Peter J. Goadsby, M.D., David Hall, Ph.D., Ulrich Meier, P. Stephane Pollentier, M.D., and Lyona M. Lecko, M.D. for the BIBN 4096 BS Clinical Proof of Concept Study Gr

ABSTRACT

irup Hospital, University of Copurhagen,

Copenhagin, Denmurk (J.Cl.); the Depart-

ment of Neurology, University of Essen, Essen, Germany (H.-C.D.): the Disputment of Neurology, University Hexpital, Münchir, Germany (LMHL); the inotifiate of feweral-

LMLS and Borbringer Ingelhore Phan-ma, Ingelhore, Germany (U.M., S.P.). Ad-

tress represe requests to Dr. Olsse at the

trup, Coperduger, Decembris, or at jeoligi-glectruptump idélementific N Singl J Med 2009;150 L150 JD

Calcitonin gene-related peptide (CGRP) may have a causative role in mig fore hypothesized that a CGRP-receptor amagonist might be effective of migraine attacks,

In an international, multicenter, double-blind, randomized clinical tri ogs. Louise: (F.J.C.), Nothingue Ingilliani. In an international, multiconter, double-billed, randomined clinical in Processionistas, Relatività, Com. (D.H., BS, a highly specific and potent nonpeptide CGED-receptor antagoni with migraine received one of the following: placebo or 9.25, 0.5, 1, 2 of BIRN 4096 BS intravenously over a period of 10 minutes. A group-a University of Copenhages, Department of Sire treatment-assignment design; was used to minimize the marrier Nearlings Gustup Magnet, 2008 Got-named.

The 2.5-mg done was selected, with a response rate of 66 percent, as 27 percent for placebo (P=0.001). The BIBN 4096 BS group as a whole rate of 60 percent. Significant superiority over placebo was also observ to most secondary end points; the pain-free rate at 2 hours; the rate spense over a period of 24 hours; the rate of recurrence of headache; i nauses, photophobia, phonophobia, and functional capacity; and the ingful milef. An effect was apparent after 30 minutes and increased or hours. The ormall rate of advicor events was 25 percent after the 2.5-mg and 20 percent for the BIBN 4096 BS group as a whole, as compared wit placebo. The most frequent side effect was puresthesis. There were no

The CGRP antagonist BIBN 4096 BS was effective in treating acute attack

shared with ergot derivatives and triptans.31 In humans BIBN 4096 BS caused only minor adverse events³² and had no constrictor effect on the middle cerebral, radial, or superficial temporal artery or on regional cerebral blood flow, blood pressure, or heart rate.33,34 It antagonized the extracerebral effect of infused CGRP in humans.33 BIBN 4096 BS has not shown vasoconstrictor activity in several animal models or in human studies, and it is the first migraine-specific medication that is not a vasocon-

Ex. 1025, 1108; Reply, 7-8

3304 A SAUL J MED STEEL WASHINGTON THE THE THE PARTY TO A 2004. Lilly Exhibit 1025, Page 3 of 9. IPR2018-01422



strictor.

Prior Art Clinical Studies Disclosed the Vascular Safety of CGRP Antagonism (Ex. 1025)

THE REW EMPLANTS POTENTIAL SENSESSINE ORIGINAL ARTICLE Calcitonin Gene-Related Peptide Recepto Antagonist BIBN 4096 BS for the Acute Treatment of Migraine Jes Olesen, M.D., Hans-Christoph Diener, M.D., Ingo W. Hussteck, M. Peter J. Goadsby, M.D., David Hall, Ph.D., Ulrich Meier, Ph.D., Stephane Pollenties, M.D., and Lyona M. Lesko, M.D., for the BIBN 4096 BS Clinical Proof of Concept Study Group ABSTRACT Calcitonin gene-related peptide (CGRP) may have a causative role in migraine. We thereirup Hospital, University of Copurhagen, five hypothesized that a CGRP-receptor antagonist might be effective in the treatment Copenhagin, Demnut (J.O.); the Departof migraine attacks, ment of Neurology, University of Essen, Essen, Germany (H.-C.D.): the Disputment of Neurology, University Prospital, Münster, Germany (LMHL); the troottable of Neuron In an international, multicenter, double-blind, randomized clinical trial of BIRN 4096 ogs (militer (F), G.), Northergen bysilinen in miternational, multicenter, double-blind, randomized clinical trial of EEE/14996.

Processionals, Statelier, Cons. (D.H.,

BS, a highly specific and potent nonpeptide CGEP-receptor antagoniat, 126 patients. LMLS and Bodyinger Equitorin Plan with migraine received one of the following: placebo or 0.25, 0.5, 1, 2.5, 5, or 10 mg me, Ingelligine, Germany (U.M., S.P.). Adv. of BIRN 4096 BS intravenously over a period of 10 minutes. A group-sequential adaptrop reprint requests to Dr. Olsen at the University of Capathages, Department of the treatment-assignment design was used to minimize the mariber of patients of Nearling Gents, 1000 Government accord. trup, Coperduger, Decembris, or at jeoligi-glectruptump idélementific N Singl J Med 2009;150 L150 JD The 2.5-mg done was selected, with a response rate of 66 percent, as compa 27 percent for placebo (P=0.001). The BIBN 4096 BS group as a whole had a re rate of 60 percent. Significant superiority over placebo was also observed with to most secondary end points: the pain-free rate at 2 hours; the rate of sustain spense over a period of 24 hours; the rate of recurrence of headache; improve nauses, photophobia, phonophobia, and functional capacity, and the time to ingful relief. An effect was apparent after 30 minutes and increased over the r hours. The overall rate of adverse events was 25 percent after the 2.5-rag dose of t and 20 percent for the BOBN 4096 BS group as a whole, as compared with 12 per placebo. The most frequent side effect was puresthesis. There were no serious **A**:

We confirmed the favorable safety and tolerability results reported in a previous phase 1 study.32 The overall rate of adverse events was low. All events

Ex. 1025, 1109; Ex. 1306, ¶33; Reply, 7

Dr. Charles's testimony:

- So isn't that the point is that the reader would say, "Well, I don't know if this is safe or not based on the data sample that I have here in this Exhibit 1025"?
- No. I think the reader would . . . be reassured by the fact that – that there were no demonstrable changes in – in heart rate, blood pressure, and there were no vascular adverse effects reported

STREET, MED YEAT WARRESTS MARINE TI, 2004 3304 Lilly Exhibit 1025, Page 3 of 5 IPR2018-01422

The CGRP antagonist BIEN 4096 BS was effective in treating acute attacks of mig

Ex. 2272, 93:22-94:6



Tan 1995 Did Not Raise Safety Concerns

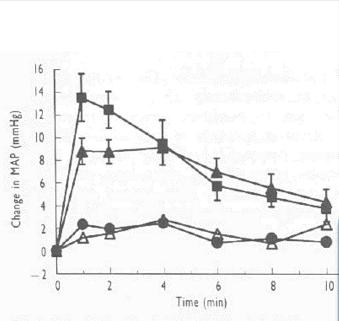


Fig. 2. Effect of Img/rat () or 3mg/rat () MAb C4.19
2mg/rat MAb C4.19 Fab' fragment () or 2mg/rat normal mouse
Fab' fragment () on baseline MAP. Mean results are plotted with
standard error bars (n = 4-6). Some error bars have been omitted
clarity.

MAb C4.19 IgG at 1 mg/rat increased baseline MAP slightly but significantly (mean increase 2.4 mmHg; Fig. 2). Increasing the dose of MAb C4.19 IgG to 3 mg/rat raised MAP by 13.5 mmHg (95% CI 7.7 to 19.3; P = 0.02). A maximum response was observed at 1 min followed by gradual recovery over 10 to 15 min (Fig. 2). MAb C4.19 Fab' frag-

Ex. 1022, 568; Ex. 1305, ¶58; Ex. 1306, ¶42; Reply, 10-11

significantly. Like the whole IgG, the MAP increase due to MAb C4.19 Fab' fragment reached a maximum at 1 min, with recovery within 10 to 15 min (Fig. 2).

Ex. 1022, 568; Ex. 1305, ¶58; Reply, 11

Effect of haCGRP₈₋₃₇ on blood pressure responses

HαCGRP₈₋₃₇ (100 nmol/kg) increased baseline MAP slightly but significantly (mean increase 3.3 mmHg).

Ex. 1022, 569; Ex. 1305, ¶59; Reply, 11



Tan 1995 Did Not Raise Safety Concerns

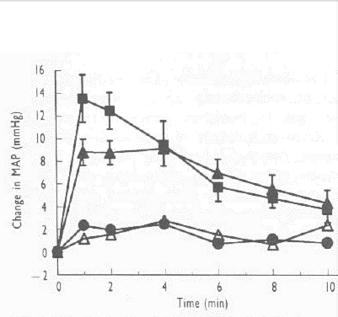


Fig. 2. Effect of Img/rat (♠) or 3mg/rat (♠) MAb C4.19 2mg/rat MAb C4.19 Fab' fragment (♠) or 2mg/rat normal marked fragment (♠) on baseline MAP. Mean results are plotted standard error bars (n = 4-6). Some error bars have been omitted clarity.

Dr. Ferrari's cross-examination:

- Q: And sumatriptan was observed to cause transient increases in blood pressure in some patients; is that correct?
- A: I don't think that increase in blood pressure has ever been a major concern for sumatriptan.

Ex. 1303, 25:11-17; Reply, 11

Dr. Charles's testimony:

44. In my opinion, the transient blood pressure change in anesthetized rats observed in Tan 1995 would not have deterred a POSA from generating a humanized anti-CGRP antagonist antibody. From over a decade of experience with triptans, a POSA would have understood that such transient changes in blood pressure in clinical settings are a manageable event. For example, sumatriptan was known to cause a transient change in blood pressure in some patients. (Ex. 1282, 1521.) Despite this, triptans were considered "very safe" as of November 2005 because clinicians were able to select appropriate migraine patients and treat them with a minimal risk of safety concerns. (See Ex. 1308, 1673.) Indeed,



Ex. 1306, ¶44; Reply, 11

Tan Did Not Raise Safety Concerns

PhD 1909 Application of monoclonal antibodies to the investigation of the role of calcitonin gene-related peptide as a vasodilatory neurotransmitter 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 Keith Kwan Gonville and Caius College, Cambridge 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 A dissertation submitte 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, 3, 11-12



Lilly, Exhibit 1287

Anti-CGRP Antagonist Antibodies Were Reported to Be Safe

Enclosure:

D5

re: EP 1 957 106 of July 11, 2014 Reitstötter Kinzebach

HYBRIDOMA Valorse 12, Number 1, 1993 Mary Ann Liebert, Inc., Publishers

> Monoclonal Antibody to Rat α-CGRP: Production, Characterization, and In Vivo Immunoneutralization Activity

H.C. WONG,¹ Y. TACHÉ,¹ K.C.K. LLOYD,¹ H. YANG,¹ C. STERNINI,¹ P. HOLZER,² and J.H. WALSH¹

¹Center for Ulear Research and Education, V.A. Wadnowski Medical Center, and Department of Medicale and Brain Research Institute, UCLA. Los Angeles, CA 90073. ²Department of Experimental and Citated Proceedances University of Cons. ASMID. Associa-

Spicen cells from a Rob NY cells to induce hybri and hybridoms produciwere produced from the contained approximately immunodiffusion analysis the ID₃₆ for rat α-CORF respectively. Protein A, the portal release of sorintravenous infusion of a national content of antibody (25 mg/sg) also in hearn rate caused by it that CORP monoclonal. Effects on the Cardiovascular System. Intravenous injection of rat α -CGRP decreased MAP and increased heart rate (Table 2). Intravenous injection of non purified CGRP monoclonal antibody (25 mg/kg) 30 min before that of rat α -CGRP (0.8 μ g/kg) completely inhibited the cardiovascular effects of the peptide (Table 2). The monoclonal antibody had no significant effect on MAP and heart rate (n=6).

and neuronal elements in the gastrointestinal tract. These results show that CGRP monoclorial antibody #4901, which is relatively specific for rat a CGRP, is useful for in vivo immunoneutralization of CGRP and is also an excellent reagent for immunohistochemical localization of a- and #-CGRP in mammals.

INTRODUCTION

Calcitonin gene related pepolde (CGRP) is a 37 amino acid peptide which retains high sequence homology in different species. In humans and rats, two genes have been isolated which encode the precursor of peptides bearing close structural homology. Rat a CGRP (or CGRP-II) differ by one amino acid in position 35 (1,2). The respective human α - and β -CGRP (for CGRP-II) differ by one amino acid and have four and three amino acid differences respectively with the rat CGRP counterparts (1) (Table 1). Functional, immunological and pharmacological studies have established that gastric and pancreatic CGRP immunoreactive fibers are derived from primary afferent neurons located in the donal root ganglia which predominantly express the a form (3-6). CGRP has been shown to be released upon stimulation of gastric sensory fibers by acute capasition injection.

13

Ex. 1033, 101; Ex. 1305, ¶62; Ex. 1306, ¶43; Reply, 12



Anti-CGRP Antagonist Antibodies Were Reported to Be Safe

D21

re: EP 1 957 106 of July 11, 2014

Journal of Jermanological Miniteds, 154 (1990) 87-94

30M 657W

Monoclonal antibodies distinguishing α and β forms of calcitoni gene-related peptide

D.P. Andrew, T.D. Bidgood, C. Bose, D. Brown, G. Galfre and M. Sherwood Cethrols Lincold, 216 Book Road, Shoops SLI 4EK, U.K. (Received 9 April 1990, revised received 11 July 1990, accepted 16 July 1990)

A panel of 18 monoclonal antibodies was raised to the human calcitonin gene related peptide (CGR Of these mabs, seven were specific for a CGRP and five for \$\beta\$ CGRP, while the remainder reacted with both α and β CGRP. Nine different epitopes on CGRP were defined with these mabs. In addition, the mabs were tested in various combinations to develop a series of two site assays specific for α or for β CGRP as well as assays able to detect both.

New service California proportional mention is and it: Mesopologial antibody

Calcitonin gene-related peptide (CGRP) is a member of the family of peptides encoded by the calcitonin gene (Amara et al., 1982). Human CGRP is a 37 amino acid peptide which occurs in two forms, α and β , with the β form differing in three amino acids (Swenberg et al., 1985). In this paper we describe the derivation of high affinity monoclonal antibodies (mabs) to non-overlapping epitopes on CGRP and the development of assays specific for α and β CGRP as well as an assay for total CGRP. Currently, CGRP is measured in biological fluid by RIA using conventional anti-

Correspondence to: D.P. Andrew, Cell Biology, Colinch. Limited, 216 Bath Read, Slough SL1 40N, U.K. (Tal.: (0753) 14655, eur. 2064).

Abbryckstore: 85A, benise series albumin: CORP. caluttomin gove-related populds; DMSM, Dolberco's modified Eagle endium; ELISA, eutyme linked immunistrat; PCA. Found's complete adjustme FIA, Freund's incomplete adlovant; HRPO, horse radish peroxidate; PBS, phosphate beffered saline, SHRPO, streptovidir, botte radith petoxidase, TMB, tetramethal beautime

Here we chose a two site assay to achieve high sensitivity, high sample throughput and to minimise interference by peptide fragments of t molecule under study. These are important or siderations since CORP is present at low les (pg/ml) in the plasma (Mason et al., 1986) a fragments of CGRP have also been reported biological fluid (Winalawansa et al., 1987). A t site assay for CGRP has been described us conventional antisera raised to different parts the CGRP molecule (Seth et al., 1988).

Materials and methods

Synthetic peptides and currier conjugates

Amino acid sequences of the various pepti used in this work are shown in Table I. Whole and \$ human and rat CGRP, as well as rat human amylin, were obtained from Bachem Peninsula Laboratories. Other peptides w synthesised in-house on an Applied Biosyste Peptide Synthesiser using the FMOC protocol.

0022-1759/90/90550 © 1990 Elsevier Science Publishers B.V. (Riceregical Division)

low levels of CGRP present in the blood. Although the immunised rats had high levels of circulating antibodies to rat CGRP, they did not any signs of physical or behavioural show abnormality.

Ex. 1055, 93; Ex. 1305, ¶65; Ex. 1306, ¶49; Reply, 12

Dr. Balthasar's testimony:

- So when Andrews says that there were no signs of physical or behavioral abnormality, what he is referring to is the animal did not die or pass out, right?
- A: Yeah, I could only speculate on what they would be looking at and measuring to be able to make that statement, but I think that most institutional animal use committees would require assessment of a wide range of parameters to evaluate safety of treatments.



Ex. 2273, 138:15-139:3

Purported Safety Concerns Did Not Deter Researchers

outside of Boundershafter for America 1997 - 1997 - 1997 - 1997 - 1997 1998 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 -

Nucleic Acid Aptamers for Target Validation and Therapeutic Applications

P. Sbannon Pendergrast, H. Nicholas Marsh, Dilara Grate, Judith M. Healy, and Martin Stanton

Archemic Copustion, Cambridge, Messachmetts

In the simplest view, automore can be throught of as nucleic acid analogs to antibodies. They are able to bird specifically to proteins, and, in many cases, that binding leads to a modulation of postein activity. New aptamens are rapidly generated through the SEEX Systematic Evolution of Ligands by Exponential endebasest) poscess and have a very high target affinity and specificity (picomoles to nanomoles). Furthermore, apromes composed of readlised readcotists have a long in vivo half-life thoses to days), are rootoxic and nontrinesurogenic, and are ex-By produced using standard nucleic acid synthesis methods. These proportion trake optamos ideal for target volidation and as a new class of the operation. As a target validation tool, aptioners provide important information that complements that associated by other methods. For example, siRNA is widely used to demonstrate that protein later feoult in a cellular assau can lead to a biological effect. Aptemers extend that information Inshowing that the close-dependent modulation of protein activito can be used to derive a thorapeutic benefit. That is, astorners can be used to demonstrate that the protein is a good target for drag development. As a new class of therapeutics, aptomess bridge the gap between small molecules and biologics, blue biologics, biologically active aptamers are upinly disconnect, have no class-specific tenicity, and are adopt at disrupting protein protein interaction. Like small molecules, aptamers can be ration ally engineered and optimized, are nonimmonogenic, and are

ADDRES CORESPONDENCE AND REPROT ENQUESTS TO: P. Shannon Periferguat, Archemic Corp., 1 Hampshire Street, Cambridge, MA 02139 (enails perdergrasis) archemic.com). produced by scalable chemical procedures at moderate cost. As such, aptomers are emerging as an important source of new therapeutic molecules.

Kirt Wotos: Aptimer, target vid vascular disease, cancer.

APTAMER DISCOVERY APTAMER DISCOVERY

bind to molecular t with high offinity are replicably from 15 so 40 can be composed of DNA a chemically modified strain 2'-O-methyl, phosphorothio pairing delines aptomer so ing primarily of short helic ed longs. Stable tentary stru binutions of these secon optames to bind to targets gen bending, and electrists moniber of possible tertany to bind with high affinity via bonding, and electrostatic is molecule, peptide, or probcenging from 10 pM to 10 r Aptamers can recognize the ficity. For instance, an aptar with up to 20,000-fold great does to its closely related (FGF) -1. -1. -5. -6. and aptamers distinguish berns bees of a protein family, or tional or conformational sta

attended to the second

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 the SELEX (Systematic Evolution of Ligands by Exponential enrichment) process and have a very high target affinity and specificity (picomoles to nanomoles). Furthermore, aptamers composed of modified nucleotides have a long in vivo half-life (hours to days), are nontoxic and nonimmunogenic, and are easily produced using standard nucleic acid synthesis methods.

The conceptual farmework and process of aptamorgeneration enterged from pieucering experiments by independent groups, both of whom published their work in 1990. There and Gold described a process of in vito selection, dubbed 58EEY Cypternatic Evolu-

Ex. 1309, Abstract; Ex. 1305, ¶51; Reply, 9



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Purported Safety Concerns Did Not Deter Researchers

Poster presentations 923

F022

Inhibition of neurogenic blood flow increases in the rat cranial dura mater by a CGRP-binding Spiegelmer

Karl Messlinger', Markus Trvelizserly, Thomas Denekar', Axel Vater', Britta Wlecks' & Sven Klusensam', Truttlate of Physiology & Pelneyhydriology, University of Erlangers Nurviderg, Germany, and NeXXAON Pharms AG, Bettin, Germany

Background Calditorin generodated peptide (CGRP) has a key function in the pathogenesis of prinary headaches. Elevated concentrations of CGRP are found in jugular vota blood samples during migraine attacks. CGRP polarised from trigorinal afforms is the main voxedilator in the meningse that mediates neurogenic blood slow changes.

Objective In an autimal model of ringentinevascular activation and mentinged blood flow the inhibitory effect of a webligh-affinity CGRP-binding RNA-Spiegelmer, which is a biostable aptamer compensed of mirror image nucleotides, was examined.

Methods Increases in meningual blood flow caused by portodic local electrical stimulation of the exponent raterantial dura mater were analysed using laser Doppler flowmerty. The CGRP-blanding Spingolmer was applied topically (10°–10° m) or lx. (5 mg/skg).

Results The Spiegelner caused dose-dependent, significant inhibition of the evoked blood flow responses to alout 50% of the control. Topical application was most effective. Band blood flow and systemic arreital presente were suchtanged. Conclusion Neurogenic blood flow increases in the meninges are reduced by binding of the released CCRP to the Spiegelners thereby preventing it from artistant yearthat CCRP receptors. The Spiegolner may upon a new therapeutial strategy in diseases that are linked to excessive CCRP release such as migrature and other primary behadehts.

Keywords: headache, migraine, CGRP, Spiegelmer, meningcal blood flow

F023

Successful treatment for allodynia accompanied with migraine attack using intravenious injenction of Mecobalamin

Jun Terrando

Teramoro Nemydogy Clinic, Nageye, Japan

Objective Migraine attack with allodynia is reported to be not offective for triptans. But we succeeded in providing rapid relief for such patients.

Patients and methods. Nine migratine patients without aura, who ordinarily showed efficacy for relptins, committed our clinic with inverse headache in spite of the use of reptims and with numbness of the face or temporal. The duration between triptain intube and consolitation was within 4th, 500 g of Microbalamin was given intraveniously with 20% glucose of 20 ml. The change in the symptoms was investigated 10–18 min artise.

Results Skin allodynia completely recovered in seven cases (77.8%), remarkably in one (11.1%) and moderately in one (11.1%). Severe headache almost completely recovered in

three (33.3%), and moderately in six (66.6%). These continued until the expected time when the attack wer Conclusion. It is unknown whether these results were the efficacy of Mecobalamia obsect to the additionaback office of retigians. This is the first report of ringiby allodynta with migratine, We occurrented this there only for its speed but also for its being easy to perfany dector with no side effects.

Keywords: migraine, allodynia, Mecobalamin

024

Rapid relief for cranial neuralgias using intravenous injection of Mecobalumin

Jun Teranacto

icameto Neurology Cliule, Nagoja, Japan

Objective Although Vitamin $B_{\rm eff}$ is known to be effectioninglass, not no general clinically. In the present sit examined the quickness of the efficacy of Mecobala candal metrolgias.

Patients and methods Corold neuroligies of 221 cours (origentical 138, occipital 566, greater occipital and origentical neuroligia syndrome (GCP18-17) were examined. The 2nd male cause and 457 female. The agest ranged from with the mean of 50 & 1.08. For the patients only rece

and make cases and 422 termines in a ages ranged from with the mean of 56 of a 169. For the patients only rec' by Valletx's point of tendernose, 500 µg of mercobaland glucore 20 ml (for diabetic patients, 0.9% of saline) we intravenously. After 10 min, the change in tendern observed.

Results Moroholomin was remarkably effective in 2 (4545), mederately in 610 (94.663), and not offective (O.D.F.). The ratio of offective coses in each neural 72.27s in integer and entrolgia, 72.27s in greater or 2.25% in micro-cecipital, 6.00% in greater or articular and in combinations of each excipital neuralgia. GOTS was among 12 (268).

Conclusion When neurolga is docrossed, for some patient is multinitud in a gast state and will run generally good condition, so Mecobalamin, which is a type of Vitamin B., is very useful. Benefood points as is not only rapidly effections, but also easy in use model staff. No side-reflects were seen, and the dru roundby yields for patients.

Keywurdsi trigeminal neuralgia, occipital neuralgia balamin, greater occipital and trigeminal neuralgia sy (GCTS)

F029

Preference for rizatripton 10-mg wafer versus eletrip 40-mg tablet for acute treatment of migraine

Mijarol J. A., Laimez, Suefan Bererk, Jehan Kinggé, Giavai Alla Chrismopher Alleni, Naveen A. Roof, Mescadi Rachili & Kain Terapiai Chuke, Universidad de Velenia, Separia, Separia Municio, Grunzey, Suembo Necodogle Service, Sarrellar, Norsa Valintering et Dunis, India, and Works & Co. Las., No. 188.

Objective To compare patient preference for rizatriping wafer vs. eleiriptan 40-mg tablet for acute treatr

Objective In an animal model of trigeminovascular activation and meningeal blood flow the inhibitory effect of a new high-affinity CGRP-binding RNA-Spiegelmer, which is a biostable aptamer composed of mirror-image nucleotides, was examined.

Results The Spiegelmer caused dose-dependent, significant inhibition of the evoked blood flow responses to about 50% of the control. Topical application was most effective. Basal blood flow and systemic arterial pressure were unchanged. **Conclusion** Neurogenic blood flow increases in the meninges are reduced by binding of the released CGRP to the Spiegelmer, thereby preventing it from activating vascular CGRP receptors. The Spiegelmer may open a new therapeutical strategy in diseases that are linked to excessive CGRP release such as migraine and other primary headaches.

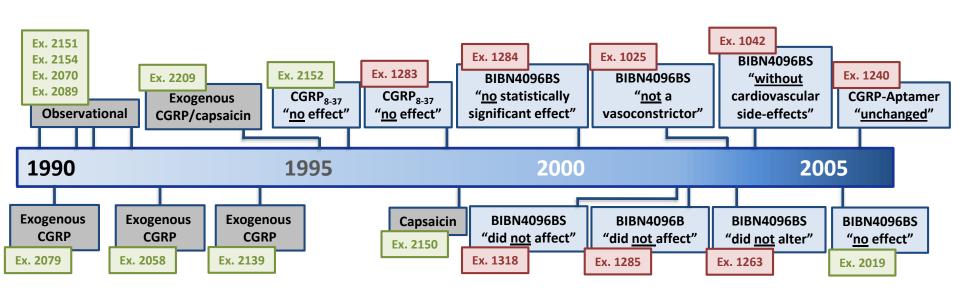
Ex. 1240, 923; Ex. 1305, ¶54; Ex. 1306, ¶¶17, 31; Reply, 9

Blackwell Publishing Ltd Crymmight, 2005, 28, 863–1020
 IPR2018-01422

Lilly Exhibit 1240, Page 1 of 1 Eli Lilly & Co. v. Teva Pharms. Int'l GMBH



Teva's Purported Safety Concerns Were Resolved by November 2005



Lilly Exhibit

Teva Exhibit

Ex. 1306, ¶¶20-38; Reply, 7-9, 13-14



Teva's Purported Safety Concerns Were Resolved by November 2005 (Exs. 1025, 1042, 2019)

Dr. Charles's testimony:

Q: ... You would agree that the clinical safety of targeting CGRP for therapeutic use had not been established as of 2005, correct?

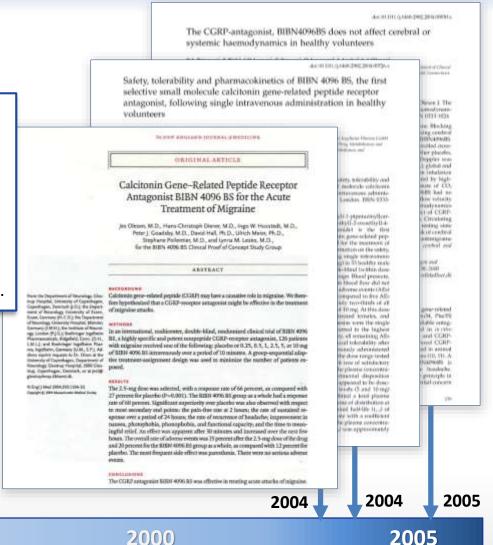
I do not agree with that, no. A:

Q: And what part do you disagree with?

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

1995

Ex. 2272, 40:11-20





1990

Ex. 1306, ¶¶33-36, 38; Reply, 7-8

Researchers, Including Teva's Experts, Praised "CGRP Antagonists" Before November 2005

Migraine: new treatment options from molecular biology Ankse H.Stam^{*}, Joost Hoars, Rune R.Frants, Michel D.Ferrari and Arr: MiM van den Maagdenberg Migraine is a common, disabling, multilectorial, opisodic neurovascular diserter of largery unknown obology. The disease is typically characterized by recursor attacts of headaches and associated autoeomic and reurologic symptoms. Current scale and prophylacisi: treatment options are for from optimal and in many cases, empirically chosen. Clearly improved treatment is desperatory recolled. Now drug targets may emerge from molecular research as the unswelling of the redocular basis of resisions should improve our understanding of the discess, notably why putions experience altacks so frequently. The Anti-two response genus discovered in families with benique-jic regrater encode on transporters, emphassing that dystanction of ion transport may be all integrations facility in relevance. We refer to the experience of the considered an expert largets for the development of future antinograms chaigs. Molecular biologic research will increasingly become important trunderstanding the pathophysiology of migrains and in: identifying potential excludials targets for novel teamers. Figure Riv. Neuroleographics (US), NO. 661 (US). Migrane in a conserve, streeting, multi-proposition have at true SE days at requires Secretal, extendic proposedular disorder of - propose and one 1% have at least 1 day of sedenous energy (c). The those is repically integrate per mon. Characteristics for recurrence actuals; specing from s him from to several days, of shadding book. "Direct between when, and resolved accounted and adults. Disposite obers for experience was provided rate surrations. Since expenses painters for the Solvenaneast House-the Society in 1988. regional to specific changates, to in insperses the ... and its vertical flows in 2008 to to it. distinguish shis sharder from southertran. Migrate-study-are opinals illusational by trediche ind other phinsip finalishe so- zeisoner, sinlainel, suissing hadistiss o

manife will be discussed.

HEISMONISTON SCHOOL

Dr. Ferrari's statements in 2005:

Calcitonin gene-related peptide antagonists

In patients with migraine, CGRP levels are elevated. CGRP infusion can trigger a migraine attack and triptans block the 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 doubleblind, 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.

1284 Cabible 1289 EV Lifts & Co. v. Teve

pleaspholes. This type of eigenes is colled migrative without seek for approximately a dust of patients the impairs attack is reconsumed.

dennes. In this rectine current contracted moderator to enter whenly, leating A-728 spiriture, or will be moral extraor the treatment. This are approximed by physical artistics and that liver searcing from molecular foreign, when accompanied by manine, photoapholis or

The 1-year penateurs of expains in Western - or preveled by equates had receiving times

14-13 years old his breaks, attough exacts town. Less other, mentes to aphear symptoms of singular rate that is any age. Aloning native are requirement and rates; enter some Lys as assignment, the resolute stands frequency. It May at requirement have bett right of acceptance of the resolute orders decision. Thirting lates different languagement pairs are preferred to the container orders decision.

is 24 to 11. Approximately 5% of the general interior of response was enfountemental into

convertes in 17th recent (F-9%) in versional constitution in the most programs with small 15-10% in course (i) in this tage of annex of Asia symptomic version for becomes 5 one adoption in 10-12 years with the visitor and 40 constitution for both demandation.

Lilly

Ex. 1290, 657; Ex. 1306, ¶40; Reply, 8

Absolute Risk of Stroke in Migraine Patients Was Very Low

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Dr. Ferrari's testimony:

"Given the complex relationship between migraine and stroke, a POSA would have looked unfavorably on developing a new therapeutic that could worsen that troubling link."

Relation between migraine and stroke

A complex bidirectional relation between intgraine, mosely neigrative with most (MA), and bechannic service to known. A cerebral infarction can occur during a MA, and MA is a risk factor for incharante stroke, particularly in young reposturious serious somen. Conveniely, croshral inchannia can imitate MA. Both inchannic service and MA might be consequences of many underlying vascular disorders. Despite the relation bowers intgrains and stroke, neignates as a primary

Migratur and sends are two commonly occurring daunden stas wern so have bele to common. Migraine to a berage dromler due persons demaghous blic to optically warm before age 46 years and affices 12% of the ... In the dovers cases of "final magnature" represent " share gulates with a 3 to 1 female propositionics. mosters neurological disurbances, characterise related disorders, or a syndrome due to other disorders to sell undear. The shappoors of reagrates to purely clinical and serios extenta have been proposed by she Insernational Headache Society (IHS):

To common service to an acrass more than secure in 2 per 1000 people per year at a mean ago of 70 years. oh a 2 es 3 male prepondennoe. Characterned by a focal delicts of yadden ensex, sende to readily diagnosed. by use of neurotreating ordinasus. Confed infaction occurs in 80% of uroles and intracondeal harmorham to 20%. The cause of both upon of artike to diverse; in individual partenu, jurnicularly disse who are young. the cause to community unknown even after essential Siveretgarton.

Dopte these difference, many studies have suggested a complex hidrontenal relators between religrative and semile," trackaling esignative as a cause of seroles, redignatese us a rink factor for or as a correspondence of certified techarmia, and respective and certified tedaenta sharing a common cause.

Charce-was probably the time or recognise than engineer. complications of restral negrative? could cause a movie when he wone that "any of the yespoma occurring during 'resgnene ophidulestque' hearn persusent's life rolder, litri; reponed a case of "optololism: returnee with repeated assacio fillowed by dead? In a man aged 53 years who had had regrame usudo-web ophshalters and dorphasts: auto stree childhood and who died after 2 mondos of Self-ended headache; vonaid disnortunous, and right or left. hemplogs. The case to epically referred to as the time case of leshal enterations scroke, but in the absence of amopie, she prestre cause of doub to unknown."

After the fine report and better the first 1913 dusticants," many cases of "magnatious trainess" were . and duration of mass have also been associated with reperued, including abunders as varied as frenkes - migrations intimus." Cerebral analography, which is occurring its magnaturatin", "umion with magnatume. Instead to Induce magnatus assades, carries a 7% stak of

hos/mining children on 1604 Spenter bits

lastra delicto walvaz omio".

In our consciours passers of indianation; indianos are large or focusion made of healache assessment torouble be usual, strate or embrate correct or autocared and toyolve ibn caronal and/or she basilar sermentes. There is migratic. Whether intigrative to a strude-create, a group of the countriers papers; of amends changes; throubouts, embolum, spaces, dissection, and normal america have all been reported. Whereas in rases of done cases the repealthy of regrees to doubtle, repeated assets of severe exigratus could lead to final arrestal tetrary compatible to sparse tradecal by subunchestal harmorhage on

There are no good date on the textdence of originity infunctions. The single largest sendy' before the HIS classification found 7 (1%) migrations returns arosing 264 fine combrel tellerature, communidate on an Incidence of 3 per 100 000 per year in the UK. However, the crusal relation between shore nowless and originate in highly debusable because only one pieters had coreless hypersensive, and one had widespread wherems.

field delets, such as lorntampta or homopic scourm due so a possener control array refers, but other sentional infaron affeoting any large away as well as angle or maltple lacasur relates have also been reported. Simplarly, all varieties of restral infarce, and technistic optic recorpalities have been described as

Much diversity in the location and uppe of inflaton to reflected to the meantringing limitings; most potent have outspitud indirects, but single and multiple indirects of any me and loanse have been repended Angiography is optically normal, but spann and octaton of large or small arortes have from agenet 2 at lase duectors and areunous,"

Vaccomentoer medications such as engagentse or etpuns migh courthus, but in some reported cases, reignations infarction was a mindiagnosis." Bessblockers known to occasionally increase dor frequency

Strames", "urales with headache", and even "large commons.

antomphy, one had educardnosphy, since were

The most common distical stars is a homometropy

which could be commone with sympoments engineer.

Eli Lilly & Co. v. Teva Pharms. Int'l GM

IPR2018-014

Nemigis I nedminion Petigota filmi obsetta France Original Millianson Mills. and Resulted Familie

Ex. 2212, ¶59

contraceptives (RR 34.4, 32.7-36.1). However the absolute risk of stroke in young women with migraine is low: 18 per 100 000 per year. 67,73 A recent meta-

Ex. 2157, 535; Ex. 1306, ¶59; Reply, 15

Dr. Ferrari's cross-examination:

- Q: Okay. 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?
- In 2005 there was no known association.



Ex. 1303, 193:3-10; Reply, 15; Ex. 2157, 536; Ex. 1306, ¶59

The Prior Art Contradicts Teva's Hypothetical **Application of the "Spare Receptor Theory"**

British Journal of Pharmacology (2004) 143, 1006-1071

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Noncompetitive antagonism of BIBN4096BS on CGRP-induced responses in human subcutaneous arteries

* Majid Sheykhrade, Henrik Lind & Lars Edvinson

Department of Pharmacology, The Danish University of Pharmacological Sciences, Universiting after 2, DK-2100 Co O. Dennark and "Department of Internal Madicine, Lond University Hospital, 22102 Lond; Swalon

- We investigated the antagonistic effect of 1-pependinacarbonicists. N-[2-[3anino-1-[4-44-position]]-pepending(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-pependinacy(b)-4-(1.4-dh)dra-2-ora-3(2H)-quincadins)) (BBDN49988) on the calcitonic percentant popular (CGRP-inition) regimes by using towards imaginate and EURA-2 technique in human subcarantees arteries returned in association with abdominal surgery.
- 2. BIBN4098BS, or the concentration of 1 psi, but no significant office on the CGRP-induced relacution in these vessels.
- 3. At the concentration of Highs, BIBNAPWARS had a competitive antagonistic-like behaviour characterized by purallel rightward shift in the log CGRP concentration-tension curve with no depression of the E-
- 4. At the higher concentrations (0.1 and 1 pso, BHINMONIS had a concentration-dependent acoupation an agreeatic effect on the CGRP-induced areponies.
- 5 The efficient and potency of CGRP was significantly greater as the analty fluxes diameter - 200 µm) himon subcataments arraries compared to the larger sines.
- 6. The apparent agentin equilibrium absorbation constant, K4, for CGRP, receptors in the human. decreases arience was approximately 1 tot. Analysis of the relationship between margine occupancy and response to CGRP judicates that the receptor reserve is relatively small.
- 7. Using reverse transcripture-polymense thain reaction (RT-PCR), the presence of miRNA sugarners emoding the calciumin mecanics-like receptor, receptor activity modifying process (BAMP). BAMP2: BAMP3: and morphox component promin were demonstrated in human subcatanous arteries, indicating the presence of CGRP, 4ke receptor and the necessary component
- 8. In conclusion, the inhibitory action of BEBN 100 GBS at the low concentration (10 petr on the CGRP-tension curve (but not intracellular calcium concentration (Ca²) It resembles what is seen with a reversible competitive arrangement. However, at the higher concentrations (R.I. and Lubt). BURN-4000 BE, acts as a solicitive noncompetitive tabilities of CGRP, recognize in human solicities one

British Journal of Photomorphy (2004) 143, 1866-1873, doi:10.1036/sj.hip.0705967 Keywork: Affinity: calcium graved and pepide: BIBN 000005; burner sebutuaneous artery

Abbreviation: 8E8N409685, 1 piperidinana bozanián, N/2 ([Amino-1]]444 pridato (I-1) piperidin (I-1) (Amino-1]444 pridato (I-1) [Ca'], introofable cakings concentration, CGRP, calcitosis gene-related poptide, CRC, assersponse carrie, CRLR, calcitonia receptor-like receptor; E.E.,..., relative vessel cosponse to agentic effects dimine tetracetic and DGTA, othere gloci-bid-ammonly) effect-N.N.N.N.-armapetic apparent receptor agonal against against an experient against affaity — logik.D confugical sub-vectors; #.#., relative receptor squares occupancy; RAMP, margies activity mode RCP, receptor compound protein, RT-PCR, reverse transcription polynomies chain reaction

Introduction

Calcitoms gene-telanal popula (CGRP) immunotasctive notes have been demonstrated throughout the county and peripheral nervous system. As a neurotromenitur CGRP in found prodominantly in the sensory serve fitters marrowing.

*Author for correspondence; Ecoloi: mode/offreigh. Advance verbar publication, 11 October 2004

blood venuts located both peripherally and centrally (Unkhum et af., 1986; Holiei. 1980). Upon stimulation, CGRP con bereleased from these morse fibres both at sove and at vive and cause vinodilatation. For intance, this occurs both in cardiovascular system following incluents (Kaliner, 1990), thating reignaine haudache (Goudsby et al., 1990) and following substructured hormorchage that et al., 1990)

Teva's arguments:

"As Dr. Foord explains, in the CGRP receptor system, less than 1% of receptors needed to be bound by ligand to elicit a full response in the cell. EX2230, ¶¶38-42, 94; EX2062, 74; EX2063, 15; EX2064, 537."

POR. 31

magnitude of response produced by an agonist (efficacy). In our study, approximately 27% of all receptors must be occupied by CGRP to elicit a half-maximal response (EC₅₀), indicating the presence of a relatively small CGRP₁-receptor reserve pool in the human subcutaneous arteries. The term

Ex. 2065, 1071; Ex. 1305, ¶¶41-42; Ex. 1300, 69:4-8; Reply, 17



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

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

golar win peptide levels determined prior to and after administration of either samutopean or dibyth bicracterion of the originateal gauginor led to a frequency-dependent increase in curebral blood flow, with a mean minimum of 43 ± 9% at a minutes frequency of 20 per second. There was a marked reduction in these responses by come 90% efter administration of either menantistan or dibodromparamine. Tripereinal penglion tripulation at a frequency of 5 per second also led to a release issu the crustal circulation of calcitomis gene-related popeide (CGRP) with the level rising from 67 a 5 to 82 a 5 peoplither on the side of scinulation. These increases were also markedly strangement by both samutripus and dihydrocrassumme. Human multin were conducted as part of the overall evaluation of sunstriptes for the constraint of acute enigenies. In T of 8 partners responding to indicate easier summittee. ton administration, alevated CGRP levels (60 ± 8 penal/liner) were correlated, with the headathe being refleved (40 # 8 peoplition). These data characterise some aspects of the carebrovascular physiology of the teleprocovascular system and determinate important interactions between this voters; and the effective settinispoint agrees sense interactions. and diffyrdroningonumine and than such interactions can be represented in assistad models

> Goaldy PJ. Edwards L. The representate toters and regrains studies charactering control and neutropeptide changes seen in humans and care. Ann Neural 1995;55:48-36

There is little doubt from a clinical transpoint that the trigernical version is interactly involved in the expression of migraine [1]. The connections of the migrainal system with the craval vessels [2] have led to the concope of the transmissional system [5]. This system constant of the cracked vessels and their trigonous inpervation, implying a functional network that may have a role both in normal phesiology and in discose. Many aspects of this relationship remain uncharacterized and new offective magazine meanments provide a challenge to existing ideas and an imperor to further study-

Stimulation of the trigerestal gaughten (VG) leads to both direct (antidrorpic) and indirect (orthodromic) disages in cerebral blood flow. Activation of the gasglion increases blood flow via a reflex (triggenia)/viacufor reflex; that eswerses the becomen, with its efforces path being through the seventh cragal serve [1]. The

From the "Department of Meanings, The Printe Hann Hospital, Lotte Bay Stellers, Australia, and the "Department of Internal Medi-tion, University Hospital, Local, Swedon.

gene-related papride (CGRP) [15, 16] can be frued Received days 7, 1993, and as sexual form Jul 16. Accepted for publication Let 17, 1992.

severally cranial nerve is the main paramyrepurhene ou

flow for the cerebral arteries. It can increase blood flow

independent of metabolic needs (5) through classic as

mannic gaughs, the sphenopalatine and one gaughs

353, via a nicoticic receptor [7]. The manutimer for

both the extraoerebeal (8) and the cerebral (9) parts of

the effect is likely to be variative intestinal peptide

(VIP). Indeed, spheropalatine gaugion minulation

above can also increase cerebral blood flow again wels-

out any effect on cerebral metabolism (10, 11). More

specifically, the remaind distribution of these fibers

flerough the ethenoidal nerve can also be activated to

The stigerated system can also autross bland flow

via antidromic activation and release of vascactive sub-

motion. Both agintance P (SP) (13, 14) and calcinosis

recruse cerebral blood flow [12].

Address interagonalised to Dr Grantily, Department of Neurolius The Prince | Story Hospital, Little Bay, NSW 2016, Australia.

48 Copyright # 1909 by the American Neurological Association

IPR2018-01422

Lilly Exhibit 1044, Page 1 of 9

Ex. 1044, Abstract; Ex. 1306, ¶67; Reply, 17

Dr. Charles's testimony:

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"); Ex. 1008, ¶¶36-45.)



Ex. 1306, ¶67; Reply, 17

Ligand Cross-Binding Did Not Undermine Motivation

Pierangelo Geppetti
Jay Guido Capone
Marcello Trevisani
Paola Nicoletti
Giovanni Zagli
Maria Resalia Tola

Bosowest 23 February 2005 Accepted in present form 23 February 2009 Published online: 8 April 2005

P. Grypetti - J.G. Capone - M.R. Tola Boadache Center, U.D. Naurology, Department of Neurosciene, Actionals Universitá-Ospadale S. Arma, Fernan, Buly

P. Guguetti (Silv + M. Turonani - P. Niurdetti (J. Zagli)
Clatical Pharmacology Urst.
Department of Chinal Cultr Medicine and
Sorgary, University of Processes,
Visite Personent v. 1-30(139 Florence, Ruly
- exall piperspade perpectation (I. I.
Int. - 379-055-4271(239)
Text - 379-055-4271(239)

Neurogenic inflammation: mechanism differences The term 'neuropenic inflammation' re

prouthammatiny responses produced by the common of peripheral terminals of a subset of primary sensory neumin and the subsequent referee of the neuropoptides, epicitionin gene-related poptide (CGRP) and the activitations, substance P (SP) and necessitalin A (SKA) [1]. The neunius that peoduce inflammation comprise a heterogeneous cell population with A-delta and C fibrus, defined as polymodal inciceptions because they sense thermal, chemical and high-fitroshold mechanical stimuli. These neurons express on their glasma membrane a large panel of excita-

tory and inhibitory receptors and channels, and some of

mount importance. Capualcin produces hurning pain by stimulating TRPVI and by referaing sensory neuropeptales courses neurogenic inflammation. However, high concerniations/doses of capsaicin have the ability, after an initial excitatory place, in describing the sensory nerve terminals, thus reducting the transmission of sensory/pain signals and abolishing neurogenic inflammation [3, 4]. This specific feature of capsaicin hos greatly contributed in define the role of this subset of sensory nerves in pathophysiological models of human diseases and has been

Adrenomedullin (AM) Calcitonin Amylin (AMY) **CGRP** Composition CALCR AMY-1: CALCR+RAMP1 CALCRL+RAMP1 AM-1: CALCRL+RAMP2 AMY-2: CALCR+RAMP2 AM-2: CALCRL+RAMP3 AMY-3: CALCR+RAMP3 Transduction pathway G_s/G_a G_s G_s/G_a G_s Selective agonists Human CT AMY α-CGRP AM Selective antagonists BIBN4096BS (+++) AMn22-52 SB-273779 (+) Salmon CT≥human Salmon CT≥AMY≥ CGRP>AM≥ AM-1: AM>>CGRP> Potency CT≥AMY, CGRP>AM CGRP>human CT>AM AMY≥salmon CT AMY>salmon CT AM-2: AM≥CGRP> AMY>salmon CT

Ex. 2059, 63 (annotation added); Ex. 1306, ¶72; Reply, 18



Tan 1995 (Ex. 1022): IgG "Clearly Diffuses" to the Site of Action

Name Street of POS 88, 543-573 Printed or Great Wilson

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

WHY K. C. TAN, Morris J. BROWN, Richard J. HARGREAVESY, Sara L. SHEINEARDY Deersh A COOK! and Raymond G. HILL!

Could Phormacology Line, Lifemensity of Combridge Clinical School, Addenbooms's Ho Carbridge, U.K., and 1 Merck. Sharp and Datme Research Laboratories, Neurosciens Gers, Hirlan, Esser, U.K.

Board If Jan, TAguer 1995; scopner 16 August 1995.

I Calcinote gene-related poptide (CGRP) is localand in provincedur sensory neurons and in a percent unillator. We intestigated the utility of immuolitebade as an in vivo technique for probing the role « CGRP as an endogenous vasodilator.

2. The effects of an anti-CCHP monoclonal antibody Milk coded C4.1% and in Full fragment on CGRP-induced changes in blood pressure and skin find flow were studied in percolarbitenesuetheiled rats. Antidromic skin vasodilatation in the rat bind gave was incasured by laser Doppler.

3. The stone response relationship for the hypotensive effect of intravenous rat a CGRP (raCGRP) was milety shifted rightward by MAh C4.19 IgG (regret; intravenously) and Fall' fragment (regret; intravenously). The C-terminal fragment of house sCGRP (hsCGRP4.11) she blocked the epotencia effect of caCGRP.

4 WAS C4.19 Full fragment (Zing:rat; intrawoody; and heCGRPage (100 mml/kg; intra-woody; but out MAb C4.19 IgG (up to Sungrat; threemendy) or normal moune Fab fragment 27g rat; intravenously), blocked the increased skin had flow response to antidrosoic stimulation of the

The mean percentage changes in skin blood flow accounts that to MAb C4.19 Eab' fragment were spilicantly different from these that he necessal New Fab' fragment (separated 1-test; P<0.05) but no from these due to haCGRPaux

The results demonstrate the pharmacekinotic change of Fab' fragment over 1gG for incommi-

CGRP released from primary afferent nerves by capsaicin in vitro [11]. The most likely barrier to

CGRP in mediating skin racedilatation.

INTRODUCTION

Calcitonin generalated postde (CGRP) is book and in performation primary afferent sources and a

a petert vasodéater spense studied [1-3 importance of CGRP flow has energed from 9-37 Diagnest of Sar which sets as a CGS 53. The hypermiest in or amenderand and a by hat GRP and DLT a sunamed hypermi congresse to operat road [8]. The hypoteness w lation and exogenous t by hat CottPa, or. Thus to be a major momento gene vanidikanon al the rat. HaCGEP, costs has been lived blood fire industri capuacte [9] burness tated pow after arrivecoose perve st area inhi-The evalence obtained seggmen that CGRP the 'sffermi' vasodias sensitive pressure aftern

blockade studies in vive and support the role

Dr. Balthasar's testimony:

1021, 705. Recognizing that "time must be allowed for the MAb C4.19 to diffuse

CGRP. 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

into the synaptic cleft," Tan 1994 reported that "the concentration of the antibody

had reached equilibrium in the synaptic cleft after 45 min[utes]." Ex. 1021, 709.

Thus, well before 2005, both Tan 1994 and Tan 1995 disclosed that full-length

anti-CGRP antagonist antibodies successfully distributed to the synaptic cleft and

effectively inhibited the activity of endogenous CGRP.

which with the send water, blind for your present above previous popular for beginn mounts

Personal Park, the other the fine time and same property is not a south contract the same particular parties. Co. from provided partie. Or continue server, h_{ear}, assumming a last that the amounts in price ref proces: CCSP for a column processed opposits. New orders: Non-Cornel Session, Narapan Rad, Indonés Ann, CTIO NG, US. Propositions: In Euro. 6. ≤ 1µs. Hom: Cornel Session, Narapan Stat. Serbita CNI Staj. Sac US.



Ex. 1305, ¶21; Reply, 20

Ex. 1022, 571; Ex. 1305, ¶20; Reply, 20

Tan 1995 Provided Guidance to Improve Immunoblockade

has been (1991 St. 163-57) (French in Great Britany

Calcitonin gene-related peptide as an endogenous asodilator: immunoblockade studies in vivo with an anti-calcitonin gene-related peptide monoclonal antibody and its Fab fragment

Wart K. C. TAN, Morris J. BROWN, Richard J. HANGREAVESY, Sara L. SHEPHEARDS. Secret A COOK! and Raymond G. HELL!

Direct Phonoscology Unit, University of Combridge Clinical School, Addenbriole's Hospital, Controlpe, U.K., and 1 March Sharp and Dahme Research Laborations, Neuroscience Research Sens Horlow, Estex, U.K.

Served If June Skepar 1995, accepted 15 August 1995.

I Calcitonia gene-related poptide (CGRP) in localind is perivascular sumony neurons and is a potent uniflator. We investigated the utility of immunolickade as an in vivo technique for probing the role of CGRP as an endogenous vasodilator.

I The officers of an anti-CCRP monoclosul antibody MAS coled C4.19; and its Fab' fragment on CERP-induced changes in blood pressure and skin loof flow were studied in pentoharbitumemurbetted rats. Antidromic skin rasodilatation in for see kind pare was measured by laser Doppler

3. The dese-response relationship for the hypotensive effect of intravenous rat oCGRP (coCGRP) was solarly shifted rightward by MAE C419 IgG linging intravenessly) and Fab' fragment Ingust intravenuesly). The C-terminal fragment of terms aCGRP (haCGRPairs) also blocked the inpotential effect of raCGRP.

6 MAb C4.19 Fab' fragment (2 mg/rat; iteramody) and hacGRP_{a,y}, (100 omilikg intra-mody), but not MAb C4.19 IgG top to Jungitati Starreously) or normal mouse Fab fragment Engrat; intravenumby), blocked the incremed skin find flow response to antidromic stimulation of the province acres.

3. The mean percentage changes in skin blood flow persenters due to MAb C419 Fab' fragment note spallenely different from those due to scental ** Fab' fragment (unpaired f-nest; P < 0.0% but ne from those due to hat GRP

the results demonstrate the pharmacokowtic stratege of Fat' fragment over IgG for immere-

blockade studies in sise and s CGRP in mediating skin varietil

INTRODUCTION

Calcitoria gene-related peptid used in persyancials primary after a potent vasofilator in man species mudwit [1-3]. Some reportance of CGRP is the r flow has emerged from studies w 8-37 fragment of human aCGI which acts as a CGRP more 52 The hypotemics emperor to in against and compount

by hirOGEP, p. (n. 7) Europeans CGEP produces

a systemed hypotrasion that recent the depressor response to special cord stornalation in the pethod not [8]. The hypotimise responses to lation and evoperom CGRF are by hoCGRPs 1+ Than endogento be a major neurotransmitter th princ caushistation after spend of the rate HaCGRPs argiven by blood flew induced by intrade captaion [4] Increased skin blo hind pew ofter antidrorse stemi enous nerse is also inhibited by to The evidence obspired from the a suggests that CGRP is an impo the 'efferted' tanoniamy fund

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

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

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

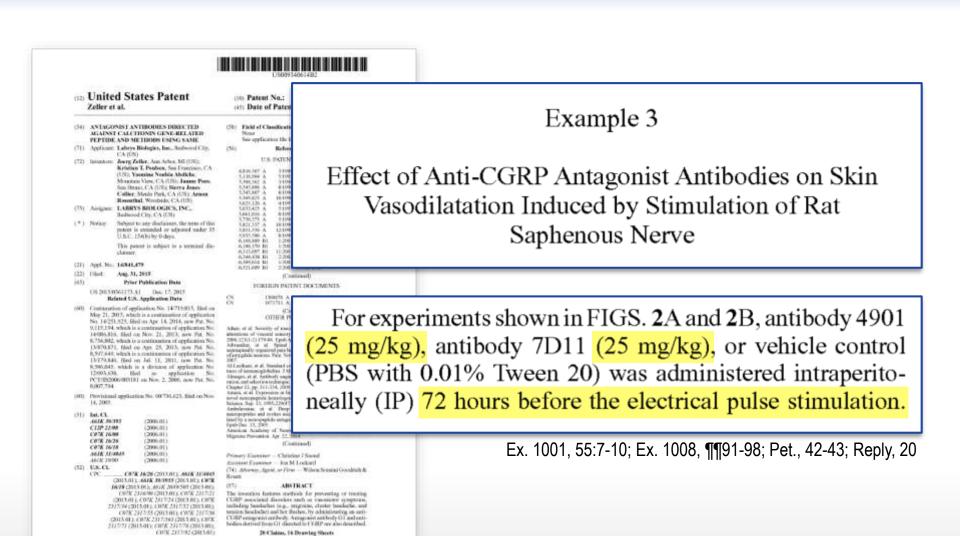
Ex. 1022, 571; Ex. 1008, ¶122; Ex. 1305, ¶¶24-29; Pet., 39-42; Reply, 20

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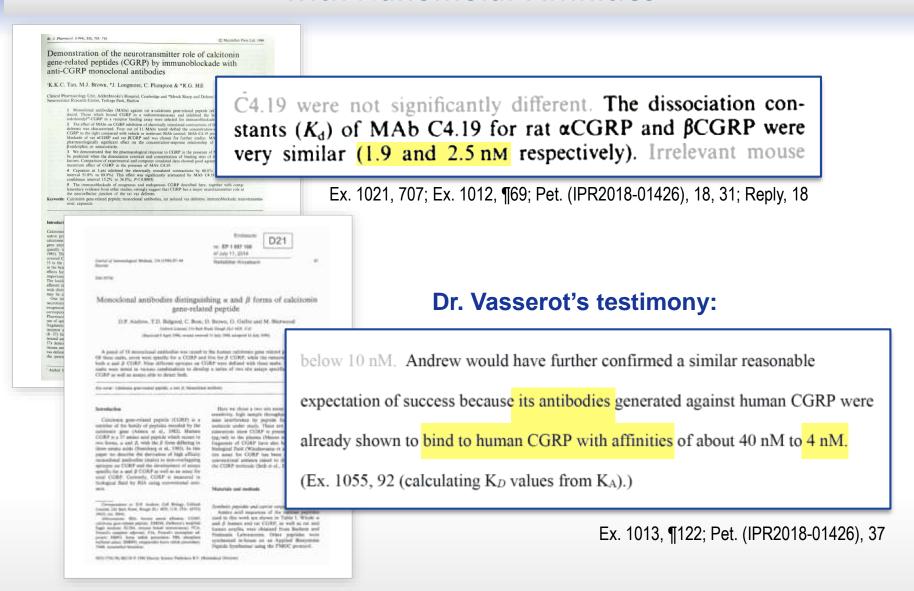


Teva Followed Tan's Express Guidance





Multiple Prior Art Studies Reported Anti-CGRP Antibodies with Nanomolar Affinities





A POSA Would Have Been Motivated to Make Anti-CGRP Antibodies with the Claimed Affinities

Dr. Tomlinson's statements in 2004:

NEWS AND VI

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

Ex. 1266, 521; Ex. 1327, ¶78; Reply (IPR2018-01426), 18

Next-generation protein drugs

lan M Tomlinson

Ankyrin repeats generate high-affinity protein binders with biophysical proporties that may favor therapeutic applications.

constitutes an ideal drug and the answer would probably include the words 'specificity, affinity, solubility, stability and safety' along with the phrases 'cheap to manufacture, eas to formulate, simple to deliver and the right pharmacokinetic profile.' Ironically, many drugs on the market fail to deliver in one or more of these areas because of their sub-opti mal biophysical malirup. Even blockbuster biologics, such as therapeutic antibodies! suffer from drawbacks, such as the require ment for an expensive mammalian cell production system and the need for intravenous. intramuscular or subcutaneous injection (with molecular weights of around 150,000, they are too large to be administered by any other route). Clearly, there is room for improvement. In this issue, Binz et al. describe a natural scaffold, ankyrin repent protein, that has promising biophysical properties for therapestic application. Ankyrin reposts are one of several new types of scalfold being developed for a new generation of

An ideal drug would have the following qualities; it would have very high affinity and equilities; it would have very high affinity and exquilities specificity for its tanget; it could be manufactured by the backet-lood in bactric or yeast; it would be both interestibly sub-ble and remarkably stable; it could be delivered to any part of the humans hody by any route of administration; and, once there, it would hang around long enough to have the delived therapostic effect. Achieving all their good has been particularly difficult for protrin drugs.

Currently, protein drugs come in all shapes and sizes: some are recombinant human proteins (for instance, insulin, growth hormone

Ian M. Toodhoon is Chief Scientific Officer of Domintis Limited, 315 Cambridge Science Park, Cambridge CB4 0WG, UK,



and erythropoletin), others are monoclonal antibodies (for instance, Remicade (infliximabi, Johnson & Johnson, Kenilworth, NJ, USA), Ritusan (rituximab; Genentech; S. San Francisco, CA, USA) and Erbitux (cetuximab) ImClone, New York, NY, USA) and still others are viral or bacterial proteins used as vaccines to elicit a specific immune response. Nature did not evolve proteins for manufacture exvive. For this reason, many human proteins produced in recombinant form are difficult to manufacture and some cannot be expressed at all in microbial cell culture. Furthermone, the serson half-life and tissue distribution of endogenously expressed proteins is carefully controlled in vivo to optimize their biological activity. Most human proteins are not

Figure 1. All in a bind. Since of air anotherists of the 33 amino audios feed added chairmal in three ordering repeats (size in the second ordering repeats (size in this e) and, using processor and page, anotherists to mannouse binding preterin. The co-crystal abuselune confirms the goodstate for using of the engineered arrivpts in page 1 arrivpts of the mannouse binding.

designed to be administered from our body. Recumbinant proteins therefore he rapidly cleared and thus require in injection (thus, the growing interted on the servan half-life by, for epolyethylene glycol conjugation).

Antibodies have proved useful a protein therapeutics because they favorable pharmacolinetic profile single injection, they can persist fitime in the bloodstream, maintain biological activity for several weeks, antibodies have also evolved to he from mammalian cells and, for a ressons, cannot be expressed in you terial cell culture.

Given the limitations of current protein therapies, scientists are starting to develop more tailored approaches to drug design whereby you first assemble a list of the vartual properties you want the drug to have and them engineer a drug with precisely those properties. Over the past three years, several new bistech companies have been see inc. If

thrit engineer a drug with precise properties. Over the past three years new bistoch companies have been exploit the sac of 'well-behand' hun teim a scaffolds to create a range of prutein drugs that have improved the properties (see Table 1). This appreced in through the following steps: fire a human protein that is well expressed teria and/or yeast and has good by imprepricies lockbullity, atability and second, create a reperiorite by intuitivestiy into the loop regions at it scaffold, prefensibly in a way that close out the overall situature of the protein the protein the protein the properties.

Dr. Tomlinson's cross-examination:

For therapeutic antibodies that act by binding a target antigen, is strong binding affinity to that antigen a desirable characteristic?

A: Yes.

Ex. 1301, 211:16-21; Reply (IPR2018-01426), 18

And as of 2005, a person of ordinary skill could use affinity maturation techniques to improve binding affinity stronger than one nanomolar, correct?

A: Yes.

NATURE BIOTECHNOLOGY VOLUME 22 NUMBER 5 MAY 200

Ex. 1301, 213:21-25; Reply (IPR2018-01426), 18



A POSA Would Have Been Motivated to Make Anti-CGRP Antibodies with the Claimed Affinities

Teva's arguments:

"[A] POSA would not have concluded that Tan 1994's anti-CGRP antibodies had K_D s of 10 nM or less, which defeats Lilly's second alleged 'reason' to make the claimed antibodies. ... But, as Dr. Tomlinson explains, Tan 1994 was not designed in a manner draw conclusions regarding affinity. EX2226, ¶¶104-109."

POR (IPR2018-01426), 42-43

Dr. Balthasar's testimony:

Although these concerns are addressed below, it is important to note that the technique used to measure the affinity of antibody C4.19 has little bearing on the motivation to develop humanized anti-CGRP antagonist antibodies for treatment of migraine or other conditions. In general, Tan 1994 and Tan 1995 helped to validate CGRP as a therapeutic target and would have motivated development of at least single-digit nanomolar-range anti-CGRP antagonist antibodies for therapeutic use.



Ex. 1327, ¶71; Reply (IPR2018-01426), 18

Near-Simultaneous Disclosure

APPLICATION NUMBER: 60/753,044 FILING DATE: December 22, 2005

TREATMENT OF MIGRAINE WITH ANTI-CGRP ANTIBODIES

FIELD OF THE INVENTION

The present invention is in the field of medicine. More specifically, the invention relates to antibodies to CGRP and the use of such antibodies for therapy and prophylaxis of migraines.

affinities characteristics as listed in Table 3. Neither monoclonal antibody nor Fab bound to amylin or adrenomedullin (tested at 500 nM). The anti-CGRP monoclonal antibodies and the anti-CGRP Fab tested specifically bind to rat and human α-CGRP and human β-CGRP.

Preferably an antibody of the invention to be used for therapeutic purposes would have the sequence of the framework and constant region (if a constant region is included) derived from the mammal in which it would be used as a therapeutic so as to decrease the possibility that the mammal would illicit an immune response against the therapeutic antibody. Humanized antibodies are of particular interest since they are considered to be valuable for therapeutic application and avoid the human anti-mouse antibody response frequently observed with murine antibodies. Additionally, in humanized antibodies if the

Ex. 1127, 1, 18, 32; Pet., 57

A R L E DE BULL R R DE L'ECA MA R DICHE LO SPENDI DE LE CREA UNITED STATES REPARTMENT OF COMPARISON Carlott Stones Farner and Stationaria Office February 01, 2803 IBS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM BE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK VICE OF THOSE PAPERS OF THE BILLOW IDENTIFIED PATENT. ICATION THAT MET THE REQUIREMENTS TO BE GRANTED A PPLICATION NUMBER: 60753,044 ILING DATE: December 22, 2005 THE COUNTRY CODE AND NUMBER OF YOUR PRIORITY APPLICATION, TO BE USED FOR FILING ABROAD UNDER THE PARIS CONVENTION, IS 0560733,040

Ex. 1127; Pet., 57

Nov. 14, 2005 L Dec. 22, 2005

2005: Aug.

Sep.

Oct.

Nov.

Dec.



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



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, 21

Antibody Format (e.g., fragments)	Fab, Fab', F(ab')2 , Fv, single chain (ScFv), fusion proteins	Ex. 1301, 27:25-28:6; Ex. 1001, 12:40-46; Pet., 22; Reply, 23
Sequence Mutations	20 ²²⁰	Ex. 1301, 92:8-10; Reply, 22
Antibody Class	IgA, IgD, IgE, IgG, IgM	Ex. 1301, 37:16-39:11; Reply, 23
Binding Affinity	2 pM-250 nM	Ex. 1001, 5:54-65; Reply, 22



Teva's Secondary Considerations Lack Nexus to the Claims



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, 24

Dr. Rapoport's cross-examination:

- Q: So let's just I think you said you didn't consider whether it preferentially binds to CGRP as opposed to amylin, correct?
- A: Right.
- 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, 141:16-20, 142:1-8; Reply, 24



Teva's Secondary Considerations Lack Nexus to the Claims

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."

Teva's claims: Reply, 24

We claim:

1. A human or humanized monoclonal anti-CGRP antagonist antibody that preferentially binds to human α -CGRP as compared to amylin.

We claim:

1. A human or humanized monoclonal anti-CGRP antagonist antibody that (1) binds human α -CGRP and (2) inhibits cyclic adenosine monophosphate (cAMP) activation in cells.

We claim:

1. A human or humanized, monoclonal anti-CGRP antagonist antibody that (1) binds human α -CGRP and (2) inhibits human α -CGRP from binding to its receptor as measured by a radioligand binding assay in SK-N-MC cells.

We claim:

1. An isolated human or humanized anti-CGRP antagonist antibody with a binding affinity (K_D) to human α -CGRP of 50 nM or less as measured by surface plasmon resonance at 37° C.

Wimalawansa (Ex. 1096):

reached and before CGRP antagonist, humanized anti-CGRP monoclonal antibodies, or both, can be evaluated as thera-

disease. The role of CGRP antagonists and humanized monoclonal antibodies should be explored with respect to control of pain and inflammation, type II diabetes, and in conditions with intractable hypotension, such as septic shock syndrome.

Ex. 1096, 567, 570; Reply, 24

Ex. 1001 ('614), claim 1;

Ex. 1001 ('951), claim 1;

Ex. 1001 ('881), claim 1;

Ex. 1001 ('649), claim 1



Teva's Secondary Considerations Lack Nexus to the Claims

Teva's claims:

We claim:

 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.

Wimalawansa (Ex. 1096):

reached and before CGRP antagonist, humanized anti-CGRP monoclonal antibodies. or both, can be evaluated as thera-

We claim:

 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.

disease. The role of CGRP antagonists and humanized monoclonal antibodies should be explored with respect to control of pain and inflammation, type II diabetes, and in conditions with intractable hypotension, such as septic shock syndrome.

Ex. 1096, 567, 570; Reply, 24

Ex. 1001 ('210), claim 1;

Ex. 1001 ('211), claim 1



Teva's Evidence of Industry Acclaim Is Deficient

NEWS

IN this section



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Crotor's disease fishiles rears approval in Europe

Migraine drug race turns its final corner, FDA decisions in sight

Administratives (EDA) is wishely serticipated to approve a trio of moreoclonal anditroly bradis) drugs for preventing reignate, in what could be a new maje; the disease incament. The mills block calcilenis generalated popular (CCRP), a recompositio that is active during migrates attacle and implicated in the transmission of pain signals and the sensory disturbances that deline this conston membraical sliveries. All, flow companies developing anti-COSP antibodies have blockbuder hopes for their mirrales insuleants-although, so clearners Acoustic must be we much difference in officiery brivers competitors, their advertages may largely be haved on doving and Impactors.

Het up will likely be enmursuly (Atmorig) Its manufacturer, Amazus of Threshand Chile Childrenia, serroussed on January 22 that the drug extretioned placers in a phase 5 told of patients with opiositic migratus travelessly triol and either not moreon conditati infectio has to four other y Insultments. A manufatory decision on a is expected by mid-filter

Next, the FOA will blicky rule on county from Yes Permanential o Tikns, lorad, in hore, and a verdict die by late September for galaxies upon it from offindingelis. A feathartí CCRP to Al nexalt from Alder Sketharmacesticsker Washington, could then bit the market and all lead one prophylactic CGRP-axis small tradecularistal sevent others for at ment) might neithe tierterhind (SaMe II)

Anti-CGIP agents are the first de paymed by drug companies with the parpose of provening migralous. For ockers and antideproparts to unit and belalinum neutrinolius, all rais rentites insulments were initially lic other indications and later reperposed phylactics against relgration. This now i amilwdy mignáne drugo also stande a that their mechanisms of actions on well stend-artike triptane, which were the for front acude entigration of tacks, on a m premise that later proved to be false. Yh budies previate originates relief by blocking the

al reducing the number of days in which individuals experience migrains attacks, with few rignificant side effects among the 10,000 or so people beated with the therapies in date.

In fact, accoming to Peter Gouldry, a head actor neurologiei si ilte Kirgh College Lenslen. who has been involved in totals of all linux on Albe and reported on two late last year (NIEM ST). 1119-2102 mil 2129-2115, 2017), flumb 588 in the afficure or followbill by data for indicatories and COSP in Altraciable belonfor than any other Totally deliverable to show matery construction relation that they differentiate in any work of was," for says.

dinical dictors, will bliefy determine which, it any, drug comes to dominate the field, uppe cially among the three products expected to win amount this calendar year. Amoun and it

Teva's arguments:

"Lilly's expert, Dr. Charles, has himself praised the claimed humanized anti-CGRP antibodies—repeatedly. Dr. Charles has touted the claimed antibodies as:

'very exciting and compelling, EX2182, 207"

POR. 49

First up will likely be erenumab (Aimovig)

Lilly of Indianapolis. A fourth anti-CGRP mAb, eptine-zumab from Alder Biopharmaceuticals of Bothell, Washington, could then hit the market in 2019, and at least one prophylactic CGRPantagonizing small molecule (and several others for acute treat-ment) might not be far behind (Table 1).

"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, a neurologist at the University of California, Los Angeles (who consults for Alder, Amgen and Lilly). "That, to me, is very exciting and compelling."

Ex. 2182, 207; Reply, 25

blend your idlation and pair semitimies. consist from the place 5 trials of the CGRF- half-life of more than 40 days, and seems by induced by CGMP on the trigominal gauglion, . Improximable superied to date, All antibudies . work with either single monthly injections or

SAFERY BESTSCHROLOGY MOLLING SE SENSERE & MARCH 2015.



Teva's Purported Evidence of Licensing Does Not Support Patentability

Dr. Stoner's cross-examination:

- Q: Do you consider the settlement and license agreement to be a patent portfolio license, you, Dr. Stoner?
- A: I was aware that the license related to all of these patents which are necessary to practice the Alder product.
- Q: When you say "all of these patents," you mean that at least 188 patents and applications listed in schedule 1.14 in 65 countries and eight families? When you say "all these patents," is that what you meant?
- A: Yes, all these related patents.
- Q: ... if just claims 1 through 7 and 15 through 20, which are the challenged claims of the 614 patent, if just those claims were canceled, Alder Bio would still owe the same consideration under this agreement because Alder Bio admits that it infringes the remaining claims or the 614 patent and all claims of the 187 additional licensed patents, correct?
- A: That's certainly a reasonable interpretation of this paragraph.
- Q: And to that same effect, if 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 ...



Detailed Analysis



Teaching Away Requires Criticizing, Discrediting, or Otherwise Discouraging Investigation



Galderma Labs., L.P. v. Tolmar, Inc., 737 F.3d 731, 738 (Fed. Cir. 2013)

"[N]or do these articles indicate in any way that the side effects would be serious enough to dissuade the development of a 0.3% adapalene product....A teaching that a composition may be optimal or standard does not criticize, discredit, or otherwise discourage investigation into other compositions."

Reply, 16



Sanofi-Aventis U.S. LLC v. Immunex Corp., IPR2017-01884, Paper 96 at 20, 21 (PTAB Feb. 14, 2019)

"We are not persuaded that the potential risk of side effects would have deterred a person of ordinary skill in the art from developing a way to block both IL-4 and IL-13 signaling. [] First, we note the literature cited by Patent Owner's expert Dr. Finkelman characterizes the side effects as theoretical."

"The problem with Patent Owner's argument is that the law does not require the prior art to explicitly suggest humanizing MAb230. ... Petitioner need not show that MAb230 was the only option or even the best option for a person of ordinary skill in the art. On the contrary, Petitioner may show that MAb230 was a 'suitable option from which the prior art did not teach away."

Reply, 9-10



Lilly Need Not Identify a Specific Antibody to Humanize

Teva's argument:

"Lilly never articulated which prior art antibody a POSA would have humanized in order to arrive at the claimed antibodies."

Sur-reply, 24



Abbott GmbH & Co., KG v. Centocor Ortho Biotech, Inc., 971 F. Supp. 2d 171, 184 (D. Mass. 2013)

A POSA would have "the motivation or attempt to combine the teachings of the prior art references to make a human, high-affinity, neutralizing antibody to IL-12" when the prior art disclosed neutralizing mouse and humanized antibodies to IL-12 and "methodology to achieve the functional result."

Pet., 31



The Prospect of Creating a "Potential Therapeutic" Is Sufficient Motivation



Sanofi-Aventis U.S. LLC v. Immunex Corp., IPR2017-01884, Paper 96, 19-20 (PTAB Feb. 14, 2019)

"We are also persuaded that Petitioner has shown that a person of ordinary skill in the art would have had a reason to humanize Hart's MAb230 using Schering-Plough's humanization technique to create a potential therapeutic for allergic diseases with a reasonable expectation of success."

Reply, 5



Abbott GmbH & Co., KG v. Centocor Ortho Biotech, Inc., 971 F. Supp. 2d 171, 185 (D. Mass. 2013)

"Based on the jury's implicit factual findings, the Court concludes that there was clear and convincing evidence of a need to create a human, neutralizing, high-affinity antibody to IL-12. A person of ordinary skill in the art at the time knew that the overproduction of IL-12 was causing diseases, and that an antibody that neutralized IL-12 could be therapeutic."

Reply, 5



Sanofi-Aventis v. Immunex Is Highly Analogous

Sanofi v. Immunex	The instant case			
Prior art antibody blocked IL-4 and IL-13 activity. (<i>Immunex</i> , IPR2017-01884, Paper 96, 18; Sur- Reply, 5)	Tan: MAb C4.19 IgG blocked "the hypotensive effects of exogenous rαCGRP <i>in vivo</i> ." (Ex. 1022, 570; Pet., 17.) Wong: antibody 4901 "is extremely effective in vivo as an immunoneutralizing agent." (Ex. 1033, 104; Pet. 34.) Wimalawansa: disclosed humanized anti-CGRP antagonist antibodies for use in treating several diseases including migraine, inflammation, and cardiogenic shock. (Ex. 1096, 567, 570 ("humanized monoclonal antibodies should be explored"); Pet. 19, 26.)			
The prior art disclosed that anti-IL-4R antibodies "could advantageously be humanized and thus used for long term treatment of allergic disorders." (<i>Immunex</i> , Paper 96, 19.)				
Potential risk of side effects not a deterring factor in the prior art. (<i>Immunex</i> , Paper 96, 20.)	Wong: Antibody 4901 "had no significant effect on MAP and heart rate." (Ex. 1033, 101; Reply, 12.) Teva's experts contemporaneously praised CGRP antagonists as "promising, new antimigraine drugs without vascular side effects." (Ex. 1290, 657; Ex. 1297, S119; Reply, 8) Doods: "we expect that CGRP antagonists will be effective anti-migraine drugs" (Ex. 1024, 422; Pet. 26.)			
Claims do not require therapeutic efficacy. (<i>Immunex</i> , Paper 96, 23-24.)	Claims do not require therapeutic efficacy. (Ex. 1001; Pet., 38 n.2; Reply, 4-5.)			



Phigenix Is Inapposite

Teva's argument:

"Under a similar challenge to composition of matter claims, as here, the Board held the petitioner to its 'therapeutic utility' motivation arguments. *Phigenix v. ImmunoGen*, IPR2014-00676, Paper 39, 16 (P.T.A.B. Oct. 27, 2017)"

Sur-reply, 3-4

Phigenix	The instant case			
Claims recite a specific antibody conjugated to a specific toxin (Herceptin-maytansinoid)	Claims recite broad genera of humanized anti-CGRP antagonist antibodies			
Key prior art human clinical study showed toxicity with a relevant immunoconjugate	Human clinical trial with relevant CGRP pathway inhibitor (BIBN) showed no toxicity			
Toxicity of Herceptin was identified in later prior-art human studies	Later prior-art human studies resolved purported safety concerns			
Tight nexus between objective indicia evidence and narrow claims that required a "specific antibody, linker, and toxin"	Objective indicia evidence lack nexus to extremely broad claims			



Teva's REOS Arguments Are Irrelevant



Senju Pharm. Co. v. Lupin Ltd., 780 F.3d 1337, 1346-47 (Fed. Cir. 2015)

"In composition claims 12–16 of the '045 patent, there is no limitation denoting the function of the composition and we decline to import this limitation into the claims."

Pet., 38 (n. 2); Reply, 19



Sanofi-Aventis U.S. LLC v. Immunex Corp., IPR2017-01884, Paper 96 at 23 (PTAB Feb. 14, 2019)

"We agree with Petitioner that the pertinent question is not whether there is a reasonable expectation that the antibodies will actually be therapeutically effective. Rather, the question is whether a person of ordinary skill in the art would have reasonably expected to arrive at the claimed invention."

Reply, 19



Teva's Evidence of Industry Acclaim Is Deficient



Bayer Healthcare Pharm., Inc. v. Watson Pharm., Inc., 713 F.3d 1369, 1376 (Fed. Cir. 2013)

"[I]ndustry praise of what was clearly rendered obvious by published references is not a persuasive secondary consideration."

Reply, 24-25



Anti-CGRP Antagonist Antibodies Had Already Been Generated



PharmaStem Therapeutics, Inc. v. ViaCell, Inc., 491 F.3d 1342, 1362 (Fed. Cir. 2007)

"Admissions in the specification regarding the prior art are binding on patentee for the purpose of a later inquiry into obviousness."

Pet., 6, 33

Teva's specification:

CGRP synthesis, production or release. Anti-CGRP antagonist antibodies are known in the art. See, e.g., Tan et al., Clin. Sci. (Lond). 89:565-73, 1995; Sigma (Missouri, US), product number C7113 (clone #4901); Plourde et al., Peptides 14:1225-1229, 1993.

Ex. 1001, 26:13-17; Pet., 6

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. General techniques for production of human and mouse antibodies are known in the art and are described herein.

Ex. 1001, 27:61-67; Pet., 6-7



Tan's Anti-CGRP Antagonist MAb C4.19

B. J. Photocoli 1994; 313, 751-712 D Macmilian Plans Lat. 1948 Demonstration of the neurotransmitter role of calcito gene-related peptides (CGRP) by immunoblockade w anti-CGRP monoclonal antibodies K.K.C. Tan, M.J. Brown, *J. Longmove, C. Phampton & *R.G. Hill Classed Phorocoology Unit, Addressrooks's Haspital, Conducting and "Month Street and Dalmer Rac Seasonment Research Cover, Technic Park, Hadison 1 Microclinal artibodies (MANs) agriest yet s-calcinete generalised popular (s/CSRP) is a redeference-county and adolesced (schemescounty and adolesced in-benefit industrials)²² CGRP in a receptor handing away were selected for introductional-selections.

The four MAbs C4.19, C4.6, R1.50, R2.73 bound CGRP by ELISA and RIA. All four MAbs cross-reacted with the α and β forms of rat and human CGRP by ELISA. CGRP

Ex. 1021, 706; Ex. 1012, ¶69; Pet. (IPR2018-01426), 18

I The offers of NAA's on CORP publishes of absencedly extended means deletes was characterized. Four nut of 11 MAIs used defeat the assessment CGRP to the right compared with vehicle or innividual MAIs control. MAIs C4.19 people blockade of rar aCGRP and rar MGRP and mis chosen for hather studies. MAN CA19 had no ingually against affect on the concernation-regions returnality of terrorisms, to

3. We disconstructed that the plantacological supreme to CCRP is the pressure of MAS C4 IX could be predicted when the dissociation constant and communication of hading size of the archesty and traver. Comparison of experimental and computer concluded data decreed good agreement for 60°,, and maximum affect of CORP in the presents of MAO CAVA.

4. Capacity at Law (oblided the describally standard corrections by 66.9%, (67 testival 51.9%, to 66.9%). This office was significantly attenued by MAh C4.99 to confidence interval 15.2% to 36.9%, (7<0.0003).</p>

5. The improvided of exoptions and endogrous CORP described here, right beyondary endouce from other studies, strongly regges that CORP has a major microsis. the accondition positive of the net use defense

Keywords: Calcitum generalistic papride remuchoul autibodies, on inclosed on deferes

Calcionar governance people (CGRP) is produced by afterastre processing of the primary in RNA transcripts of unknieser gene (Remedyld er al., 1965). A second CGSP gene encoding austher Wilansian and popular was spine. questly identified (Amara et al., 1981; Steenbergh et al., 1983; This peptide (KXIRP) defens from the originally disworld CCHEP (at GRP) by only our atoms and or position If as the set. United calcinoses, CGRP is presently beading the frain and peopleral nervous tissue. Diverse histogical effects have been enrithered to CORP has its physiological reportunes remains to be retaileded in more regan inventors. The hardingson of CGRP-the ammanorments in printers offeren account intersecting more different moons and wide distribution of UGRP binding sites suggest that CGRP

may be a physiologically deportant temperaturality.

One important anterior that most be fidabled for any
menostropology to that modulation of the effects of the reignance passing approximates for drops should have corresponding offices on responses to never strendships. Phoreacological blackade is normally accorded through the one of specific company antiqueness. A traveler of Command fragments of COSP have been demonstrated to believe as respon aringment (Mineralt et al., 1981). The C-treatest (8-17) (regreen) of boson aCGRP has been well characteriord and in commercially available. However, CORP (1-17) depositions variable extensions potents or different lessen and is a relatively poor assignment in the rai sedent van Arthreus preparation (Dense et al., 1990). This has led no the penedution that multiple comprise subseque state the

Autor for compendent

CGRP. An alternative approach to git ado to the use of authories which his

burnanchinitade may be a more grown approach no assumptions have to be made concurring receptor multiplicity and the relative selectivity of receptor entagonals. The moon objective of the present study was to correspon

resembleday passive of the ox soluted tax delices as a CORF from server was achieved to matrix. Copropole is the pumpost larger the genes Capacion which selective idition of primary affirms morne

1981). It has been widely sood on a p investigate the 'effected function of cean inviewed by Maggi & Meli, popular stored in terror terrorally who ore various effecter functions. Both inhibit the nerve-recliated contraction delenes. It is flurefore reasonable to b pany he assisted to accentistion panetics of the sec on defense.

Analysis of the effects of individual index in other difficult because of the encopepides by superiors in my tachekenen co-retraced with CGRF of basingsal response in g. dilutation of arterest

trically stimulated oscilated was deletered neurokeats. A uncl authoriz P exhance contractions (Mactalii et al., 1987) in

anti-peptide (TSH) MAb as a control. We were also able to confirm the specificity of MAb C4.19 in immunocytochemistry experiments. Pre-incubation of the MAb C4.19 with 1 µM

Ex. 1021, 709; Ex. 1012, ¶69; Pet. (IPR2018-01426), 18

C4.19 were not significantly different. The dissociation constants (K_d) of MAb C4.19 for rat α CGRP and β CGRP were very similar (1.9 and 2.5 nm respectively). Irrelevant mouse

Ex. 1021, 707; Ex. 1012, ¶69; Pet. (IPR2018-01426), 18, 31; Reply, 18



Tan 1995 Discloses the Benefits of Anti-CGRP Antagonist Antibodies

Calcitonin gene-related peptide as an endogenous visodilator: immunoblockade studies in vivo with an anti-calcitonin gene-related peptide monoclonal antibody and its Fab' fragment

Vant K. C. TAN. Morris J. BROWN, Richard J. HANGREAVER, Sars L. SHEPHEARDs.

Search A. COOK? and Raymond G. HEL!

Check Phorococcing Unit. University of Combridge Child School, Additionally International Control, Morris Starp and Dahme Research Endominists. Neuroscionis Research Control, Holland, U.K.

Musel (Forellague 1992, suspend of Augus 1995)

I. Chilmens gene-related peptide (CGRP) is localind in perivascular survivey neutrons and is a patent smillater, We investigated the utility of immunolockade as an in wive technique for probing the role of CGRP as ar endingerous vasodilator.

3. The effects of an anti-C CRP mesockoral artifield, SAN: caded C L19 and its Fab fragment on CRP-induced changes in blood present and skin fool from were studied in periodial biommuthetined rais. Antiferroint skin raisofilatation is for me skind pain was measured by laser Dopples femants.

3. The form-response relationship for the hypotensise dirty of intraveness rat a CGHP (ref GRP) was smilett shilled rightward by Male CA19 [gG legical intravenessly]; and Falt fragment degree intravenessly. The Corresion Prognett of lumn a CGRP (hat GRP_{d-12}) also blacked the shitting effect of prCGRP.

4 MA CA19 Fab fragment (Imprort intramody, and hxCGRP_{2-N} (100 models); intramody), but and MA CA19 [GG (a) to Nighter. Warroughly or normal mouse Fab fragment "Registal improvements), blocked the increased white land flow represents of artificturity relaxabilities of the spheres, neares.

 The mean percentage changes in skin blood flor principes due to MAA CA19 Falt fragment nets quilleantly different from those due to recental more Falt fragment (unpaired r-test; P=0.05) has no fact.

ne from those due to hat GRP_{n, re}.

5 The results demonstrate the pharmacokowtic strange of Fab' Sengment over IgG for immuno-

Mockade studies in vive and sa CGRP in mediating skin vasodila

INTRODUCTION

Calcatents gree-related peptide used in pervisional primary after a pointst weedfalson in man a species studied [1–3]. Some responsable of CORPs in the rather than amongst from studies with a studies of the studies o

5] The hypotensive imperior to integration CGRI in assesthetized and compous rate may be blocked by hatCGEP, at (6, 7) Exagences CGEP produces a systemed hypotrasion that research the depressor response to special cord stimulation in the pithod nat [8] The hypotentine responses to spend conf stemlation and evoponess CGRP are markedly infulered by hoCORPs at This endogenous CGRP appears to be a major nearconnection that readules reurogene: convoluntation after spend cord stimulation in the car. HeCGRP, region by the intracessor must has been found to robbit the increased skin blood flow induced by settadermal CGRP and cognature [4] Increased with blood flow in the rat hind pew ofter antidrome stimulation of the napherous more to also subband by beCGRP_{8, 17}[9, [0]]. The evidence obtained from the out of baCGRP_{8, 17} reggerit that CGRP is an experiant medicity of the 'offerest' nanohistory function of expensivesession primary afferent occurse.

and bradykinin. The present investigations have been performed with an MAb with inherent advantages of defined specificity, known affinity, reproducibility and unlimited availability. This study has

Ex. 1022, 572; Ex. 1008, ¶60; Pet., 18; Reply, 3

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Queen (Ex. 1023): Humanization Techniques Were Routine

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(75)	Inventors		L. Queen, Los Altos; , Belmont, both of CA		2 0365 997 0 125 023 0456216	10/1991	(EP) . (EP) .	
(73)	Assignee:	Protei CA (U	in Design Labs, Inc., (S)	Fremont,	0460167 1-0519 596 1-0592 106	12/1992 4/1994	(EP)	
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(21)	Appl. No.	08/48	1,537		WO 89/01783 WO89/09622	3/1989	(WO) . (WO) .	
(22)	Filed	Jun. 7	, 1995		WO 90/87861 91/89967	7/1990		
			S. Application Data		WO 91/09966 WO 92/11018 WO 92/11383	7/1991 7/1992 7/1992		
(63)	Dec. 19, 19 ation-in-par 1990, now application abandoned.	No. U7/ which	of application No. 07/63 Pat. No. 5,530,101, whice certion No. 07/590,274, fit od, which is a continual 310,252, filed on Feb. 1 is a continuation in-part	h is a continu- ed on Sep. 28, ion-in-part of 3, 1989, now of application	WO92/11018 WO93/02191 WO 93006231 WO94/11509 WO 96/05/29	7/1992 2/1993 4/1993 5/1994 2/1996	(WO) . (WO) . (WO) . (WO) .	
			ed on Dec. 28, 1988, now			OTHER	PUBLIC	CATIONS
(51) Int. CL ⁷ A61K 39/395 (52) U.S. Cl. 435/69.6; 435/172.3; 435/328; 530/387.3; 530/388.2; 424/133.1; 424/143.1			George et al Current Methods in Sequence Comparison and Analysis in Macromolecular Sequencing and Synthesis 127–148, 1988.*					
(58) Field of Search 424/133.1, 143.1; 435/328, 69.6, 172.3, 530/387.3, 388.2			Barton et al Protein Sequencing Alignment and Database Screening Protein Structure Prediction. 31-63, 1996.*					
(56)		Ref	erences Cited		(List continued on next page.)			
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oglobulin to the antigen, such as a protein or other and containing an epitope.

30 Claims, 55 Drawing Sheets

Lilly Exhibit 1023, Page 1 of 147

Perhaps most importantly, non-human monoclonal antibodies contain substantial stretches of amino acid sequences that will be immunogenic when injected into a human patient. Numerous studies have shown that after injection of

Ex. 1023, 1:44-47; Ex. 1008, ¶¶128-129; Pet., 29

ity to a predetermined antigen. These humanized immunoglobulins should remain substantially non-immunogenic in humans, yet be easily and economically produced in a manner suitable for therapeutic formulation and other uses.

Ex. 1023, 2:30-33; Pet., 35

In accordance with the present invention, novel means of designing humanized immunoglobulins capable of specifically binding to a predetermined antigen with strong affinity are provided. These improved methods produce immuno-

Ex. 1023, 10:57-60; 1013, ¶54; Pet. (IPR2018-01426), 21-22, 37



IPR2018-01422

The Prospect of Creating a "Potential Therapeutic" Is Sufficient Motivation

Dr. Vasserot's testimony:

"A POSA would have been particularly motivated to make a humanized antibody when its murine counterpart antibody had been shown to exhibit functional properties that could be useful in treating a disease. [] Routine humanization techniques known in the art would have provided a reasonable expectation for a POSA to obtain a humanized antibody with similar desirable properties. All of these were present for CGRP."

Ex. 1009, ¶¶70-71; Pet., 29; Reply, 5

- Q: So AME is the type of company that would take Tan 1994, humanize Tan's antibody, and take it to clinic?
- A: We have done worse than that.
- Q: You have done worse than that. What have you done that's worse than that?
- A: We have started projects with less data than that.

Ex. 2191, 99:8-100:1; Reply, 5



The Prospect of Creating a "Potential Therapeutic" Is Sufficient Motivation

Teva's sur-reply argument:

"Lilly then points to Dr. Tomlinson's acknowledgment that he "humanized antibodies all the time" as evidence of motivation in 2005. Reply, 5. But Dr. Tomlinson was discussing his humanization activities from 2007 to 2016, not prior to 2005. EX1301, 55:1-13."

Sur-reply, 7

Dr. Tomlinson cross-examination:

Q: I'd like to consider the time frame before the earliest filing date of September 14, 2005. So before September 14, 2005, when was the – I guess the – the latest time before that date that you humanized a murine antibody or murine antibody fragment?

A: ... during my time at the MRC I was working literally alongside the people that were doing the work on humanizing antibodies. ... I spent a lot of time discussing humanization with colleagues at, for example, Genentech, and other companies that were doing a lot of humanization at the time under license from the MRC.

Ex. 1301, 55:16-56:23



Prior Art Clinical Studies Disclosed the Vascular Safety of CGRP Antagonism (Ex. 2019)

doi:10.1017/j.1468-2982.2004.00830.x

The CGRP-antagonist, BIBN4096BS does not affect cerebral or systemic haemodynamics in healthy volunteers

KA Petersen¹, S Birk¹, LH Lassen¹, C Kruuse¹, O Jonassen², L Lesko² & J Olesen¹

Tomick Bradiche Ceiter, University of Copenhages and Department of New Augus Geotrop University Magnitud Department of Christole Physiologies and Nedern Medicia, Gloding University Hospiel, Demanik, Berlinger Ingellein Phormic actives Inc., Bilgebill, Garnetics.

CGRP-antags

the recentor of vasocon@rict Seven bealths over study. I 2.5 mg or 10 used to meas regional cereb SPECT. The d resolution ad IP,CO3, and influence on in the middle

(PetCO₂), and adverse events were monitored regularly. BIBN4096BS had no influence on global or regional cerebral blood flow, or on the blood flow velocity in the middle cerebral artery. There was no effect on systemic haemodynamics and adverse events were minor. We conclude that there is no effect of CGRPreceptor blockade on the cerebral or systemic circulation in humans. Circulating

and adverse en receptor blockade on the cerebral or systemic circulation in humans. Circulating CGRP is therefore not likely to exert a vasadilatory activity in the resting state and the use of BIBN 4096BS for acute migraine seems to be without risk of cerebral vasoactivity. These data suggest that BIBN405656 is the first specific antimigraine drug without vasuartive effect. LIBBN408685, CGRP-entogonism, confront and systemic langualguanics, migratur

Dr Konneth A. Petersen, Danish Headache Center, University of Caperlingen and Department of Neurology, Clostrup University Hospital, KAS Clostrup, DK-2699 Clastrop Demank. Tel. +15 43232296, for +15 43233960, e-soil hapterscribballnet.# Receival 5 February 2004, screpted 29 May 2004

Introduction

Calcitonin gene-related peptide (CGRP) is probably one of the most potent vasodilators of human arterics (1-4). The vasoactive function of the neuropeptid is mediated through a receptor complex (5). Binding to this complex leads to an intracellular increase in cyclic miclostides and vasodilatation. CGRP probably plays a protective role against vasospasm following subarachnoidal haemorrhage in both animals. and humans (6, 7). CCRP is likely to play a causative role in migraine headache 96, 99.

6/8/actor/# Publishing Lat Ciplanique, 2014, 28, 179-147

Peptide fragments of calcitonin gene-relates peptide, e.g. CGRP. -- and [Asp31, Pro34, Phe35 CCRP have so far been the only available antag enists of CGRP. They have been used in invidstudies to characterize CGRP function and CGRI receptor properties. BEBN40968S is a nevel CGRP amagonist. It has been well characterized in anim studies and can be used safely in humans (10, 31). phase-2 study gave proof that BBBN4896BS effective in treating acute migraine headache BIBN4096BS therefore represents a new principle in acute migraine trentment (11). One potential concer

Eli Lilly & Co. v. Teva Pharm

Ex. 2019, Abstract; Ex. 1306, ¶36; Reply, 8

Dr. Ferrari's cross-examination:

So in healthy volunteers, blocking the CGRP pathway had no clinically meaningful effect on blood pressure, correct?

...in healthy volunteers under physiological circumstances, there is admittedly no effect on the parameters you just mentioned.



Ex. 1303, 91:19-92:20; Reply, 8

Prior Art Clinical Studies Disclosed the Vascular Safety of CGRP Antagonism (Ex. 1042)

doi:10.1111/j.1468-2982.2004.00726.x

Safety, tolerability and pharmacokinetics of BIBN 4096 BS, the first selective small molecule calcitonin gene-related peptide receptor antagonist, following single intravenous administration in healthy

M Iovino¹, U Vibras Parmo & Co. KG, Ingels Plantacolineties, Phinacolineties,

Cephalals

acute migraine. The objective of this study was to obtain information on the safety, tolerability and pharmacokinetics of BIBN 4096 BS following single intravenous administration of rising doses (0.1, 0.25, 0.5, 1, 2.5, 5 and 10 mg) in 55 healthy male and female volunteers. The study was of single-centre, double-blind (within dose levels), placebo-controlled, randomized, single rising dose design. Blood pressure, pulse rate, respiratory rate, ECG, laboratory tests and forearm blood flow did not reveal any clinically relevant, drug-induced changes. Sixteen adverse events (AEs)

reveal any clinically relevant, drug-induced changes. Sixteen adverse events (AEs) were reported by eight of 41 volunteers after BIBN 4096 BS compared to five Alfa reported by four of 14 volunteers after placebo. Approximately two-thirds of all AEs related to active treatment occurred at the highest dose of 10 mg. At this dose level, all Alis were confined to the three BBN 4096 BS-treated females, and consisted mainly of transient and mild puresthesias. Paresthesias were the single most frequent AE, whereas fatigue was the AE which occurred in the highest number of subjects. Only two AEs were of moderate intensity, all remaining AEs were of mild intensity. No serious Alls were reported. The local tolerability after intravenous administration was good. In summary, intravenously administen BIBN 40% BS revealed a very favourable safety profile over the dose range tested in both genders. Generally well tolerated at all dose levels, it was of satisfactor tolerability in female subjects at the highest dose of 10 mg. The plasma concentr tion-time courses of BIBN 4096 BS showed multicompartmental disposition characteristics. Mean maximum concentration (Cnn) values appeared to be dos proportional. Based on the results from the two high dose levels (5 and 10 mg with sufficient individual subject data, BIBN 4096 BS exhibited a total plasm clearance (CL) of approximately 12 1/h and an appearent volume of distribution steady state (V,,) of approximately 201, resulting in a terminal half-life (t,c) approximately 2.5 h. Inter-individual variability was moderate with a coefficien of variation of approximately 45% based on the area under the plasma concentration-time curve (AUC) values. The mean renal cleanance (CL_e) was approximately

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IPR2018-01422

Lilly Exhibit 1042, Page 1 of 12

Ex. 1042, Abstract; Ex. 1306, ¶35; Reply, 8

Dr. Charles's testimony:

- Q: Any a study showing that there were no adverse events in healthy volunteers would be reassuring for you with respect to patients who have a history of ischemia?
- A: Yes... information about the vascular consequences of a compound in healthy volunteers is reassuring about the use of these compounds in the setting of ischemia.

Ex. 2272, 96:22-97:7



Tan 1995 Did Not Raise Safety Concerns

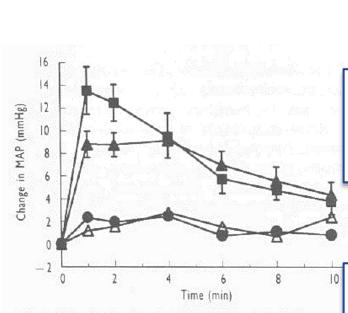


Fig. 2. Effect of l mg/rat (●) or 3 mg/rat (■) MAb C4.19 2 mg/rat MAb C4.19 Fab' fragment (△) or 2 mg/rat normal m Fab' fragment (△) on baseline MAP. Mean results are plotted standard error bars (n = 4-6). Some error bars have been omitted clarity.

Teva's arguments:

"Moreover, at 3 mg/rat, MAb C4.19 raised [mean arterial pressure] nearly 13-fold, while having minimal, if any, effect in the saphenous nerve assay. EX1022, 568, Figure 2, 569; EX2230, ¶¶52, 78."

POR, 24

Dr. Foord's cross-examination:

- Q: Is it fair to state that at the one-minute mark, the monoclonal antibodies C14, c4.19 at 3 milligrams per kilogram, raised mean arterial pressure around 1.1-fold versus baseline, as reported in Tan 1995?
- A: Yes.

Ex. 1300, 129:21-130:4; Reply, 11



Tan 1995 Did Not Raise Safety Concerns

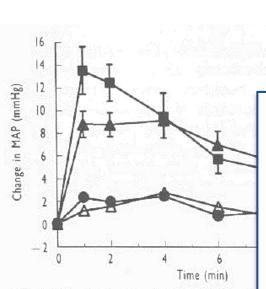


Fig. 2. Effect of Img/rat (♠) or 3mg/rat (■) arg/rat MAb C4.19 Fab' fragment (♠) or 2m Fab' fragment (♠) on baseline MAP. Mean restandard error bars (n = 4-6). Some error bars helarity.

Dr. Balthasar's testimony:

57. Because full-length IgG antibodies have half-lives on the order of weeks, a POSA would have understood that the minor blood pressure increase observed had no relationship to the half-life of Tan's C4.19 antibody. Ex. 1022, 568. Because the observed transient and minimal impact on blood pressure was not tied to the long half-life of MAb C4.19, Tan 1995's blood pressure study results would not have raised any concerns about long-term blood pressure increases upon anti-CGRP antagonist antibody administration.

Ex. 1305, ¶57; Reply, 11



Tjen-A-Looi (Ex. 2084) Is Not Relevant

Dr. Balthasar's testimony:

CGRP and somatostatin modulate chronic hypoxic pulmonary hypertension

STEPHANIE TJEN-A-LOOI, ROLF EKMAN, HOWARD LIPPTON JOHN CARLY, AND INGRIGERD KEITH

Department of Comparative Biosciences, School of Veterinary Medicine, and Dep Wildlife Ecology, University of Wavensin, Madison, Wisconsin 55706; Departm and Neurochomistry, University of Lund, Lund, Sweden; and Departments of L. and Pharmacology, Louisiana State University, New Orleans, Louisiana 70112

Tjen-A-Losi, Stephanie, Relf Ekman, Howard Lippton, John Cory, and Ingegerd Krith. CCRP and sometstatis modulate chessis hypexic palmeany hypertension. Am. J. Physiol. 363 (Heure Circ. Physiol. 32): 14681-1460, 1992.— Choosic hypoxic gulmonary hypertension (PH), associated with increased polanosary esterial pressure (PPA) and right ventricular impertupity (RVH), correlates significantly with cofcitonia gene-ralated paptide (OGRIP) and comptomatin (SOM) levels in lung and blood. CGRIP's role in regulation of PPA in chronic hypoxis and its potential interactions with SOM were investigated. CGRP, its antibudy (ab) and blocker. CGRP-(8-37), SOM-54, SOM-26, and SOM-sh, respectively. were infused into the pulmonery circulation of hypobaric by poxia note for 4, 8, and 16 days. Thereafter, under personarbital sodium correthesis. PPA was measured in the right ventricle and main pulmonary artery. Cheosic CGNP influion presented PH at all times, whereas incremensultalization and records black ing enscerbated PH. SOM-38 also esscerbated while SOM-14 and SOM-so decreased PRL RVR generally refrected the PPA. Radiointropassansy confirmed successful infusion of the peptides with negligible postize degradation in the pumps though cut 16 days and aboved complete immunorestralization of CGRP with its ab. Pautide levels in lung tissue suggest inhibition of CGHI* release by SOM-28 and increased plasma SDM with CGRP infusion to vites pharmacological studies suggest that CGRP exerts a recuptor coediated consideracycle, normacertific vasodilatory effect in the lung which is independent of endothelium derived relaxing factor and does not involve ATPdependent potassium channels. We essolute that endogenous CGSP plays an important role in palmonary pressure homeostasis during hypoxia, by directly diluting polinonery vescelature, thus anultorating the development of chronic hypoxic pulmentary hypertension in rate

extr; long tissue and blood peptide levels; indicinamentatory; pulmonary arterial pressure

custonic hypoxic pulmonary hypertension (PH) is characterized by increased pulminary atterial pressure. The rise in pressure is based on vasoconstriction, accompanied by polycythemia (12) and structural remodoling. The structural changes include medial thickening of pulmonary arteries and arterioles, and hyperplasis of the constituent cells (46), almost invariably accompazóed by right ventricular hypertrophy (RVH). Hypoxic ventilation not only causes pulmonary vasoconstriction but also enhances the pressur response to many constricter substances (1). Hypexia has also been shown to impair the spontaneous vasodilation that follows vasoconstriction caused by substances such as KCl and beadykinin (1).

In addition, PH can be oneliomted by general agents including the #-adrenoreceptor antagonist metipranolol (42), aspirin (25), diethylrarbamazine (40) via kuko-

triese inhibition, heparin sodi rived growth factor inhibition, bradykinia (22) via pulmonary

The pulmonary neuroendocble of responding to acute but cytosis of small membrane-box tion the regulatory peptide peptide (CGRP), a pulmonary peptide bormone localized to (SOM) (525)

The present study was don dispulseonary effects of the n 80M to better understand th duced by prolonged hypercia.

MAYERIALS AND MICTIODIS

Chronic infusion. Male Sunos 200-g weight ratur were used for th their antagonists were chronical Alast caractic microperup models periods of 4, 8, and 16 days, ser chosen according to used for infusi Model 2ML1 and 2ML2 morage a required a higher dilution (4 ag/al) soaked overnight in bacteriasty with the infessed substance at 40 tion. Leophilized antiscrem and Cappel no. 5012-12855 ware reco water and dikted in sterile salita: mili; poptides and blocker ware-dika our havitravies (I enginel). With the anarchesia (1:20 mg/kg km, Fort C ein was rengulated with a PE-1 0.61 mm/ fitted to a PE-68 cath sobcotaneous Alies consotic mine the scapula. The PR-10 cutherer for immediate delivery to the pur right heart. The incluies was clossted with Neosports centmes (h h postsurgery), the rate were pla ambient nom eir (permosia) er ig with hypobaric hypoxia therometr tional concentration of O_c in lang of Wisconsin). The hyperin chard feeding and cleaning. Hypexia rate infesions: a-CGRP (not: Pesingul Backen Bioscience ps. H-2205) eddet anti-est a CGRP serum RAS-6000N) at 0.25 al-ner-1 (8 : 37)] at 6 ag mit 2 h 1, 80% H-1490) at 20 ag-mit 1 h 2, Suchen Riencience no. H-1955) a enti-SOM senso (Iruntar un. 200

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In Tjen-A-Looi, the researchers analyzed rats under conditions that would not be encountered in any reasonable clinical setting. First, Tjen-A-Looi placed the rats under investigation in hypobaric chambers with only a 10% oxygen concentration, roughly half of the oxygen concentration of ambient air. Ex. 2084, H681. Tien-A-Looi notes that the hypoxia conditions were designed to impair vasodilation responses in rats, and would have the effect of artificially enhancing blood pressure responses. Ex. 2084, H681. Second, Tjen-A-Looi continuously infused CGRP, rabbit anti-rat αCGRP serum, or CGRP₈₋₃₇ into the pulmonary circulation of hypoxic rats for 4, 8, or 16 days, respectively. Ex. 2084, H681. Chronic infusion over days is not a reasonable approximation of how drugs are typically dosed in practice. Thus, a POSA would have understood Tjen-A-Looi to have little relevance for assessing potential side effects of the compounds administered.



Ex. 1305, ¶67; Reply, 11

Tjen-A-Looi (Ex. 2084) Observed a Stronger Pulmonary Arterial Pressure Increase with CGRP₈₋₃₇

CGRP and somatostatin modulate chronic hypoxic pulmonary hypertension

Transmission approximation of

STEPHANIE TJEN-A-LOOI, ROLF EKMAN, HOWARD LIPPTON JOHN CARY, AND INGEGERD KEITH

Department of Comparation Biocenness, School of Veterinary Medicine, and Department of Department of comparation of Wisconsin, Marinon, Wisconsin 53708; Department of Psychiatry Winting Ecology, University of Land, Land, Seeden; and Departments of Psychiatry and Neurochemistry, University of Land, Land, Seeden; and Departments of Internal Medicine and Pharmacology, Louisiana State University, New Orleans, Louisiana 70112

Tjen-A-Loui, Stephanie, Relf Ekman, Howard Lippton, John Cury, and Ingegerd Krith. CCRP and someto statis modulate channic hyperic pulmanary hypericosion. Am. J. Physiol. 263 (Heure Circ. Physiol. 22: 1969)-1960, 1992.— Choosic hypoxic gulmonary hypertension (PH), associated with increased polanosary esterial pressure (PPA) and right ventricular impertupity (RVH), correlates significantly with cofcitonia gene-related poptide (CGRP) and novementation (SOM) levels in long and blood. CGRP's tole in regulation of PPA in cheenic hypoxia and its potential interactions with SOM were investigated. CGRP, its antibudy (ab) and blocker. CGRP-(8-37), SOM-54, SOM-26, and SOM-sh, respectively. were infused into the pulmonery circulation of hypobaric by poxia nets for 4, 8, and 16 days. Thereafter, under personarbital sodium correthesis. PPA was measured in the right ventricle and main pulmonary artery. Cheosic CGNP influion presented PH at all times, whereas incommutatingtion and receptor block-ing encorbated PH. SDM-28 also exacerbated while SOM-16 and SOM-so decreased PRL RVR generally refrected the PPA. Radiointropassansy confirmed successful infusion of the peptides with regligible postize degradation in the pumps though est 16 days and showed complete immunonestralization of CGRP with its ab. Pautide levels in lung tissue suggest inhibition of CGHI* release by SOM-28 and increased plasma SOM with CGRP infusion. In vites pharmacological studies suggest that CGRP enems a measure confused considerately, contrascertific vasodilatory effect in the long which is independent of endothelium derived relaxing factor and does not involve ATP-dependent notamium charpels. We conclude that endogrous-CGSP plays an important role in palmonary pressure homeostasis during hypoxia, by directly diluting polinonery vescelature, thus annitorating the development of chronic hypoxic pulmentary hypertension in rate

extr; long tissue and blood peptide levels; indicinamentatory; pulmonary arterial pressure

CHRONIC HYPOXIC pulmonary hypertension (PH) is characterized by increased pulminary arterial pressure. The rise in pressure is based on vasoconstriction, accompanied by polycythemia (12) and structural remodoling. The structural changes include modial thickening of pulmonary arteries and arterioles, and hyporplasis of the constituent cells (46), almost invariably accompanied by right ventricular hypertrophy (RVH). Hypoxic ventilation not only causes pulmonary vasoconstriction but also enhances the pressor response to many constricter substances (1). Hyperia has also been shown to impair the spontaneous vasodilation that follows vasoconstriction caused by substances such as KCl and beadykinin (1).

In addition, PH can be smellorated by general agents including the \$-adrenoreceptor antagonist metioranolol (42), aspirin (25), diethylcarbamazine (40) via leuko-

triese inhibition, heparin sedium (26) via plan-rived growth factor inhibition, and hydrolasine (bradykinin (12) via pulmonary vasodilation.

The primorary neuroendocrine cell (PNEC) ble of responding to acute hypoxia with increacytosis of small membrane-bound vesicles (18) th tain the regulatory poptide calcitonin gene peptide (CCRP), a primorary vanodilator (35), peptide hormone localized to PNEC is some

The present study was designed to evaluate dispulmonary effects of the neuropoptides CG 80M to better understand the mechanism of duced by prolonged hypercia.

MATERIALS AND MICTHORS

Chronic infusion, Male Samo Sprague-Dunley to Galaxies required, make musto dependent takes as 200-g weight range were used for the experiments. Pap their antagonists were chronically infrared using in Alast ceractic meripence models (feed), 2001, and Alari camada mienerano medala (1902), 2001, and 20 periodo de 4, 8, md 16 days, sespectively. The pass chosen according to need for infrare twent from an enter of project and enter of project and enter of project and enter of the 2004 is required to higher efficiency (4 april 10 mil or 100 mil or soulded community in forcementation earlier (1 mil off) and with the infrared substance at an enter (1 mil off) and with the infrared substance at an enter (1 mil off) and with the infrared substance at an enter (1 mil off) and with the infrared substance at an enter (1 mil off). tion. Lyophilized antiscrem and normal rabbit ser Cappel no. 5012-1280) were reconstituted in dutill water and dikend in sterile salitat containing buckets sall, poptides and blacker were diluted in startle saller ing backtracks (I english). With the out under between arcethesia (1:20 regrisp ins, Fort Dodge/Haver), the it ein sus consulated with a PE-10 cuthster (ID 0.38 0.61 most fitted to a PE-68 calbester that was come subestancess Ainci carsotic minipussy pinced in the net the scapule. The PK-10 cutheter was aftered into the se-

for immediate delivery to the pulmonery crecibition via the right heart. The incision was closed with 3-0 silk sciures and rested with Neosparis centment (Peopera). After recovery (5 h post-suggery), the rate were placed uncentrained in cages in It is posturately, our rate were tracen incommitteen in came analysis room of commontal or in cages on a presence chamber with hypothetic hypothetic through the present presents. (80) must higher fractional conventionation of on, in analysing case, 10%, fortuna, 110%, of Wasserstein. The hypothechamber was operate code a day for feeding and decoing. Hypexin rate secrived one of the following infosione a CORP (not; Pesituals Laboratories no. 6006 and Backets Bioscience no. H-22001 at a rate of 10 ag-rat-1-k-1 ndirit anti-est « CGRP serom (Peninsula Laboratories no nellin ordreni errori errori (Perimoni l'ascentorio no. RAS-600NO et 0.25 pl.ne." (h."), CHRP blocker [CGRP-08 371] at 6 ng. ns. "h.", 80M-14 (Bachen, Bioseleire no. H-1490) et 20 sg. ns." (h."), 80M-28 (proteoatostorio, Buchen Riescience us. H-4850) at 2 ag-ret. 1-h 1, and rabbit anti-SOM serion (Iruntar ins. 20067) at 0.4 al rat 1. h 1. The

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CGRP antibody, infused into the pulmonary circulation, inactivated the endogenous circulating CGRP by immunoneutralization and enhanced the PPA by 22% at day 16. Furthermore, CGRP blocker, CGRP-(8-37), an inactive form of CGRP, prevented CGRP from binding to its receptor and eliminated the dilatory effect of endogenous CGRP, thus enhancing the PPA in hypoxia by 44%. These observations indicate that endogenous CGRP plays an important role in the homeostasis of PPA and, consequently, in PH.

Ex. 2084, H687; Ex. 1305, ¶68; Ex. 1306, ¶45; Reply, 11



CGRP Deletion Did Not Produce Safety Concerns



- (19) United States
- 62) Patent Application Publication (10) Pub. No.: US 2002/0162125 A1
 - (83) Pub. Date:
- (54) METHODS AND COMPOSITIONS FOR THE MODULATION OF NEUROGENIC INFLAMMATORY PAIN AND PHYSICAL OPIATE WITHDRAWAL
- (70) Investory: Anne-Marie Salmon, Paris (FR); Sasuma Sekino, Kanagawa (IP); Marino Picciotio, Guilford, CT (US); Jean-Pierre Changeau, Paris (FII)

Correspondence Address: Finnegon Handerson Facubese Garrett & Doorner 1300 I Street, N.W. Workington, DC 20005 (US)

10/091,127

Belated U.S. Application Bute

(90) Provisional application No. 60/273,349, filed on Mar.

Publication Classification

- (51) Int. Cl.⁷ ARIK 6TREE (52) U.S. CL 506(3; 500:10
- ABSTRACT

A method of successing for a compound that is an entagonist of calcitonin gene related poptide (of CGRP) is provided. The method comprises exposing a makent mouse to a compound. The pretent money has a genome that comprises a honorygous disruption of the of GSP gene, wherein the discaption results in the restner mouse lacking desectable levels of endogenous or XIRP as consumed to a wild type mouse. The resource of the motivat mouse to a nociceptive inducing stientus is determined. A difference in response compand to a wild type mouse is indicative of the compound functioning to alter of GRP activity. In a partiered embodiment, the disruption comprises the insertion of a transgene. A compound identified by the method is also nervaled. The compound is useful for antiforning negrogenic inflammatory pain audior physical opiate withdrawal

[0069] The targeting construct was performed from the CT/CGRP gene (15), and the chimera mice were obtained as described (15). α CGRP --- and +/+ mice are derived from backcrosses on the C57B16 strain after mating of heterozygous +/- mice. Homozygous mutant mice, from all generations, are healthy, fertile and do not present obvious abnormalities. The body temperature is the same in mutant and wild type mice, and no differences in the body weight of the two lines were observed during development.

Ex. 1027, ¶[0069]; Ex. 1306, ¶47; Reply, 12

- 8. The compound of claim 6, which is a monoclonal antibody.
- 9. A method for ameliorating neurogenic inflammatory pain comprising:

administering a compound capable of specifically inhibiting aCGRP activity to an animal having neurogenic inflammatory pain symptoms in an amount sufficient to inhibit the aCGRP activity in the animal so that symptoms of neurogenic inflammatory pain are ameliorated.



Ex. 1027, claims 8 & 9; Reply, 12

CGRP Deletion Did Not Produce Safety Concerns

Molecular and Cellular Neuroscience 14, 99–120 (1999). Article (Directe, 1999,0767, wavefable online at http://www.idealibrary.com.on $101b_b1^0$

MCN

Mice Lacking α-Calcitonin Gene-Related Peptide Exhibit Normal Cardiovascular Regulation and Neuromuscular Development

Jonathan T. Lu, *Young-Jin Son, † Jongho Lee, * Thomas L. Jetton, † Masakazu Shiota, † Lisa Moscoso, † Kevin D. Niswender, † Arthur D. Loewy, † Mark A. Magnuson, ‡ Joshua R. Sanes, † and Ronald B. Emeson* ‡

"Department of Plansmodings and "Department of Malecular Physiology and fliephysics, Vanderbild University School of Modeline, Nanhelle, Tanescuse 37222; and Unpartment of Austrony and Narondology, Windington University Malecular School, Sc. Louis, Missouri (3316)

ca-Calcitonin gene-related peptide (nCGRP) is a plelotropic poptide neuromodulator that is widely expressed throughout the central and peripheral nervous systems. CGRP has been implicated in a variety of physiological processes including peripheral vasodilation, cardiac acceleration, nicotinic acetylcholine receptor (AChR) synthesis and function, testicular descent, nociception, carbohydrate metabolism, gastrointestinal motility, neurogenic inflammation, and gastric acid secretion. To provide a better understanding of the physiological role(s) mediated by this peptide neurotransmitter, we have generated oCGRPnull mice by targeted modification in embryonic stem cells. Mice lacking oCGRP expression demonstrate no abvious phenotypic differences from their wild-type littermates. Detailed analysis of systemic cardiovascular function revealed no differences between control and mutant mice regarding heart rate and blood pressure under basal or exercise-induced conditions and subsequent to pharmacological manipulation. Characterization of neuromuscufar junction morphology including nicotinic receptor localization, terminal sprouting in response to denervation. developmental regulation of AChR subunit expression. and synapse elimination also revealed no differences in aCGRP-deficient animals. These results suggest that aCGRP is not required for the systemic regulation of cardiovascular hemodynamics or development of the neuremuscular junction.

INTRODUCTION

Calcitonin gene-related peptide (CGRP) is a 37-aminoacid neuropeptide produced via tissue-specific alternative splicing of the calcitantin/uCGRP primary RNA

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transcript (Amara et al., 1982, 1984; Rosenfeld et 198-0. While calcitonin neRNA production is limited to the C-cells of the thyroid gland, transcripts are widely expressed in discrete or throughout the central and peripheral nervous (Amora et al., 1982; Rosenfeld et al., 1983). In a human beings, posttranslational processing of min and CGRP proposionsones is predicted to the generation of six distinct peptides including nin and amino- and carboxyl-terminal poptides from the calcitonia prohormone. The oCGRP more is postranslationally modified to yield and N- and C-terminal peptides and biological a have been ascribed to all but the carbonyl-terminal of pro-CGRP (Burns et al., 1992). A second iso CGRP, referred to as \$4CGRP or CGRP II, is end a separate gene focus and has been shown to strate an overlapping but nonideotical pattern of sion throughout the nervous system (Amara et a

Based sipon its anatomical distribution and his ies, CGRP is thought to play important roles i nomic, somatosensory, integrative, and moor fu (Nawai et al., 1985; Riesse et al., 1992, 1995; Riosa al., 1985; Shofissch and Janobowitz, 1985a.lij. lines of evidence suggest that CGRP may partie the regulation of cardiovascular hemodynamics, immanoreactivity; has been focalized in almost all months of the company of the contraction o

organs involved in cardiovascular regulation, including peripheral perivascular nerves, epicardial arteries, and smoatrial and atriovenoricular nodes, as well as CNS regions vital for the regulation of cardiovascular homeo-

> Lilly Exhibit 1288 ES Lilly & Co. v. Teva Pharms, Int'l GMBH

cells. Mice lacking α CGRP expression demonstrate no obvious phenotypic differences from their wild-type littermates. Detailed analysis of systemic cardiovascular function revealed no differences between control and mutant mice regarding heart rate and blood pressure under basal or exercise-induced conditions and subsequent to pharmacological manipulation. Characterization of neuromuscu-

 α CGRP-deficient animals. These results suggest that α CGRP is not required for the systemic regulation of cardiovascular hemodynamics or development of the neuromuscular junction.

Ex. 1288, Abstract; Ex. 1306, ¶48; Reply, 12



Purported Safety Concerns Did Not Deter Researchers

Nucleic Acids Research, 2003, Vol. 32, N

Short bioactive Spiegelmers to migraine-associate calcitonin gene-related peptide rapidly identified to novel approach: Tailored-SELEX

Axel Vater, Florian Jarosch, Klaus Buchner and Sven Klussmann*

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Received August 7, 2000; Herried and Accepted September 10, 2000

ABSTRACT

We developed an integrated method to identify aptamers with only 10 fixed nucleotides through ligation and removal of primer binding sites within the systematic evolution of ligands by exponential enrichment (SELEX) process. This Tailored-SELEX approach was validated by identifying a Spiegelmer ('mirror-image aptamer') that inhibits the action of the migraine-associated target calcitonin generelated peptide 1 (cr-CGRP) with an ICso of 3 nM at 37°C in cell culture. Aptemers are oligonucleotide figands that can be generated to bind to targets with high affinity and specificity. Stabilized aptemers and Splegelmers have shown activity in vivo and may be used as therapeutios. Aptamers are isolated by an vitro selection from combinatorial nucleic acid fibraries that are composed at a central randomized region and additional fixed primer binding sites with -30-49 nt. The identified sequences are usually not short enough for efficient chemical Spiegelmer synthesis, post-SELEX stabilization of aptamers and economical production. If the terminal primer binding sites are part of the target recognizing domain, fruncation of aptamers has proven difficult and Inborious. Tailored-SELEX results in short sequences that can be tested more rapidly in biological systems. Currently, our identified CGRP binding Splegelmer serves as a lead compound for its vivia

INTRODUCTION

Since the invention of se eiter selection of oligonachotides from combinatorial nucleic acid fibraties, also known assystematic evolution of ligands by exponential enrichment (NELEX), the use of these melecules (sermed artument) as therapeuties, e.g. for the specific interruption of discuserelated protein postein interactions, has been predicted and aspired (1-3). Aptumers esselly shore binding constants to their respective postein or peptide targets in the same range as most receptor-ligand interactions and exte bit a high specificity (4-6).

In order to some aptament from the bench to several busifies bove to be taken. The most prominer the issues of aptomer subility in biological I perduction costs. Subdistation of optomers against nucleuses has been improved by the introduction of elmodified nucleic acid filtraries (pre-SELEX modif combination with post-SELEX modifications, that be the substitution of the RNA's 2'-Oil group (7-10). It strategy, chiral principles were introduced into th process in order to generate muchaine revision apto basis of r-RNA or r-DNA, so-called Spiegelmen-German 'Spiegel', recaving mirror) (11). Spiegemens an identified through in virus selection of an unusualit or ti-DNA library against the minor-image cos returnisomers of a drug target. The selected aptioner are then symbolized in their areasual enteriorneric ation as L-RNAs or L-DNAs. Following the rules of s these Spiegelmen bind to the sunsed target of intenthe uptimers bind to the mirror-image selection targe Aptamers with pre- and post-SELEX modifications Spiezelmen-have been reported to be stable for my biological fluids (11,14).

For both strategies, the ability to chemically syn fend condidates is critical, since neither post-SELEN apsatters ner Spiegelmers can be syntholized en due to the lack of appropriate encystes. However, and Spiegelmers that are identified through the SELEX process usually comprise 60-90 at, since typically selected from modeic acid fibraries with long randomized regions plus lived primer sites of on each side. Standard chemical objectionacteotide however, is only efficiently applicable up to 60 decreasing yields and escalating production enti-Incorporated base.

Therefore, the identified lead oligonaclootides non and experimental transation before they can be further tested in biological systems (15). Whether or not the to given feat agranter or Spiegelmer will eventu may not be insessers. The flutking fixed region puriscipate in forming the scalfold that surround interface and may then sex simply be omitted (2

enrichment (SELEX) process. This Tailored-SELEX approach was validated by identifying a Spiegelmer ('mirror-image aptamer') that inhibits the action of the migraine-associated target calcitonin generelated peptide 1 (α -CGRP) with an IC₅₀ of 3 nM at 37°C in cell culture. Aptamers are oligonucleotide ligands that can be generated to bind to targets with high affinity and specificity. Stabilized aptamers and Spiegelmers have shown activity in vivo and may be used as therapeutics. Aptamers are isolated by

In order to prove the efficiency of Tailored-SELEX, we carried out an *in vitro* selection approach against the optical antipode of the neuropeptide calcitonin gene-related peptide 1 $(\alpha$ -CGRP) of rat. α -CGRP has been recognized as a potent vasodilator and has recently attracted attention as a novel target in acute migraine treatment (19+22).

Wimalawansa, S.J. (1996) Calcitonin gene-related peptide and its receptors: molecular genetics, physiology, pathophysiology and therapeutic potentials. Endocr. Rev., 17, 533-585.

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The uniform wish to be known that, to their spirion, the time two authors should be approbable joint first Author-

Nucleic Acids Bawarch, Vol.31 No.21 & Oxford Enterries Press 2003: all rights reserved

Ex. 1082, Abstract, 2 (citing Wimalawansa as ref. 19);

Ex. 1306, ¶17; Reply, 9

Teva's Purported Safety Concerns Were Resolved by November 2005 (Ex. 2151)



Dr. Ferrari's cross-examination:

- Q: Exhibit 2151 does not study the effects of CGRP antagonism in healthy humans, correct?
- A: Correct.
- Q: And it doesn't study the effects of CGRP antagonism in migraine patients?
- A: Correct.
- Q: And, in fact, it doesn't study the effects of CGRP antagonism at all, correct?
- A: Correct.

Ex. 1303, 111:11-20; Ex. 2151; Reply, 13

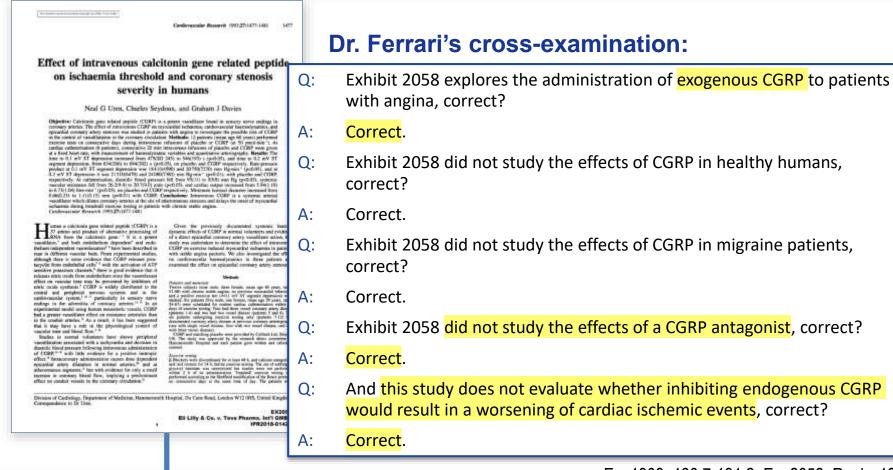
1990

1990 1995 2000 2005

Lilly

Ex. 1306, ¶¶22, 38; Reply, 8, 13

Teva's Purported Safety Concerns Were Resolved by November 2005 (Ex. 2058)



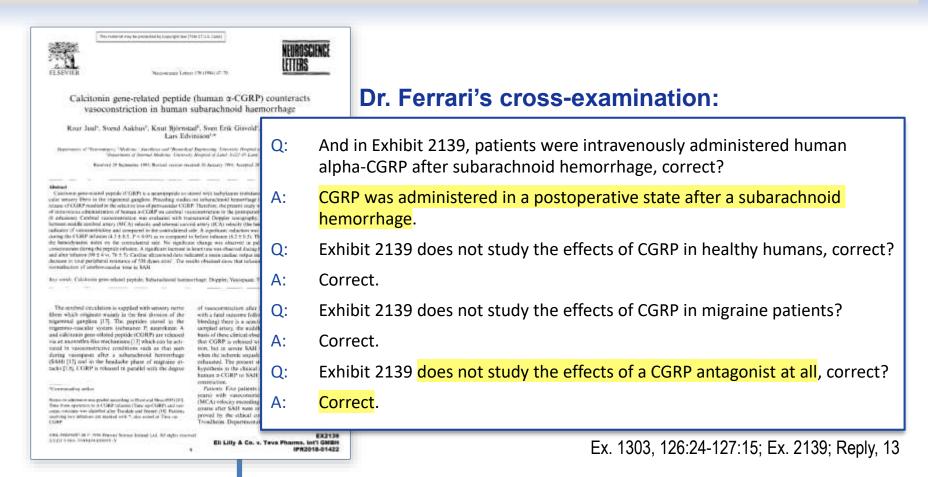
1993

Ex. 1303, 130:7-131:2; Ex. 2058; Reply, 13

1990 1995 2000 2005



Teva's Purported Safety Concerns Were Resolved by November 2005 (Ex. 2139)



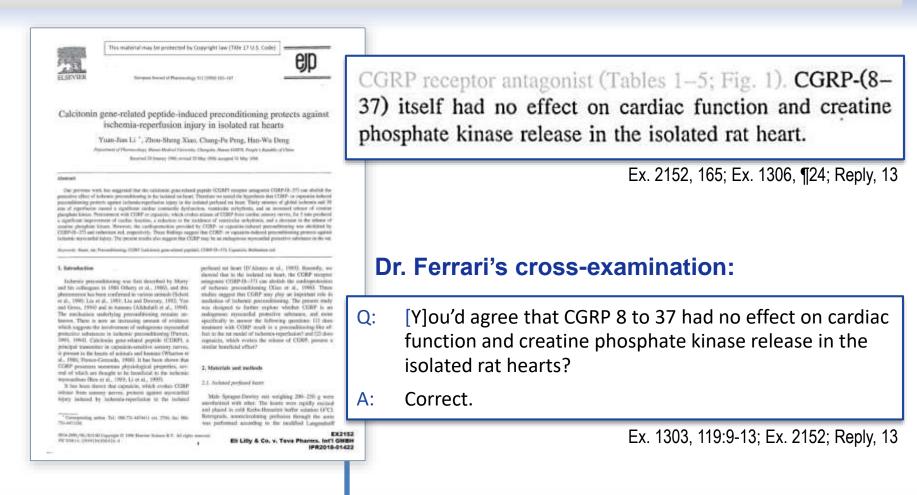
1994

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Ex. 1306, ¶¶21, 38; Reply, 8, 13

Teva's Purported Safety Concerns Were Resolved by November 2005 (Ex. 2152)



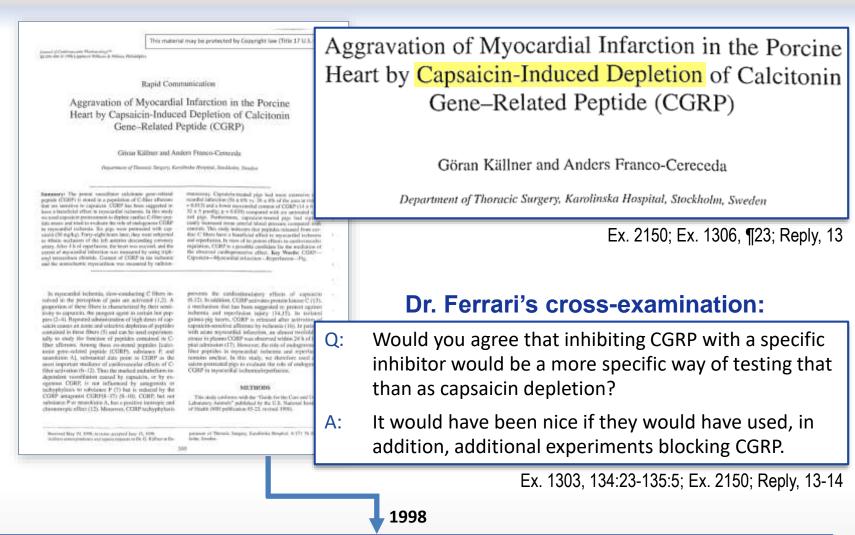
1996

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Lilly

Ex. 1306, ¶¶24, 38; Reply, 8, 13

Teva's Purported Safety Concerns Were Resolved by November 2005 (Ex. 2150)



1990 1995 2000 2005

Lilly

Ex. 1306, ¶¶23, 38; Reply, 8, 13-14

Teva's Purported Safety Concerns Were Resolved by November 2005 (Ex. 1283)

CGRP-antagonist CGRP(8-37), administered either locally by retroinfusion, or systemically by intravenous infusion, did not influence the postischaemic cardiac function or infarct size, which may suggest that locally released CGRP does not function as a cardioprotective agent in this experimental model.

Ex. 1283, 498; Ex. 1306, ¶27; Reply, 14



1998

1990 1995 2000 2005

Lilly

Ex. 1306, ¶¶27, 38; Reply, 8, 14

Teva's Purported Safety Concerns Were Resolved by November 2005 (Ex. 1284)

reduction of the infarct size. The cardioprotective effects of CGRP were blocked by the novel CGRP antagonist BIBN4096BS (20 nmol·kg⁻¹·h⁻¹). Although cardiac ischemia resulted in an almost 50 % increase in plasma CGRP levels in blood sampled from right cardiac ventriintravenous infusion of the CGRP antagonist BIBN4096BS before occlusion until the end of reperfusion had no statistically significant effect on the infarct size.

Ex. 1284, Abstract; Ex. 1306, ¶28; Reply, 14

DESCRIPTION AND PROMPTS FRANCISCO DESCRIPTION OF THE PERSON. Original Research Effects of calcitonin gene-related peptide and BIBN4096BS on myocardial ischemia in anesthetized ratu Day Mr. Will : Puter A. ray (WESTON). Rest N. (DOCON) : Continuousland Resetting. Backmann Resetting Planta N.J. Bidealogic birks. District Atlanta, Geometri Department of Phintage-theory, Academ. Made cal Cinery, Electronic of Americans, Molecules of Fig. 1703 AT Americans. The Americans-BBNANCE: research bilintains operation topay INTRODUCTION ADIC The configuration effect of extreme game-Calcolin greenhee populy (CDRF) is a lit arised popular (CORP) was innergood in an inchessor owner and popular that in professional could to make METRODS, belong-operated logary months smarry souther. It can be whereif from both not privated by if not hill mak coming acrey such. He could not positional acress of story require sim billhood by 40 min of experience a seminated. CORF-comming, more than have been alreaded on. The time-one sizes of very the west massed by designed the sentencester system, to execute a sing-2.1. 5-reptosylementary attends to deserving the lablood speaks, in particular the connects section, and fact are. Please maint phospetimes look and arried the simulate and attenuational water "" discrepant by proper of a possible ploughth-name (CSN) CCMF is a point visualitate popular and it even positive information and frameput effects in our and his most of the A that force stower to exact community polests Ex. A radiotestocology was used to describe plants CORP levels. RESELTS, Decreeous atlanta of tarriform activey in testand broker, peechs, and be-CCRO* () lessor kg *1-ts *7; KI man helion sucheaux secul the end of experience restored interes size by 20 % a . Their consump creation *** . Brushman, COSE appears to be a more power considere to the conditionness. 1.9. The reduction in select rise was accompared by persons also corporal with the large-feature cona Romani in concluming levels of senation phosphickinson. some "1". It passes with some represented reference. behavior of the same does of CORF consequency from the in street one list increase of places CGRP level mamet of imperfector until the and instead a 40 % is 3 %. oftenned states 24 is after tempted admission. This rise: rejection of the inferences. The coefficiences of the rate must from the sellen extrate of CCSO in response to of CURP new blocked by the royal CURP anagonal the reduction in respectful perfector """. CGSP tra-STENSONESS CELL MARKET THE TILL ARREST COMMIT been tened in periods with christic stallor sterios comed induction modes in an arrang W. W. premier or plants CORP involv in bland sumpled from right yaedlar neminbe commune after discuss. If was discuss to dilute commade articles, or the sale of affectmentals determine and asthe laterature relative of the COMP amagents thing the court of repeateds induces during exercise BSENSWERS before contains until the end of reportation ted on surerically egothesis office on the relact size. We previously reported on the first would reclause CONCLUSION: The prices study decreebed that wineter CORF assurem: Bibliograph, T. B. C. (R' - R') - N - 2-13 Senten (- 1.5 C Expedigel (d. from the Device of Street-Sept. Most Stad Mobile Compiperatus lawboost perest assess 1-1/11/1-2 discount-Married Barris, Phones, 1974, 1744 Companions or Most N 000000, 49 (c) holicograms (societ) a consider (4 t.1. 4 display) No of This beauty. He is that starts. part 13H i-planting in Epiperine character treat tree, and the heavings against on the forcest \$00000 (). Assigned \$100.00.00. which presents tigh affects and solutivity for furner CCRP employ 111. For the positive CCRP (Feg. car-

2001

1990 1995 2000 2005

Ex. 1306, ¶¶28, 38; Reply, 8, 14

Teva's Purported Safety Concerns Were Resolved by November 2005 (Ex. 1285)

90 minutes followed by reperfusion after 2 weeks of pacing. After 6 weeks of pacing, LV pressure (-11 \pm 6%), LV dP/dt (-53 \pm 5%), and mean arterial pressure (-15 \pm 4%) decreased (P < 0.01), while left atrial pressure (+19 \pm 3 mm Hg from 7 \pm 1 mm Hg) and heart rate (+53 \pm 16%) increased (P < 0.01). Infusion of the α -CGRP receptor antagonist \alpha - CGRP[8-37] (30 \text{ \text{ug/kg/min, iv}}, which blocked the exogenous α-CGRP challenge, did not affect any of these indices. Regional blood flow, as measured by the microsphere technique, in the nonischemic myocardium, as well as cerebral and renal vasculatures were unaltered during the infusion of α-CGRP[8-37]. Plasma concen-

unchanged after 6 weeks of pacing as compared with control. Thus,

we conclude that endogenous α-CGRP does not appear to play a major role in the regulation of cardiac and peripheral vascular dynamics in the late stage of heart failure.

Ex. 1285, Abstract; Ex. 1306, ¶29; Reply, 14

OWNERS G. ARTICLE

Effects of Inhibition of α-CGRP Receptors on Cardiac and Peripheral Vascular Dynamics in Conscious Dogs with Chronic Heart Failure

Your Tang Klain, MD; John J. Maffae, MS, Laurence K Haudt, DFM, Dockl B. Gillarns, DFM. Asseph J. Lynch Jr., PhD, Richard J. Hargrooves, PhD, Keyneth S. Kuhlan, PhD, Robert J. Goold, PhD, and Stefenie A. Kone, PhD

Abilitati. Warter endogeness cricinos generatas i pepate OCCUPY player a rate in basic failure to practice. Some diagn news toy pystake and nome, strict and sensing nine elebrary. Herefirement recordings and response in a CTARF chickings move obtained for bandons in the connection man. Exped puring 1740 features is one that included. The comment artest was excluded for 40 minutes followed by reperfusive after 2 weeks of parting. After 6 weeks of parting, 1.V premium; 1.1 in \$50, 1.V \$500 (1.0 After 6.0 recent artested processes (1/15 × 4%) decreased (A × 60%), while field according to the Linux High Rang Tu Linux High and flux in man (1/15). A 1974 il minerand JF - 1014, between of the se-CORF exceptor on tagement se-CORF file [16]. The large lagrants are large set to the control of the control completes representate, as well as applied and read coordinates are weathered during the refusion of a CEEP 8-11. Planta converse takens of CLEAP Point both provide and covering state tempto over analysis offer 1 matrix of provide as companied with county Than. or contribute that endingerous as A CRFF that not approximation or our role of the regulation of revitae and paradismit variable discussion. in the late stage of heart between

Key Wards: calciform gave releast populis, CORF, reyounded bland thes, regional bland flow, percelleparents, Serve Salam, 1,17

of Confessor Photocol 75 2803.02 639-6611

Report, indicated that a column properties of peptide (COMPER-17), the popular fragment antigonist of the COMP receptor, June and products regardinate effects in the cardional-

Nazarrač bi patikacio, koti 19, 2005 acaptur Bay 25, 2005. Piero Riccia Essecuti Lubermino, Wya Pape, Pomprismo.

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heart factors produced was more reverse floor floor induced by

atther rapid pacing alone or remotery untry cochasion and reperfession." It is conservable that in the presence of beyond

did reference produced by correspy artery outlesson, the sa-

dition of capit pacing would further increase the energy de-

must of the meanthrose representant, provide beyond the gendual, irreversible reportedable cell damage via the initial-

steed energy supply and demand. Thus, the current study should soften more closely the progression of severe heart fail

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hours, was abroated by the total stage of hours failure, blood

samples were collected directly from both coverage siturcard

To directly address this mean, the effects of a CORPA

in different frees those saider screenl, average conditions

Cardinne Plennen" + Italane 43, Nomen 5, November 2003

2003

1990 1995 2000 2005

Ex. 1306, ¶¶29, 38; Reply, 8, 14

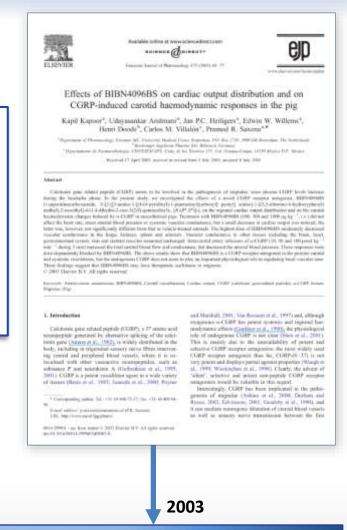


Teva's Purported Safety Concerns Were Resolved by November 2005 (Ex. 1318)

In conclusion, our study clearly demonstrates that BIBN4096BS is an effective antagonist at vascular CGRP receptors in anaesthetised pigs, but has little haemodynamic effects of its own, a finding that negates a major physiological role for CGRP in cardiovascular regulation. The potent blockade of the carotid haemodynamic effects of CGRP does suggest that BIBN4096BS may be effective in migraine treatment.

1995

Ex. 1318, 76; Ex. 1306, ¶30; Reply, 14





1990

2005

2000

Teva's Purported Safety Concerns Were Resolved by November 2005 (Ex. 1263)

But & David Photocopy & Serving 1991, 94, 311, 217 Effects of the Culcitonin Gene-Related Pentide (CGRP) Receptor Antagonist BIBN4096BS on a-CGRP-Induced Regional Haemodynamic Changes in Anaesthetised Rats Ellipseetine Arabusta' Shores P. Saberg, Jose S. G. Helippe, Street W. William, Science St. Hilland and France St. Streets'

of the antagonism produced by BIBN4096BS. Moreover, the fact that BIBN4096BS did not alter baseline haemodynamics suggests that endogenously produced CGRP does not play an important role in regulating the systemic and regional haemodynamics under resting conditions.

Ex. 1263, Abstract; Ex. 1306, ¶30; Reply, 14

In conclusion, the present investigation demonstrates that: (i) exogenously administered α -CGRP dilates several regional vascular beds in a dose-dependent manner; and (ii) endogenous CGRP does not play an important role in regulating systemic and regional haemodynamics.

Ex. 1263, 296; Ex. 1306, ¶30; Reply, 14

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reconstructions (Editoring of all 1900), a remaint that that it brights official by the concepts and animalizate On the basis of the above, the propose study set out to analyse to manufactured tree, the effects produced by solice scene) administrative of ROSS-6000E on 10 Employing trick has malponed to involges by the posterial tadisease his side effects; and GI for examp and regions

2004

1990 1995 2000 2005

Ex. 1306, ¶¶30, 38; Reply, 8, 14



Teva's Purported Safety Concerns Were Resolved by November 2005 (Ex. 1240)

Objective In an animal model of trigeminovascular activation and meningeal blood flow the inhibitory effect of a new high-affinity CGRP-binding RNA-Spiegelmer, which is a biostable aptamer composed of mirror-image nucleotides, was examined.

Results The Spiegelmer caused dose-dependent, significant inhibition of the evoked blood flow responses to about 50% of the control. Topical application was most effective. Basal blood flow and systemic arterial pressure were unchanged.

Ex. 1240, 923; Ex. 1306, ¶31; Reply, 9

Inhibition of savengenic blood flow increases in the rul trural duty mater by a CCRP-banding Springshow

had blackings", Makan Yeshnadi Alpana Dandari And Shari Beng Witche' is hive University Scotter of Residing is Arthodoxyching, Critically in University Samuring Commercial WO ECO (Samuri Al, Arthodoxyching)

Background Colinson generalized popular (COSF) for a maked conscionregions of CCDIF are found to jugader year Mined. semples during inagnitis attacks, CGMF interestd from prigorsind allower is the main rand below in the emitiges than and ten mangark that this dunye.

Objective in an autoral evolet of trigonomenously within tion and montioped blood flow the inhabiture office of a new Eigh-effinite CERF-brocking RNA-bytopilmer, which is a Noskills optioner composed of solvenizings epidothics, since

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Objective Migration attack with albeideous to reported to be not also the for implant. But we was ended to providing stead relative such patients

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Slaped either for tractal remarks as a stop retracement importune of Miscohalamin

Objective Although Vicense R., in Leaves to be effective the tennilgas, ner so greenti distratio. In the present study, we reasoned the gate trees of the efficient of Merchalastic in-

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Lilly Exhibit 1240, Page 1 of 1 Eli Lilly & Co. v. Teva Phanns. Int'l GMBH

2005

1990 1995 2000 2005

Ex. 1306, ¶¶31, 38; Reply, 8, 9

Researchers Praised "CGRP Antagonists" **Before November 2005**



Available online at www.sciencedirect.com







Review

Calcitonin gene-related peptide and its role in migraine pathophysiology

Udayasankar Arulmani^a, Antoinette MaassenVanDenBrink^a, Carlos M. Villalón^{c,b}, Pramod R. Saxena^{c,4}

*Department of Phiremic ology, Combinencedor Bassardi Sontons *COBERT, Environ MC, University Medical Contra Sontonion, PUA, Star 1758.

Acceptan 2000 ER. Flu Verharbank

*Departements de Termacobiologia. COVESSEF-PR. Cala. de los Essories 233. Col. Geogles-Capa. Missio D.F. 14330. Masio

Accepted 1 John 2804

CORC, a nearppeptide related from activated trigonisal seasony nervos, dijetos (structurial blood vessels and transmits vascular acciosption. Therefore, it is proposated that: (i) CGRP may have an important sole in enignine parkophysiology, and (ii) inhibition of trigominal CGIP release or CGIP-instaced cruzial vascilitation may abort migrator. In this regard, triptane americante migrator bradache presently by constricting the dilated control blood vessels and by intelliging the Figureinal CGRP release. In order to explore the potential sole of CGRP in express pathsphysiology, the wheest of a selective CGRP receptor amagement was obligatory. The introduction of sh-poptide attractigations in established migraine models that are professive of actionignmen activity here above that HIBNAPARM is a potent CORP program antagonist and that it has antiquigative potential. Indeed, a recordly published clinical study has reported that \$100,040085 is a flactive is coming some engages attacks without eignificant side offices. The present review will discous mainly the potential role of COMP in the strophysiology of migrains and the various treatment modulities that are currently available to target this strategyphide. C 2004 Election B.V. All rights reserved.

Newtot: Animpsins day; BBN49686; CORP; Myniss

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2	Calcin	onin gene-related poptide													 							398
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IPR2018-01422

ESE: Meprimenostratilg/Month

Lilly Exhibit 1031, Page 1 of 16

Dr. Saxena's statements in 2004:

faceted disorder. The encouraging results obtained in a "proof of concept" study with BIBN4096BS, administered i.v., in the acute treatment of migraine holds significant promise to suggest that orally effective CGRP receptor antagonists will become available in the not too distant future. An important advantage of CGRP antagonists over the triptans can be their use in patients with coronary artery disease. Moreover, migraine research is beginning to be focussed on the development of preventive medications and it would be worthwhile to explore whether inhibition of CGRP synthesis, release or its effects may reduce the frequency of migraine attacks. It is evident that further

Ex. 1031, 326; Ex. 1306, ¶39; Reply, 14-15



^{*} Consequending, endoor, Tel.: +56: 10:408: T5:30'47; fac: +56: 10:408: 94:56. E-mit aldere: provinsjenzenseral (FR, Senno.

Absolute Risk of TIAs in Migraine Patients Was Low

Teva's arguments in Sur-reply:

"[A] patient need not have a stroke or myocardial infarction for the concern over CGRP inhibition to be pertinent. A POSA would have been concerned with 'common' ischemic episodes, such as transient ischemic attacks (TIAs) and angina, expecting that long-term loss of CGRP's protective effect would lead to the development of more serious events, e.g., stroke or myocardial infarction."

Sur-reply, 20-21

Dr. Charles's testimony:

- O: Now, would you agree that 300,000 TIAs per year is a common incidence?
- Again, it depends on your definition of of 'common.' You know, if you compare that, A: for example, with the number of migraine attacks per year, it's relatively uncommon.

Ex. 2272, 67:3-9

Ex. 2272, 56:17-23

- Q: Okay. In your experience, do ischemic episodes occur frequently in healthy individuals?
- Again, I would have to say that it depends on the definition of ischemia, but . . . in this A: particular context, I would say no, that ischemic is not something that routinely occurs in healthy individuals.



Angina May Not Be Caused By Ischemia

Dr. Charles's testimony:

Q: Would you review angina as an ischemic episode?

A: No.

Q: Why not?

A: Because you can have angina that . . . isn't necessarily ischemic.

Ex. 2272, 55:9-16

Q: Okay. And I think I asked you earlier, but I'm going to ask you again. Is it your opinion that angina is a type of ischemic episode?

A: I think that angina is a clinical syndrome that can be caused by ischemia but may also occur as a consequence of other mechanisms.

Ex. 2272, 74:21-75:2



Tan 1995 (Ex. 1022) Shows MAb C4.19 Effective In Vivo

Dr. Charles's testimony:

Sand Street (1995), 88, 363-577 (French in Group Street).

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

Wash K. C. TAN, Morris J. BROWN, Richard J. HARGREAVESY, Sars L. SHEPHEARDS, Sepondi A. COOK? and Raymond G. HELL?

Direct Promocalogy Unit, University of Combridge Clinical School, Addendmole's Hispool, Controller, U.K., and 1 March Sharp and Dahme Research Laboratories, Neuroschool Research Gene, Harlow, Essex, U.K.

Stored Principles (ML screen) & August (ME)

 Chittonis gene-related peptide (CGRP) is localied in perivascular sensory neurons and is a petent unifilate. We irrestigated the utility of immunolischale as an in wise technique for probing the role of CGRP as an endogenous vasoditator.

3. The effects of an anti-CCRP mesocologial antibody SAN: code CA19: and its Full fragment on CRP-induced changes in blood present and skin food from new studied in periodiarbitonmentation of an Auditomic skin casofilization in to rat kind pain was measured by laser Doppler femants.

3. The fore-response relationship for the hypotensise dirt of intravenous rat of GHP (see GRP) was smilet; shilled rightward by MAE CA19 IgG legical intravenously, and Paly Brightser, Jegus; intravenously, The Corresion Tragenets of learn at GRP (hat GRP_{A-N}) also blacked the shitting of the Corresponding to the property of the Corresponding to the property of the property of the photonic effect of proCGRP.

5.50A CA19 Fab fragment [2] region; seriment); and haCGRP_{4, to} [100 mmlkg; intrament); but not MAL CA19 [pG (a) to Yingirat. Strenously) for instead missie Fab fragment Captas immeriously). Bocked the increased white had the response to areidromic stimulation of the spream areas.

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the county demonstrate the pharmacokowtic situating of Fab' fragment over 1gG for immuno-

Meckade studies de vive and support the role of CGRP in mediating skin vaco

INTRODUCTION

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[15] The hypotenties response to qualificate and evoquence GGP are markedy inhibited by het GGP, ... This embogrous GGP appear to be a stage memoranteristic that mechanic sensition and a stage memoranteristic that mechanic sensition in the rat. Het GGP, ... ration 50 the intrascense must have been found to indust the intrascense indeed the indused the indused the indused him below the memoral CGP, and opposite the proposition of the indused the indused him indused the indused with the indused him indused the indused of the indused him indused to the interest opposite the indused him indused to the indused him indused

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and a slightly longer (two-hour) duration before stimulation, a 16% block in increased blood flow was observed. (Ex. 1022, 569.) In the third study condition.

blood flow response. (Ex. 1022, 569.) But with a higher 3 mg dose of MAb C4.19

Ex. 1008, ¶57; Pet.,18; Reply, 20

Dr. Balthasar's testimony:

under the curve). Ex. 1022, 569. When further nerve stimulation was performed

at two hours after a 3 mg/rat antibody dose was administered, a 16% improvement

in AUC compared with baseline was observed. Ex. 1022, 569. A POSA would

Ex. 1305, ¶25; Pet.,18; Reply, 20

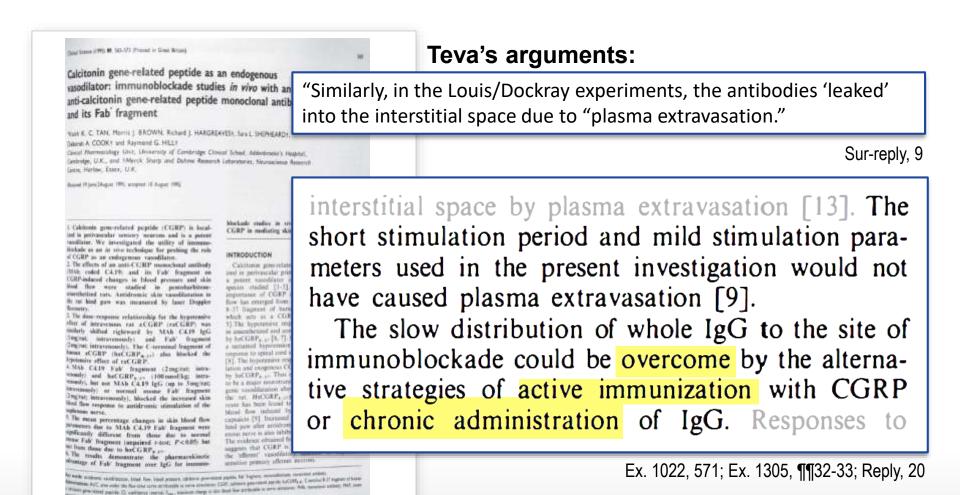
Dr. Tomlinson's testimony:

- Q: And so you would agree that trends can be seen in the absence of statistical significance, correct?
- A: Trends are trends.

Lilly

Ex. 1301, 165:6-9; Reply, 20

Tan 1995 Offers Express Guidance to Improve Immunoblockade





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Tan 1995: MAb C4.19 "Clearly Diffuses" to the Site of Action

Teva's assertion:

"But the art shows that in a carcass (a crude mix of leftover body parts), 'assignment of a site, or sites, of antibody localization was not possible.' Thus, Lilly fails to show that a full-length antibody would distribute into interstitial spaces with additional time."

Sur-reply, 8

Dr. Balthasar's testimony:

carcass. Ex. 1247, 3969, 3972. A POSA would have understood that the rat carcass evaluated in Covell includes the muscular tissues remaining after the other organs have been removed, and thus would have included hind leg muscles and tissues where the rat saphenous nerve is located. Ex. 1022, 567 (describing the saphenous nerve as located in the "right hind limb"), 571 (noting that the carcass "includ[es] muscle and skin"). Accordingly, the carcass tissue data of Covell approximates what a POSA would have expected for antibody distribution times in Tan's rat saphenous nerve assay.



Ex. 1305, ¶27; Reply, 20

Tan's Guidance to Improve Immunoblockade Is Consistent with Well-Known Pharmacokinetic Principles

Teva's arguments:

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"But the art shows that in a carcass (a crude mix of leftover body parts), 'assignment of a site, or sites, of antibody localization was not possible.' Thus, Lilly fails to show that a full-length antibody would distribute into interstitial spaces with additional time."

Sur-reply, 8

Not K. C. TAN, Morris J. BROWN, Richard J. HARGREAVER, San L. SHEPHEARCH Dearth A. COOK! and Raymond G. HLLS Carel Phornacology (Art. University of Combridge Clinical School, Additional Centrality, U.K., and 19Myck Shorp and Deline Research Lateratories, 5 (post, Horbos, Essex, U.K., Based If JimcTAgan 195, suspend 16 August 195)

 Calcinum power-related poptide (CGRP) is localied in printenestar sensory nearons and in a potent station. We investigated the utility of immunolicitate as an in-row rechnique for probing the role of CGRP as an embagration varieditate.

2. The effects of an artis's CLRP musus/mail autilities 19th; colds CA19; and its Fab' fragment as CRP-induced changes is blood pressure and skin food flow were statisted in persubarbitionaustricitied rats. Amidomosis skin vasofilization in the six bind gave was measured by laser Doppler Benutry.

3. The slaw response relationship for the hypotronics that of hetrocenses and a CGRP (not GRP) was makely shifted right-and by MAB CA19 IgG Tegratic intracensority) and Fab frequents Tegratic intracensority. The Cereminal Gragment of Issues (CGRP (het GRP_{A-1})) also blocked the Impositive shifted of a CGGRP.

4-MA CA19 Fab frequent (2 mg/rat) introsoully and het GRP₂. (100 mm/lkg intromedy, hat not MAO CA19 IgG may 6 Sug/rat strummely, not moread means Fab fragment Tagrat, strumment), Mocked the necessar shat had fee response to arridromic stimulation of the sphene means.

5. The mean percentage changes in this blood flow actournes due to MAb C4.19 Eas' fragment were opticately different from those due to normal flow Fab' fragment (sepaired 1-6-5), P<0.05 Set to flow these due to baCGRP_{2,2}.

The results demonstrate the pharmacekinetic risunage of Fab' fragment over 1gG for immuni-

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[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 lgG. Moreover, the steady-state interstitial to plasma concentration ratio in the carcass was 0.86 for Fab' fragments compared with 0.18 for whole lgG.

Attempts were made in the present study to improve the likelihood of success with IgG by increasing the dose 3-fold and doubling the time allowed for antibody distribution. The data of



Ex. 1022, 571; Ex. 1305, ¶¶26-29; Reply, 20

Tan 1995: MAb C4.19 "Clearly Diffuses" to the Site of Action

Dr. Balthasar's testimony:

...what Covell did, which at the time was a major advance, is develop a A: physiologically based model of antibody disposition. And that's why this paper is so well-known in the field. And as part of the work that was done, they considered sites of antibody disposition, so tissues for antibody distribution to that were represented. And these tissues, then, were broken down into subspaces that were physiologically relevant for those tissues, including capillary plasma, interstitial spaces, and cell associated spaces. And they used this theoretical mathematical framework, which is called a physiologically based model, to describe antibody disposition with time in these different regions within the tissues. So it's a combination of use of experimental and theoretical work to be able to predict and understand disposition in different spaces. And it really, again, is the basis for an entire field of physiologically based modeling in antibody pharmacokinetics.

Ex. 2273, 94:5-95:6



Tan 1994 Would Inform Potential Effects of Anti-CGRP Antagonist Antibodies *In Vivo*

Dr. Balthasar's testimony:

- Q: For example, the tissue bath experiment with the vas deferens, it didn't have a vascular endothelial layer, correct?
- A: I don't know that that's correct. I think that probably the tissue section would include, you know, sections of vascular endothelial. The way I would picture it is it's a chunk of tissue.

Ex. 2273, 78:14-21

- Q: And that 1994, the Tan 1994 tissue bath study doesn't represent a synapse?
- A: Are you saying that there is not synapses within the tissue preparation?
- Q: I think that's what I'm saying.
- A: My expectation would be that there would be neuromuscular junctions and synapses present within the tissue preparation.

Ex. 2273, 79:11-20

- Q: Now, it's fair to say that you wouldn't consider the in vitro experiment or tissue bath experiment of Tan 1994 to be representative of what would occur when administering an antibody to a whole animal?
- A: Yeah, I think it's a demonstration of activity that where the findings would be helpful in informing or understanding or predicting potential effects of in vivo, but as the in vitro system, it's not exactly equivalent to an in vivo system.



Other Anti-CGRP Antagonist Antibody Studies Had Established In Vivo Effectiveness (Exs. 1048-1050)

Dr. Charles's testimony:

own anti-CGRP antagonist antibodies). For example, Louis and colleagues used active immunization and demonstrated that anti-CGRP antagonist antibodies can effectively inhibit CGRP-induced inflammation *in vivo*. (Ex. 1048, 257.) Louis

1048, 259.) Later, Dockray and colleagues used the same technique and further confirmed that the amount of anti-CGRP antagonist antibodies in antisera correlated with protection against extravasation. (Ex. 1049, 258-59, 261-62.)

51. Another publication by Louis confirmed the antagonistic effects of passive immunization using a rabbit polyclonal antiserum to CGRP. (Ex. 1050, 582.) The administration of the antiserum significantly blocked CGRP-induced

Lilly

Ex. 1008, ¶¶50, 51; Pet. 11

A POSA Would Have Been Motivated to Make Anti-CGRP Antibodies with the Claimed Affinities

Dr. Balthasar's testimony:

αCGRP. Ex. 2226, ¶104-107. I disagree. RIA assays were often designed to

allow appropriate assessment of the affinity of an unlabeled ligand with the use of

a radiolabeled tracer that is structurally different from the ligand of interest.

Ex. 1327, ¶73; Reply (IPR2018-01426), 18-19

Source	pK_i/pK_d	Comments	References
Human			
CL/RAMP1 (293 EBNA cells)	10.74	pK_i	30
CL/RAMP1 (Cos 7 cells)	10.05	pK_d	10
SK-N-MC (CL/RAMP1)	10.35	pK_d	41
	10.8	pK_i	13
	11.4	pK_i	14
Rat			
CL/RAMP1 (293 EBNA cells)	8.8	pK_i	30
Brain	8.8	pK_i	
Spleen	8.5	pK_i	13
Marmoset			
Cortex	10.2	pK_d	41
	10.2	pK_i	
Total brain	9.9	pK_d	
	10.4	pK_i	
Dura mater	10.3	pK_d	
Spleen	9.7	pK_A	
	10.0	pK_i	



Ex. 2068, 35-37; Ex. 1327, ¶74; Reply (IPR2018-01426), 18-19

A POSA Would Have Been Motivated to Make Anti-CGRP Antibodies with the Claimed Affinities

Teva's arguments:

"Lilly is wrong because the art teaches a disconnect between binding and activity: the anti-CGRP antibody MAb R1.50 'clearly showed the greatest [binding] activity' among the tested antibodies to rat α CGRP, yet it 'blocked rat α CGRP poorly. Thus, Lilly's argument that 'single-digit nM affinities are typically obtained as a 'general rule' is amiss with regard to anti-CGRP antibodies."

1 Monoclonal antibodies (MAbs) against rat a-calcitonin gene-related peptide (arCGRP) were produced. Those which bound CGRP in a radioinmanneassay and inhibited the brinding of 2-1 to Jodonisats[s] "-CGRP in a receptor binding assay were selected for immunoblockade experiments."

- 2. The effect of MAbs on CGRP inhibition of electrically stimulated contractions of the rat soluted van deference was chiracterized. Four out of 11 MAbs tested shifted the consentration-response curve of CGRP to the right compared with white or irrelevant MAb control. MAb C4 to produced equipment blockade of rat xCGRP and cat gCGRP and was shown for further studies. MAb C4 10 produced equipment produced to the rate xCGRP and cat gCGRP and was shown for further studies. MAb C4 10 had no pharmacologically significant effect on the concentration-response relationship of sopremaline, rat F-endopphin or somnatoration.
- 3. We demonstrated that the pharmacological response to CGFP in the presence of MAb C4.19 could be predicted when the dissociation constant and concentration of binding sites of the antibody ever known. Comparison of experimental and computer simulated data showed good agreement for EC_w and maximum effect of CGFP in the presence of MAb C4.19.
- 4 Capsaicin at LμM inhibited the electrically stimulated contractions by 6 interval 518% to 693%). This effect was significantly attenuated by MAb confidence interval 15.2% to 36.8%, P<0.00031.</p>
- 5 The immunoblockade of exogenous and endogenous CGRP described he lementary evidence from other studies, strongly suggest that CGRP has a mujor the neuroeffector junction of the rat vas deferens.

Keywords: Calcitonin gene-related peptide; monoclonal antibodies, rat isolated van deferei sion, capsuicin

stroduction

Calcitonin gene-related peptide (CGRP) is produced by alternative processing of the primary mRNA transcripts of the calcitonin gene (Rosenfide et al., 1983). A second CGRP gene encoding another 37-amin caid peptide was subsequently identified (Amaia et al., 1985). Steaheshey he et al., 1983). This peptide (RCGRP) youlve one amino and at position 53 in the rat. Unlike calcitonin, CGRP is grimarly) localized in the brain and peripheral nervous tissue. Diverse boological effects have been attributed to CGRP but its physiological importance remains to be established in many organ systems. The localization of CGRP-like immunoroactivity in primary afferent tearnors innervating many different issues and the wide distribution of CGRP brinding sites suggest that CGRP may be a physiologically important encorassmitter.

may be a physiotogically important neurocoadisticate.

One important criterion that must be fulfilled for any neuronal contrainment in that modulation of the effects of the exceptions patient enurorizamenter by drugs should have corresponding effects on response to never the corresponding effects on response to never through the new of appoint proportion and produce and fragments of CGRP have been demonstrated to behave an exception antagonists (Mineualt et al., 1991). The Cereminal (8–37) fragment of human a CGRP has been well characterized and in commercially available. However, CGRP (8–37) demonstrates variable antagonistic potency in different issues and it a retainvely poor antagonist in the rat isolated vas deferrent preparation (Demnis et al., 1990). This has led to the postulation that multiple exceptor subtypes sent for

Author for correspondence

CGRP. An alternative up ade is the use of antibod biological activities of p Immunoblockade may be clucidation of the physiol no assumptions base to b plicity and the relative se

The major objective of I the role of CORP as a penuroeffector junction of model for neutronamistic GRP from nerves was saidin. Capazionis is the put the genus Capacions what ulation of primary affere 1991). It has been widely investigate the "efferent" ones (reviewed by Maga capacion-seniority serves) and the activation of capacion-seniority serves the training of the control of the control of the capacity of the control of the capacity of th

tides in often difficult because of the co-release of several neuropeptides by capasien in many tissues. In particular, tachykimus co-released with GGRP often produce a similar biological response (e.g. dilatation of arteries). In the eletrically stimulated isolated vas deferens, neurokima A and supstance P enhance constructions (Moritoki n nl., 1987) in

Sur-reply (IPR2018-01426), 24

MAbs tested, including MAb C4.19, C4.6 and R2.73 described above, shifted the concentration-response curve of CGRP to the right compared with vehicle or irrelevant MAb control. 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 which clearly showed the greatest activity in these assays and in the ELISA. Although raised in mice immunized with rat

Ex. 1021, 707; Ex. 1327, ¶72; Reply (IPR2018-01426), 18



A POSA Would Have Been Motivated to Make Anti-CGRP Antibodies with the Claimed Affinities

Dr. Balthasar testimony:

For example, Tan 1994, Tan 1995, and Wong performed *in vitro* and *in vivo* testing with their anti-CGRP antagonist antibodies at 37°C and successfully confirmed their biological activity at that temperature. Ex. 1021, 705 (conducting tissue bath experiment at 37°C); Ex. 1022, 567 (conducting blood pressure experiment in animals at a body temperature of 37°C); Ex. 1033, 98 (disclosing that antibody 4901 was selected based on its ability to bind at 37°C); Ex. 1033, 97 (conducting blood pressure experiment in animals at a body temperature of 36-37°C). Therefore, a POSA would have understood that using a temperature of 37°C did not adversely affect the beneficial properties of these prior art anti-CGRP antagonist antibodies.

Lilly

Ex. 1327, ¶77; Reply (IPR2018-01426), 18; see also Ex. 1013, ¶124 (Pet. (IPR2018-01426), 38-39)

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

Dr. Tomlinson's cross-examination:

- Q: And so can you identify for me the half-life value that would be suitable or unsuitable for antibody fragments within the scope of Claim 1?
- A: I think it's you know, having worked at Domantis for, whatever, six, seven years, I think it's pretty clear that an unformatted antibody fragment is not going to be effective as a human therapeutic against that target. I think that's obvious to anyone who works in the field or worked in that field at the time.

Ex. 1301, 134:14-25; Reply, 23



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

Dr. Tomlinson's cross-examination:

- Q: You would agree that there's about a five[-]thousand[]fold difference between fremanezumab's binding affinity of 2.2 picomolar and the upper end of claimed range 10 nanomolar?
- A: Ten divided by 0.0022, yeah, 5,000.
- Q: And you would agree that Claim 1 of the '211 patent also covers humanized anti-CGRP antagonist antibodies having femtomolar binding affinities [below] the 2.2 picomolar affinity of fremanezumab?
- A: Yes.
- Q: Well, you cite two antibodies, correct?
- A: Yes.
- Q: And one has an affinity of 2.2 picomolar and the other has an affinity of 31 picomolar, correct?
- A: Yes.
- Q: And those do not cover or represent the full range of affinities covered by the 211 patent's claimed range extending up to 10 nanomolar, correct?
- A: No. They're just two antibodies within that range.



Ex. 1301, 102:10-22, 104:7-19; Reply, 22-23

Teva Failed to Establish Unexpected Results

Brief Communication

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

Objective.—To review the efficacy of naratriptan as preventive treatment in 27 patients with chronic migraine refractory to other commonly used preventive therapies.

Background.—The treatment of chronic migraine often poses a major challenge to the clinician. Even when given expert care, patients with chronic migraine may continue to have daily or near-daily headaches.

Methods.—Clinical records and headache calendars were reviewed of 27 patients fulfilling the following inclusion criteria: (1) aged 18 to 65 years; (2) diagnosis of chronic migraine (formerly transformed migraine), ac-

cording to the criteria proposed by Silberstein et al. (3) previous failure of at least 4 seribed as part of a management program that included nonpharmacological measu acute care medication, and detoxification from overused medication; and (4) have at less than 2 consecutive months. The dose of naratriptan prescribed was 2.5 mg twice of lowing outcomes: (1) frequency of headache, (2) intensity of paln. (3) number of days ache, (4) headache index (frequency times intensity), and (5) proportion of patients pattern of pain after 6 months of treatment.

Results.—There was a staffstically significant reduction in the frequency of he days versus 24.1 days at baseline, P<001), 6 months (9.1 days, P<001), and 1 year (treatment with maratriptan was initiated. There was also a statistically significant reducer of the severe pain at 1 month (5.6 days versus 12.5 days at baseline, P<0.01), and 1 year (2.6 days, P<0.01), a finitally, there was a staffstithe headache index at 2 months (33 versus 56.4 at baseline, P<0.001), 6 months (19.5 P<0.001).

Of the 26 patients who continued to use naratriptan daily for at least 6 months, sodic pattern of pain (migraine). At 1 year, 11 (55%) still continued to experience q lapsed to chronic migraine, and 2 (10%) were lost to follow-up. No patients had into ing the treatment period, and no one stopped treatment due to adverse events.

Conclusion.—Naratriptan may have a role in the preventive treatment of intrac spective, controlled studies should be considered.

Key words: chronic migraine, chronic daily headache, transformed migraine, narati prophylactic treatment

Abbreviations: CDH chronic daily headache, CM chronic migraine (Headache, 2003;43:482-489)

From the Department of Neurology, Columbia University College of Physicians and Surgoons, New York, NY (Dr. Rapoport). The New England Center for Headache, Stanforth, Coun (Drs. Rapoport, Bigal, Sheftell, and Tepper); the Department of Neurology, Albert Einstein College of Mediciae. Broux, NY (Dr. Bigal); the Department of Neurology, University of Anticquia, Medelin, Colombia (Dr. Noley); and Primario Unita Operativa di Neurologia e Neurofisiopatologia, A. O. G. Rummo, Beneventa, Italy (Dr. Feleppa).

Address all correspondence to Dr. Alan M. Rapoport, 778 Long Ridge Road, Stanford, CT 96902.

Accepted for publication December 29, 2002.

482

Teva's arguments:

"Studies have confirmed that Ajovy® reduces incidences of MOH, a phenomenon nothing in the prior art suggested."

POR. 54

Dr. Rapoport's statements in 2003:

ment. Fourth, some of the patients stopped overusing acute care medication during the study, and at least a portion of the benefit they received reasonably could be attributed to analgesic discontinuation rather than naratriptan alone. Finally, since some patients were

Ex. 1294, 487; Ex. 1306, ¶¶88-89; Reply, 26



Teva's Purported Evidence of Commercial Success Does Not Support Patentability



Pain Point Med. Sys., Inc. v. Blephex, LLC, IPR2016-01670, Paper 44 at 19-21 (PTAB Feb. 28, 2018)

"Although these exhibits indicate some circumstantial evidence of sales, and a potential market for the BlephEx device, what Patent Owner has not produced is any substantial evidence of market share."

Reply, 26-27

Teva's arguments:

"Third-party investment analysts, Leerink Transformation Partners, have forecasted that the migraine antibody market will break the blockbuster barrier by 2025 and that the entire class of drugs will be worth \$4.5 billion by 2022, and a staggering \$6.9 billion by 2025. EX2085, 2-3."

POR, 55-56; Reply, 26-27



Dr. Charles (Tan 1995)

Teva's assertion:

the unreliability of Tan's results. EX2191, 118:12-119:1; POR. 3. Dr. Charles—a clear outlier among the experts—testified that C4.19 "showed a 16% reduction in skin blood flow" in a saphenous nerve assay. EX1008, ¶122; POR, 15. But given Dr. Charles' gross mischaracterization of prior art in these proceedings (EX2192, 182:21-183:12; 154:18-20), his opinion must be given little weight. POR, 3-4.

Sur-reply, 6-7

Tan 1995 (Ex. 1022):

n=4) after 60 min (Fig. 5a). Further nerve stimulation performed at 2h after 3 mg/rat MAb produced an AUC which was slightly smaller compared with baseline stimulation, but not by more than 16% (n=2).

Ex. 1022, 569; Ex. 1008, ¶57; Pet., 17-18

Dr. Vasserot's testimony:

may be "14 times more rapid for Fab' fragments than for whole IgG.")) But with a longer period between treatment and nerve stimulation and a higher dose, a 16% block in increased blood flow was observed. (Id.) In view of these results, Tan

Ex. 1009, ¶77; Reply, 20

Dr. Balthasar's testimony:

Fab' fragment significantly blocked the effects of CGRP. Ex. 1022, 569, 570. The full-length antibody significantly blocked the hypotensive effects of exogenous CGRP in rats and showed 16% reduction in skin blood flow in the rat saphenous nerve assay under the experimental conditions used. Ex. 1022, 569, 570. Tan's in

Ex. 1305, ¶22; Reply, 20



Dr. Charles (Wimalawansa)

Teva's assertion:

**Wimalawansa states that humanized anti-CGRP antibodies 'should' be developed

and used." EX1008, §62. But Wimalawansa says nothing of the sort, instead

POR, 4

Wimalawansa (Ex. 1096):

disease. The role of CGRP antagonists and humanized monoclonal antibodies should be explored with respect to control of pain and inflammation, type II diabetes, and in conditions with intractable hypotension, such as septic shock syndrome.

Ex. 1096, 570; Ex. 1008, ¶74; Pet., 19; Reply, 2

Dr. Charles's testimony:

for diseases associated with CGRP, (Ex. 1096, 567.) Wimalawansa concludes that humanized anti-CGRP antagonist antibodies "should be explored" for a variety of clinical conditions. (Ex. 1096, 570.)

Ex. 1008, ¶74; Pet., 19



Dr. Charles (Olesen)

Teva's assertion:

533: EX1025, 1108: EX1042, 647: EX2272, 83:22-84:13. What is more. Olesen specifically warned against relying on its study for cardiovascular safety: "our data base was too small for us to assess cardiovascular safety." EX1025, 1109; POR, 27; EX2212, ¶22. Dr. Charles blatantly ignored this warning

(EX1306, ¶34), but Dr. Balthasar confirmed that Olesen's statement is consistent

Sur-reply, 16

Dr. Charles's testimony:

34. 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. 2212, ¶22.) 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. 1306, ¶34; Reply, 7

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. 1306, ¶40; Reply, 8

Dr. Charles (Triptans)

Teva's assertion:

EX1306, ¶44 But triptans' mechanism of action and pharmacokinetics differ from that of antibodies and Dr. Charles has not explained the basis for equating the two classes of molecules. Moreover, because triptans were used as a treatment for acute migraine, physicians would not have been concerned with triptans' long-term effects. EX2212, ¶21; EX1031, 322; EX1040, 176. Even then, the

Sur-reply, 17-18

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. 1306, ¶12; Reply, 7



Dr. Charles (CGRP-Binding Aptamer)

Teva's assertion:

short half-life—"hours to days," not "weeks"—and would not have been informative on the safety of long-acting antibodies. EX1309, Abstract; EX2272, 114:6-115:5. Second, aptamers are not "analogs to antibodies," as Lilly simplistically argues. Reply, 9. Aptamers "bridge the gap between small molecules."

Sur-reply, 18

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, 9

Dr. Charles's testimony:

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.)

Ex. 1306, ¶17; Reply, 9

Dr. Balthasar's testimony:

requiring only weekly or biweekly dosing. Ex. 1309, 231. Indeed, 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").

Ex. 1305, ¶51; Reply, 9



Dr. Charles (Purported Safety Concerns)

Teva's assertion:

2901. Any increase in the incidence or severity of, e.g., TIAs, would have been a very serious concern. Dr. Charles ignores such concerns, and he has offered no rebuttal to Dr. Ferrari's testimony about the likelihood that CGRP inhibition would worsen common ischemic episodes in migraineurs.

Sur-reply, 21

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. 1306, ¶19; Reply, 13



Dr. Charles (Purported Safety Concerns)

Teva's assertion:

Even Lilly's EX1284 demonstrates CGRP's cardioprotective role: CGRP reduced infarct size in an ischemia rat model by up to 89%, while BIBN4096BS blocked "[t]he cardioprotective effect of CGRP." EX1284, 591-592, Figure 3.

Notably, Lilly omitted this unfavorable information, and its expert refused to even acknowledge it as "germane" during cross-examination. EX2272, 20:1-21:3.

Sur-reply, 11

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. 1306, ¶28; Reply, 13-14



Dr. Charles (Purported Safety Concerns)

Teva's assertion:

Even Lilly's EX1284 demonstrates CGRP's cardioprotective role: CGRP reduced infarct size in an ischemia rat model by up to 89%, while BIBN4096BS blocked "[t]he cardioprotective effect of CGRP." EX1284, 591-592, Figure 3.

Notably, Lilly omitted this unfavorable information, and its expert refused to even

acknowledge it as "germane" during cross-examination. EX2272, 20:1-21:3.

Sur-reply, 11

Dr. Charles's testimony:

- Q: Now, you didn't mention that outcome in your declaration, correct?
- A: I did not because it was not germane to the point that I was actually making.
- Q: And the point that you were making was that in 2001, Wu and colleagues showed that endogenous CGRP did not affect myocardial infarcts?
- A: Yes.

Ex. 2272, 20:16-23



Dr. Charles (Risk of Stroke/MI in Migraine Patients)

Teva's assertion:

8 Revealing his bias, Dr. Charles even refused to acknowledge that "angina"

is an ischemic event. EX2272, 55:9-11. The art says otherwise. EX2212, §32:

Sur-reply, 20 n.8

Dr. Charles's testimony:

Q: Would you review angina as an ischemic episode?

A: No.

Q: Why not?

A: Because you can have angina . . . that isn't necessarily ischemic.

Ex. 2272, 55:9-16

Q: Okay. And I think I asked you earlier, but I'm going to ask you again. Is it your opinion that angina is a type of ischemic episode?

A: I think that angina is a clinical syndrome that can be caused by ischemia but may also occur as a consequence of other mechanisms.

Ex. 2272, 74:21-75:2



Dr. Charles (Spare Receptor Theory)

Teva's assertion:

Lilly and Dr. Charles ignore the relevance of receptor reserve and argue that one would need to antagonize "only elevated or inappropriate levels of CGRP" to effectively treat migraine, there is no evidence in the record that supports this conclusion. Reply, 17 (emphasis in the original); EX1306, \$67.

Sur-reply, 22

Dr. Charles's testimony:

67. 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"); Ex. 1008, ¶¶36-45.)

Ex. 1306, ¶67; Reply, 17

attacks. (Ex. 1043, 185; Ex. 1044, 48, 52-53.) Researchers also reported that following effective treatment of migraine attacks (i.e., with sumatriptan), the elevated CGRP levels returned to normal. (Ex. 1044, 48, 52-53.) Meanwhile,

Ex. 1008, ¶38; Pet., 10



Dr. Charles (Cross-Reactivity)

Teva's assertion:

As for Dr. Charles' belated testimony on cross-reactivity, all he now does is state—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." EX1306, ¶71; Reply, 18. Dr. Charles misses the point: one cannot equate receptor and ligand antagonism without considering the differences between the two. EX2230, ¶83.

Sur-reply, 23

Dr. Charles's testimony:

72. 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+RAMP I	AM-1: CALCRL+RAMP2 AM-2: CALCRL+RAMP3
Transduction pathway	G_dG_g	G_r	G_{i}/G_{ij}	G _i .
Selective agonists	Human CT	AMY	tr-CGRP	AM
Selective antagonists	***	***	BIBN4096BS (+++) SB-273779 (+)	AMn22-52
Potency	Salmon CT2humun CT2AMY, CGRP>AM	Salmon CT≥AMY≥ CGRP>human CT>AM	CGRP>AM2 AMY2salmon CT	AM-1: AM>CGRP> AMY>salmon CT AM-2: AM>CGRP> AMY>salmon CT

(Ex. 2059, Table 1 (highlighting added); Ex. 2230, ¶34.) 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. 1306, ¶¶72, 74; Reply, 18

Dr. Vasserot (Motivation)

Teva's assertion:

unravel. As Lilly's expert Dr. Vasserot admitted, a POSA would have needed to see much more in the way of safety and efficacy beyond what Tan disclosed before having any meaningful reason to embark on the costly and burdensome endeavor

to humanize a murine anti-CGRP antibody. EX2191 65:2-71:19, 75:4-13; 97:15-

106:19. This is exactly what Wimalawansa, Lilly's second primary reference, says:

POR, 7

Dr. Vasserot's testimony:

- Q: So AME is the type of company that would take Tan 1994, humanize Tan's antibody, and take it to clinic?
- A: We have done worse than that.
- Q: You have done worse than that. What have you done that's worse than that?
- A: We have started projects with less data than that.

Ex. 2191:99:8-100:1; Reply, 5



Teva's Experts - Dr. Ferrari

Dr. Ferrari's testimony:

of my research, I am an author on over 450 peer reviewed publications. My research efforts have included investigation of the possibility of therapeutically targeting the CGRP signaling pathway, including developing and conducting clinical trials of therapeutics targeting the CGRP pathway. These efforts began in the early 2000's.

Ex. 2212, ¶6

below), including practical experience in conducting clinical trials. In particular, I played an instrumental role in the clinical design and testing of BIBN4096BS for its efficacy and safety in treating acute migraine. Earlier, I also played an instrumental role in the clinical design and testing of the class of drugs known as triptans for their use in treating acute migraine starting in the late 1980's.

Ex. 2212, ¶11

Teva's arguments:

not prior to 2005. EX1301, 55:1-13. Similarly disingenuous is Lilly's allegation that "Teva's experts conceded that a POSA would have found it appropriate to use humanized antibodies throughout drug development, including binding assays, in vitro testing, and animal studies." Reply, 5-6. The transcripts illuminate the truth:

- Dr. Tomlinson stated that a POSA would have humanized an antibody to be tested *only* when "[g]iven sufficient motivation to do so
 which at the time wasn't the case," for CGRP. EX1301, 204:4-15;
- Dr. Ferrari admitted that he is "not an expert in [the drug development] field." EX1303, 54:25-55:6;

Sur-reply, 7



Teva's Experts – Dr. Ferrari

Dr. Ferrari's testimony:

CGRP is one of the most potent microvascular vasodilator substances identified to date, and a POSA would have expected that sequestering CGRP risked causing deleterious side effects on the vascular system via prevention of CGRP-mediated vasodilation to rescue viable penumbra tissue in cardiac and cerebral ischemic events. This concern would have been particularly problematic for anti-CGRP

Ex. 2212, ¶12

Dr. Ferrari's statements in 2005:

quent 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. 1306, ¶40; Reply, 8



Teva's Experts - Dr. Ferrari (Olesen)

Dr. Ferrari's testimony:

events" were observed. EX2015, 1104. However, Olesen also cautioned that their study did not assess whether BIBN4096BS has any "vasoconstrictor properties" because "[its] data base was too small," and therefore Olesen could not conclude whether BIBN4096BS was different from the triptans in that regard. EX1025, 1109. Further, Olesen infused BIBN4096BS once for only 10 minutes, which is

Ex. 2212, ¶22

Dr. Ferrari's statements in 2005:

leagues 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 head-ache 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. 1306, ¶40; Reply, 8



Teva's Experts – Dr. Ferrari (Lassen)

Dr. Ferrari's testimony:

65. Dr. Charles also asserts that the Lassen publication's results "led to the conclusion that 'CGRP antagonism' was a therapeutic principle for treating migraine." EX1022, ¶62. I disagree with this characterization of Lassen because, as with Tan 1995, the Lassen publication would not have provided a clinician with an expectation that an anti-CGRP antibody could be of clinical use. Lassen observed that administering CGRP causes "migraine-like" symptoms in migraineurs. EX1047, 59. But a POSA would have understood that this data does not prove that CGRP has a physiological role in migraine, and a study of how CGRP functions (such as Lassen) does not provide an understanding of what would happen if CGRP activity were blocked. This distinction is important

Ex. 2212, ¶65

Dr. Ferrari's statements in 2005:

Calcitonin gene-related peptide antagonists

In patients with migraine, CGRP levels are elevated. CGRP infusion can trigger a migraine attack and triptans block the release of CGRP [22] 24]. Therefore, CGRP antagonists may be effective in the treatment of acute migraine. Olesen and col-

Lassen LH, Haderslev PA, Jacobsen VB, Iversen HK, Sperling B, Olesen J, CGRP may play a causative role in migraine.

Cephalalgia 22, 54–61 (2002)

Ex. 1290, 657; Ex. 1306, ¶40; Reply, 8



Teva's Experts – Dr. Ferrari (Tan)

Dr. Ferrari's testimony:

CGRP receptor antaponism. 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. 2212, ¶70

Dr. Tan's statements:

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 I have suggested several therapeutic targets for CGRP blockade, including inflammation and migraine. Conversely, CGRP itself may be beneficial in

Ex. 1287, 247; Reply, 3, 11-12



Teva's Experts - Dr. Ferrari (Wong)

Dr. Ferrari's testimony:

- 51. A number of publications also disclosed their findings, in studies of CGRP function in rats, that administering an anti-CGRP antibody leads to an increase in blood pressure:
- Wong 1993: in testing a new anti-CGRP antibody, Wong 1993 noted that administering that antibody to rats "completely blocked the intravenous rat α-CGRP-induced decrease in blood pressure and increase in heart rate in rats." EX1033, 102.

Ex. 2212, ¶51

Wong (Ex. 1033):

Effects on the Cardiovascular System. Intravenous injection of rat α -CGRP decreased MAP and increased heart rate (Table 2). Intravenous injection of non purified CGRP monoclonal antibody (25 mg/kg) 30 min before that of rat α -CGRP (0.8 μ g/kg) completely inhibited the cardiovascular effects of the peptide (Table 2). The monoclonal antibody had no significant effect on MAP and heart rate (n=6).

Treatment ³	MAP (△ mm Hg)	HR (△ beats/min)
α-CGRP	-17 ± 3	25 ± 5
Saline + α-CGRP	-22 ± 3	24 ± 7
a-CGRP	-20 ± 6	18 ± 4
CGRP Ab + α-CGRP	0	2 ± 2**

Ex. 1033, 101; Ex. 1306, ¶43; Reply, 12



Teva's Experts - Dr. Rapoport (Olesen)

Dr. Charles's testimony:

recurrence. (Ex. 1025, 1108.) In view of these clinical results on the migrainerecurrence endpoint, Olesen established that blocking the CGRP pathway was an equally viable therapeutic target for both preventative migraine applications and acute migraine treatment.

Ex. 1008, ¶43; Pet., 10

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. 1306, ¶40; Reply, 8



Teva's Experts – Dr. Rapoport (MOH)

Dr. Rapoport's testimony:

69. 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. 2235, ¶69

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. 1306, ¶¶88-89; Reply, 26

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

Ex. 1294, 487; Ex. 1306, ¶¶88-89; Reply, 26

Dr. Rapoport's cross-examination:

- Q: So as of 2005, a person of ordinary skill in the art would have known that triptans inhibit the release of CGRP, correct?
- A: Anybody reading that article [published in 1999] would have.

Ex. 1304, 90:10-15; Reply, 7



Motion to Strike



Exhibit 1287 and Related Sections of Lilly's Reply

Teva's arguments in POR:

And even if Tan 1995's antibody is the antibody that Lilly argues a POSA would have had a reason to humanize—to be sure, a POSA would not—there is no evidence of record explaining why a POSA would have (1) begun with Tan 1995, which is a basic research paper studying vasodilation in rats, particularly where Lilly's articulated motivation is *therapeutic* (not scientific) and (2) looked to modify a CGRP antibody by humanization, rather than one of the solutions posed by the other references Lilly cites. EX2224, ¶79-101; EX2230, ¶50. Indeed, the question remains: why would a POSA have started with Tan 1995, a reference that was published 10 years prior to the earliest priority date of the '614 patent?

Scientists from Merek were authors on Tan 1995, yet neither they nor Merek as a company were investigating anti-CGRP antibodies during this 10-year period.

EX2212, ¶324, 70, 76. The time-gap speaks volumes, but Lilly has chosen not to

POR, 45 (citing Ferrari's declaration Ex. 2212, ¶¶24, 70, 76)

Lilly's reply:

Teva incorrectly attempts to undermine Tan's disclosures by characterizing it as a "basic research paper" and citing purported personal knowledge of its authors.

Ex. 2212 ¶70; POR, 45. 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 investigated and used as "therapeutic agents" for migraine and other diseases.

Ex. 1287, 247 (similarly discussing human anti-CGRP MAbs as an "exciting possibility" for administration "in man"). Dr. Tan's contemporaneous statements were written with first-hand knowledge of the blood pressure results focused on by Teva and directly contradict Teva's litigation-driven position.

Reply, 11-12; Opposition to Motion to Strike, 2



Exhibit 1287 and Related Sections of Lilly's Reply

Dr. Ferrari's testimony:

70. 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 2005, that interest would have directed that POSA to CGRP receptor antagonism. 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 phenomenon, and were not vet in the general consciousness of those of us pursuing clinical neurology research.

Ex. 2212, ¶70; POR, 45

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, 3, 11-12; Opposition to Motion to Strike, 2



Exhibit 1287 and Related Sections of Lilly's Reply

Dr. Foord's testimony:

77. As stated above, the purpose of Tan 1995 was simply "to investigate immunoblockade as an alternative strategy for probing the role of CGRP as a vasodilator *in vivo*." EX1022, 566. Because Tan 1995 is only studying the role CGRP plays in vasodilation in an experimental animal, a POSA would have understood that Tan 1995 was not studying whether a CGRP antibody could be safely used for human clinical purposes. As such, and as would be expected in this type of study, Tan 1995 does not consider adverse events or side effects caused by the anti-CGRP antibody. This includes the effect of the antibody on the animal over a longer period of administration. Side effects were unimportant to Tan 1995 as the rats were likely sacrificed after the experiment, and the side effects were not relevant to confirming their basic science hypothesis—that CGRP mediates vasodilation in a whole animal.

79. The almost instant increase in mean arterial pressure after administration of Fab' or full-length antibody suggests that both are exerting an effect by binding CGRP in the systemic circulation (since the saphenous nerve assay was ineffective for a full-length antibody). A POSA would have understood that an anti-CGRP antibody would have a systemic vascular effect, leading to adverse consequences, well before it might have any local anti-CGRP effect (as in the saphenous nerve assay) for any therapeutic benefit, e.g., treating migraine.

Lilly's reply:

Ex. 2212 ¶70; POR, 45. 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 investigated and used as "therapeutic agents" for migraine and other diseases. Ex. 1287, 247 (similarly discussing *human* anti-CGRP MAbs as an "exciting possibility" for administration "in man"). Dr. Tan's contemporaneous statements were written with first-hand knowledge of the blood pressure results focused on by Teva and directly contradict Teva's litigation-driven position.

Reply, 11-12; Opposition to Motion to Strike, 3

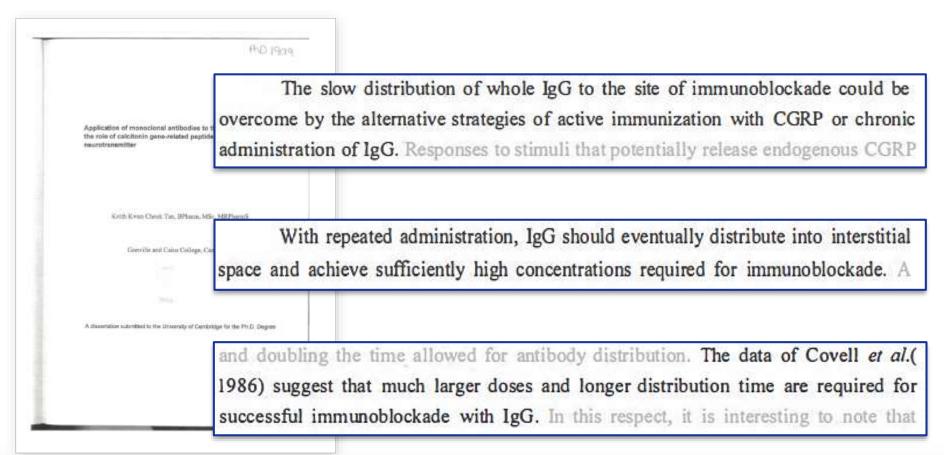


Ex. 2230, ¶¶77, 79; POR, 24

Motion to Exclude



Exhibit 1287 Is Admissible



Ex. 1287, 222-23; Opp. Mot. Excl., 2-3



Exhibit 1287 Is Admissible

Carney's declaration:

 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.

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_ALMA2142964848000
3606 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/primoexplore/sourceRecord?vid=44CAM_PROD&docId=44CAM_ALMA21429648480 003606 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

