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Petitioners,

v.

NOVARTIS AG,

Patent Owner.

Case IPR2017-00854[1]

U.S. Patent No. 9,187,405

PATENT OWNER NOVARTIS'S CORRECTED ORAL HEARING DEMONSTRATIVES

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[1] Cases IPR2017-01550, IPR2017-01946, and IPR2017-01929 have been joined with this proceeding.

Apotex Inc., et al.

Petitioners

v.

Novartis AG.

Patent Owner

Case IPR2017-00854[1]

Patent US 9,187,405

Patent Owner's Demonstrative Exhibits

May 11, 2018

[1] Cases IPR2017-01550, IPR2017-01946, and IPR2017-01929 have been joined with this proceeding.

Introduction

- Prior animal and human studies showed 1.0 mg and higher needed for any efficacy in humans. [1]
- Novel EAE experiments revealed new biomarker and that much lower doses could treat RRMS.[2]
- MS physicians and at least one MS treatment hospital doubted 0.5 mg would have efficacy. [3]
- In Phase III trials, 0.5 mg surprisingly had efficacy in RRMS, unexpectedly reaching as much efficacy as 1.25 mg. [4]
- '405 Patent claims 0.5 mg fingolimod daily to treat aspects of RRMS. [5]
- Hindsight by Petitioners' less qualified experts cannot outweigh copious contemporaneous evidence. [6]

[1] Paper 26 at 1-2, 11-12, 39; [2] *Id.* at 20-25; [3] *Id.* at 25-27, 40-41;
[4] *Id.* at 3, 25-27; [5] Ex. 1001, cls. 1-6 ; [6] Paper 26 at 42-46; Paper 63 at 12-14.

U.S. Patent No. 9,187,405

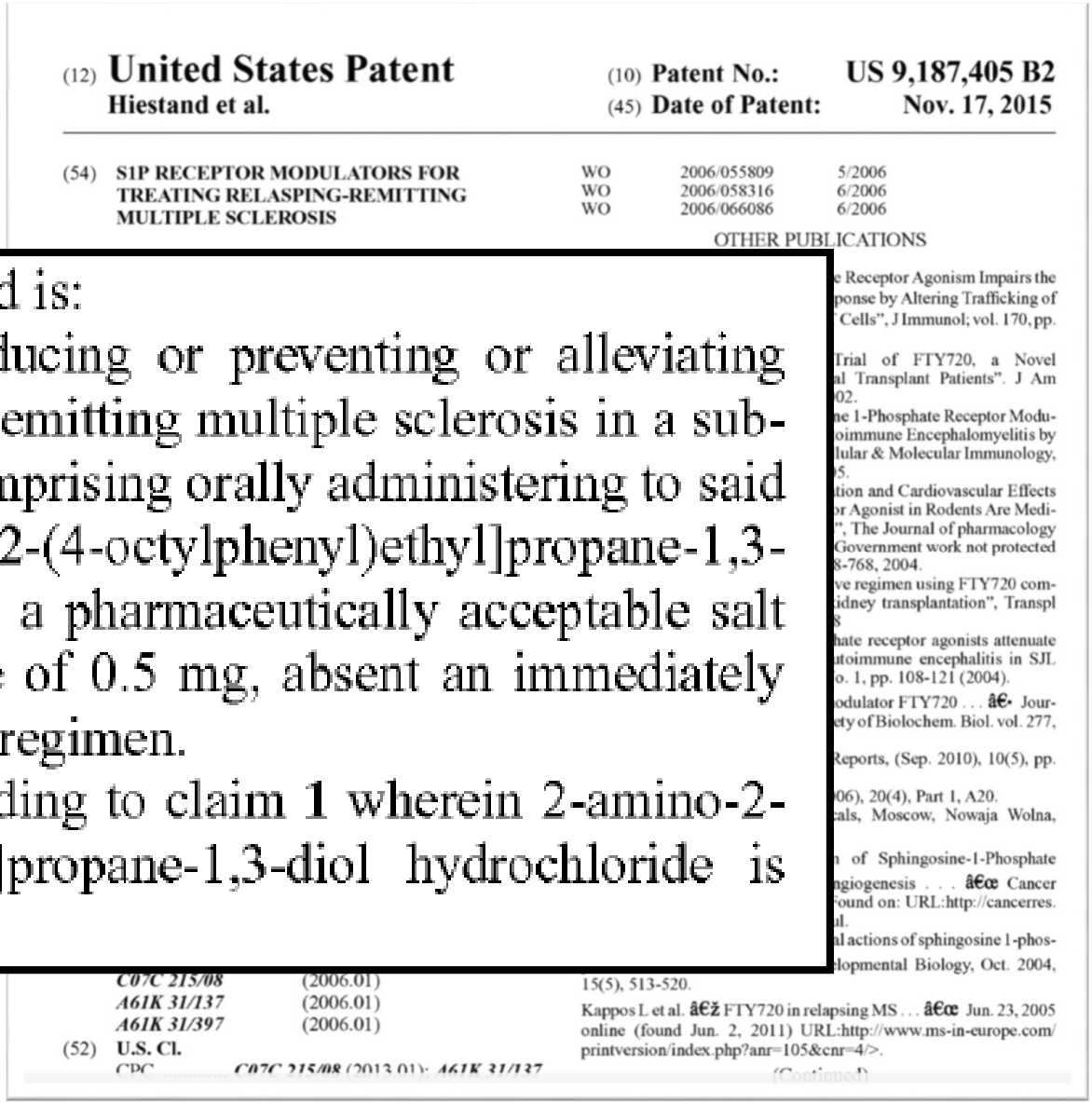
The ’405 Patent

Representative Claims of the ’405 Patent

The invention claimed is:

1. A method for reducing or preventing or alleviating relapses in Relapsing-Remitting multiple sclerosis in a subject in need thereof, comprising orally administering to said subject 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol, in free form or in a pharmaceutically acceptable salt form, at a daily dosage of 0.5 mg, absent an immediately preceding loading dose regimen.

2. The method according to claim 1 wherein 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol hydrochloride is administered.



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

(10) **Patent No.: US 9,187,405 B2**
(45) **Date of Patent: Nov. 17, 2015**

(54) **S1P RECEPTOR MODULATORS FOR TREATING RELASPING-REMITTING MULTIPLE SCLEROSIS**

WO 2006/055809 5/2006
WO 2006/058316 6/2006
WO 2006/066086 6/2006

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e Receptor Agonism Impairs the ponse by Altering Trafficking of Cells", J Immunol; vol. 170, pp.

Trial of FTY720, a Novel al Transplant Patients". J Am 02.

he 1-Phosphate Receptor Modu- oimmune Encephalomyelitis by llular & Molecular Immunology, 5.

tion and Cardiovascular Effects or Agonist in Rodents Are Medi- ", The Journal of pharmacology Government work not protected 8-768, 2004.

ve regimen using FTY720 com- idney transplantation", Transpl 8

hate receptor agonists attenuate utoimmune encephalitis in SJL o. 1, pp. 108-121 (2004).

odulator FTY720 . . . â€· Jour- ety of Biolochem. Biol. vol. 277,

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06), 20(4), Part 1, A20. als, Moscow, Nowaja Wolna,

of Sphingosine-1-Phosphate ngiogenesis . . . â€œ Cancer found on: URL:http://cancerres. l.

al actions of sphingosine 1-phos- elopmental Biology, Oct. 2004, 15(5), 513-520.

Kappos L et al. â€ž FTY720 in relapsing MS . . . â€œ Jun. 23, 2005 online (found Jun. 2, 2011) URL:http://www.ms-in-europe.com/printversion/index.php?anr=105&cnr=4/>.

C07C 215/08 (2006.01)
A61K 31/137 (2006.01)
A61K 31/397 (2006.01)

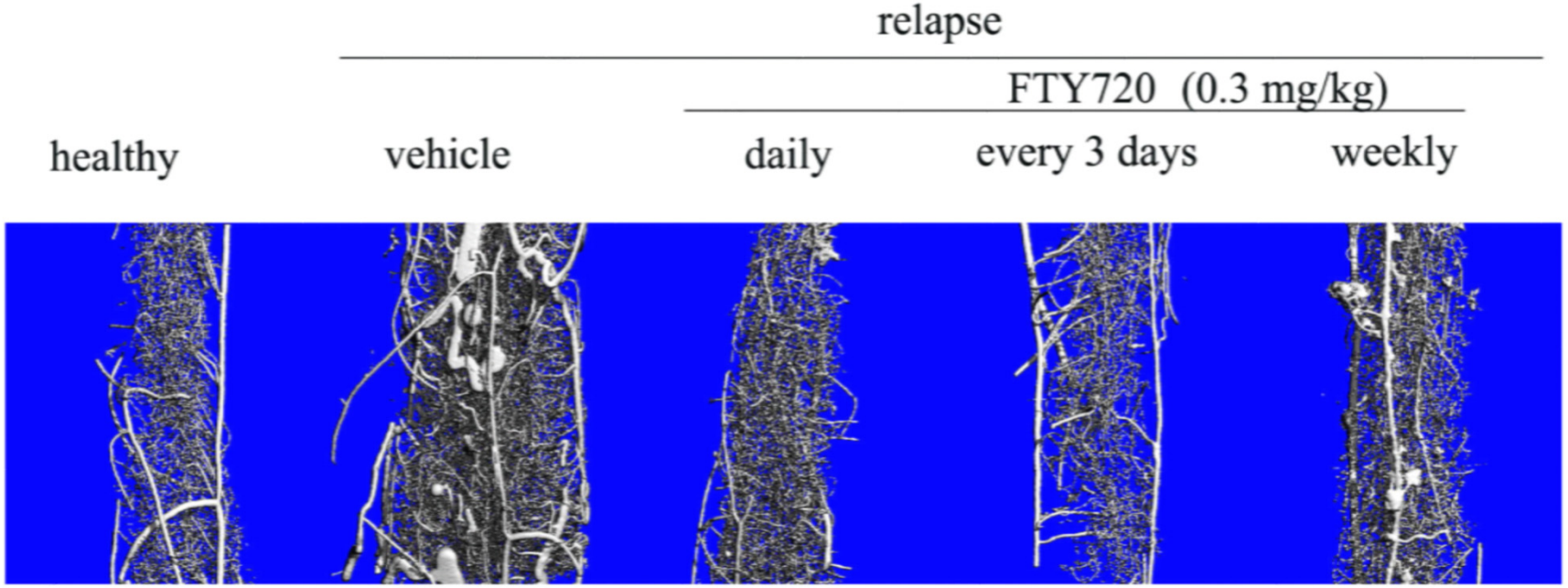
(52) **U.S. Cl.**
CPC ... *C07C 215/08* (2013.01); *A61K 31/137*

(Continued)

Ex. 1001 at cls. 1-2.

Inventors Discovered New Efficacy Biomarker

Figure 3-5 **FTY720 reduces the increased vascular density during EAE relapse.**

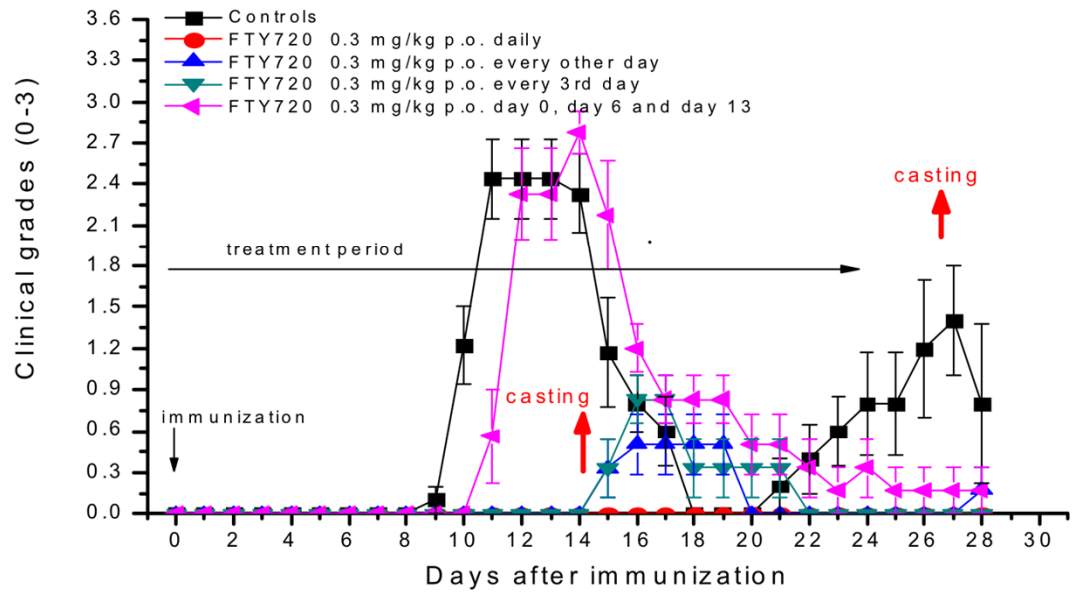


- "…the inventors were able to show…that the inhibition of angiogenesis was positively correlated with clinical efficacy in EAE." Dr. Steinman, Ex. 2022 at ¶107.

Ex. 2026 at 24; Ex. 2057 at 16; Ex. 2022 (Dr. Steinman) at ¶¶ 101-108; Ex. 2024 (Dr. Jusko) at ¶¶ 101-107.

Inventors' New Focus on Relapse Stage of MS

Figure 3-2 **Effects of various treatment schedules of FTY720 on the acute and relapse phase EAE in the Lewis rat.**

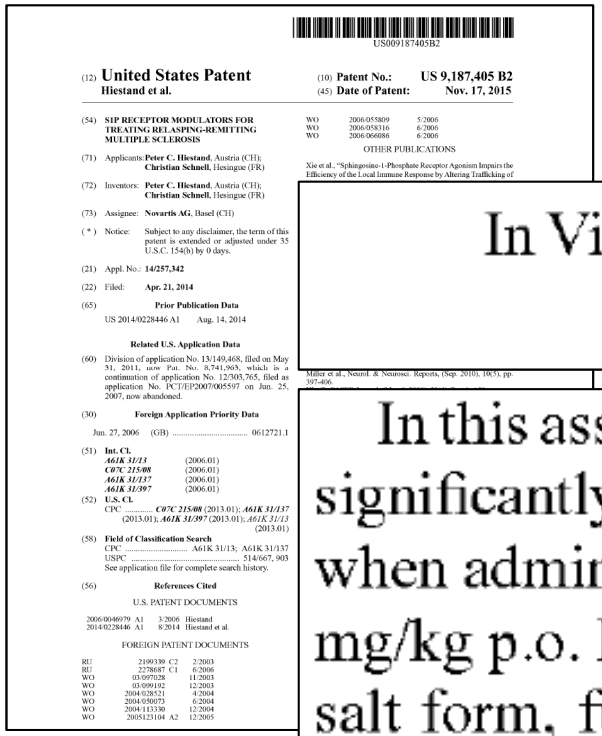


"[I]f [the inventors] had focused on the first attack like the authors in Webb and other EAE studies, they too may not have discovered that such low doses had a clinical effect. That shift in perspective appears to underpin the invention here." (Dr. Steinman, Ex. 2022 at ¶ 96.)

"The inventors' insight in focusing on later relapses in the assessment of whether a dose could be useful translates directly into how MS medicines are actually used." (Dr. Steinman, Ex. 2022 at ¶ 103.)

Ex. 2026 at 23; Ex. 2057 at 14; and Ex. 2022 (Dr. Steinman) at ¶¶101-108; Dr. Jusko, Ex. 2024, ¶¶101-107.

Unexpected Results in EAE Animal Model of MS



US009187405B2

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

(10) **Patent No.: US 9,187,405 B2**
(45) **Date of Patent: Nov. 17, 2015**

(54) **SIP RECEPTOR MODULATORS FOR TREATING RELASPING-REMITTING MULTIPLE SCLEROSIS**

(71) Applicants: **Peter C. Hiestand**, Austria (CH); **Christian Schnell**, Hesingue (FR)

(72) Inventors: **Peter C. Hiestand**, Austria (CH); **Christian Schnell**, Hesingue (FR)

(73) Assignee: **Novartis AG**, Basel (CH)

(*) Notice: 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.: **14/257,342**

(22) Filed: **Apr. 21, 2014**

(65) **Prior Publication Data**

US 2014/0228446 A1 Aug. 14, 2014

Related U.S. Application Data

(60) Division of application No. 13/149,468, filed on May 31, 2011, now Pat. No. 8,741,965, which is a continuation of application No. 12/303,765, filed as application No. PCT/EP2007/005597 on Jun. 25, 2007, now abandoned.

(30) **Foreign Application Priority Data**

Jun. 27, 2006 (GB) 0612721.1

(51) **Int. Cl.**
A61K 31/13 (2006.01)
C07C 215/08 (2006.01)
A61K 31/137 (2006.01)
A61K 31/397 (2006.01)

(52) **U.S. Cl.**
CPC ***C07C 215/08*** (2013.01); ***A61K 31/137*** (2013.01); ***A61K 31/397*** (2013.01); *A61K 31/13* (2013.01)

(58) **Field of Classification Search**
CPC A61K 31/13; A61K 31/137
USPC 514/667, 903
See application file for complete search history.

(56) **References Cited**

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2014/0228446 A1 8/2014 Hiestand et al.

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WO 2004/113330 12/2004
WO 2005/123104 A2 12/2005
WO 2006/055809 5/2006
WO 2006/058316 6/2006
WO 2006/066086 6/2006

OTHER PUBLICATIONS

Xie et al., "Sphingosine-1-Phosphate Receptor Agonism Impairs the Efficiency of the Local Immune Response by Altering Trafficking of

Miller et al., Neurol. & Neurosci. Reports, (Sep. 2010), 10(5), pp. 397-406.

In Vivo: Relapsing Experimental Autoimmune Encephalomyelitis (EAE)

In this assay, a S1P1 receptor modulator, e.g. Compound A significantly blocks disease-associated neo-angiogenesis when administered to the animals at a dose of from 0.1 to 20 mg/kg p.o. For example, Compound A, in the hydrochloride salt form, fully blocks disease-associated angiogenesis and completely inhibits the relapse phases when administered daily at a dose of 0.3 mg/kg p.o. The same effect is obtained when Compound A, in the hydrochloride salt form, is administered p.o. at 0.3 mg/kg every 2nd or 3rd day or once a week.

Ex. 1001 at 10:33-11:2; Paper 26 at 20.

Person of Ordinary Skill in the Art

Person of Ordinary Skill in the Art

POSA Definition

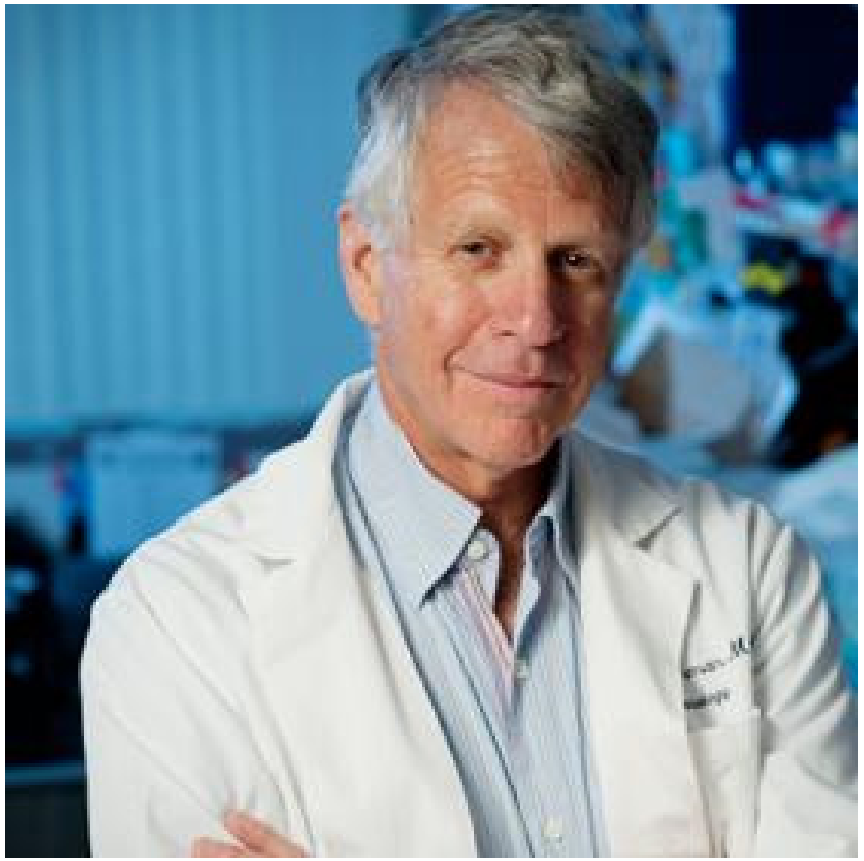
> On the record before us, we find that one of ordinary skill in the art may be part of a multi-disciplinary research team including 1) a Ph.D. with expertise in the area of neurology and/or an M.D. having several years of clinical experience treating multiple sclerosis patients, and who would be knowledgeable about the multiple sclerosis medical literature, and 2) a pharmacologist with experience in drug development.

Paper 11 (Institution Decision) at 9; Paper 26 at 44; Paper 63 at 2.

Patent Owner's Experts Eminently Qualified

Dr. Lawrence Steinman [1]

- **M.D. Physician / MS researcher**
- **Professor, Stanford University, Chair of Interdepartmental Program in Immunology**
- Helped discovery MS medicine Tysabri®
- Designs and studies MS medicines "bench to bedside"
- Extensive experience interpreting EAE animal model data in the context of MS drug development



[1] Ex. 2022 (Dr. Steinman) ¶¶ 12-21; Ex. 2023 (Steinman CV); Paper 26 at 6. [2] Ex. 2005 (Dr. Jusko) ¶¶ 7-13; Ex. 2006 (Jusko CV); Ex. 2024 (2nd Jusko) ¶ 40; Paper 26 at 7. [3] Ex. 2003 (Dr. Lublin) ¶¶ 8-17; Ex. 2004 (Lublin CV); Paper 26 at 6-7.

Patent Owner's Experts Eminently Qualified

Dr. William Jusko [2]

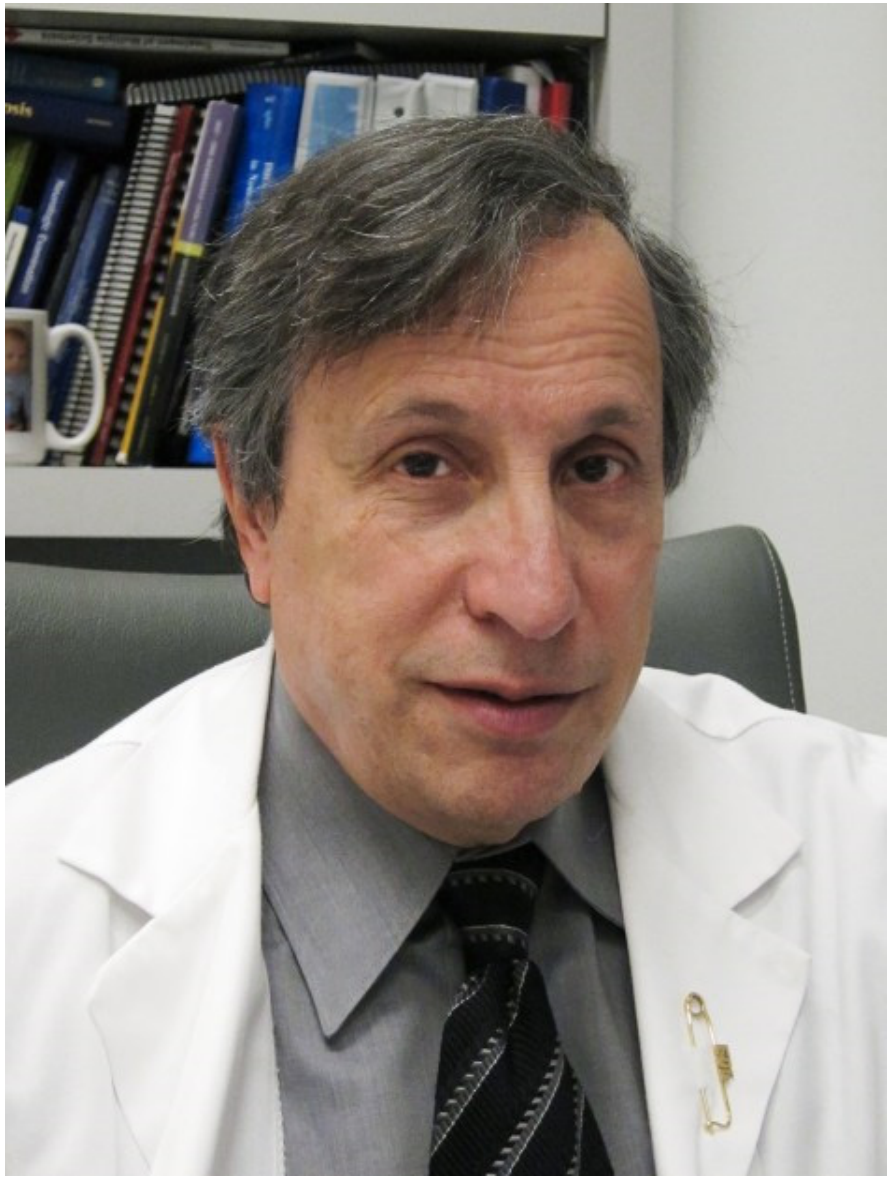
- **Ph.D., Pharmacologist**
- **Distinguished Professor, State University of New York at Buffalo, New York**
- Experienced with immunosuppressants
- Extensive experience with pharmacology of fingolimod, PK/PD
- Published papers on pharmacology of fingolimod in rats and monkeys

[1] Ex. 2022 (Dr. Steinman) ¶¶ 12-21; Ex. 2023 (Steinman CV); Paper 26 at 6. [2] Ex. 2005 (Dr. Jusko) ¶¶ 7-13; Ex. 2006 (Jusko CV); Ex. 2024 (2nd Jusko) ¶ 40; Paper 26 at 7. [3] Ex. 2003 (Dr. Lublin) ¶¶ 8-17; Ex. 2004 (Lublin CV); Paper 26 at 6-7.

Patent Owner's Experts Eminently Qualified

Dr. Fred Lublin [3]

- **M.D., MS Physician**
- **Professor of Neurology and Director of Center for MS at Icahn School of Medicine, Mt. Sinai, New York**
- First-hand experience in determining doses in MS clinical trials
- Member of Clinical Trial Advisory Board, DSMB, and Principal Investigator for fingolimod trials
- Principal or Co-Investigator for clinical trials related to many MS medicines



[1] Ex. 2022 (Dr. Steinman) ¶¶ 12-21; Ex. 2023 (Steinman CV); Paper 26 at 6. [2] Ex. 2005 (Dr. Jusko) ¶¶ 7-13; Ex. 2006 (Jusko CV); Ex. 2024 (2nd Jusko) ¶ 40; Paper 26 at 7. [3] Ex. 2003 (Dr. Lublin) ¶¶ 8-17; Ex. 2004 (Lublin CV); Paper 26 at 6-7.

Petitioners' Experts Inexperienced in Key Aspects of Art

Dr. Giesser:

— M.D., MS clinician

— Professor of Clinical Neurology, UCLA

— Not a pharmacologist

— No animal research experience, including EAE

— No experience with clinical dose design

— No experience with fingolimod except prescribing it (did not read Gilenya® Label before this case)

Dr. Benet:

— Ph.D., pharmacologist

— Professor of Bioengineering and Therapeutic Sciences, Schools of Pharmacy and Medicine, University of California

— No experience with fingolimod

— No publications involving MS or EAE

— No experience performing EAE animal model studies

— Alleged consulting on three MS drugs 15-20 years ago

Paper 26 at 44-46; Paper 63 at 2; Ex. 1002 (Dr. Giesser) ¶¶ 1-4; Ex. 1047 (Dr. Benet) ¶¶ 1-11; Ex. 2100 (Benet Deposition) at 37:6-17, 43:9-46:2, 47:1-6.

Dr. Giesser Admits to Facts That Defeat Petition

- The law requires determination of scope and content of prior art when attempting to prove obviousness.
- Dr. Giesser did not review the scope and content of the prior art.
- Dr. Giesser limited her opinion to ”references supplied by counsel.”
- No rebuttal opinion from Dr. Giesser.
- **Dr. Giesser employed impermissible hindsight.**
- **Dr. Giesser’s opinion should be given no weight.**
- **Accordingly, the Petition is fatally defective and should be denied in full.**

Paper 26 at 28-30; 42-44; Paper 63 at 1.

Dr. Giesser Did Not Review the State of the Art

No literature searches to review state of the art.

"References were supplied by counsel."

10:49:12 BY MS. LOVE:

Q Did you perform any searches of the literature other than -- strike that.

Have you performed any literature searches in your work related to this matter?

A I looked up an article subsequent to one that was published during the time period referred to in the declaration.

Q What article was that?

A There is an abstract published by Kappos, I believe, in 2005. The full paper resulting from this abstract was published in September 2006.

Q Other than that, have you performed any searches for literature?

A No.

Q Okay. How did you get the references that are cited in your declaration?

A References were supplied by counsel.

Ex. 2039 (Dr. Giesser Transcript) at 49:17-50:9; Paper 26 at 28-31.

Dr. Giesser Ignored Webb Even Though On Face of Patent

Dr. Giesser ignored Webb in her Declaration, but reviewed it before her deposition, even though it was on the face of the '405 Patent.

Q Did you review a paper by Webb et al. dated 2004?

A I believe I have reviewed that article.

Q When did you review it?

A Last week.

Q How did you come to receive it?

A This was supplied by counsel.

Q Were any other articles supplied by counsel for your review?

A I have stated the articles I have reviewed in my declaration.

Q Were any other articles not in your declaration supplied by counsel for your review?

A No. Other than Webb.

Ex. 2039 (Dr. Giesser Transcript) at 67:1-68:15; Paper 26 at 42.

Law Supports Disregarding Dr. Giesser's Opinion

- Dr. Giesser "did not perform an analysis of the art as a whole." Paper 26 at 42, quoting *AstraZeneca*.
- Dr. Giesser only considered "references supplied by counsel."
- The *AstraZeneca* court found that an expert considering only "a selection of prior art ***handpicked*** by" counsel had "fatally undermine[d]" the credibility of the putative expert, giving his opinion no weight. Paper 26 at 43.
- In *Warner Chilcott*, the obviousness attack was "entirely hindsight driven" as it is here. *Id.*
- The experts there "picked and chose from the already-narrowed list of references that lawyers provided, and worked backwards using improper hindsight." That analysis was simply "legally incorrect." *Id.*

State of the Art

Review of state of the art is first step in analysis under 35 U.S.C. § 103.

KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 406 (2007) (citing *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17-18 (1966)); Paper 8 at 23.

Multiple Sclerosis

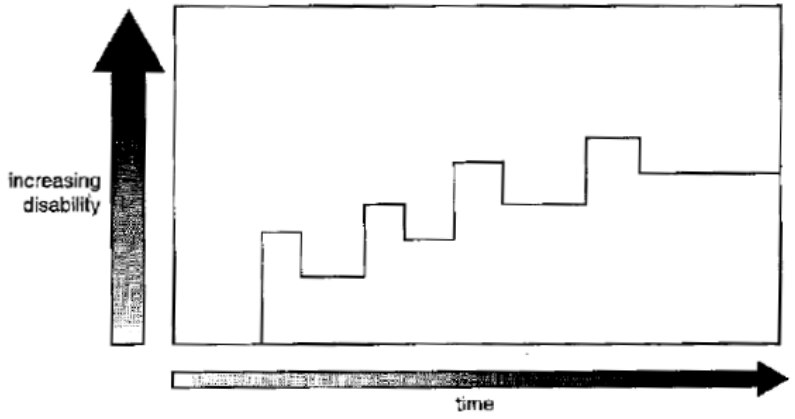
- "The **symptoms of multiple sclerosis are diverse** and can include tremor, paralysis, loss of bladder or bowel control, fatigue, pain, loss of cognitive function, disturbances in vision and speech, emotional changes, and nystagmus." Thomson, Ex. 1005 at 158; Ex. 2022 (Dr. Steinman) ¶¶ 24-27; Paper 24 at 7.

- Finding medicines to treat MS is challenging:
  —MS is a life-long disease (there is no cure) and **medicines need to be used over extended period** of time
  —**High level of inter-patient variation** makes it difficult to identify a positive signal in clinical trials
  Ex. 2025 (Dr. Lublin) ¶¶ 23-31; Paper 26 at 25.

Efficacy in RRMS Means *Sustained* Therapy

"RRMS is a life-long condition. … Disability thus accumulates over time. As a result, MS doctors focus on sustained, consistent relapse prevention and slowing progression of the disease." Dr. Steinman, Ex. 2096, ¶ 43.

46. The following graph from Lublin et al., *Defining the clinical course of multiple sclerosis: Results of an international survey*, 46 Neurology 907 (1996), shows the disease course of RRMS, as understood as of 2006 (Ex. 2010 at 908 (Fig. 1).):



"Fingolimod held promise too, but only if it could provide consistent, sustained benefits to patients." Ex. 2096, ¶ 44.

Ex. 2003 ¶ 46; Paper 8 at 32-33; Paper 63 at 6-7.

"Perplexities" of Fingolimod

- Pro-drug with long half-life.
- Inhibits movement of lymphocytes out of lymph nodes, but MOA for MS unknown.
- "However, the **effect of fingolimod on cell trafficking is not directly tied to its therapeutic effect**." Ex. 2024 (Dr. Jusko) ¶ 42.
- "The **mechanism by which fingolimod exerts therapeutic effects in multiple sclerosis is unknown**, but **may involve reduction of lymphocyte migration** into the central nervous system." Ex. 2040 (GILENYA Label) at 12; Ex. 2024 (Dr. Jusko) ¶ 38.
- "A skilled pharmacologist would be **cautious in judging the clinical therapeutic benefit of administering fingolimod** because one would not want to expose a patient to the risk of side-effects without confidence that the dose provided sufficient benefit." Ex. 2024 (Dr. Jusko) ¶ 40.

Dr. Jusko, Ex. 2024 at ¶¶ 37-44; Paper 26 at 8.

Early Biomarker for Effect - Lymphocyte Suppression

"Many scientists believed that…'lymphocyte sequestration is a convenient surrogate marker of the pharmacodynamic effect of FTY720[.]'" Dr. Steinman, Ex. 2022 ¶ 41 (*quoting* Thompson, Ex. 1005 at 162.)

BUT:

"Studies showed, however, that only substantial lymphocyte suppression provided any clinical benefit." Dr. Steinman, Ex. 2022, ¶ 5.[1]

[1] *See also*, Ex. 2024 (Dr. Jusko) ¶¶ 53, 55-57, 59, 62, 63, 65-75; Ex. 2022 (Dr. Steinman) ¶¶ 55-66, 74-85; Paper 26 at 8, 10-14, 16-19.

State of the Art – Chiba Patent

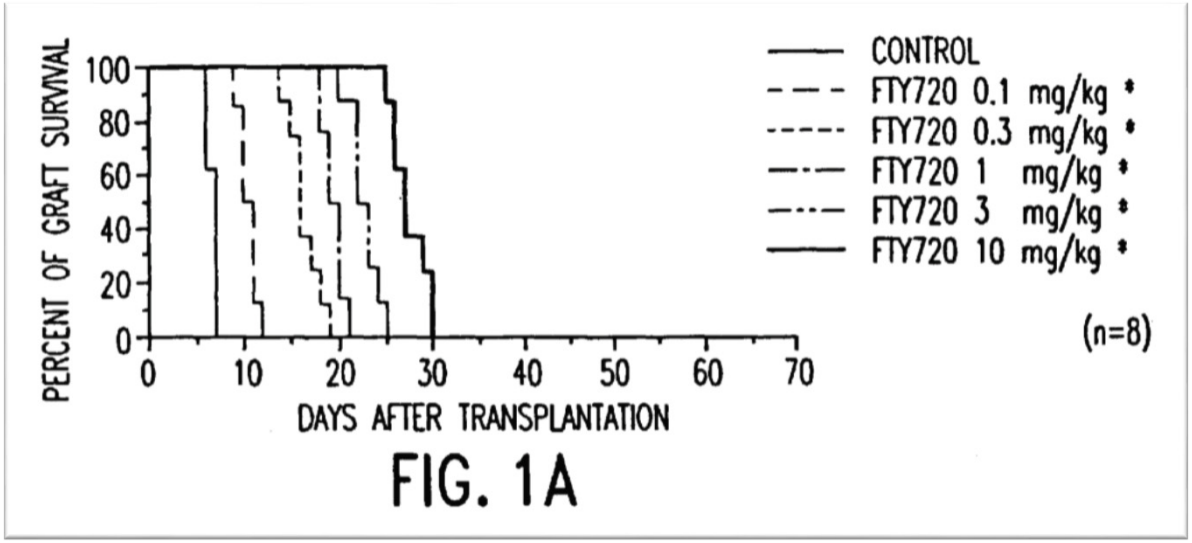
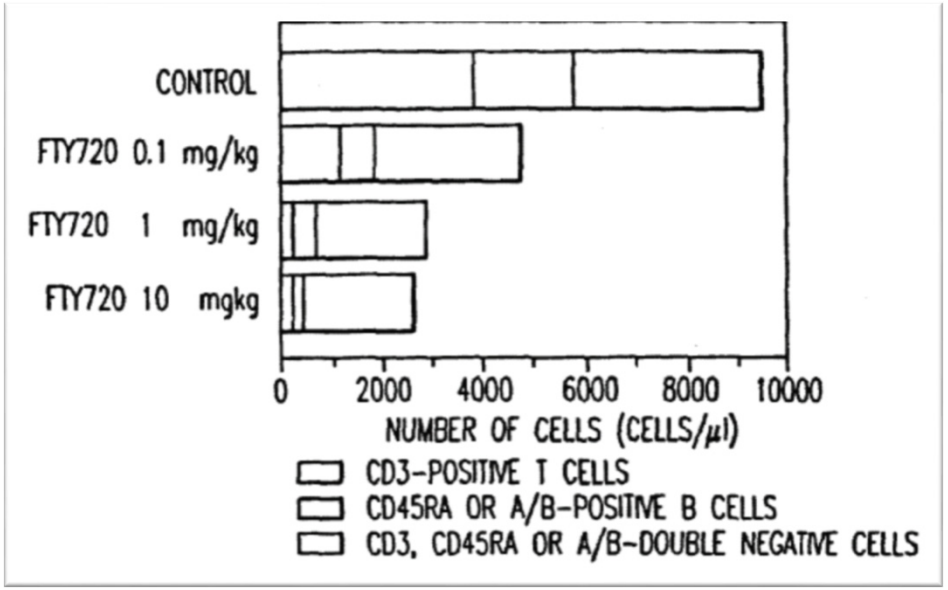


FIG. 1A

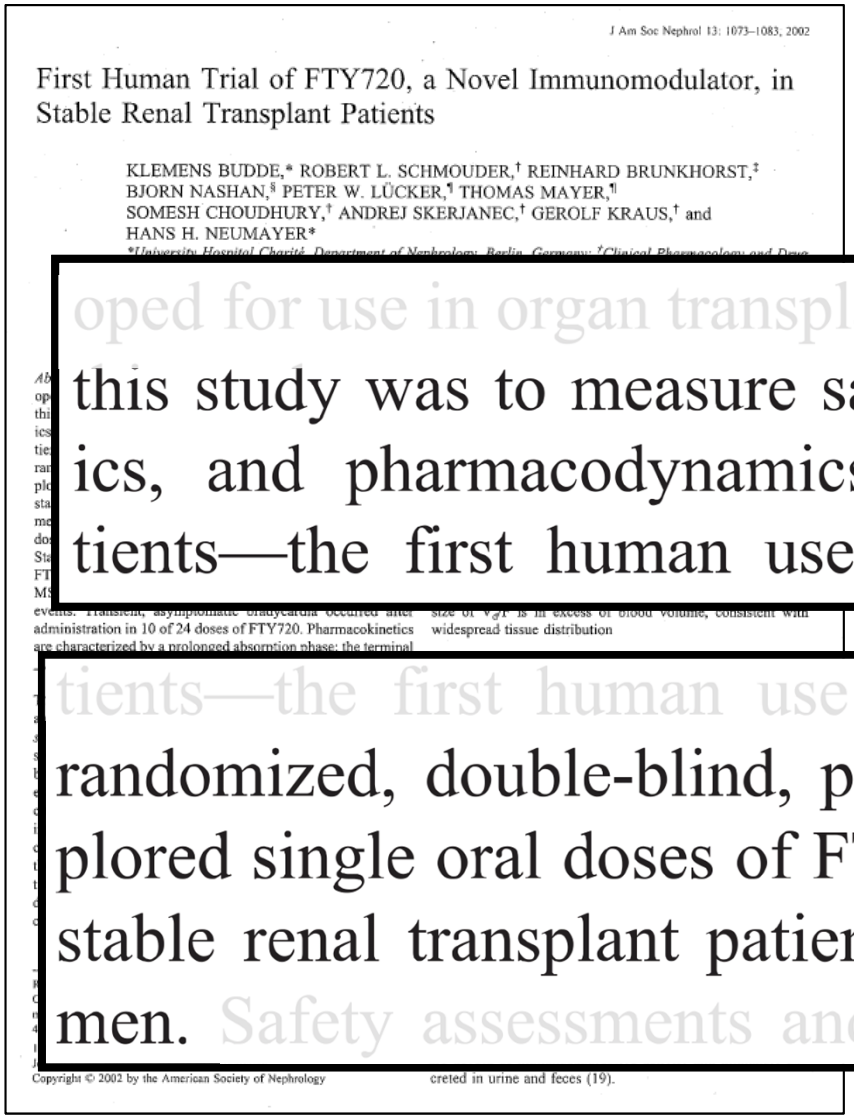
—> Increasing doses of fingolimod show increased effect on graft survival in transplant animal model.

—> Increasing doses of fingolimod show increasing reduction of lymphocytes in periphery.



Ex. 1006 (Chiba), Fig. 1A, Fig. 11; Ex. 2022 (Dr. Steinman) ¶¶ 41-46; Paper 26 at 8.

Budde 2002: Single-Dose Phase IA Safety Study



J Am Soc Nephrol 13: 1073–1083, 2002

First Human Trial of FTY720, a Novel Immunomodulator, in Stable Renal Transplant Patients

KLEMENS BUDDE,* ROBERT L. SCHMOUDER,† REINHARD BRUNKHORST,‡ BJORN NASHAN,§ PETER W. LÜCKER,¶ THOMAS MAYER,¶ SOMESH CHOUDHURY,† ANDREJ SKERJANEC,† GEROLF KRAUS,† and HANS H. NEUMAYER*

oped for use in organ transplantation. The primary objective of this study was to measure safety, single-dose pharmacokinetics, and pharmacodynamics in stable renal transplant patients—the first human use of FTY720. This study used a randomized, double-blind, placebo-controlled design that explored single oral doses of FTY720 from 0.25 to 3.5 mg in 20 stable renal transplant patients on a cyclosporine-based regimen. Safety assessments and blood samples were taken pre-

administration in 10 of 24 doses of FTY720. Pharmacokinetics are characterized by a prolonged absorption phase; the terminal

widespread tissue distribution

creted in urine and feces (19).

Ex. 1008 (Budde) at 1073; Paper 26 at 9-10.

Kahan 2003: Multi-Dose Phase IB Safety Study

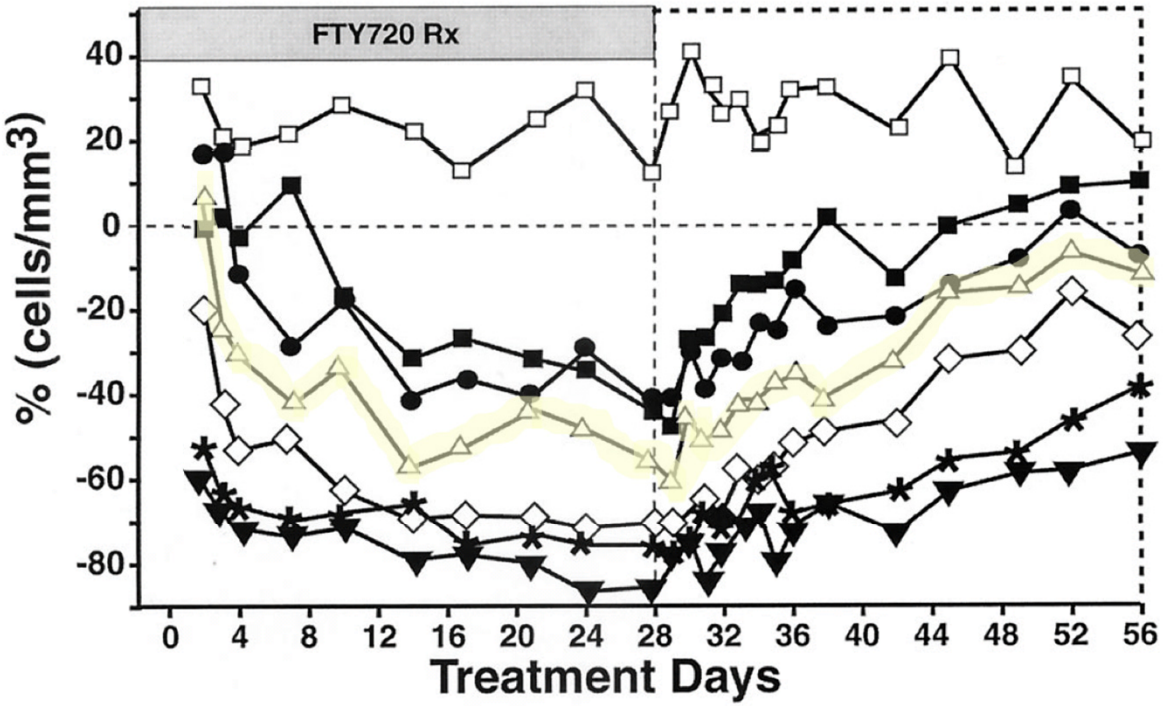


FIGURE 1. Impact of dose on the kinetics of percent change from baseline of the absolute lymphocyte count by study day during FTY720 treatment (28 days) and posttreatment (days 29–56) periods. (*open squares*) Placebo; (*filled squares*) 0.125 mg; (*filled circles*) 0.25 mg; (*open triangles*) 0.5 mg; (*open diamonds*) 1.0 mg; (*asterisks*) 2.5 mg; (*filled triangles*) 5.0 mg.

Ex. 1031 (Kahan 2003) at 1081; Ex. 2022 (Dr. Steinman) ¶ 57; Paper 26 at 10-12.

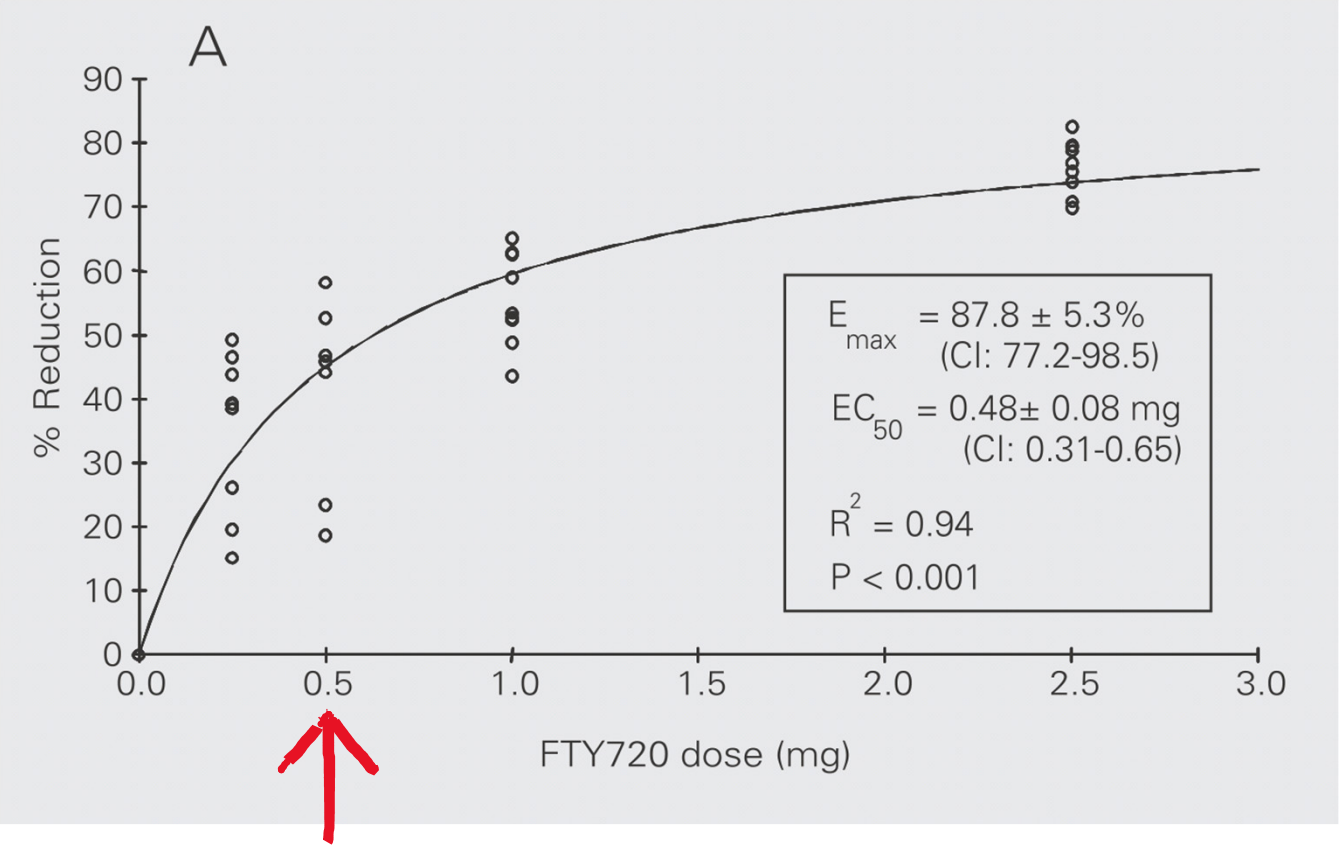
Kahan 2003: FTY ≥ 1.0 mg/day => 85% Lymphopenia

Results. **FTY720 doses greater than or equal to 1.0 mg/day produced a significant reduction in peripheral blood lymphocyte count by up to 85%, which reversed within 3 days after discontinuation of study medication. Compared with placebo-treated patients, FTY720 subjects did not show a major increase in adverse events or a change in renal function. Pharmacokinetic measurements revealed that FTY720 displayed linear relations of doses and concentrations over a wide range, but had no effect on CsA exposure.**

Ex. 1031 (Kahan 2003) at 1079; Ex. 2022 (Dr. Steinman) ¶ 57; Paper 26 at 10-12.

Park 2005: Teaches Away from Low Doses

High inter-patient variability at low doses.

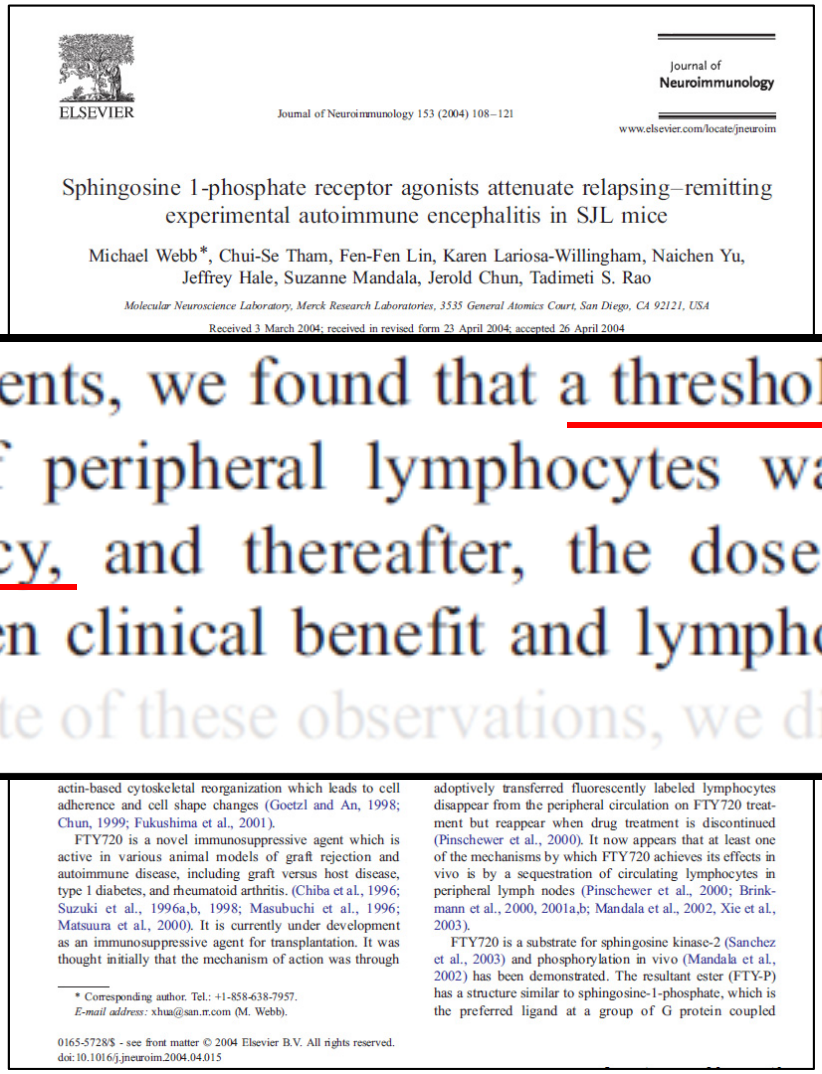


42% average lymphocyte suppression in 0.5 mg group, Ex. 1019, Table 3, p. 689

Ex. 1019 (Park 2005) at 690; Ex. 2022 (Dr. Steinman) ¶ 62; Paper 26 at 12-14.

Webb 2004: Teaches a Threshold of 70% Suppression

Paper from Merck Research Laboratories



ELSEVIER

Journal of Neuroimmunology 153 (2004) 108–121

Journal of Neuroimmunology

www.elsevier.com/locate/jneuroim

Sphingosine 1-phosphate receptor agonists attenuate relapsing–remitting experimental autoimmune encephalitis in SJL mice

Michael Webb*, Chui-Se Tham, Fen-Fen Lin, Karen Lariosa-Willingham, Naichen Yu, Jeffrey Hale, Suzanne Mandala, Jerold Chun, Tadimeti S. Rao

Molecular Neuroscience Laboratory, Merck Research Laboratories, 3535 General Atomics Court, San Diego, CA 92121, USA

Received 3 March 2004; received in revised form 23 April 2004; accepted 26 April 2004

In dose response experiments, we found that a threshold of about 70% depletion of peripheral lymphocytes was required to see any efficacy, and thereafter, the dose–response relationship between clinical benefit and lymphopoenia was very steep. In spite of these observations, we did

actin-based cytoskeletal reorganization which leads to cell adherence and cell shape changes (Goetzl and An, 1998; Chun, 1999; Fukushima et al., 2001).

FTY720 is a novel immunosuppressive agent which is active in various animal models of graft rejection and autoimmune disease, including graft versus host disease, type 1 diabetes, and rheumatoid arthritis. (Chiba et al., 1996; Suzuki et al., 1996a,b, 1998; Masubuchi et al., 1996; Matsuura et al., 2000). It is currently under development as an immunosuppressive agent for transplantation. It was thought initially that the mechanism of action was through

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E-mail address: xhua@san.rr.com (M. Webb).

doi:10.1016/j.jneuroim.2004.04.015

adoptively transferred fluorescently labeled lymphocytes disappear from the peripheral circulation on FTY720 treatment but reappear when drug treatment is discontinued (Pinschewer et al., 2000). It now appears that at least one of the mechanisms by which FTY720 achieves its effects in vivo is by a sequestration of circulating lymphocytes in peripheral lymph nodes (Pinschewer et al., 2000; Brinkmann et al., 2000, 2001a,b; Mandala et al., 2002, Xie et al., 2003).

FTY720 is a substrate for sphingosine kinase-2 (Sanchez et al., 2003) and phosphorylation in vivo (Mandala et al., 2002) has been demonstrated. The resultant ester (FTY-P) has a structure similar to sphingosine-1-phosphate, which is the preferred ligand at a group of G protein coupled

Ex. 2014 (Webb) at 118; Paper 26 at 16-19.

Kataoka 2005: (A Different Lab) Cites (Not Refutes) Webb

Article

FTY720, Sphingosine 1-Pho
Experimental Autoimmun
Cell Infiltration

Hirotoshi Kataoka[1], Kunio Sugahara[1], Fukunari[3] and Kenji Chiba[1, 4]

FTY720, a sphingosine 1-phosphate receptor blood lymphocytes and exerts immunomodu disease models. In this study, we evaluated FTY720-phosphate [(*S*)-FTY720-P] on expe Prophylactic administration of FTY720 at 0. and therapeutic treatment with FTY720 si histological change in the spinal cords of LEW with rat EAE, the development of proteolipid protein-induced EAE in SJL/J mice was almost completely prevented and infiltration of CD4$^+$ T (*S*)-FTY720-P. When FTY72 EAE was markedly inhibited CD4$^+$ T cells were decreased myelin oligodendrocyte glyc not only a prophylactic but EAE appears to be due to inflammation site. *Cellular &*

Key Words: FTY720, S1P re

substantial axon loss and neurodegradation (41). It has been reported by Webb M, et al that administration of either FTY720 or FTY720-P to SJL mice with established relapsing EAE results in a rapid and sustained improvement (42); however they did not analyze the relationship between the therapeutic effect of FTY720 and the infiltration of T cells into the CNS.

42. Webb M, Tham CS, Lin FF, et al. Sphingosine 1-phasphate receptor agonists attenuate relapsing-remitting experimental autoimmune encephalitis in SJL mice. J Neuroimmunol. 2004; 153:108-121.

Introduction

2-Amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol hydrochloride (FTY720), a new class of immunomodulator, sequesters circulating mature lymphocyte into secondary lymphoid tissues and thymus by long-term down-regulation of S1P receptor type 1 ($S1P_1$) on lymphocytes, and exerts immunomodulating effect (1-6). It has been previously reported that a potent immunosuppressive natural product, ISP-I can be isolated from a culture broth of *Isaria scinclairii*, a kind of vegetative wasp (7-9). The chemical modification of ISP-I led to a novel synthetic compound, FTY720 that has more potent immunomodulating activity and less toxicity than ISP-I (10-13). FTY720 has been shown to be highly effective in prolonging allograft survival in various experimental allograft models (1-4, 14, 15). A striking feature of FTY720 is the induction of a marked decrease in the number of peripheral blood lymphocytes, especially T cells, at doses that prolong allograft survival (1-4). FTY720-induced

[1]Research Laboratory III (Immunology), Pharmaceutical Research Unit, Research and Development Division, Mitsubishi Pharma Corporation, Yokohama, Japan;

[2]Research Laboratory I (CNS), Pharmaceutical Research Unit, Research and Development Division, Mitsubishi Pharma Corporation, Yokohama, Japan;

[3]Discovery Technology Laboratory I, Pharmaceutical Research Unit, Research and Development Division, Mitsubishi Pharma Corporation,

Ex. 1029 at 446, 448.

Kappos 2005: Teaches No Dose Lower Than 1.25 mg

O141
FTY720 in relapsing MS: results of a double-blind placebo-controlled trial with a novel oral immunomodulator
L. Kappos, E. W. Radü, J. Antel, G. Comi, X. Montalban, P. O'Connor, O. Bettoni-Ristic, T. Haas, R. Preiss, A. Korn
on behalf of the FTY720D2201 Study Group

FTY720 is an oral immunomodulator (sphingosine-1 phosphate receptor (S1P) modulator) that reversibly sequesters tissue damaging T and B cells away from blood and the central nervous system to peripheral lymph nodes. FTY720 has demonstrated both preventive and therapeutic efficacy in several animal models of MS.

Methods: We report the clinical and MRI results of an international, multicenter, double-blind study to evaluate efficacy, safety and tolerability of two doses of FTY720 and placebo (PL). 281 patients with active relapsing MS were randomized to receive PL (n = 93), 1.25 mg (n = 94) or 5.0 mg FTY720 (n = 94) q. d. for 6 months. Patients had monthly cranial MRI scans and 3-monthly neurological assessments by a neurologist otherwise not involved in their care.

Results: Clinical and MRI baseline characteristics were balanced amongst groups. The primary outcome, mean (median) total number of Gadolinium(Gd)-enhancing lesions in monthly post baseline MRI scans was 14.8 (5.0), 8.4 (1.0) and 5.7 (3.0) for PL, FTY 1.25 and 5.0 mg groups ($p < 0.001$ 1.25 vs. PL, $p = 0.006$ 5.0 vs. PL). Similar, clearly significant effects favoring both FTY720 groups vs. PL were found for Gd-enhancing lesion volume, new T2 lesions and change in T2 lesion volume (only 5 mg qd sign. better than PL). The proportion of relapse-free patients (70.0, 86.0 and 86 %; $p = 0.007$ 1.25 mg vs. PL, $p = 0.008$ 5 mg vs. PL), annualized relapse rate (0.77, 0.35 and 0.36) and time to first relapse were significantly better in both FTY720 groups vs. PL. There was no compelling dose-related difference in efficacy on MRI or clinical endpoints. Treatment was generally well tolerated with 255 (91 %) of patients completing study and 249 (89 %)

in both FTY720 groups vs. PL. There was no compelling dose-related difference in efficacy on MRI or clinical endpoints. Treatment was generally

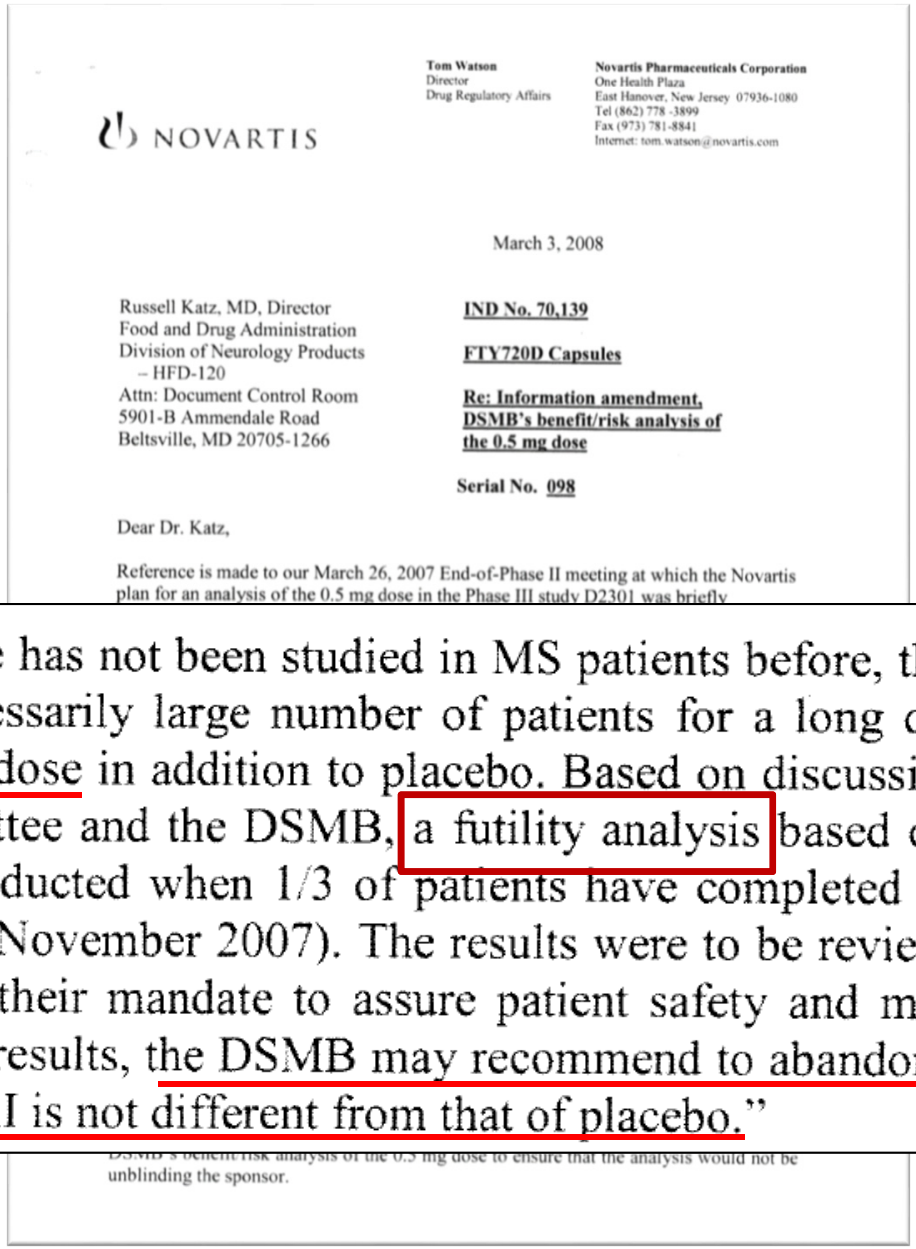
safety evaluations strongly suggest that FTY720 has the potential to be an efficacious disease modifying treatment for relapsing forms of MS with the additional benefit of once daily oral administration.

Study supported by Novartis Pharma AG Basel.

- Clinical and MRI results of study in RRMS of 5.0 mg, 1.25 mg, and placebo.
- "[C]learly significant effects favoring both FTY720 groups…" were reported.
- Mild adverse events were more common in 5 mg group.

Ex. 1007 at II/41; Paper 26 at 20.

The Phase III Trial: Futility Analysis Only for 0.5 mg



Tom Watson
Director
Drug Regulatory Affairs

Novartis Pharmaceuticals Corporation
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NOVARTIS

March 3, 2008

Russell Katz, MD, Director
Food and Drug Administration
Division of Neurology Products
– HFD-120
Attn: Document Control Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

IND No. 70,139

FTY720D Capsules

Re: Information amendment, DSMB's benefit/risk analysis of the 0.5 mg dose

Serial No. 098

Dear Dr. Katz,

Reference is made to our March 26, 2007 End-of-Phase II meeting at which the Novartis plan for an analysis of the 0.5 mg dose in the Phase III study D2301 was briefly

unblinding the sponsor.

- "Since the 0.5 mg dose has not been studied in MS patients before, there is a risk of exposing an unnecessarily large number of patients for a long duration to a potentially ineffective dose in addition to placebo. Based on discussions with the study Steering Committee and the DSMB, a futility analysis based on MRI data was planned to be conducted when 1/3 of patients have completed 6 months in study D2301 (planned November 2007). The results were to be reviewed only by the DSMB as part of their mandate to assure patient safety and monitor study conduct. Based on the results, the DSMB may recommend to abandon the 0.5 mg dose if its effect on MRI is not different from that of placebo."

Ex. 2064 at 2; Paper 26 at 26.

Mt. Sinai IRB Skeptical of 0.5 mg Efficacy

Curovic-Perisic" <valentina.curovic-perisic@novartis.com>
Cc: "Bencosme, Yadira" <Yadira.Bencosme@mssm.edu>;"Lublin, Fred (MSH)" <fred.lublin@msnyuhealth.org>
Subject: Re: Novartis 2302 IRB Deferral

Dear Valentina, please see below re Dr. Miller's IRB deferral. Thanks, Sylvia

----- Original Message -----
From: "Farrell, Colleen" [colleen.farrell@mssm.edu]
Sent: 06/22/2007 05:50 PM
To: "Weber, Michele (MSH)" <michele.weber@msnyuhealth.org>;"Miller, Aaron (MSH)" <aaron.miller@msnyuhealth.org>;Karen Webster <Karen-1.Webster@novartis.com>
Cc: "Bencosme, Yadira" <Yadira.Bencosme@mssm.edu>;"Lublin, Fred (MSH)" <fred.lublin@msnyuhealth.org>;sylvia.burns@novartis.com
Subject: Novartis 2302 IRB Deferral

I received the posting today from the IRB for the board meeting on June 19th.

"The IRB cannot approve this project without adequate justification for the use of the 0.5 mg dose of fingolimod. No studies have been provided at any phase that shows this dose may be safe and effective. The IRB can contact the FDA directly for their recommendations regarding this low dose, if the Investigators prefer. Please address in a memo to the IRB."

Ex. 2063 at 2; Paper 26 at 26-27.

Consistent Evidence: No POSA Thought 0.5 mg Would Be Effective

Teaching Away [1]

- MS is a variable disease that needs sustained therapy.
- Webb — 70% lymphopenia needed to show any efficacy in EAE.
- Park – 0.5 mg results in highly variable effects.
- Kahan and Park — 0.5 mg produces only 42% (Park) or 50% (Kahan) average suppression.

Skepticism of Experts [2]

- Futility analysis for only 0.5 mg at Phase III.
- DSMB could abandon 0.5 mg arm if no different than placebo.
- Mt. Sinai IRB refuses to join PIII trial based on skepticism that 0.5 mg would have any efficacy.

Unexpected Results [3]

- Inventors saw unexpected biomarker and surprising EAE rodent model results.
- Phase III trial surprisingly showed efficacy of 0.5 mg dose, and at similar level as 1.25 mg application date.

[1] Paper 26 at 33-34; Paper 63 at 5-8. [2] Paper 26 at 40-41; Paper 63 at 9-12. [3] Paper 26 at 39-40; Paper 63 at 9-12.

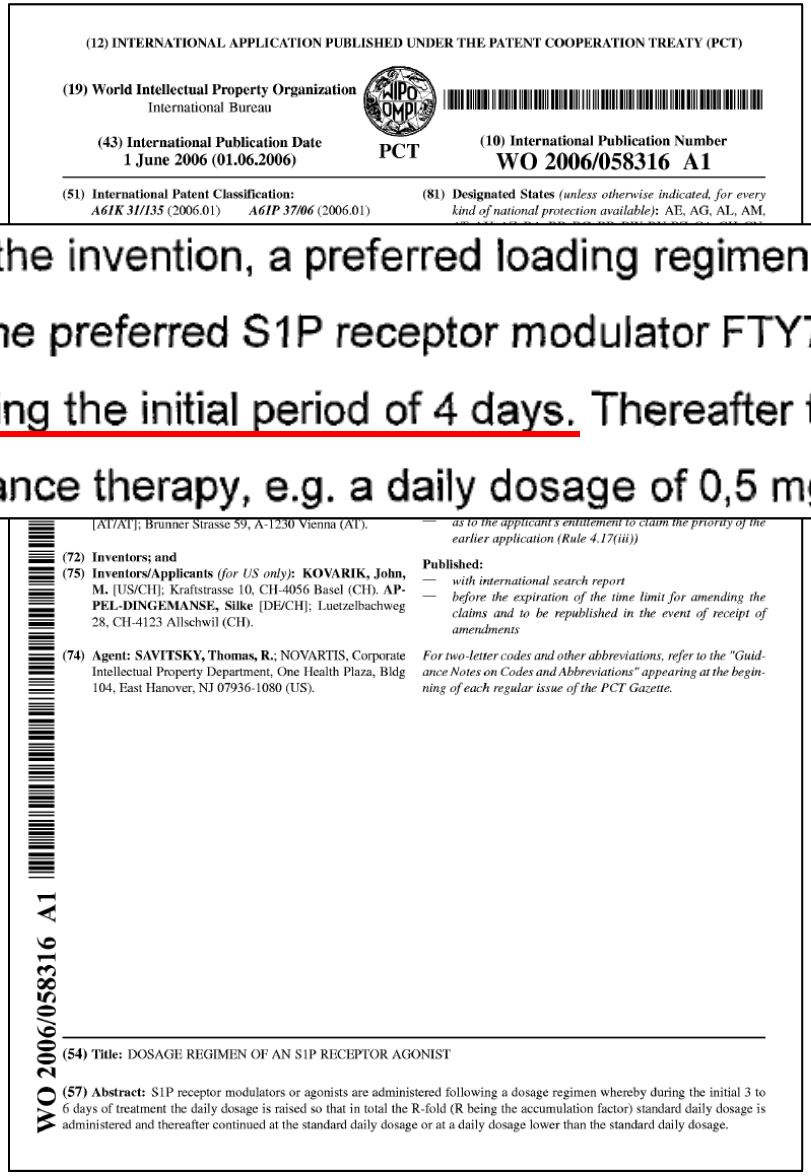
Ground I

GROUND I:

Kovarik + Thompson

Kovarik Patent Application - Loading Dose Regimens

In a further embodiment of the invention, a preferred loading regimen of a S1P receptor agonist or modulator, e.g. the preferred S1P receptor modulator FTY720, may also be e.g. 0.5mg/1mg/1.5mg/2mg during the initial period of 4 days. Thereafter the treatment is continued with the maintenance therapy, e.g. a daily dosage of 0,5 mg.



(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

PCT

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1 June 2006 (01.06.2006)

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WO 2006/058316 A1

(51) International Patent Classification:
A61K 31/135 (2006.01) *A61P 37/06* (2006.01)

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM,

[AT/AT]; Brunner Strasse 59, A-1230 Vienna (AT).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **KOVARIK, John, M.** [US/CH]; Kraftstrasse 10, CH-4056 Basel (CH). **APPEL-DINGEMANSE, Silke** [DE/CH]; Luetzelbachweg 28, CH-4123 Allschwil (CH).

(74) Agent: **SAVITSKY, Thomas, R.**; NOVARTIS, Corporate Intellectual Property Department, One Health Plaza, Bldg 104, East Hanover, NJ 07936-1080 (US).

as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2006/058316 A1

(54) Title: DOSAGE REGIMEN OF AN S1P RECEPTOR AGONIST

(57) Abstract: S1P receptor modulators or agonists are administered following a dosage regimen whereby during the initial 3 to 6 days of treatment the daily dosage is raised so that in total the R-fold (R being the accumulation factor) standard daily dosage is administered and thereafter continued at the standard daily dosage or at a daily dosage lower than the standard daily dosage.

**Record does not reflect that highlighted term refers to alternatives. The record reflects the term means incremental doses over initial four days.

Ex. 1004 at 15; Paper 26 at 51-52; Ex. 2022 (Dr. Steinman) ¶¶ 164-68.

Kovarik: Loading Dose "Increased Stepwise"

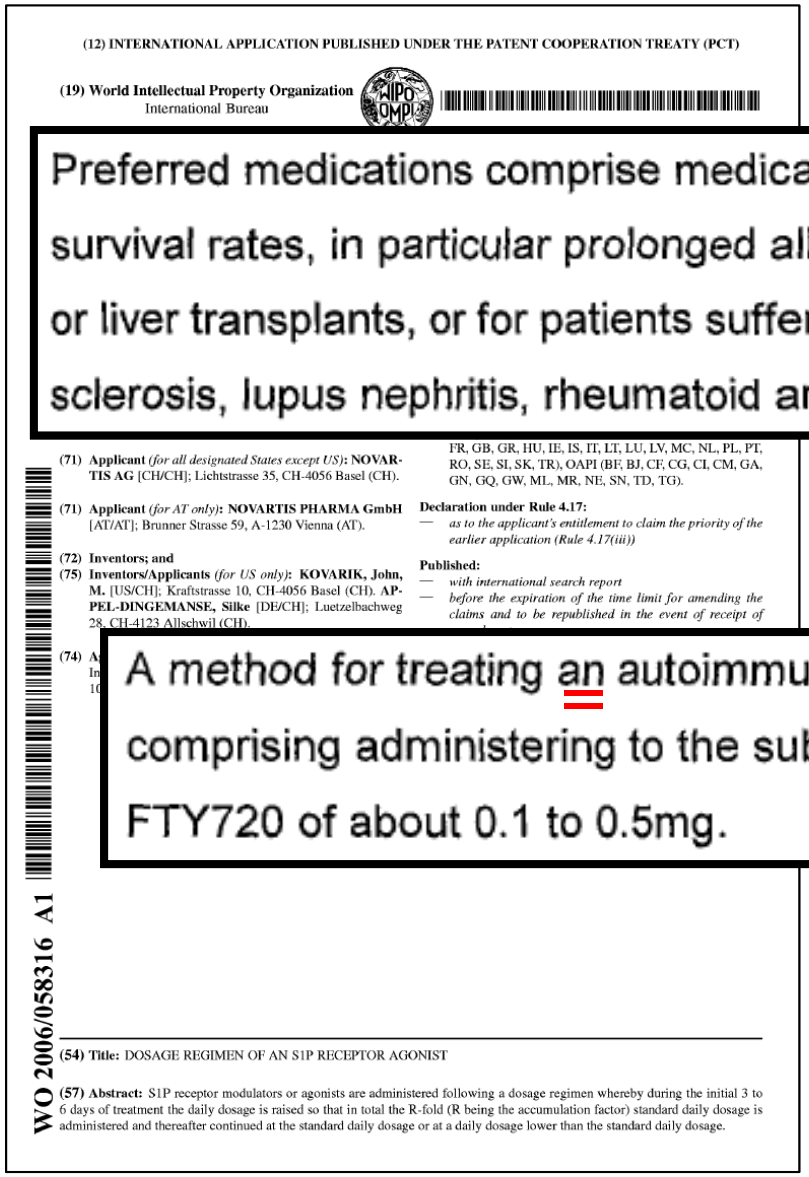
Preferably, the dosage of the S1P receptor modulator or agonist during the initial 3 to 6 days, of treatment is increased stepwise. Thereafter the treatment is continued with the maintenance therapy with the standard daily dosage or with a lower daily dosage. When the treatment is continued at a lower daily dosage, it may be e.g. about 1/50 to ½, preferably 1/50 to 1/10, of the standard daily dosage of the S1P receptor modulator or agonist.

Preferably, the total dosage of said S1P receptor modulator or agonist during the initial 3 to 6 days, preferably 4 or 5 days, most preferred 4 days, of treatment is increased incrementally from 3- to 21-fold, more preferred from 4 to 12-fold, particularly about 10-fold, the standard daily dosage of said S1P receptor modulator or agonist. For example, the loading dose may be 1; 1.5-2; 2-3; and 3-4 fold the standard daily dosage, on day 1, 2, 3 and 4, respectively.

According to a preferred embodiment of the invention, the highest loading regimen dose instalment on the last day of the loading regimen, e.g. on day 4, is 4x the maintenance dose of the S1P receptor modulator or agonist. The instalment doses on days 1, 2 and 3 of the loading regimen may be e.g. about ¼; ½; and ¾ of the highest instalment dose of the S1P receptor modulator or agonist.

Ex. 1004 at 14; Paper 26 at 51-52; Ex. 2022 (Dr. Steinman) ¶¶ 164-68.

Kovarik Does Not Link MS with 0.5 mg Fingolimod



(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

Preferred medications comprise medication for transplant patients providing prolonged survival rates, in particular prolonged allograft survival rates especially for renal, heart, lung or liver transplants, or for patients suffering from autoimmune diseases, e.g. multiple sclerosis, lupus nephritis, rheumatoid arthritis, inflammatory bowel diseases or psoriasis.

(71) **Applicant** *(for all designated States except US)*: **NOVARTIS AG** [CH/CH]; Lichtstrasse 35, CH-4056 Basel (CH).

(71) **Applicant** *(for AT only)*: **NOVARTIS PHARMA GmbH** [AT/AT]; Brunner Strasse 59, A-1230 Vienna (AT).

(72) **Inventors; and**
(75) **Inventors/Applicants** *(for US only)*: **KOVARIK, John, M.** [US/CH]; Kraftstrasse 10, CH-4056 Basel (CH). **APPEL-DINGEMANSE, Silke** [DE/CH]; Luetzelbachweg 28, CH-4123 Allschwil (CH).

FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declaration under Rule 4.17:
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of*

A method for treating an autoimmune disease in a subject in need thereof, comprising administering to the subject, after a loading regimen, a daily dosage of FTY720 of about 0.1 to 0.5mg.

WO 2006/058316 A1

(54) **Title:** DOSAGE REGIMEN OF AN S1P RECEPTOR AGONIST

(57) **Abstract:** S1P receptor modulators or agonists are administered following a dosage regimen whereby during the initial 3 to 6 days of treatment the daily dosage is raised so that in total the R-fold (R being the accumulation factor) standard daily dosage is administered and thereafter continued at the standard daily dosage or at a daily dosage lower than the standard daily dosage.

Ex. 1004 at 14, 17; Paper 26 at 36.

Thomson Only Mentions 0.5 mg from Budde

Emerging therapy review

FTY720 in multiple sclerosis: the emerging evidence of its therapeutic value

Andrew Thomson

Core Medical Publishing, Knutsford, UK

The absorption phase of FTY720 is prolonged, characterized by a t_{max} of >12 h C_{max} (R^2=0.966; P<0.001) and AUC (R^2=0.916; P<0.001) were dose-proportional over the dose ranges (0.25–3.5 mg) All FTY720 groups showed a temporal pattern of relative lymphocyte sequestration, seen at the latest 6 h postdose. No clear dose response, but the highest doses showed a more pronounced reduction in lymphocyte numbers. Lymphocyte counts returned to ~80% baseline values 24 h postdose Almost all lymphocyte subgroups declined following FTY720 treatment, with CD4+ and CD45RA+ cells being affected the most. Natural killer cells, granulocytes, and monocytes were not influenced by FTY720	0.25 (n=6), 0.5 (n=6), 0.75 (n=3), 1 (n=3), 2 (n=3), or 3.5 mg (n=3), or placebo (n=8)	Randomized, double-blind, placebo-controlled, two-center, single-dose study in 20 stable renal transplant patients (mean age 43.2 y)	Budde et al. 2002; Budde et al. 2003

Paper 26 at 49-50, 53; Ex. 1005 at 163.

Kovarik & Thomson Fail to Teach 0.5 mg for RRMS

Reference Lacking: [1]	Kovarik (Ex. 1004)[2]	Thomson (Ex. 1005)[3]
Not teach 0.5 mg to treat RRMS.	X	X
Ref. not specific to any disease.	X	
Every dosing regimen requires a loading dose.	X	
No efficacy teaching for 0.5 mg daily for RRMS.	X	X
No daily dosage of 0.5 mg.	X	X

[1] Ex. 1001 at cls. 1-6 (Claim 1 is representative); [2] Paper 26 at 49-51; [3] Paper 26 at 4, 36, 49-52.

Ground I: Kovarik + Thompson – Evidence Fails to Support Theory

Dr. Giesser:

- Did not review state of the art and therefore ignorant of teaching away.
- Not a pharmacologist (*e.g.*, relies on an off-topic textbook with error in equation).
- Misreads Kovarik disclosure "an autoimmune disease."
- Misconstrues "daily" to include single dose.
- Mischaracterizes lymphopenia as a clinical end-point in MS (it is not).

Dr. Benet:

- Lacks experience with fingolimod, and performing EAE experiments.
- Over-reads certain Webb data while ignoring full teaching.
- Relies on max suppression data inappropriate for chronic RRMS treatment.
- Cannot offer opinion on meaning of preamble because he alone is not a POSA.
- Cherry-picked scaling factors with hindsight.

Paper 26 at 37, 42-46, 49-50, 54-55; Paper 63 at 2, 6-8.

Ground I – Failure of Proof

- References do not teach or make obvious the claimed invention.
  - Kovarik inapplicable to MS due to loading dose requirement – POSA would not look to loading dose patent to design a daily dose.
  - Kovarik teaches no specific regimen for RRMS, MS, or any particular autoimmune disease.
- No motivation to combine.
- Combination offers no reasonable expectation of success to a POSA in the context of the state of the art.

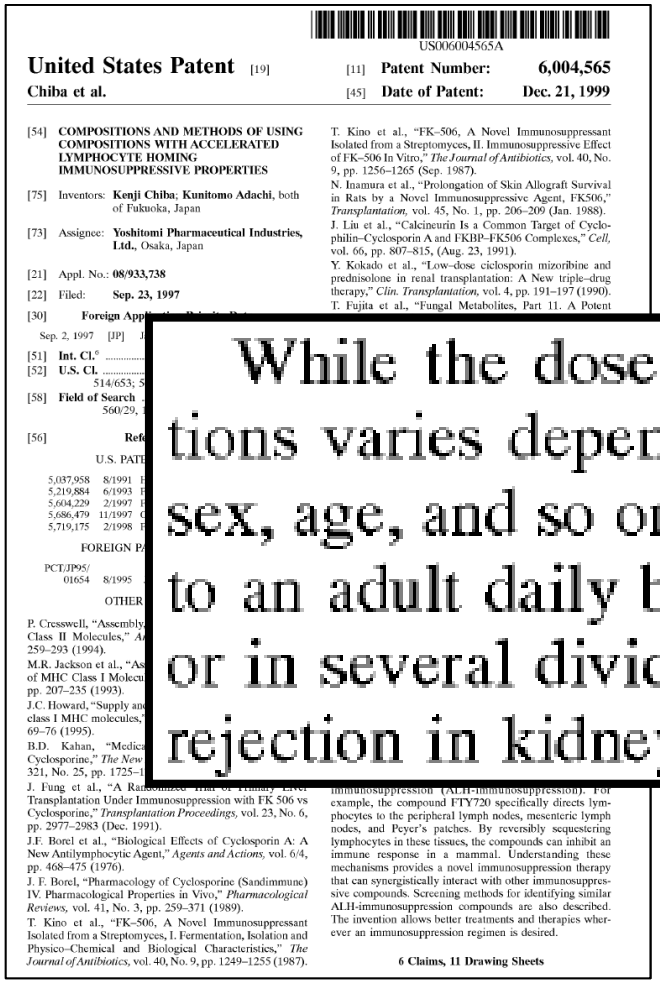
Paper 26 at 46-55.

Ground II

GROUND II:

Chiba + Budde + Kappos 2005

Chiba Discloses a 1000-Fold Range of Potential Doses



US006004565A

United States Patent [19]

Chiba et al.

[11] **Patent Number: 6,004,565**

[45] **Date of Patent: Dec. 21, 1999**

[54] **COMPOSITIONS AND METHODS OF USING COMPOSITIONS WITH ACCELERATED LYMPHOCYTE HOMING IMMUNOSUPPRESSIVE PROPERTIES**

[75] Inventors: **Kenji Chiba**; **Kunitomo Adachi**, both of Fukuoka, Japan

[73] Assignee: **Yoshitomi Pharmaceutical Industries, Ltd.**, Osaka, Japan

[21] Appl. No.: **08/933,738**

[22] Filed: **Sep. 23, 1997**

[30] Foreign Application Priority Data

Sep. 2, 1997 [JP] J

[51] **Int. Cl.**[6] .....

[52] **U.S. Cl.** 514/653; 5

[58] **Field of Search** 560/29,

[56] **Ref**

U.S. PATE

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T. Fujita et al., "Fungal Metabolites, Part 11. A Potent

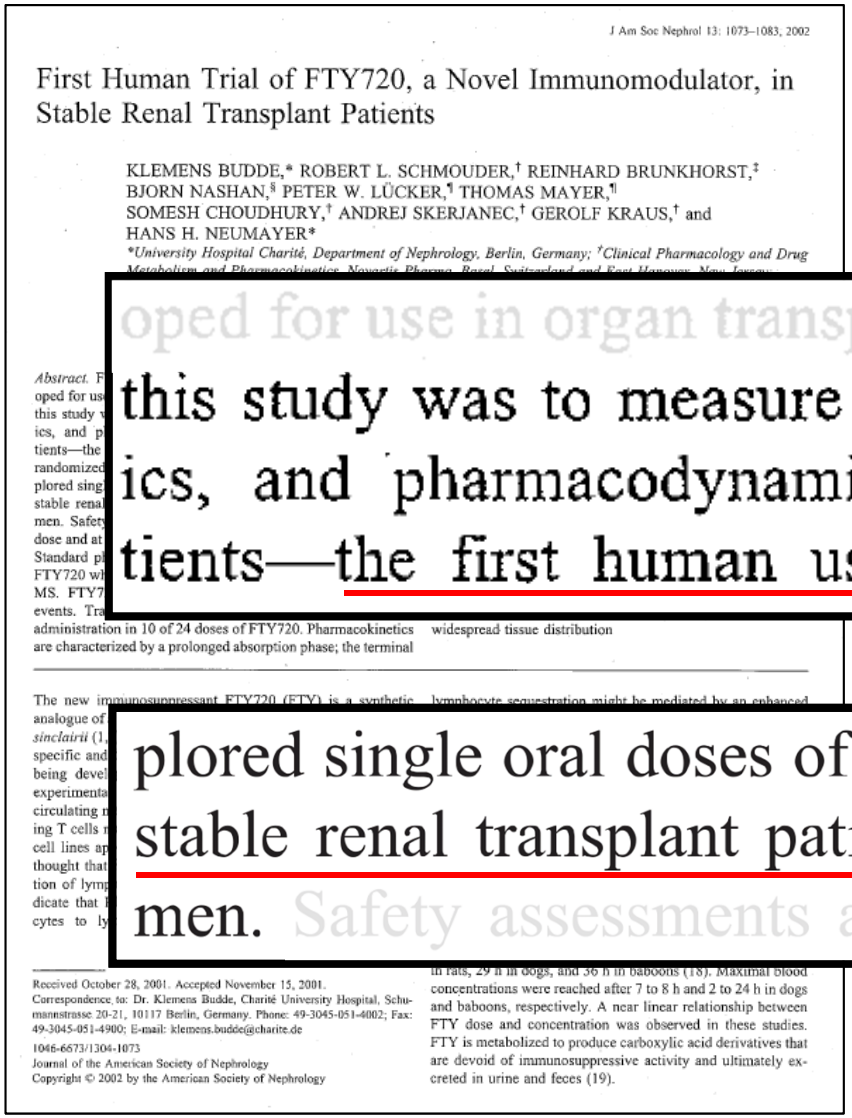
immunosuppression (ALH-immunosuppression). For example, the compound FTY720 specifically directs lymphocytes to the peripheral lymph nodes, mesenteric lymph nodes, and Peyer's patches. By reversibly sequestering lymphocytes in these tissues, the compounds can inhibit an immune response in a mammal. Understanding these mechanisms provides a novel immunosuppression therapy that can synergistically interact with other immunosuppressive compounds. Screening methods for identifying similar ALH-immunosuppression compounds are also described. The invention allows better treatments and therapies wherever an immunosuppression regimen is desired.

6 Claims, 11 Drawing Sheets

While the dose of the compounds used in the compositions varies depending on disease, symptom, body weight, sex, age, and so on, they may be administered, for example, to an adult daily by 0.01–10 mg (potency) in a single dose or in several divided doses, for example when suppressing rejection in kidney transplantation.

Ex. 1006 at II/41; Paper 26 at 56.

Budde 2002: Single-Dose Phase IA Safety Study



J Am Soc Nephrol 13: 1073–1083, 2002

First Human Trial of FTY720, a Novel Immunomodulator, in Stable Renal Transplant Patients

KLEMENS BUDDE,* ROBERT L. SCHMOUDER,† REINHARD BRUNKHORST,‡ BJORN NASHAN,§ PETER W. LÜCKER,¶ THOMAS MAYER,¶ SOMESH CHOUDHURY,† ANDREJ SKERJANEC,† GEROLF KRAUS,† and HANS H. NEUMAYER*

*University Hospital Charité, Department of Nephrology, Berlin, Germany; †Clinical Pharmacology and Drug Metabolism and Pharmacokinetics, Novartis Pharma, Basel, Switzerland and East Hanover, New Jersey,

oped for use in organ transplantation. The primary objective of this study was to measure safety, single-dose pharmacokinetics, and pharmacodynamics in stable renal transplant patients—the first human use of FTY720. This study used a

plored single oral doses of FTY720 from 0.25 to 3.5 mg in 20 stable renal transplant patients on a cyclosporine-based regimen. Safety assessments and blood samples were taken pre-

Received October 28, 2001. Accepted November 15, 2001.
Correspondence to: Dr. Klemens Budde, Charité University Hospital, Schumannstrasse 20-21, 10117 Berlin, Germany. Phone: 49-3045-051-4002; Fax: 49-3045-051-4900; E-mail: klemens.budde@charite.de
1046-6673/1304-1073
Journal of the American Society of Nephrology

Ex. 1008 at 1073; Paper 26 at 5, 9-10.

Kappos 2005: Teaches Dose No Lower Than 1.25 mg

O141
FTY720 in relapsing MS: results of a double-blind placebo-controlled trial with a novel oral immunomodulator
L. Kappos, E. W. Radü, J. Antel, G. Comi, X. Montalban, P. O'Connor, O. Bettoni-Ristic, T. Haas, R. Preiss, A. Korn
on behalf of the FTY720D2201 Study Group

FTY720 is an oral immunomodulator (sphingosine-1 phosphate receptor (S1P) modulator) that reversibly sequesters tissue damaging T and B cells away from blood and the central nervous system to peripheral lymph nodes. FTY720 has demonstrated both preventive and therapeutic efficacy in several animal models of MS.

Methods: We report the clinical and MRI results of an international, multicenter, double-blind study to evaluate efficacy, safety and tolerability of two doses of FTY720 and placebo (PL). 281 patients with active relapsing MS were randomized to receive PL (n = 93), 1.25 mg (n = 94) or 5.0 mg FTY720 (n = 94) q. d. for 6 months. Patients had monthly cranial MRI scans and 3-monthly neurological assessments by a neurologist otherwise not involved in their care.

Results: Clinical and MRI baseline characteristics were balanced amongst groups. The primary outcome, mean (median) total number of Gadolinium(Gd)-enhancing lesions in monthly post baseline MRI scans was 14.8 (5.0), 8.4 (1.0) and 5.7 (3.0) for PL, FTY 1.25 and 5.0 mg groups ($p < 0.001$ 1.25 vs. PL, $p = 0.006$ 5.0 vs. PL). Similar, clearly significant effects favoring both FTY720 groups vs. PL were found for Gd-enhancing lesion volume, new T2 lesions and change in T2 lesion volume (only 5 mg qd sign. better than PL). The proportion of relapse-free patients (70.0, 86.0 and 86 %; $p = 0.007$ 1.25 mg vs. PL, $p = 0.008$ 5 mg vs. PL), annualized relapse rate (0.77, 0.35 and 0.36) and time to first relapse were significantly better in both FTY720 groups vs. PL. There was no compelling dose-related difference in efficacy on MRI or clinical endpoints. Treatment was generally well tolerated with 255 (91 %) of patients completing study and 249 (89 %)

in both FTY720 groups vs. PL. There was no compelling dose-related difference in efficacy on MRI or clinical endpoints. Treatment was generally

safety evaluations strongly suggest that FTY720 has the potential to be an efficacious disease modifying treatment for relapsing forms of MS with the additional benefit of once daily oral administration.

Study supported by Novartis Pharma AG Basel.

- Clinical and MRI results of study in RRMS of 5.0 mg, 1.25 mg, and placebo.
- "[C]learly significant effects favoring both FTY720 groups…" were reported.
- Mild adverse events were more common in 5 mg group.

Ex. 1007 at II/41; Paper 26 at 20.

Chiba, Budde, and Kappos 2005: Do Not Teach Claimed Invention

Chiba (Ex. 1006)[1]	Budde (Ex. 1008)[2]	Kappos (Ex. 1007)[3]
• Range of 0.1 mg to 10 mg disclosed with general disclosure of autoimmune disease and transplant rejection. • 0.5 mg not disclosed specifically.	• Single, one-time dose. Not a daily dose. • No RRMS patients. • Administration to stable, renal, transplant patients taking other immuno-suppressants.	• Only discloses dosage amounts of 1.25 mg and 5.0 mg with positive results in RRMS for each dose in Phase II trial.

None of the references provides a motivation to combine.

[1] Paper 26 at 37-38, 55-56. [2] Paper 26 at 9-10; Ex. 2022 (Dr. Steinman) ¶¶ 50-54. [3] Paper 26 at 20, 56.

Prior Art Teaches Away

- A reference teaches away "when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent form the path that was taken by the applicant."

  Allergan, Inc. v. Sandoz Inc., 796 F.3d 1293, 1305 (Fed. Cir. 2015).

- When evaluating teaching away, "the prior art must be considered *as a whole* for what it teaches."

  Medichem S.A. v. Rolabo, 437 F.3d 1157, 1166 (Fed. Cir. 2006)(emphasis in original).

Paper 26 at 33-34, 37.

Prior Art Teaches Away

- Webb 2004 identifies 70% threshold for efficacy in EAE
- Park 2005 and Kahan 2003 show 70% lymphopenia achieved only at doses 1.0 mg or higher in humans
- References read as a whole teach away from 0.5 mg

Paper 26 at 10-14, 16-19, 33-35..

Webb 2004: Data in Paper Supports Conclusion

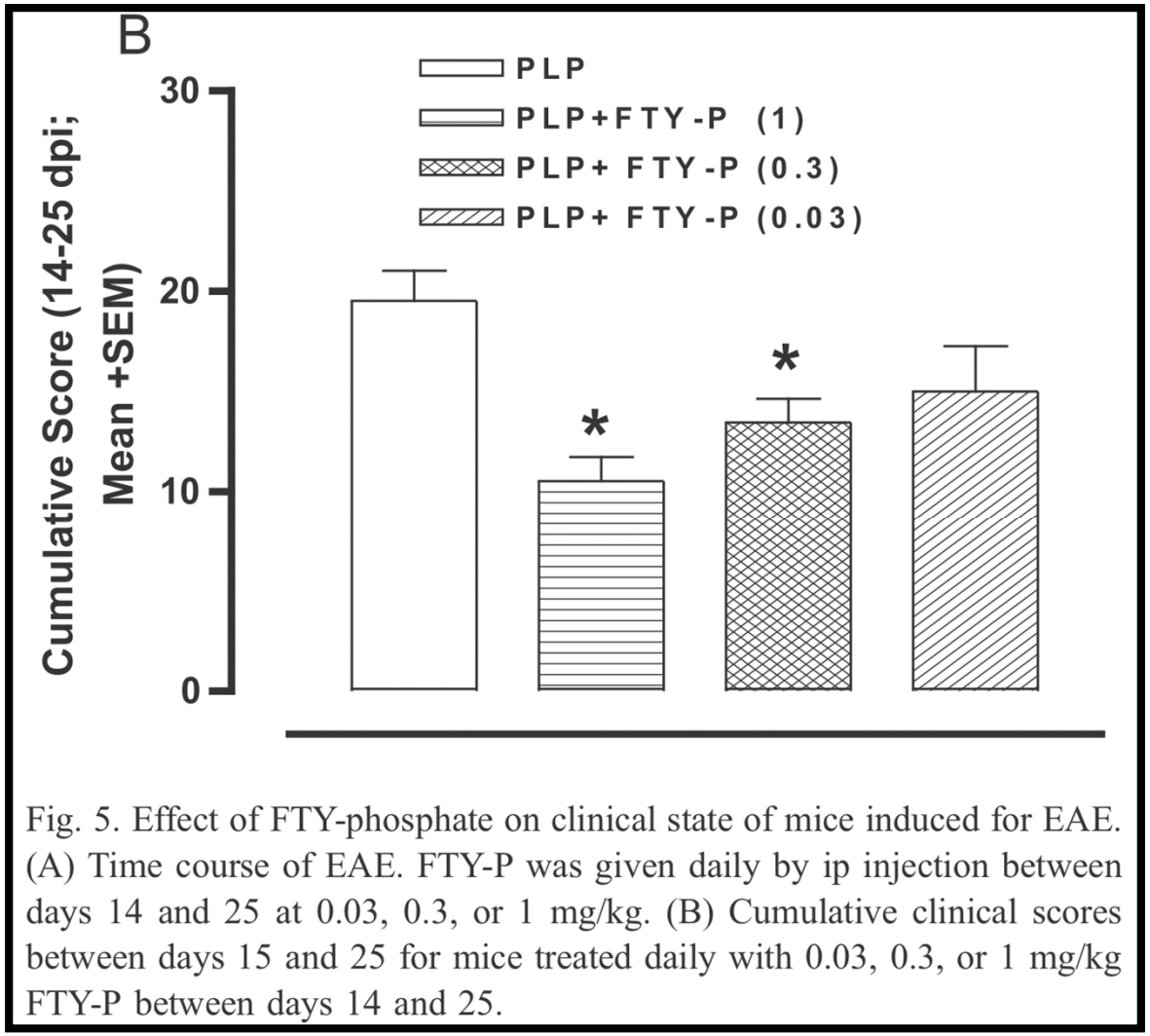


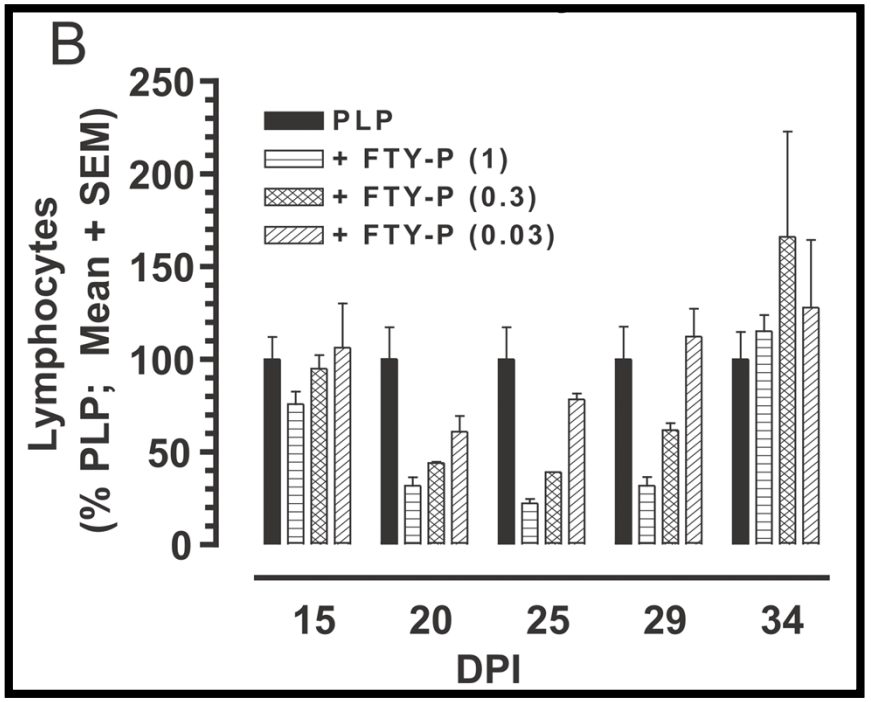
Fig. 5. Effect of FTY-phosphate on clinical state of mice induced for EAE. (A) Time course of EAE. FTY-P was given daily by ip injection between days 14 and 25 at 0.03, 0.3, or 1 mg/kg. (B) Cumulative clinical scores between days 15 and 25 for mice treated daily with 0.03, 0.3, or 1 mg/kg FTY-P between days 14 and 25.

As to Fig. 5B, Dr. Steinman says "the **lowest 0.03 mg/kg dose provided no statistically significant clinical benefit**, as shown by the absence of an asterisk over the 0.03 mg/kg bar." Ex. 2022, ¶ 81.

Ex. 2022 (Dr. Steinman) ¶¶ 80-83; Paper 26 at 16-19, 45.

Webb 2004: Figure 6 Supports 70% Threshold

Dr. Chun says: "The subjective nature of EAE clinical scoring renders distinctions of "about 70%" and 60% **virtually moot**. Our goal was to provide – in our concluding statements in the Discussion — conclusions that could be examined and **reproduced by others**. Those conclusions were not based solely on the averages reported in Figures 5 and 6 in isolation. Rather, we **drew our conclusions using all of our data** that included individual mice. We saw a **striking pattern** in that data that **only mice with about 70% or greater suppression in lymphocytes compared to baseline showed sustained clinical efficacy** produced by drug exposure." Dr. Chun, Ex. 2098, ¶ 38.



Paper 63 at 6.

Dr. Steinman: Webb Authors Meant What They Said

> 26. But a person of skill in June 2006 would have read Webb to mean what it says: "In dose response experiments, we found that a threshold of about 70% depletion of peripheral lymphocytes was required to see any efficacy[.]" (Ex. 2014 at 118.) Webb was published in a respected, peer-reviewed journal. The paper describes experiments that generated data sufficient for the authors' conclusions (Ex. 2022 at ¶ 74-85), and those conclusions resonated with similar results in transplant patients showing that fingolimod had to suppress lymphocytes by 80% to be effective (*id.* at ¶ 127).

Ex. 2096 (Dr. Steinman) ¶¶ 25-40; Paper 63 at 6.

Dr. Chun and Dr. Steinman Confirm Webb Teaching

- Dr. Chun, a co-author of Webb 2004, testified that his paper meant what it said – about 70% suppression being needed for any efficacy. (Ex. 2098, ¶¶ 2-9,17-35.)
- Dr. Chun testified he and his co-authors used judgment informed by multiple data points, not just averaged data. They considered data from individual mice, and qualitative assessments of various aspects of the EAE model. (*Id*. ¶¶ 2-8,36-41.)
- Dr. Steinman testified that a person of skill would have believed Webb as written. (Ex. 2096, ¶¶ 25-40.)

Paper 63 at 6.

Skepticism of Experts Consistent with Teaching Away

"Doubt or disbelief by skilled artisans regarding the likely success of a combination or solution weighs against the notion that one would combine elements in references to achieve the claimed invention."

WBIP, LLC v. Kohler Co., 829 F.3d 1317, 1335 (Fed. Cir. 2016).

In *WBIP*, skepticism arose from audience reaction to a presentation.

Paper 26 at 40-41.

Dr. Lublin Expected No Efficacy From 0.5 mg

2. I have been involved in clinical trials for almost every MS medication approved in the U.S. and Europe as of June 2006 and thereafter, as well as many that were never approved. I was involved in both the Phase II and Phase III human trials for fingolimod, as I describe further below.

3. The Phase III trial for fingolimod tested two doses, 1.25 mg and 0.5 mg daily. Counsel for Novartis has asked me whether the 0.5 mg dose was expected to be effective. The answer is no. I and others believed the likelihood was that 0.5 mg daily would be equivalent to placebo, *i.e.*, that it would show no efficacy. Even if it showed some efficacy, I am aware of no one who believed that dose would have the same efficacy as 1.25 mg daily. I was very surprised when 0.5 mg daily produced essentially the same results as that higher dose.

Dr. Lublin, Ex. 2025 ¶¶ 2-3; Paper 26 at 27.

Unexpected Results

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 4, 2010 VOL. 362 NO. 5

A Placebo-Controlled Trial of Oral Fingolimod in Relapsing Multiple Sclerosis

Ludwig Kappos, M.D., Ernst-Wilhelm Radue, M.D., Paul O'Connor, M.D., Chris Polman, M.D., Reinhard Hohlfeld, M.D., Peter Calabresi, M.D., Krzysztof Selmaj, M.D., Catherine Agoropoulou, Ph.D., Malgorzata Leyk, Ph.D., Lixin Zhang-Auberson, M.D., Ph.D., and Pascale Burtin, M.D., Ph.D., for the FREEDOMS Study Group*

ABSTRACT

CONCLUSIONS

As compared with placebo, both doses of oral fingolimod improved the relapse rate, the risk of disability progression, and end points on MRI. These benefits will need to be weighed against possible long-term risks. (ClinicalTrials.gov number, NCT00289978.)

Ex. 1038 at 387; Paper 26 at 27; Ex. 2025 (Dr. Lublin) ¶¶ 59-63.

RRMS Dosing Patent Recently Upheld Based Only on Unexpected Results

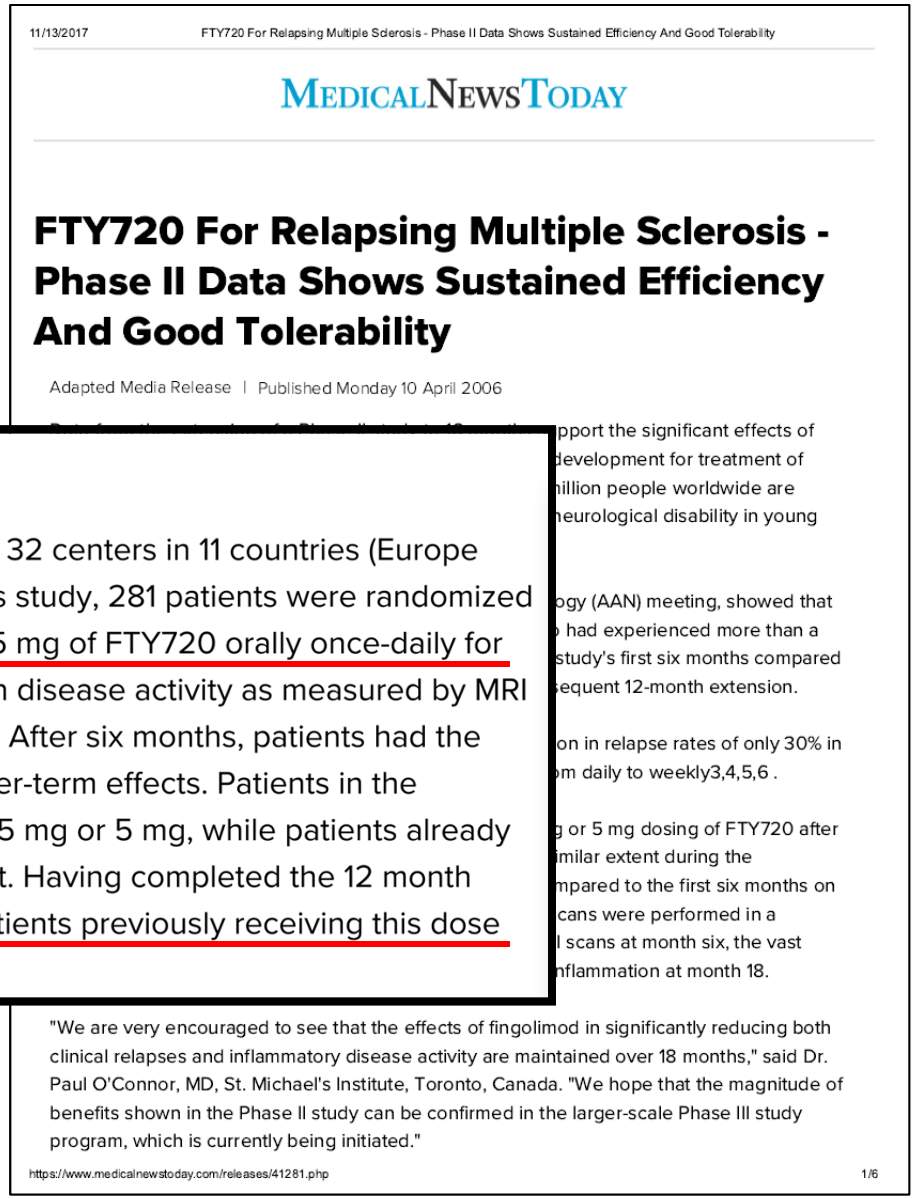
CAFD, et al. v. Biogen M.A., Inc., IPR2015-01933, Paper 63 (PTAB Mar. 21, 2017):

- Patent on 480 mg daily dose of an RRMS drug, filed after Phase II clinical trial results showing efficacy of 720 mg but lack of statistical efficacy of 240 mg and 360 mg.
- Board rejected obviousness challenge—Phase III trials showed 480 mg had similar efficacy to 720, which was an unexpected result.

- ***In the present case there is far more evidence of patentability***:
  - Prior art teaching away
  - Innovative animal model use led to invention; and
  - Unexpected results corroborated by multiple contemporaneous documents.

Paper 26 at 32-33, 39; Paper 63 at 11-12.

Chavez Press Release: Phase II Results for 1.25 mg



11/13/2017 FTY720 For Relapsing Multiple Sclerosis - Phase II Data Shows Sustained Efficiency And Good Tolerability

MEDICAL NEWS TODAY

FTY720 For Relapsing Multiple Sclerosis - Phase II Data Shows Sustained Efficiency And Good Tolerability

Adapted Media Release | Published Monday 10 April 2006

pport the significant effects of
development for treatment of
illion people worldwide are
eurological disability in young

gy (AAN) meeting, showed that
had experienced more than a
study's first six months compared
equent 12-month extension.

on in relapse rates of only 30% in
m daily to weekly3,4,5,6 .

or 5 mg dosing of FTY720 after
imilar extent during the
mpared to the first six months on
cans were performed in a
scans at month six, the vast
nflammation at month 18.

"We are very encouraged to see that the effects of fingolimod in significantly reducing both clinical relapses and inflammatory disease activity are maintained over 18 months," said Dr. Paul O'Connor, MD, St. Michael's Institute, Toronto, Canada. "We hope that the magnitude of benefits shown in the Phase II study can be confirmed in the larger-scale Phase III study program, which is currently being initiated."

https://www.medicalnewstoday.com/releases/41281.php 1/6

Phase II study design

The results are from a large Phase II study conducted at 32 centers in 11 countries (Europe and Canada). In the initial, placebo-controlled part of this study, 281 patients were randomized in equal numbers to receive either placebo, 1.25 mg or 5 mg of FTY720 orally once-daily for six months. The study evaluated the effect of FTY720 on disease activity as measured by MRI and clinical relapses as well as its tolerability and safety. After six months, patients had the option to enter the extension phase evaluating the longer-term effects. Patients in the placebo group were re-randomized to receive either 1.25 mg or 5 mg, while patients already on FTY720 continued their originally-assigned treatment. Having completed the 12 month time point, the 5 mg dose arm was discontinued and patients previously receiving this dose were continuing in the study on a dose of 1.25mg.

Ex. 2031 at 2; Paper 64 at 8; Ex. 2097 ¶¶ 8-10.

Chavez Announces a Phase III Trial to "Confirm" 1.25 mg

MEDICAL NEWS TODAY

FTY720 For Relapsing Multiple Sclerosis - Phase II Data Shows Sustained Efficiency And Good Tolerability

"We are very encouraged to see that the effects of fingolimod in significantly reducing both clinical relapses and inflammatory disease activity are maintained over 18 months," said Dr. Paul O'Connor, MD, St. Michael's Institute, Toronto, Canada. "We hope that the magnitude of benefits shown in the Phase II study can be confirmed in the larger-scale Phase III study program, which is currently being initiated."

Phase III study program

Novartis has initiated its first Phase III pivotal study called "FREEDOMS" (Fingolimod Research Evaluating Effects of Daily Oral therapy in Multiple Sclerosis). The 24-month, randomized, double-blind, placebo-controlled FREEDOMS study will include more than 1,000 patients with relapsing-remitting MS between age 18-55. Study participants will be equally randomized to either receive either 1.25 mg or 0.5 mg of FTY720 or placebo once daily for up to 24 months.

Ex. 2031 at 2; Paper 64 at 8-9; Paper 63 at 9-11.

Dr. Lublin Testified that Chavez Only Discloses a Test

Q. And you also agree that the person of ordinary skill in the art on that date would understand that that daily dose is administered to RRMS patients who have a need for reducing, preventing, or alleviating relapses who have a need for RRMS treatment, and who have a need for slowing the progression of RRMS.

Correct?

MR. TRENCHARD: Same objections.

A. No. They would understand that a study was being done to test that dose.

Paper 64 at 9-10; Ex. 1042 at 239:10-21.

Ground III

GROUND III:

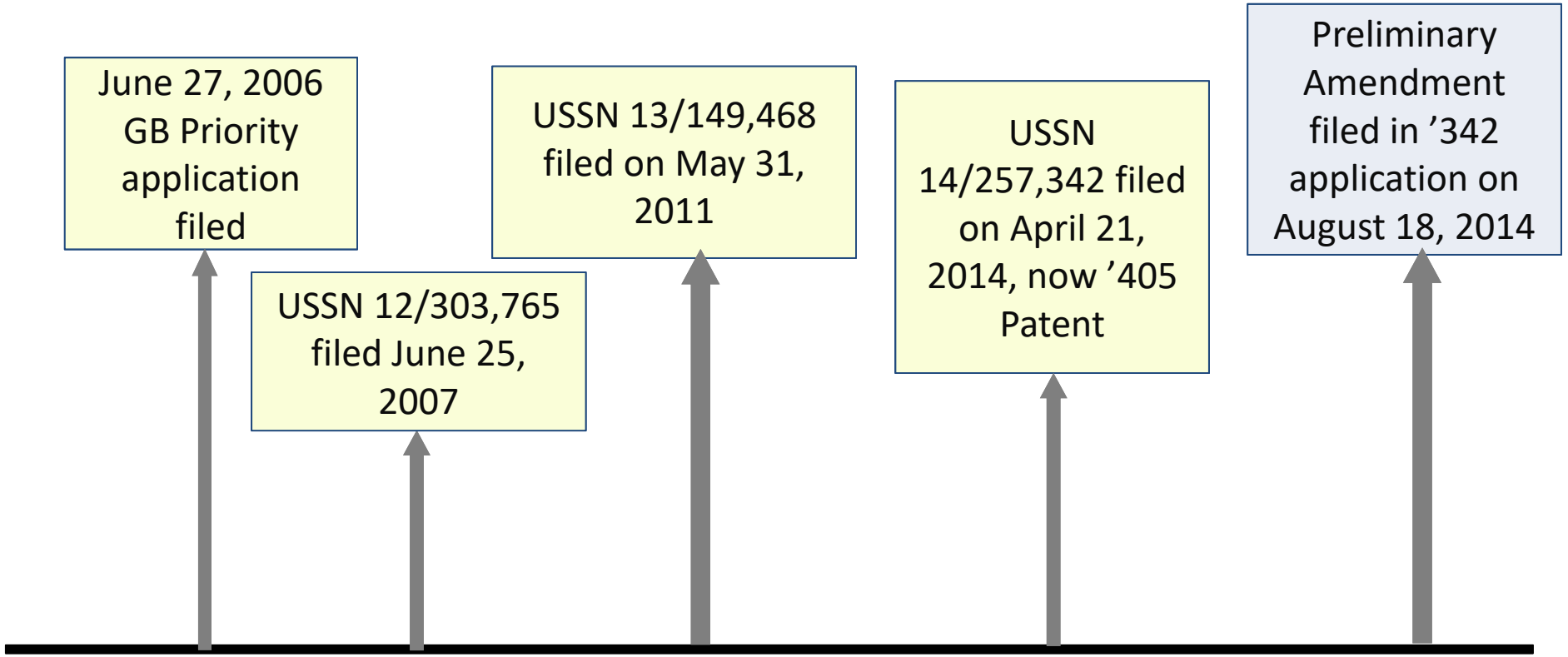
35 USC § 112 & Kappos 2010

Ground III Improper Under 35 U.S.C. § 311

- Decision in *Bioactive Labs* does not reach the present situation.
- Here, Petitioners ask Board to accord Patent Owner April 2014 filing date because negative limitation was added in Preliminary Amendment filed in August 2014, four months after filing date.
- Petitioners give no reasoning to rationalize choosing the later April 2014 filing date instead of the earliest filing date in June 2006 except for the proximity to the filing date of the Preliminary Amendment.
- There are no C-I-Ps and no new subject matter was added.

Paper 26 at 57-61; *Bioactive Labs. V. BTG Int'l Inc.*, IPR2015-01778, 2016 WL 1082772, at *3 (P.T.A.B. Feb 16, 2016).

Application Filing Timeline



- No additional subject matter added.
- No C-I-P's.

Paper 26 at 61; Paper 2 at 57-58; Ex. 1009; Ex. 1010; Ex. 1011; Ex. 1012.

35 U.S.C. § 112 Was Met as of June 2006

- Dr. Steinman testified that the specification in June 2006 would have told a person of ordinary skill in the art that the inventors possessed the entire invention – including a daily dose that excluded loading doses. Ex. 2022, ¶¶182-189.

- Dr. Jusko testified that the specification discloses a complete dosing regimen and thus a person of skill would know not to add in any other features to the prescribed dosing regimen. Ex. 2024, ¶¶173-176.

Paper 26 at 61-64.

Contingent Motion to Amend

Contingent

Motion to Amend

Motion to Amend

Proposed Claim 7. (Proposed substitute claim in place of original claim 1.) A method for reducing or preventing or alleviating relapses in Relapsing-Remitting multiple sclerosis in a subject in need thereof, comprising orally administering to said subject 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol, in free form or in a pharmaceutically acceptable salt form, wherein the subject receives a dosing regimen consisting of a daily dosage amount of ~~at a daily dosage of~~ 0.5 mg of 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol , ~~absent an immediately preceding loading dose regimen~~.

Paper 61 at 19.

Proposed Amended Claims Address All Three Grounds

- Ground III:
  - Proposed amendments obviate the predicate by deleting the negative limitation.
- Ground I and II:
  - The "consisting of" phrase closes the scope of the fingolimod dosing regimen so nothing more than 0.5 mg daily is encompassed. The narrower claims show it is even less reasonable for a POSA to believe the claim is obvious in view of the references.

Paper 61 at 14-18; Paper 64 at 11-12.

Claim Construction: "Daily Dosage"

- Petitioners argue "daily dosage" encompasses a single, one-time dose.
- Under broadest reasonable interpretation standard, this is not a reasonable position because it renders the term "daily" meaningless.
- Drs. Steinman and Jusko testify that "daily" does not mean a one-time, single dose.

Ex. 2022 (Dr. Steinman) ¶¶ 179, 183; Ex. 2096 (Dr. Steinman) ¶¶ 21-24; Ex. 2024 (Dr. Jusko) ¶ 114, 140; Paper 26 at 37; Paper 64 at 6-7.

Claim Construction: "Dosing Regimen"

- Dr. Steinman testifies:

"As of June 2006 a person of skill would have understood that the general phrase 'dosing regimen' is an umbrella term that encompasses different aspects of dosing. The definition of a dosing regimen is a schedule of doses of a therapeutic agent per unit of time, including the time between doses or the time when the doses are to be given and the amount of the therapeutic agent to be given at each specific time."

Ex. 2096, ¶ 18, underlining added.

Paper 64 at 5-6.

Claim Construction: "Consisting Of"

- "Consisting of" narrows all of the original claims.
- Petitioners' "hypothetical" claim violates meaning of "consisting of" and meaning of "dosing regimen."

> The method of claim 9, wherein the method further comprises administering to said subject a loading dose regimen immediately preceding the dosing regimen consisting of a daily dosage amount of 0.5 mg of 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,2-diol .

Paper 61 at 12-13; Paper 62 at 10-11; Paper 64 at 3-6.

Preambles Are Limiting and Require Efficacy

Dr. Giesser agrees all RRMS patients need all aspects claimed.

> the method. Thus, under the broadest reasonable interpretation of the claims of the '405 patent, any subject that has RR-MS is a subject in need of a method for "reducing or preventing or alleviating relapses in RR-MS," "[a] method for slowing progression of Relapsing-Remitting multiple sclerosis," and a method for "treating" RR-MS.

- Dr. Steinman agrees. Ex. 2096 ¶ 11.
- Presumption against claim redundancy and antecedent basis support efficacy requirement.
- No expert testimony from Petitioners to the contrary.

Dr. Giesser, Ex. 1002, ¶ 44; Paper 64 at 2-3.

The Preambles Require Efficacy

- Petitioners do not dispute that the ’405 Patent preambles are limiting.
- Petitioners cite *In re Montgomery* to argue that “method of treating claims impose no ‘efficacy requirement[.]’” (Paper 49 at 7.)
- But, the Federal Circuit in *Montgomery* assumed the claims there imposed an efficacy limitation.
- Also, the *Montgomery* claims were to only one method with one effect; no claim redundancy problem like the claims here.
- The specification here shows efficacy was at the core of the invention, unlike *Montgomery*.

Paper 63 at 2-5.

Preambles Require Efficacy

- Claims to 0.5 mg daily for the purpose of achieving, or to actually achieve the specific effects recited in the claims.
- Dr. Steinman testifies from point of view of POSA that:
  - Specification repeatedly emphasizes the invention's therapeutic benefits. Ex. 2096, ¶ 13.
  - Inventors discovered a new mechanism of action that produced certain effects. *Id*., ¶ 14.
  - Animal model example showing effects. *Id*., ¶ 15.
  - Human example in specification focused on achieving certain effects. *Id*.
  - In arguments for patentability, file history mentions balance of safety and efficacy. *Id*., ¶ 16.
  - "[A] person of skill in June 2006 would read the claims to require that the dose be administered to achieve the effects of the claimed benefits, or at least be intended to do so." *Id*., ¶ 18.

Paper 63 at 2-5.

Chavez Does Not Anticipate

- Chavez does not anticipate expressly or inherently.
- Chavez does not disclose claim preambles.
- Chavez is silent on efficacy for 0.5 mg arm.
- Dr. Lublin says efficacy is not necessarily result from using 0.5 mg.
- No expert testimony from Petitioners.

> in the Phase III trial. As I showed in my Second Declaration (at ¶¶ 48-49), commentators described the Phase III trial as designed to "confirm" the Phase II results for 1.25 mg daily, but merely to "evaluate" the 0.5 mg daily dose. That difference in language reflects a difference in expectation about the doses. It was not necessarily the case that the 0.5 mg arm of the Phase III clinical trial would have resulted in efficacy.

Dr. Lublin, Ex. 2097 ¶ 8; Paper 64 at 7-10.

Inherency

- Petitioners cite *BMS v. Ben Venue*, 246 F.3d 1368 (Fed. Cir. 2001), and *In re Montgomery*, 677 F.3d 1375 (Fed. Cir. 2012), as their primary inherency references. (Paper 62 at 5.)

- The majority in *Montgomery* held that inherency cannot be based on Phase III results "published … after [the] priority date[.]" 677 F.3d at 1378.

- Petitioners here have submitted no other evidence to suggest inherency.

Paper 64 at 7-8.

Inherency

- For a patented "process" to be inherently anticipated, it must be "*directed to the same purpose*" as the original process. *BMS*, 246 F.3d at 1376; *Montgomery*, 677 F.3d at 1381.
- Here, Chavez describes giving 0.5 mg to RRMS patients for "testing," as the undisputed testimony of Dr. Lublin shows. Ex. 2025 ¶ 48.
  - But the '405 Patent uses that dose for a different purpose: as a therapy.
- In contrast, *BMS* and *Montgomery* involved using known processes for known uses: to treat cancer (*BMS*) or hypertension and stroke (*Montgomery*).

Paper 64 at 7-10.

Dr. Benet's Animal Scaling Argument is Wrong

- Dr. Benet argues that a person of skill would seize on Kataoka's lowest effective dose in an EAE mouse (0.1 mg/kg) and scale up from that using the FDA Guidance to 0.5 mg in humans.
- Dr. Jusko shows the flaws in this methodology.
  - ***First***, the FDA Guidance is only for first-in-human use before human PK/PD data exists; here, human PK/PD data existed.
  - ***Second***, the FDA Guidance is general and does not take account of animal PK/PD data with any specific drug; here, animal PK/PD data existed.
  - ***Third***, the FDA guidance provides multiple methods for dose scaling, the weight of which point toward doses 1.0 mg or higher.

Ex. 2095 ¶¶ 1-44; Paper 63 at 7-8.

Dr. Benet Misuses FDA Guidance Scaling to Human Dose

Guidance for Industry

Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers

This guidance outlines a process (algorithm) and vocabulary for deriving the maximum recommended starting dose (MRSD) for *first-in-human* clinical trials of new molecular entities in adult healthy volunteers, and recommends a standardized process by which the MRSD can be selected. The purpose of this process is to ensure the safety of the human volunteers.

By June 2006, fingolimod had been used for years in humans, yielding extensive PK/PD data.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

July 2005
Pharmacology and Toxicology

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07/06/05

Ex. 1049 at 1; Ex. 2095 ¶¶ 4-18; Paper 63 at 7-8.

Dr. Benet's Animal Scaling Argument Is Wrong

- FDA Guidance: "identifying … 'pharmacologically active' doses (PAD) 'depends on many factors and differs markedly among pharmacological drug classes and clinical indications; therefore, selection of a PAD is *beyond the scope of this guidance*.'"

- Instead, pharmacologist would use PD data from Webb and humans to estimate doses.
  - "[P]harmacologists assume that PD markers like lymphocyte suppression apply across species, absent evidence to the contrary."
  - No such evidence here.

Ex. 2095 ¶ 8 (quoting Ex. 1049 at 12 (adding emphasis*); Id*. ¶ 9; Paper 63 at 7-8.

Dr. Benet Misuses FDA Guidance Scaling to Human Dose

Guidance for Industry

Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers

Although the process outlined in this guidance uses administered doses, observed toxicities, and an algorithmic approach to calculate the MRSD, an alternative approach could be proposed that places primary emphasis on animal pharmacokinetics and modeling rather than dose (Mahmood et al. 2003; Reigner and Blesch 2002). In a limited number of cases, animal pharmacokinetic

Dr. Jusko: "…if a pharmacologist were inclined to try to scale a human dose from the Kataoka animal data in June 2006, he would turn to actual clearance data in the relevant species. He would find the actual human and rat clearance data that was available at the time and would use it for scaling. … Scaling from rat to human would have pointed toward scaled doses for humans of 1.0 mg or higher." Ex. 2095, ¶26.

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07/06/05

APOTEX ET AL. - EXHIBIT 1049
Apotex Inc. et al. v. Novartis AG
IPR2017-00854

Ex. 1049 at 2; Ex. 2095 ¶¶ 4-18; Paper 63 at 7-8.

Dr. Benet Cherry-Picked Scaling Factors

In choosing how to extrapolate from Kataoka with the FDA Guidance, Dr. Benet chose the one formula that would yield the lowest estimated human dose.

Kataoka Dose	Body Surface Area Exponent	Conversion Factor	Formula	**Human Equivalent Dose**
0.1 mg/kg Mouse	0.67	0.075	0.1 x 0.075 x 75	**0.56 mg**
0.1 mg/kg Mouse	0.75	0.141	0.1 x 0.141 x 75	**1.05 mg**
0.1 mg/kg Rat	0.67	0.156	0.1 x 0.156 x 75	**1.17 mg**
0.1 mg/kg Rat	0.75	0.245	0.1 x 0.245 x 75	**1.83 mg**

Ex. 2095 ¶¶ 41; Paper 63 at 8.

Conclusion

- Ground I and II should be denied because Petitioners have not carried their burden of showing unpatentability. Contemporaneous evidence and expert testimony support non-obviousness of the claimed invention.
  - State of art taught away from invention and toward 1.0 mg.
  - Skepticism of experts as shown by futility analysis and IRB at Mt. Sinai refusing to join clinical trial using 0.5 mg.
  - Unexpected results in patent showing EAE animal model results and in Phase III trial result with 0.5 mg showing efficacy, and at a level similar to 1.25 mg.
- Impermissible hindsight arguments by Petitioners' less qualified experts don't outweigh contemporaneous evidence from multiple sources.
- Ground III not proper under AIA and should be denied.
- Proposed amended claims address all grounds of rejections and are novel and non-obvious over Chavez too. Petitioners have no expert testimony to support their opposition.

CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6, I hereby certify that on May 10, 2018, true and accurate copies of the foregoing PATENT OWNER NOVARTIS'S CORRECTED ORAL HEARING DEMONSTRATIVES for IPR2017-00854 was served via electronic mail, on the following counsel of record for Petitioners:

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Respectfully submitted,

Dated: May 10, 2018

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