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

MYLAN PHARMACEUTICALS INC., SAWAI USA, INC., AND SAWAI PHARMACEUTICAL CO., LTD.,

v.

BIOGEN MA INC.

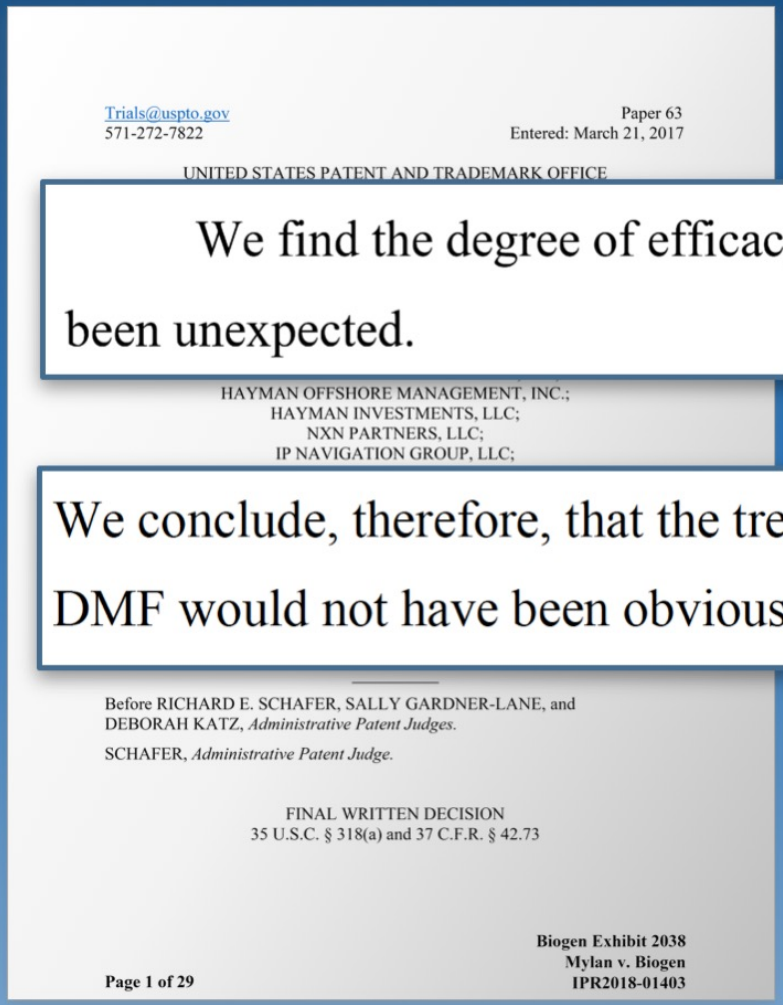
Case No. IPR2018-01403, IPR2019-00789

U.S. Patent No. 8,399,514

BIOGEN TRIAL DEMONSTRATIVES

November 13, 2019

Coalition v. Biogen MA Inc., IPR2015-01993



Trials@uspto.gov
571-272-7822

Paper 63
Entered: March 21, 2017

UNITED STATES PATENT AND TRADEMARK OFFICE

HAYMAN OFFSHORE MANAGEMENT, INC.;
HAYMAN INVESTMENTS, LLC;
NXN PARTNERS, LLC;
IP NAVIGATION GROUP, LLC;

Before RICHARD E. SCHAFER, SALLY GARDNER-LANE, and DEBORAH KATZ, *Administrative Patent Judges.*

SCHAFER, *Administrative Patent Judge.*

FINAL WRITTEN DECISION
35 U.S.C. § 318(a) and 37 C.F.R. § 42.73

Biogen Exhibit 2038
Mylan v. Biogen
IPR2018-01403

Page 1 of 29

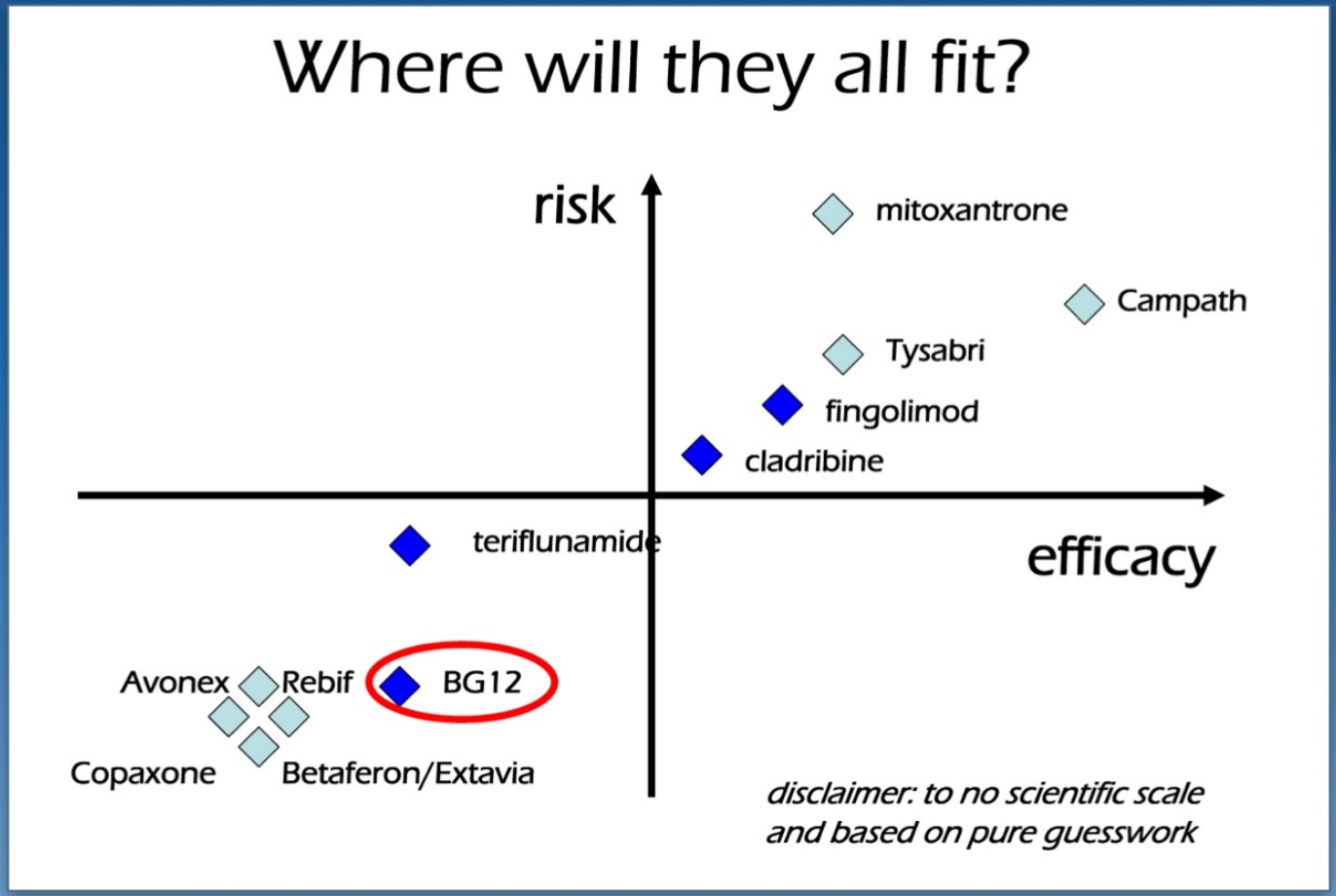
We find the degree of efficacy of the 480 mg/day dose of DMF would have been unexpected.

We conclude, therefore, that the treatment of MS patients with 480 mg/day of DMF would not have been obvious. "Objective indicia of non-obviousness 'may

Ex. 2038, 25-26

Dr. Duddy's Contemporaneous Perception

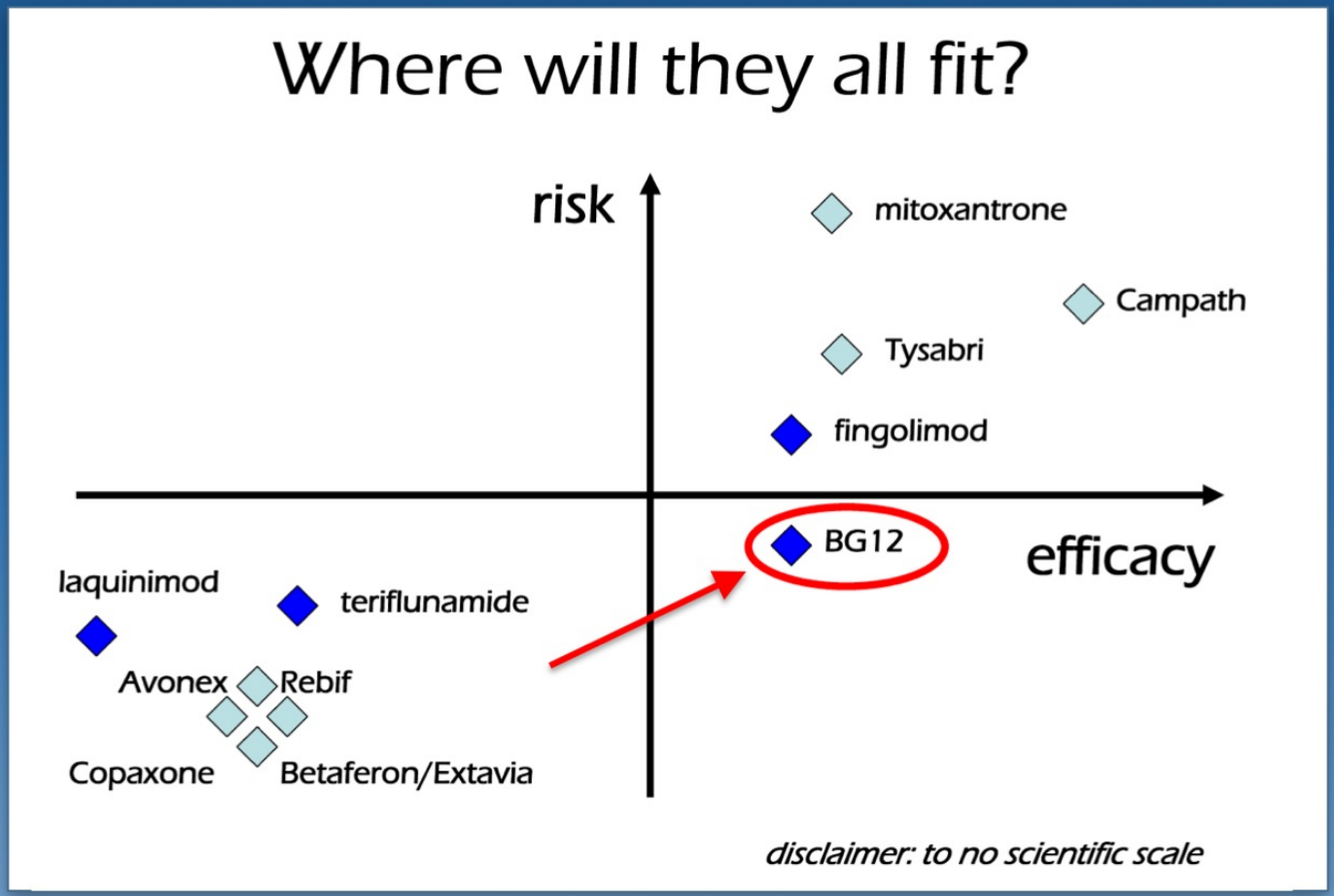
- **September 2009 (Only Phase II Results Published)**



Ex. 2058 (Dr. Duddy), ¶¶174-176 / Ex. 2124, 30

Dr. Duddy's Contemporaneous Change of Perception

- **November 2011 (After Phase III Results Known)**



Ex. 2058 (Dr. Duddy), ¶177 / Ex. 2125, 45

Dr. Duddy's Contemporaneous Change of Perception

Declaration of Biogen's Expert Dr. Duddy:

"**My perception of BG-12 completely and unexpectedly shifted** when Biogen released the results of its Phase III trials. In November 2011, I reworked that same slide, moving BG-12 into the lower right-hand quadrant reflecting the strongest overall performance (higher efficacy, lower risk) … I recall being surprised at that time at the high level of reduction in relapse rate and the strength of the MRI results given the modest magnitude of the effect in the Phase II study"

Ex. 2058 (Dr. Duddy), ¶177

Unexpected Results - Magnitude of Efficacy

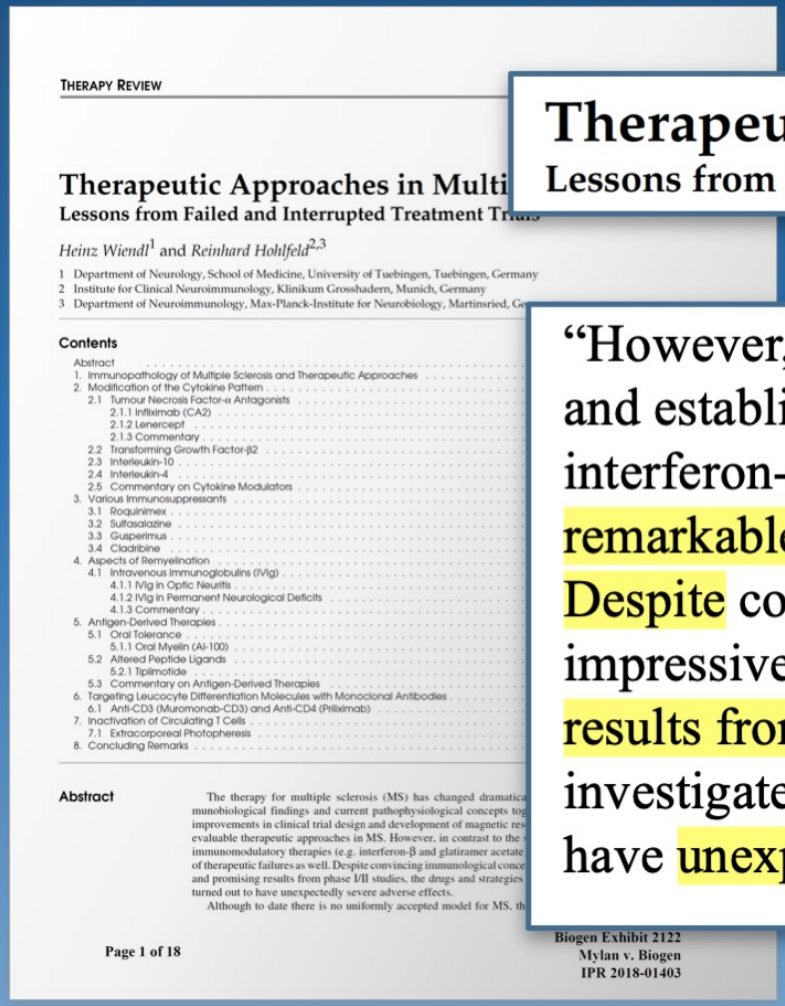
Declaration of Biogen's Expert Dr. Thisted:

"Both the DEFINE and CONFIRM studies show that the therapeutic effects on brain lesions at 480 mg/day are essentially the same as those seen at 720 mg/day. **It is stunning and unexpected to see, in two large independent studies, that increasing an ineffective dose (360 mg/day) by a small amount (120 mg/day) produces a strong therapeutic effect, and that a further, larger dose increase (to 720 mg/day) produces virtually no additional therapeutic benefit**."

Ex. 2060 (Dr. Thisted), ¶100

Unpredictability & Failures in the Art

Wiendl (2002):



THERAPY REVIEW

Therapeutic Approaches in Multi
Lessons from Failed and Interrupted Treatment Tri

Heinz Wiendl[1] and *Reinhard Hohlfeld*[2,3]

1 Department of Neurology, School of Medicine, University of Tuebingen, Tuebingen, Germany
2 Institute for Clinical Neuroimmunology, Klinikum Grosshadern, Munich, Germany
3 Department of Neuroimmunology, Max-Planck-Institute for Neurobiology, Martinsried, Ge

Contents

Abstract

The therapy for multiple sclerosis (MS) has changed dramatica
munobiological findings and current pathophysiological concepts to
improvements in clinical trial design and development of magnetic res
evaluable therapeutic approaches in MS. However, in contrast to the
immunomodulatory therapies (e.g. interferon-β and glatiramer acetate
of therapeutic failures as well. Despite convincing immunological conce
and promising results from phase I/II studies, the drugs and strategies
turned out to have unexpectedly severe adverse effects.
Although to date there is no uniformly accepted model for MS, th

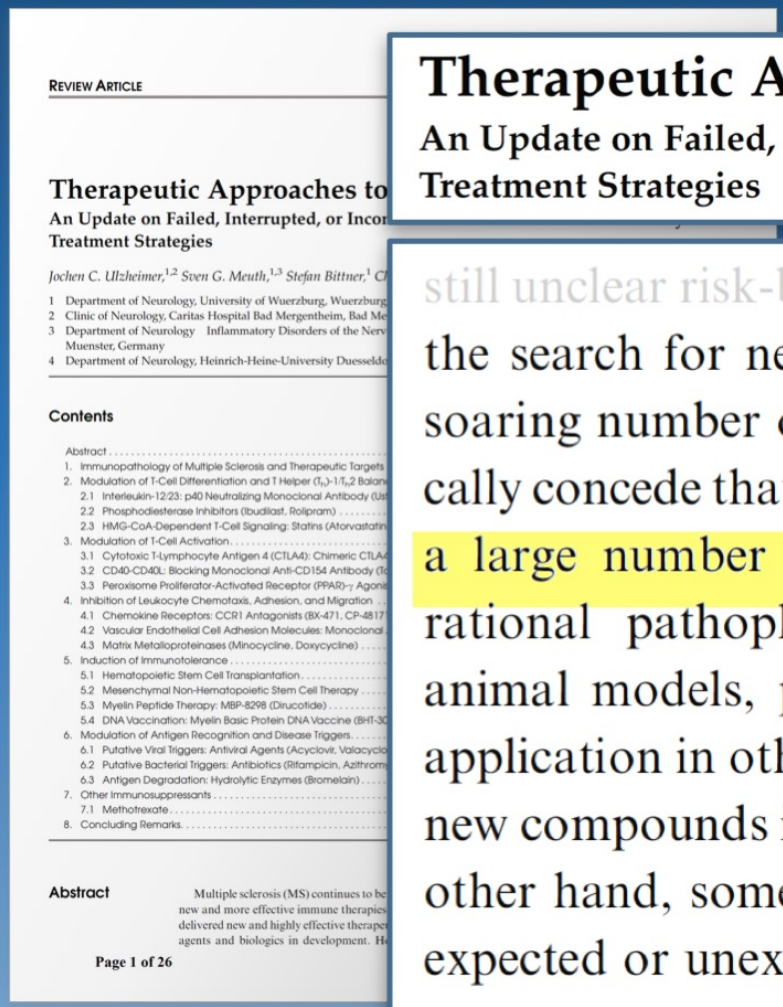
Therapeutic Approaches in Multiple Sclerosis
Lessons from Failed and Interrupted Treatment Trials

"However, in contrast to the successfully introduced and established immunomodulatory therapies (e.g. interferon-β and glatiramer acetate), there have been a remarkable number of therapeutic failures as well. Despite convincing immunological concepts, impressive data from animal models and promising results from phase I/II studies, the drugs and strategies investigated showed no benefit or even turned out to have unexpectedly severe adverse effects."

Ex. 2122, 1

Unpredictability & Failures in the Art

Ulzheimer (2010):



REVIEW ARTICLE

Therapeutic Approaches to

An Update on Failed, Interrupted, or Incon

Treatment Strategies

Jochen C. Ulzheimer,[1,2] Sven G. Meuth,[1,3] Stefan Bittner,[1] Cl

1 Department of Neurology, University of Wuerzburg, Wuerzburg
2 Clinic of Neurology, Caritas Hospital Bad Mergentheim, Bad Me
3 Department of Neurology Inflammatory Disorders of the Nerv
Muenster, Germany
4 Department of Neurology, Heinrich-Heine-University Duesseldo

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Abstract
1. Immunopathology of Multiple Sclerosis and Therapeutic Targets
2. Modulation of T-Cell Differentiation and T Helper (T_h)-1/T_h2 Balan
2.1 Interleukin-12/23: p40 Neutralizing Monoclonal Antibody (Us
2.2 Phosphodiesterase Inhibitors (Ibudilast, Rolipram)
2.3 HMG-CoA-Dependent T-Cell Signaling: Statins (Atorvastatin
3. Modulation of T-Cell Activation
3.1 Cytotoxic T-Lymphocyte Antigen 4 (CTLA4): Chimeric CTLA4
3.2 CD40-CD40L: Blocking Monoclonal Anti-CD154 Antibody (Te
3.3 Peroxisome Proliferator-Activated Receptor (PPAR)-γ Agonis
4. Inhibition of Leukocyte Chemotaxis, Adhesion, and Migration
4.1 Chemokine Receptors: CCR1 Antagonists (BX-471, CP-4817
4.2 Vascular Endothelial Cell Adhesion Molecules: Monoclonal
4.3 Matrix Metalloproteinases (Minocycline, Doxycycline)
5. Induction of Immunotolerance
5.1 Hematopoietic Stem Cell Transplantation
5.2 Mesenchymal Non-Hematopoietic Stem Cell Therapy
5.3 Myelin Peptide Therapy: MBP-8298 (Diruocotide)
5.4 DNA Vaccination: Myelin Basic Protein DNA Vaccine (BHT-30
6. Modulation of Antigen Recognition and Disease Triggers
6.1 Putative Viral Triggers: Antiviral Agents (Acyclovir, Valacyclo
6.2 Putative Bacterial Triggers: Antibiotics (Rifampicin, Azithrom
6.3 Antigen Degradation: Hydrolytic Enzymes (Bromelain)
7. Other Immunosuppressants
7.1 Methotrexate
8. Concluding Remarks

Abstract

Multiple sclerosis (MS) continues to be
new and more effective immune therapies
delivered new and highly effective therapeu
agents and biologics in development. He

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Therapeutic Approaches to Multiple Sclerosis

An Update on Failed, Interrupted, or Inconclusive Trials of Immunomodulatory Treatment Strategies

still unclear risk-benefit ratio. There is a tremendous activity in the search for new therapeutics,[1,2] which is reflected by the soaring number of publications. However, one has to realistically concede that few successful agents in MS stand apart from a large number of therapeutic disappointments.[3-5] Despite rational pathophysiologic concepts, conclusive data from animal models, promising phase I/II studies, and successful application in other autoimmune diseases, several trials testing new compounds in MS patients have shown no benefit. On the other hand, some effective treatments are associated with unexpected or unexpectedly severe adverse effects. Whereas pos-

Ex. 2120, 1-2

POR, 56-57

Unexpected Results - Magnitude of Efficacy

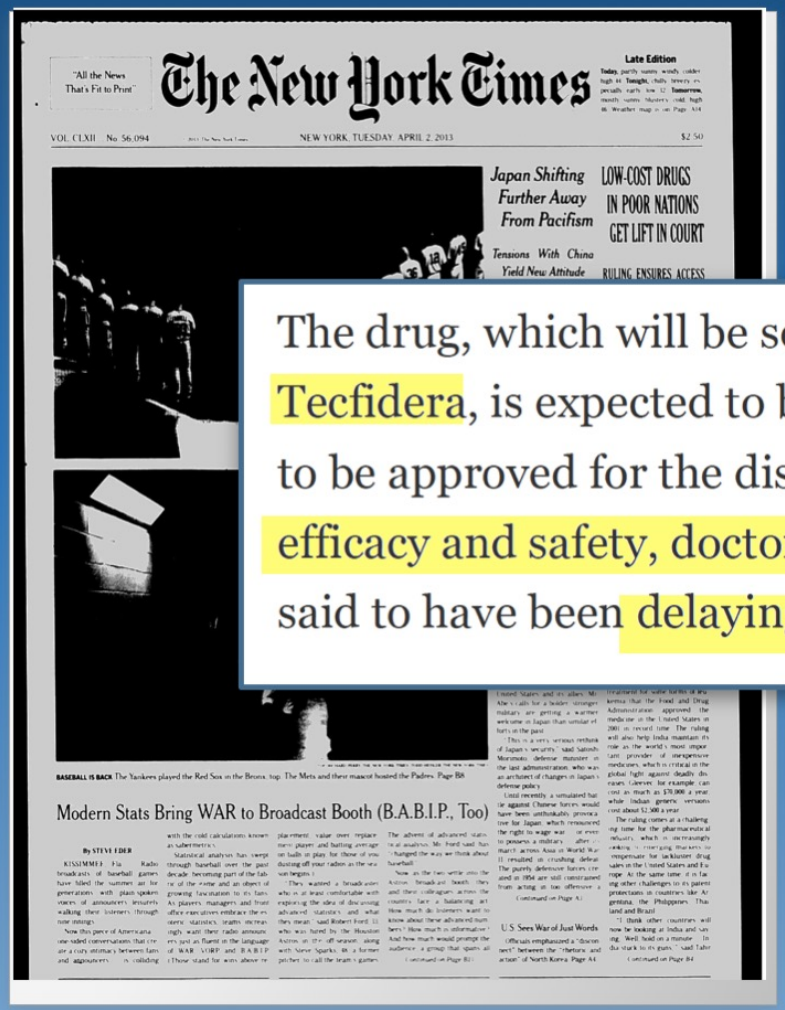
Testimony of Biogen's Expert Dr. Wynn:

Q: [Y]ou did not think that 480 milligrams would work, correct?

A: It certainly wasn't my invention, **I wouldn't have guessed that it would have worked based on the results of the Kappos trial**. I wouldn't have expected the 720 dose in the CONFIRM and DEFINE trial to show the results it did even at 720 milligrams, it seemed to outperform the Phase II trial. Phase III, and **more often than not, we see the opposite, we see drugs do better in Phase II than in Phase III**.

Ex. 1126 (Dr. Wynn), 208:15-25

Pent-Up Demand in Anticipation of Tecfidera® Launch



"All the News That's Fit to Print"

The New York Times

Late Edition

VOL. CLXII No. 56,094 NEW YORK, TUESDAY, APRIL 2, 2013 $2.50

Japan Shifting Further Away From Pacifism

Tensions With China Yield New Attitude

LOW-COST DRUGS IN POOR NATIONS GET LIFT IN COURT

RULING ENSURES ACCESS

BASEBALL IS BACK The Yankees played the Red Sox in the Bronx, top. The Mets and their mascot hosted the Padres. Page B8

Modern Stats Bring WAR to Broadcast Booth (B.A.B.I.P., Too)

By STEVE EDER

U.S. Sees War of Just Words

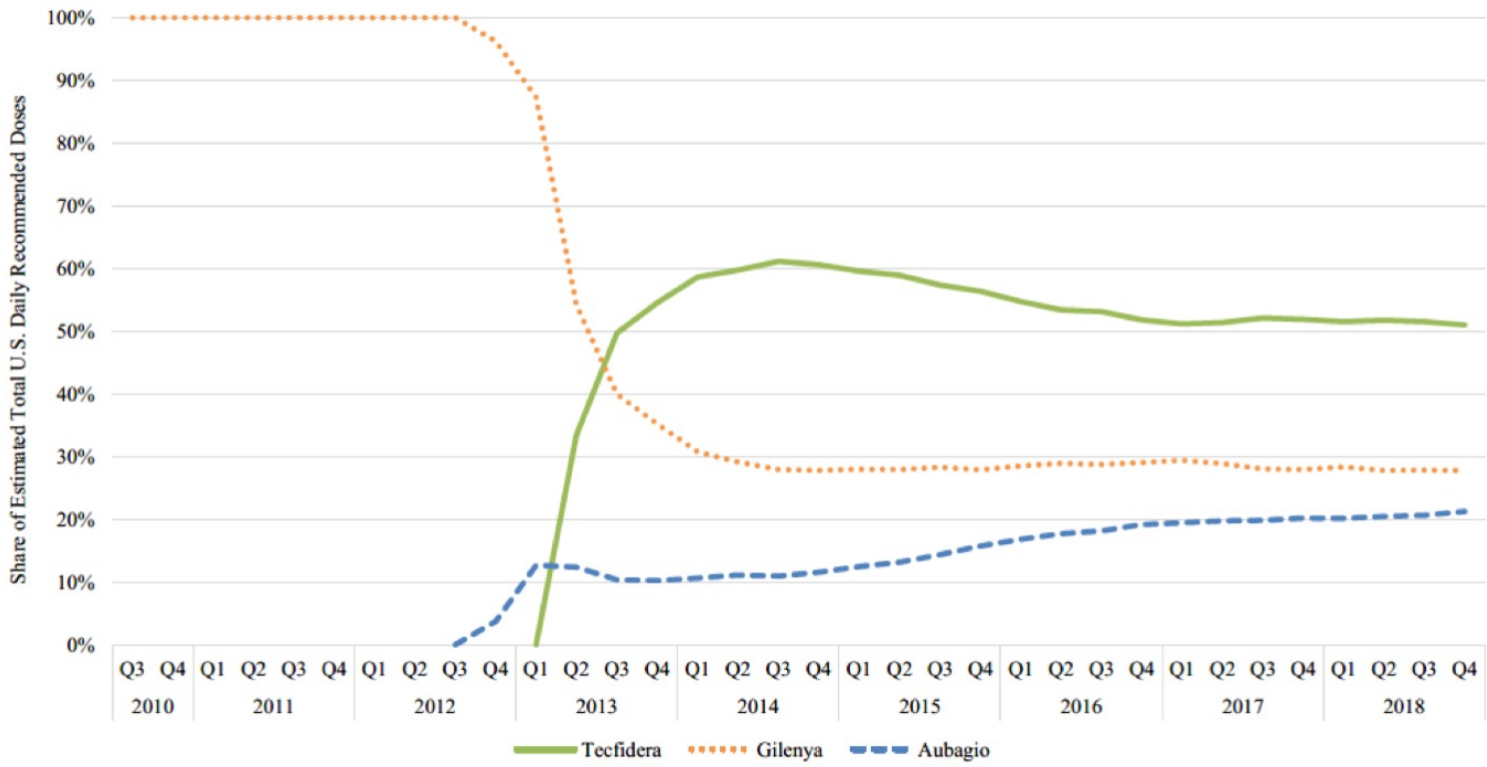
New York Times, April 1, 2013:

The drug, which will be sold by Biogen Idec under the brand name Tecfidera, is expected to be a blockbuster. It is only the third oral treatment to be approved for the disease, and it offers a tantalizing combination of efficacy and safety, doctors and Wall Street analysts say. Some patients are said to have been delaying treatment until Tecfidera is available.

Ex. 2006, 5, 11

Tecfidera® Rapidly Overtook Its Oral MS Competitors

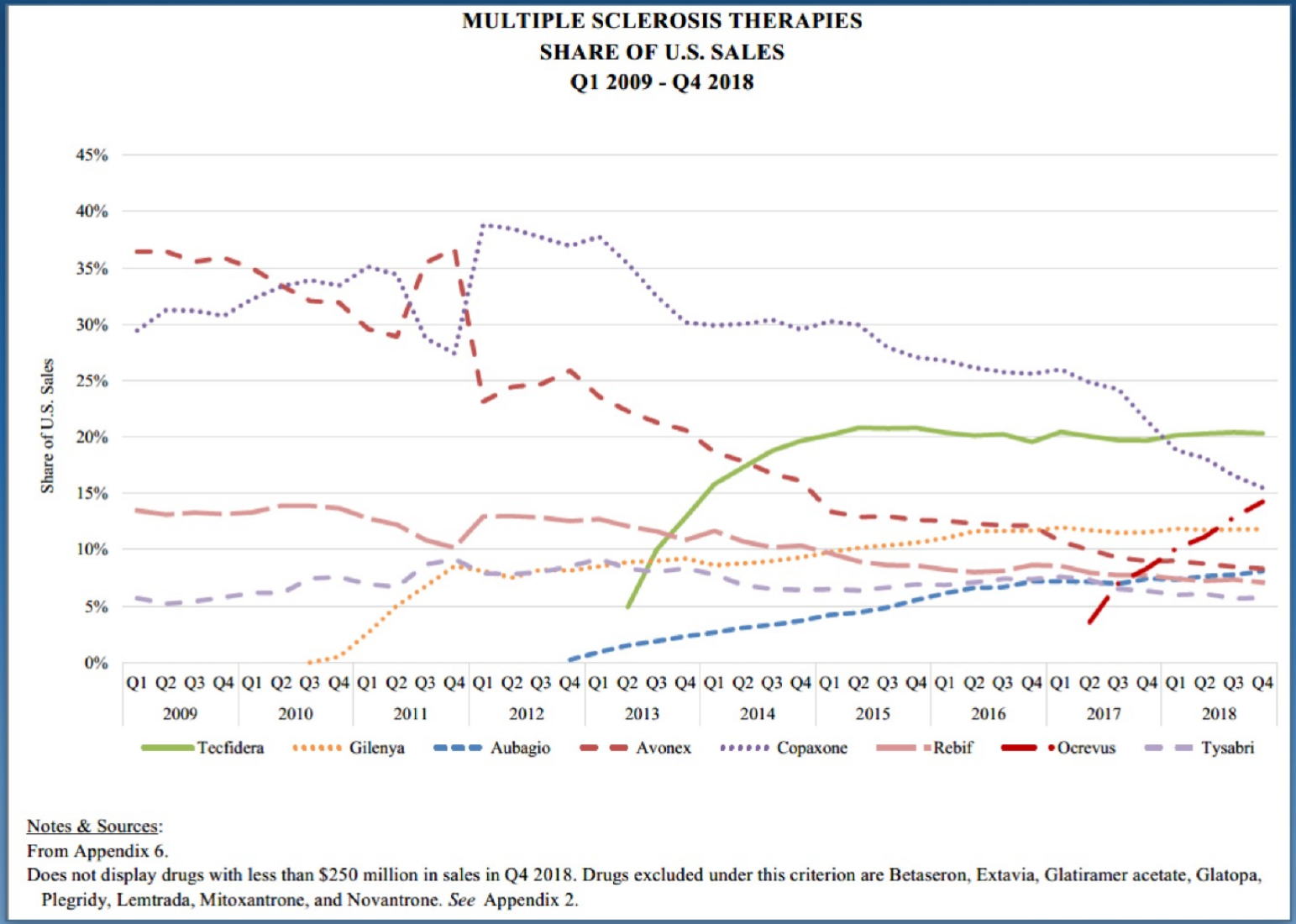
ORAL MULTIPLE SCLEROSIS THERAPIES
SHARE OF ESTIMATED TOTAL U.S. DAILY RECOMMENDED DOSES
Q3 2010 - Q4 2018



Notes & Sources:
From Appendix 15.

Ex. 2202 (J. Jarosz), ¶¶73-74, Figure 3

Tecfidera® Market Share Leads All MS Drugs



Notes & Sources:
From Appendix 6.
Does not display drugs with less than $250 million in sales in Q4 2018. Drugs excluded under this criterion are Betaseron, Extavia, Glatiramer acetate, Glatopa, Plegridy, Lemtrada, Mitoxantrone, and Novantrone. *See* Appendix 2.

Ex. 2202 (J. Jarosz), ¶74, Figure 4

Dr. Hay's Independent Economic Analysis

Admissions of Petitioner's Dr. Hay in Previous Testimony:

A: "**Tecfidera** has been a relatively **successful** oral MS drug with **3.5 billion in 2014 annual sales**, less than 2 years after its launch, despite directly competing with Gilenya and other MS drugs. Since its launch in 2012, Tecfidera has been **rapidly taking market share** from Gilenya as doctors and patients understand that **it's a better and more valuable oral MS drug.**"

Q: And for the first point about the annual sales, you rely on public data from IMS; correct?

A: Right. Which doesn't adjust for the confidential rebates and discounts …

Ex. 2230 (Dr. Hay), 109:21-110:20

Dr. Hay's Independent Economic Analysis

Admissions of Petitioner's Dr. Hay from His Own Publication:

A: "Dimethyl fumarate dominated all other therapies over the range of willingness-to-pays from $0 to $180,000 per QALY [Quality Adjusted Life Year]."

* * *

Q: What does "dominated" mean in that sentence?

A: It means it has better outcomes. So **the actual efficacy and reduction of side effects is better than any other drug at the time** based on the information we had, which is all public. We didn't have any private information. So it has better outcomes and lower cost, and for a health economist that's ideal. You don't have to struggle with a decision to adopt a drug that reduces your cost and produces better outcomes for your patients. **I mean, we call those no-brainers.** You do them.

Ex. 2230 (Dr. Hay), 66:8-67:13

’376 Patent Could Not Have Prevented Others From Developing DMF in Other Forms for MS

US006509376B1

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

(10) **Patent No.: US 6,509,376 B1**
(45) **Date of Patent: Jan. 21, 2003**

(54) **UTILIZATION OF DIALKYFUMARATES**

(75) Inventors: **Rajendra Kumar Joshi**, Zürich (CH); **Hans-Peter Strebel**, Muri (CH)

(73) Assignee: **Fumapharm AG**, Muri (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.: **09/831,620**

(22) PCT Filed: **Oct. 29, 1999**

(86) PCT No.: **PCT/EP99/08215**

§ 371 (c)(1),
(2), (4) Date: **May 10, 2001**

(87) PCT Pub. No.: **WO00/30622**

PCT Pub. Date: **Jun. 2, 2000**

(30) **Foreign Application Priority Data**

Nov. 19, 1998 (DE) 198 53 487

(51) **Int. Cl.**[7] **A61K 31/225**

(52) **U.S. Cl.** **514/547**; 514/960

(58) **Field of Search** 514/547, 960

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EP	0312697	4/1989
WO	WO 95/25102	9/1995
WO	WO 96/27369	9/1996
WO	WO 98/04250	2/1998
WO	WO 98/27970	7/1998
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M. Bacharach–Buhles et al., “Fumaric Acid Esters (FAEs) Suppress CD 15– and ODP 4–positive Cells in Psoriasis”, Acta Derm Venerol (Stockh); 1994; Suppl. 186: 79–82.
H. M. Ockenfels, et al., “The antipsoricatic agent dimethylfumarate immunomodulates T-cell cytokine secretion and inhibits cytokines of the psoriatic cytokine network”, British Journal of Dermatology, 1998, vol. 139, 390–395.
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Immunodulation durch Fumaderm, Das richtungsweisende Konzept, Charité–Berlin, Hautklinik, Symposium, Nov. 1.–3, 1996, 28 pages, 4 page english translation of pp. 23–24.

* cited by examiner

Primary Examiner—Kevin E. Weddington
(74) *Attorney, Agent, or Firm*—Sieberth & Patty, L.L.C.

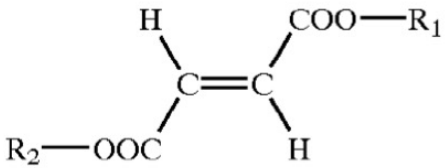
(57) **ABSTRACT**

The present invention relates to the use of certain dialkyl fumarates for the preparation of pharmaceutical preparations for use in transplantation medicine or for the therapy of autoimmune diseases and said compositions in the form of micro-tablets or pellets. For this purpose, the dialkyl fumarates may also be used in combination with conventional preparations used in transplantation medicine and immunosuppressive agents, especially cyclosporines.

16 Claims, No Drawings

MYLAN PHARMS. INC. EXHIBIT 1025 PAGE 1

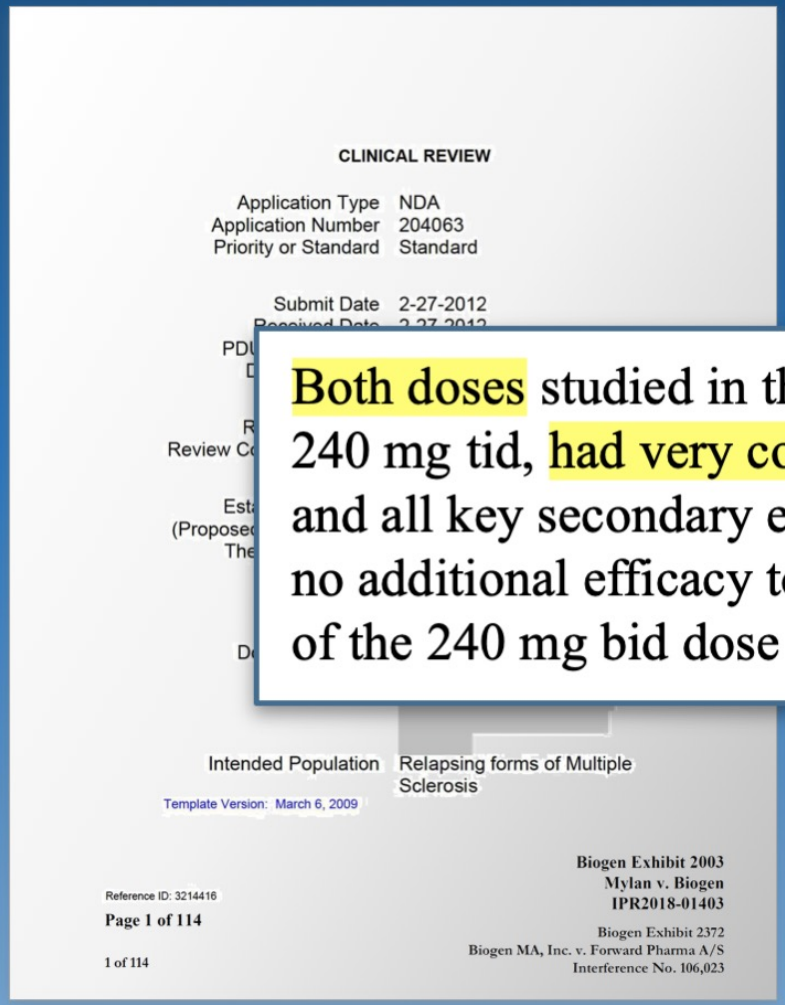
1. Pharmaceutical preparation in the form of microtablets or micropellets comprising one or more dialkyl fumarates of the formula



wherein R_1 and R_2, which may be the same or different, independently represent a linear, branched or cyclic, saturated or unsaturated C_{1-20} alkyl radical which may be optionally substituted with halogen (Cl, F, I, Br), hydroxy, C_{1-4} alkoxy, nitro or cyano, and optionally suitable carriers and excipients for use in transplantation medicine or for the therapy of autoimmune diseases such as polyarthritis, multiple sclerosis, juvenile-onset diabetes, Hashimoto’s thyroiditis, Grave’s disease, systemic Lupus erythematodes (SLE), Sjogren’s syndrome, pernicious anaemia, chronic active (lupoid) hepatitis, psoriasis, psoriatic arthritis, neurodermatitis and enteritis regionalis Crohn.

Ex. 1025, claim 1

Unexpected Results - Magnitude of Efficacy



CLINICAL REVIEW

Application Type NDA
Application Number 204063
Priority or Standard Standard

Submit Date 2-27-2012

Intended Population Relapsing forms of Multiple Sclerosis

Template Version: March 6, 2009

Biogen Exhibit 2003
Mylan v. Biogen
IPR2018-01403

Biogen Exhibit 2372
Biogen MA, Inc. v. Forward Pharma A/S
Interference No. 106,023

Reference ID: 3214416

Page 1 of 114

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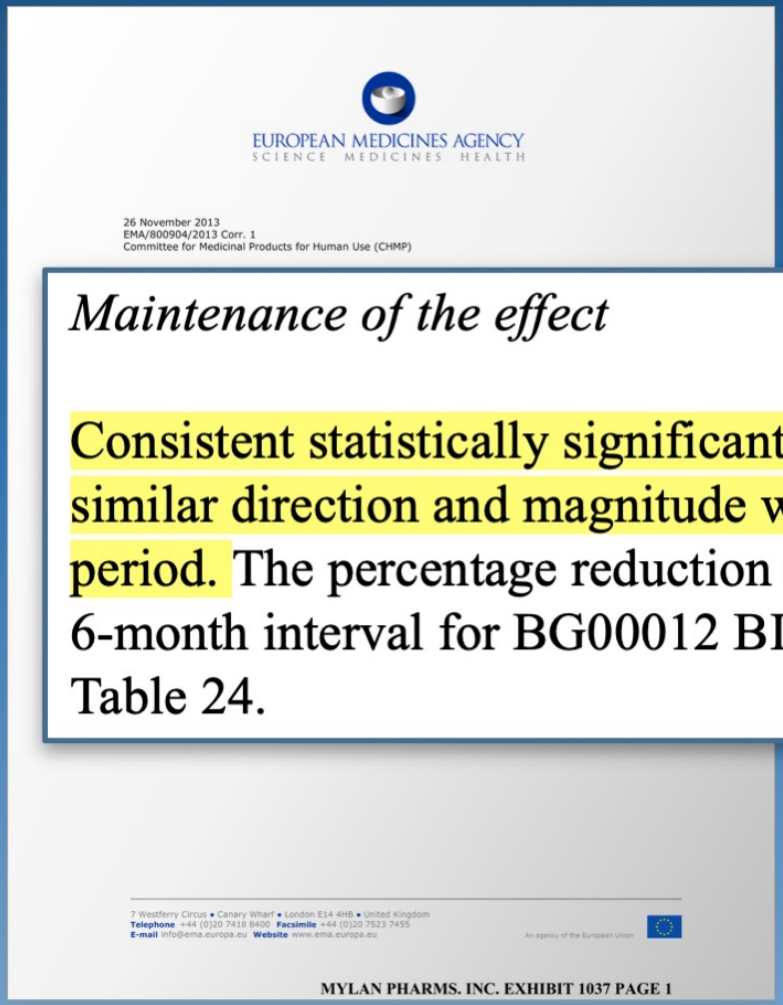
FDA Clinical Review

Both doses studied in these efficacy trials, BG-12 240 mg bid and 240 mg tid, had very comparable efficacy on the primary endpoints and all key secondary endpoints. Since the 240 mg tid dose offered no additional efficacy to the 240 mg bid dose, I recommend approval of the 240 mg bid dose only.

Ex. 2003, 8

Unexpected Results - Magnitude of Efficacy


EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

26 November 2013
EMA/800904/2013 Corr. 1
Committee for Medicinal Products for Human Use (CHMP)

7 Westferry Circus • Canary Wharf • London E14 4HB • United Kingdom
Telephone +44 (0)20 7418 8400 Facsimile +44 (0)20 7523 7455
E-mail info@ema.europa.eu Website www.ema.europa.eu
An agency of the European Union

MYLAN PHARMS. INC. EXHIBIT 1037 PAGE 1

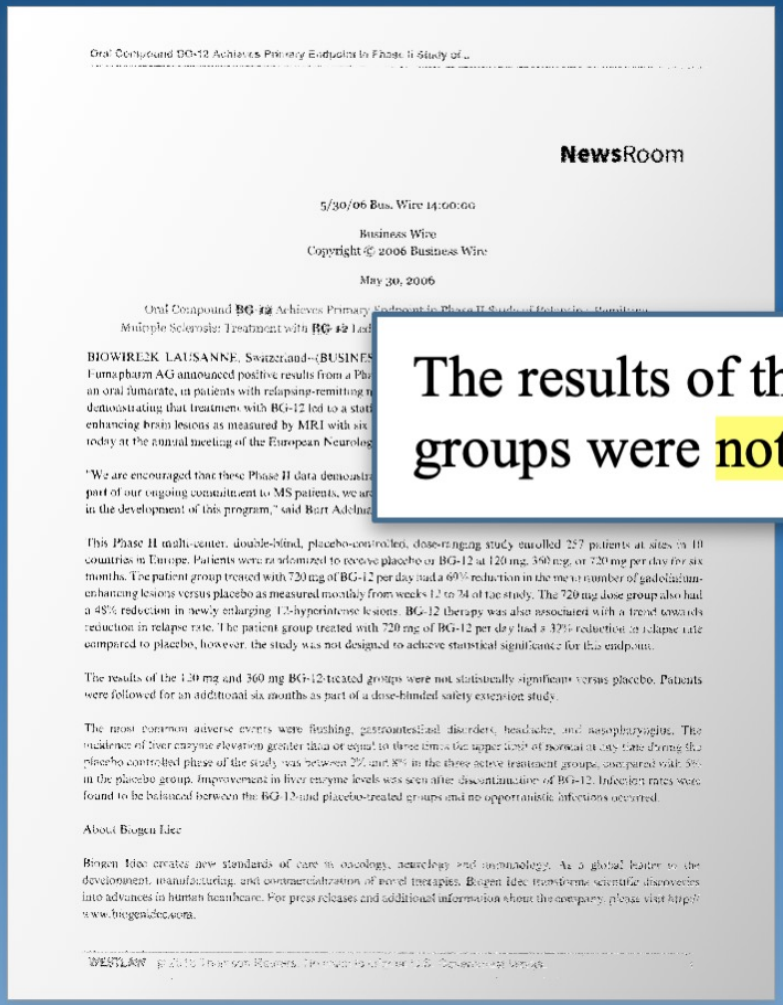
EMA Assessment Report

Maintenance of the effect

Consistent statistically significant effects with both doses of BG00012 of similar direction and magnitude were seen across the studies at each 6-month period. The percentage reduction and 95% CI in the annualized relapse rate by 6-month interval for BG00012 BID compared to placebo are presented in Table 24.

Ex. 1037,75

Petitioner's Post Hoc (Hindsight) Arguments



Oral Compound BG-12 Achieves Primary Endpoints in Phase II Study of ...

NewsRoom

5/30/06 Bus. Wire 14:00:00

Business Wire
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May 30, 2006

Oral Compound BG-12 Achieves Primary Endpoint in Phase II Study of Relapsing-Remitting Multiple Sclerosis; Treatment with BG-12 Led ...

BIOWIRE2K LAUSANNE, Switzerland--(BUSINES... Fumapharm AG announced positive results from a Ph... an oral fumarate, in patients with relapsing-remitting ... demonstrating that treatment with BG-12 led to a stati... enhancing brain lesions as measured by MRI with six ... today at the annual meeting of the European Neurolog...

"We are encouraged that these Phase II data demonstra... part of our ongoing commitment to MS patients, we ar... in the development of this program," said Bart Adelma...

This Phase II multi-center, double-blind, placebo-controlled, dose-ranging study enrolled 257 patients at sites in 10 countries in Europe. Patients were randomized to receive placebo or BG-12 at 120 mg, 360 mg, or 720 mg per day for six months. The patient group treated with 720 mg of BG-12 per day had a 69% reduction in the mean number of gadolinium-enhancing lesions versus placebo as measured monthly from weeks 12 to 24 of the study. The 720 mg dose group also had a 48% reduction in newly enlarging T2-hyperintense lesions. BG-12 therapy was also associated with a trend towards reduction in relapse rate. The patient group treated with 720 mg of BG-12 per day had a 37% reduction in relapse rate compared to placebo, however, the study was not designed to achieve statistical significance for this endpoint.

The results of the 120 mg and 360 mg BG-12-treated groups were not statistically significant versus placebo. Patients were followed for an additional six months as part of a dose-blinded safety extension study.

The most common adverse events were flushing, gastrointestinal disorders, headache, and nasopharyngitis. The incidence of liver enzyme elevation greater than or equal to three times the upper limit of normal at any time during the placebo controlled phase of the study was between 2% and 8% in the three active treatment groups, compared with 5% in the placebo group. Improvement in liver enzyme levels was seen after discontinuation of BG-12. Infection rates were found to be balanced between the BG-12 and placebo-treated groups and no opportunistic infections occurred.

About Biogen Idec

Biogen Idec creates new standards of care in oncology, neurology and immunology. As a global leader in the development, manufacturing, and commercialization of novel therapies, Biogen Idec transforms scientific discoveries into advances in human healthcare. For press releases and additional information about the company, please visit http://www.biogenidec.com.

WESTLAW

May 2006 Press Release

The results of the 120 mg and 360 mg BG-12 treated groups were not statistically significant versus placebo.

Ex. 1016, 1

Petitioner's Post Hoc (Hindsight) Arguments

Admissions of Petitioner's Dr. Greenberg:

Q: In Exhibit 2224, your article in 2008 where you reference Phase II data for BG12, there is nothing to indicate that you looked for or found baseline imbalances in Gd lesions; correct?

A: And so it's not called out in this paper, no.

Ex. 2231 (Dr. Greenberg), 141:20-142:5;
see also id., 136:15-139:13, 220:14-221:9

Petitioner's Post Hoc (Hindsight) Arguments

Testimony of Biogen's Expert Dr. Duddy:

Q: So you disagree with Drs. Fox, Gold, Ruddick, and Cohen; correct?

A: … I see it as a potential **long after the fact justification** of trying to explain away why the Phase II study showed no effect before the 720 dose and that the Phase III study showed an effect at 480 and 720.

Ex. 1125 (Dr. Duddy), 138:16-139:7

Petitioner's Post Hoc (Hindsight) Arguments

Declaration of Biogen's Expert Dr. Wynn:

"… However, **post hoc analyses amount to data hunting—hindsight attempts to create positive outcomes from negative trials. Post hoc analyses would never be accepted to make a negative study positive**. On the contrary, post hoc analyses are used by skilled artisans only to make a positive study negative should unaccounted variables be found."

Ex. 2061 (Dr. Wynn), ¶65

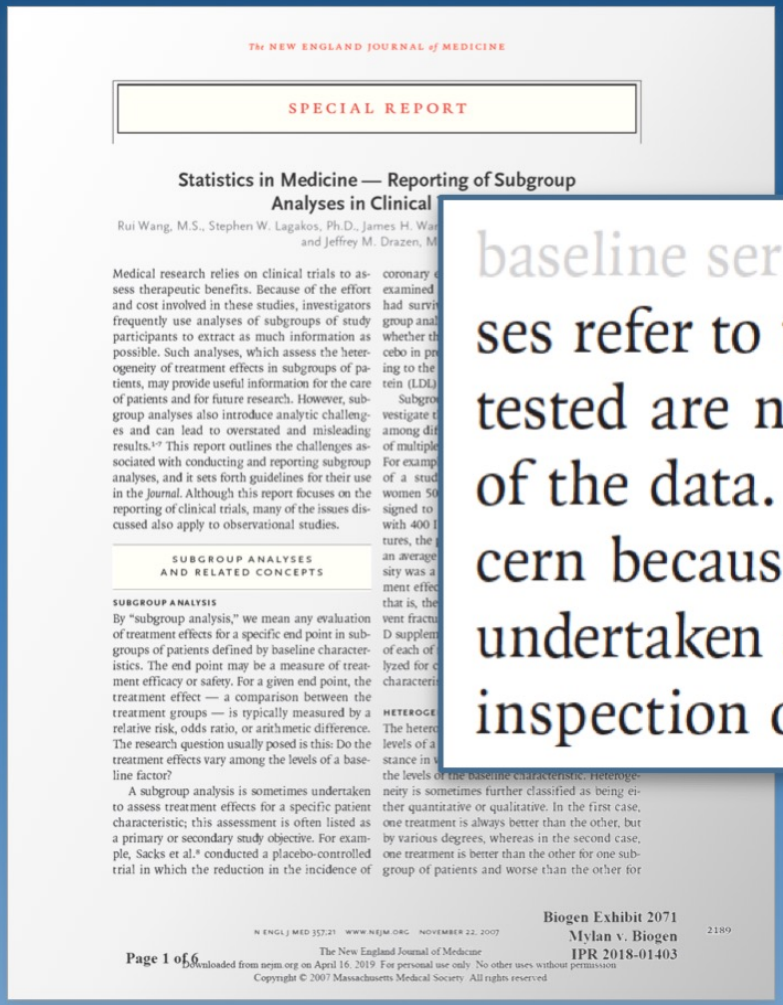
Petitioner's Post Hoc (Hindsight) Arguments

Declaration of Biogen's Expert Dr. Thisted:

"Performing additional analyses post hoc based on a review of unblinded data **is inherently unreliable and must be viewed cautiously** because such analyses **necessarily involve hindsight** and may therefore **introduce significant bias**. Conducting analyses that are motivated by the data (i.e., viewing the data and using the same data both to decide which after-the-fact analyses might produce favorable results and to carry out those analyses), rather than tested by the original study design and resulting data, is **analogous to an archer redrawing the target after the arrow has landed**."

Ex. 2060 (Dr. Thisted), ¶35

Petitioner's Post Hoc (Hindsight) Arguments



The NEW ENGLAND JOURNAL of MEDICINE

SPECIAL REPORT

Statistics in Medicine — Reporting of Subgroup Analyses in Clinical

Rui Wang, M.S., Stephen W. Lagakos, Ph.D., James H. Wa
and Jeffrey M. Drazen, M

Medical research relies on clinical trials to assess therapeutic benefits. Because of the effort and cost involved in these studies, investigators frequently use analyses of subgroups of study participants to extract as much information as possible. Such analyses, which assess the heterogeneity of treatment effects in subgroups of patients, may provide useful information for the care of patients and for future research. However, subgroup analyses also introduce analytic challenges and can lead to overstated and misleading results.[1-7] This report outlines the challenges associated with conducting and reporting subgroup analyses, and it sets forth guidelines for their use in the *Journal*. Although this report focuses on the reporting of clinical trials, many of the issues discussed also apply to observational studies.

SUBGROUP ANALYSES AND RELATED CONCEPTS

SUBGROUP ANALYSIS

By "subgroup analysis," we mean any evaluation of treatment effects for a specific end point in subgroups of patients defined by baseline characteristics. The end point may be a measure of treatment efficacy or safety. For a given end point, the treatment effect — a comparison between the treatment groups — is typically measured by a relative risk, odds ratio, or arithmetic difference. The research question usually posed is this: Do the treatment effects vary among the levels of a baseline factor?

A subgroup analysis is sometimes undertaken to assess treatment effects for a specific patient characteristic; this assessment is often listed as a primary or secondary study objective. For example, Sacks et al.[8] conducted a placebo-controlled trial in which the reduction in the incidence of

N ENGL J MED 357;21 WWW.NEJM.ORG NOVEMBER 22, 2007 2189

Biogen Exhibit 2071
Mylan v. Biogen
IPR 2018-01403

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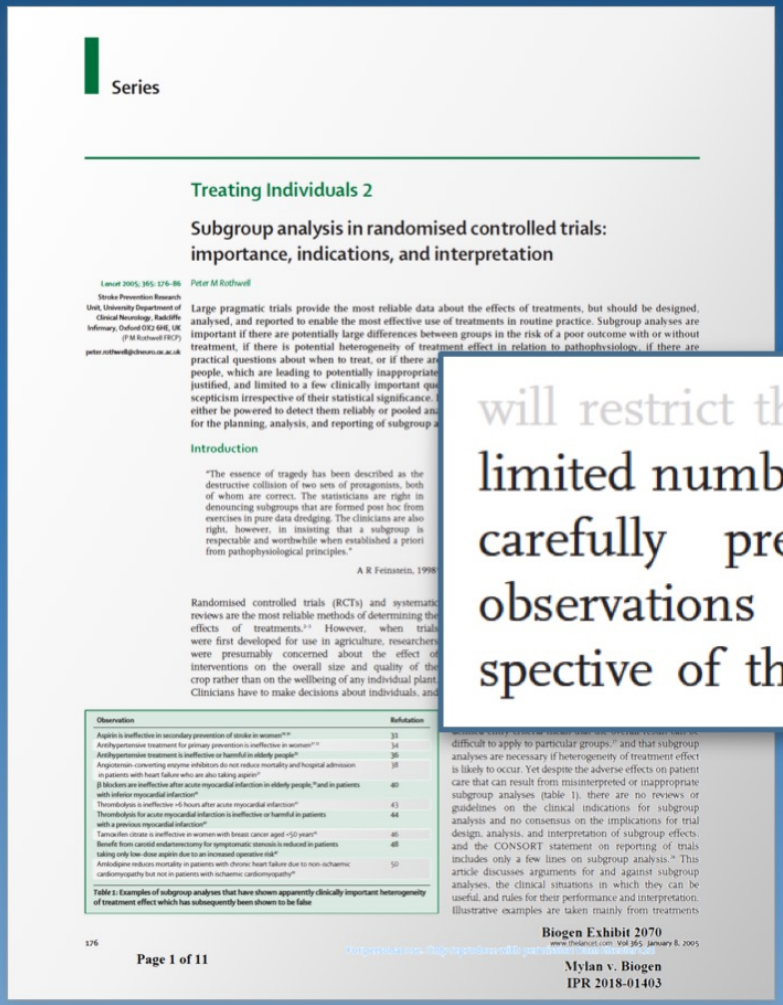
Wang (2007):

baseline serum creatinine level." Post hoc analyses refer to those in which the hypotheses being tested are not specified before any examination of the data. Such analyses are of particular concern because it is often unclear how many were undertaken and whether some were motivated by inspection of the data. However, both prespeci-

Ex. 2071, 2

Petitioner's Post Hoc (Hindsight) Arguments



Series

Treating Individuals 2

Subgroup analysis in randomised controlled trials: importance, indications, and interpretation

Lancet 2005; 365: 176–86

Peter M Rothwell

Stroke Prevention Research Unit, University Department of Clinical Neurology, Radcliffe Infirmary, Oxford OX2 6HE, UK (P M Rothwell FRCP)

peter.rothwell@clneuro.ox.ac.uk

Large pragmatic trials provide the most reliable data about the effects of treatments, but should be designed, analysed, and reported to enable the most effective use of treatments in routine practice. Subgroup analyses are important if there are potentially large differences between groups in the risk of a poor outcome with or without treatment, if there is potential heterogeneity of treatment effect in relation to pathophysiology, if there are practical questions about when to treat, or if there are people, which are leading to potentially inappropriate justified, and limited to a few clinically important qu scepticism irrespective of their statistical significance. either be powered to detect them reliably or pooled an for the planning, analysis, and reporting of subgroup a

Introduction

"The essence of tragedy has been described as the destructive collision of two sets of protagonists, both of whom are correct. The statisticians are right in denouncing subgroups that are formed post hoc from exercises in pure data dredging. The clinicians are also right, however, in insisting that a subgroup is respectable and worthwhile when established a priori from pathophysiological principles."

A R Feinstein, 1998

Randomised controlled trials (RCTs) and systematic reviews are the most reliable methods of determining the effects of treatments.[1,2] However, when trials were first developed for use in agriculture, researchers were presumably concerned about the effect of interventions on the overall size and quality of the crop rather than on the wellbeing of any individual plant. Clinicians have to make decisions about individuals, and

Observation	Refutation
Aspirin is ineffective in secondary prevention of stroke in women[9,10]	33
Antihypertensive treatment for primary prevention is ineffective in women[9,11]	34
Antihypertensive treatment is ineffective or harmful in elderly people[8]	36
Angiotensin-converting enzyme inhibitors do not reduce mortality and hospital admission in patients with heart failure who are also taking aspirin[7]	38
β blockers are ineffective after acute myocardial infarction in elderly people,[16] and in patients with inferior myocardial infarction[17]	40
Thrombolysis is ineffective >6 hours after acute myocardial infarction[18]	43
Thrombolysis for acute myocardial infarction is ineffective or harmful in patients with a previous myocardial infarction[19]	44
Tamoxifen citrate is ineffective in women with breast cancer aged <50 years[20]	46
Benefit from carotid endarterectomy for symptomatic stenosis is reduced in patients taking only low dose aspirin due to an increased operative risk[21]	48
Amlodipine reduces mortality in patients with chronic heart failure due to non-ischaemic cardiomyopathy but not in patients with ischaemic cardiomyopathy[22]	50

Table 1: Examples of subgroup analyses that have shown apparently clinically important heterogeneity of treatment effect which has subsequently been shown to be false

difficult to apply to particular groups,[3] and that subgroup analyses are necessary if heterogeneity of treatment effect is likely to occur. Yet despite the adverse effects on patient care that can result from misinterpreted or inappropriate subgroup analyses (table 1), there are no reviews or guidelines on the clinical indications for subgroup analysis and no consensus on the implications for trial design, analysis, and interpretation of subgroup effects. and the CONSORT statement on reporting of trials includes only a few lines on subgroup analysis.[4] This article discusses arguments for and against subgroup analyses, the clinical situations in which they can be useful, and rules for their performance and interpretation. Illustrative examples are taken mainly from treatments

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www.thelancet.com Vol 365 January 8, 2005

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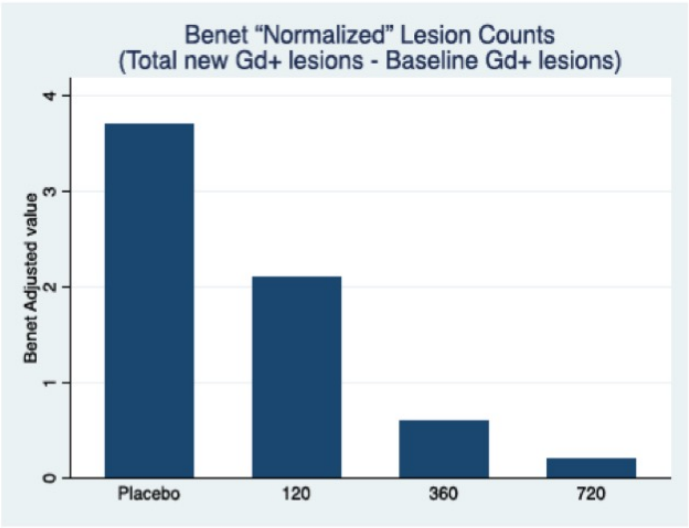
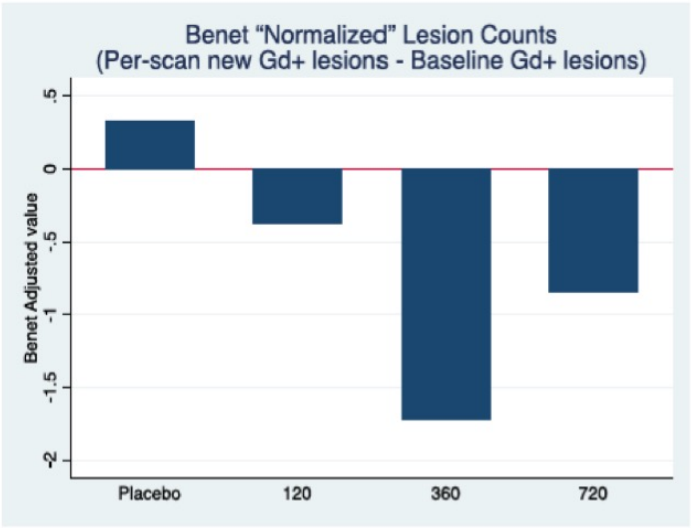
Rothwell (2005):

will restrict the use of treatment in routine practice. A limited number of clinically important analyses must be carefully predefined and justified, and post-hoc observations should be treated with scepticism irrespective of their significance. Adherence to the guide-

Ex. 2070, 9

"Dr. Benet's Subtraction Analysis Is Also Highly Arbitrary"





Declaration of Biogen's Expert Dr. Thisted:

> The particular calculations and adjustments included in Dr. Benet's declaration thus appear to have been selected based on the outcomes they produce—exactly the weakness of *post hoc* analyses . . .

Ex. 2060 (Dr. Thisted), ¶¶43, 46-47, Figure 1

Petitioner's Post Hoc (Hindsight) Arguments

Admissions of Petitioner's Dr. McKeague:

Q: And percent reduction relative to baseline, that's not one of the primary endpoints of the original Kappos study. Correct?

A: Yeah, the - - that's - - that's correct essentially.

Ex. 2064 (Dr. McKeague), 69:22-70:2

Admissions of Petitioner's Dr. Benet:

Q: And what physically is being measured or what physically does the subtraction that you did correspond to?

A: Nothing. …

Ex. 2062 (Dr. Benet), 151:3-15

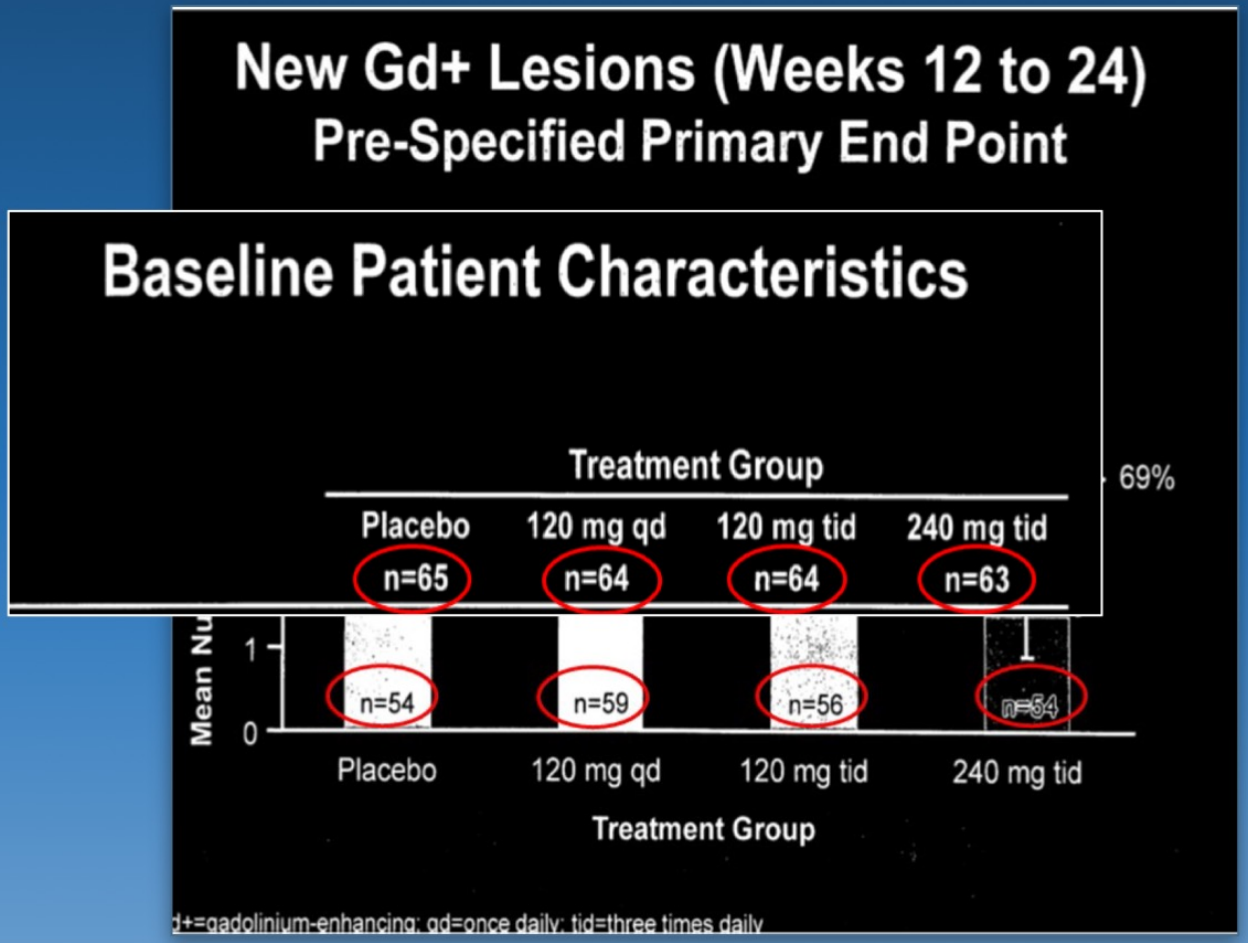
Petitioner's Post Hoc (Hindsight) Arguments

Declaration of Biogen's Expert Dr. Duddy:

"The lesion will be gadolinium enhancing ("Gd+") on T1 sequences for the first few weeks, but this stops once the blood brain barrier closes, usually by six weeks."

Ex. 2058 (Dr. Duddy), ¶18

Different Patient Populations



Ex. 2060 (Dr. Thisted), ¶¶56-58

Petitioner's Post Hoc (Hindsight) Arguments

Declaration of Biogen's Expert Dr. Thisted:

"[T]he difference in the number of patients included in the baseline slide and those included in the endpoint slide is important because the mean baseline Gd+ lesions may be driven by outlier values. Even one or two outliers having between 20-70 baseline Gd+ lesions in the 360 mg/day group compared to the other groups could account for the entire difference in mean values. The likely existence of an outlier is indicated by the size of the standard deviation reported for the 360 mg/day group, which is three times as great as for the placebo group."

Ex. 2060 (Dr. Thisted), ¶¶59, 61

Dr. Hay's Cross-Examination – Expectations in 2007

Admissions of Petitioner's Dr. Hay:

Q: There's a heading "What factors are constraining the mark[et] for multiple sclerosis therapies." Can you read that first bullet into the record so I can ask you about it.

A: "Despite experts' demand for agents that are more efficacious at delaying disease progression, the majority of MS agents that we expect to launch during [our] study period have yet to demonstrate significant improvement in efficacy over most current therapies. As a result, **most emerging therapies will capture limited patient shares and garner only modest market sales**."

Q: What do you understand that to mean?

A: That they don't think that the new drugs -- and **keep in mind that they are writing this in 2007**, so this is before the launch of -- **certainly before the launch of Tecfidera**. I think it's before the launch of Gilenya and Aubagio.

Ex. 2230 (Dr. Hay), 117:15-118:7, 118:8-14

Dr. Hay's Cross-Examination – Expectations in 2007

Admissions of Petitioner's Dr. Hay:

Q: In the conclusion they have in 2007 in Exhibit 2210 that "most emerging therapies will capture limited patient shares and only garner modest market sales," that's contrary to what you actually found in 2014 and 2015; correct?

A: Yeah, I think it -- **it isn't consistent with what we saw, you know, several years later after these drugs launched**.

Ex. 2230 (Dr. Hay), 119:22-120:7

Difficulties of Treating MS

Declaration of Biogen's Expert Dr. Wynn:

"Disease modification is the key treatment objective for the MS field, because the impact of MS over time is devastating and irreversible…. Lengthening the amount of time an individual with MS can work, participate in daily activities, maintain social roles, and remain independent is important to every MS patient, and to society at large…."

* * *

"[O]nce a patient has MS disease activity, brain damage has already occurred."

Ex. 2061 (Dr. Wynn), ¶23, 54
See also Ex. 2230 (Dr. Hay), 88:8-20, 89:15-90:18;
Ex. 2231 (Dr. Greenberg), 172:1-16

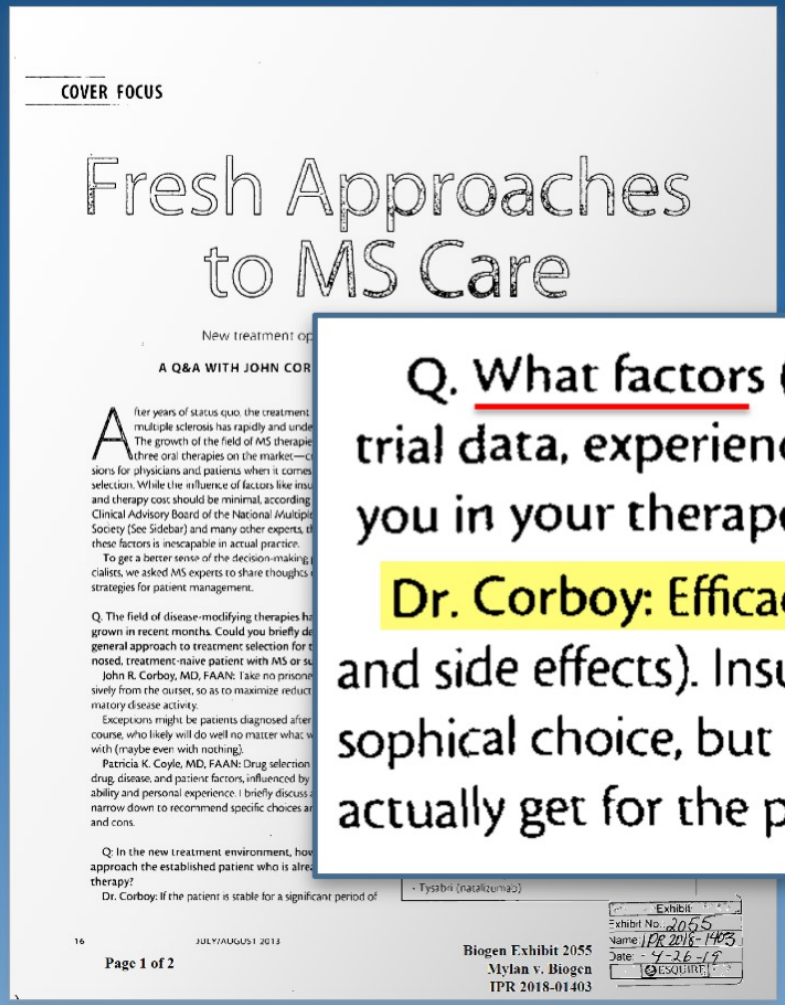
Difficulties of Treating MS

Declaration of Biogen's Expert Dr. Wynn:

- "For disease-modifying treatments for MS such as DMF, individual dose titration to determine the optimal effective dose for individual patients is not possible because disease activity varies over time within an individual patient."
- "[B]ecause the disease course is uncertain and not always observable to the patient or physician, efficacy determinations for MS drugs must be demonstrated using large groups of patients, which compare the average response of the treated group to the average response of the placebo group to determine efficacy."
- "Given the particular nature of MS and the grave consequences of undertreatment, physicians cannot, and do not, dose-titrate disease-modifying therapy to treat an individual MS patient."

Ex. 2061 (Dr. Wynn), ¶55

Published Interview of Petitioner's Dr. Corboy - Efficacy



COVER FOCUS

Fresh Approaches to MS Care

New treatment op

A Q&A WITH JOHN COR

After years of status quo, the treatment
multiple sclerosis has rapidly and unde
The growth of the field of MS therapie
three oral therapies on the market—c
sions for physicians and patients when it comes
selection. While the influence of factors like insu
and therapy cost should be minimal, according
Clinical Advisory Board of the National Multipl
Society (See Sidebar) and many other experts, t
these factors is inescapable in actual practice.
To get a better sense of the decision-making
cialists, we asked MS experts to share thoughts
strategies for patient management.

Q: The field of disease-modifying therapies ha
grown in recent months. Could you briefly de
general approach to treatment selection for t
nosed, treatment-naive patient with MS or su

John R. Corboy, MD, FAAN: I take no prisone
sively from the outset, so as to maximize reduct
matory disease activity.
Exceptions might be patients diagnosed after
course, who likely will do well no matter what w
with (maybe even with nothing).

Patricia K. Coyle, MD, FAAN: Drug selection
drug, disease, and patient factors, influenced by
ability and personal experience. I briefly discuss
narrow down to recommend specific choices ar
and cons.

Q: In the new treatment environment, how
approach the established patient who is alre
therapy?

Dr. Corboy: If the patient is stable for a significant period of

· Tysabri (natalizumab)

16 JULY/AUGUST 2013

Page 1 of 2

Biogen Exhibit 2055
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IPR 2018-01403

Exhibit
Exhibit No. 2055
Name: IPR 2018-1403
Date: 4-26-19
ESQUIRE

Q&A with Dr. Corboy (2013)

Q. What factors (insurance coverage/costs, convenience, trial data, experience) would you say are most relevant to you in your therapeutic decision-making?

Dr. Corboy: Efficacy. Efficacy. Risk. Compliance (convenience and side effects). Insurance/costs never play a role in philosophical choice, but often play a practical role in what we can actually get for the patient.

Ex. 2055, 2

Dr. Brundage's Testimony – Side Effects

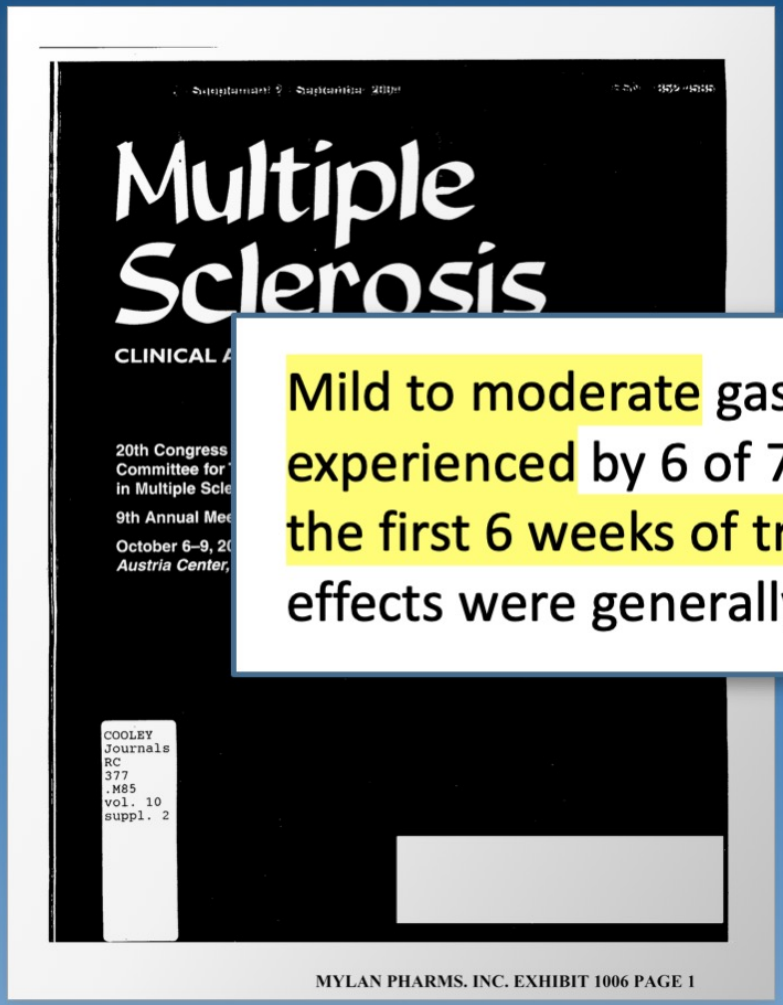
Testimony of Biogen's Expert Dr. Brundage:

Q: Okay. And so you wouldn't want to give a high dose that would cause too many adverse events; correct?

A: That is a relative statement that I cannot agree with. **When you're facing the consequences of MS, you may be quite willing to tolerate a higher frequency of some side effects for the ability to keep walking and stay out of wheelchairs**.

Ex. 1131 (Dr. Brundage), 95:8-17

Temporary Side Effects



Schimrigk 2004:

Mild to moderate gastrointestinal discomfort was initially experienced by 6 of 7 patients, but decreased gradually during the first 6 weeks of treatment in all patients. All other side effects were generally mild and transient.

Ex. 1006, 5

Temporary Side Effects

Declaration of Biogen's Expert Dr. Wynn:

"[T]he results of Biogen's Phase II study disclosed in the Kappos 2006 Slides demonstrated that 720 mg/day of DMF was **well-tolerated** and, in fact would have motivated a skilled artisan to seek potentially higher-efficacy doses. Ex. 1046 at 25-27. Accordingly, in my opinion, one of ordinary skill would not have been motivated to optimize the dose of DMF to 480 mg/day given the relative **tolerability associated with fumarate administration**."

Ex. 2061 (Dr. Wynn) ¶89

Similar Side Effects Across All Doses

Declaration of Biogen's Expert Dr. Duddy:

"…There were also the same number of serious adverse events for the 720 mg/day and 360 mg/day dose groups, both of which had fewer serious adverse events than the non-treatment (placebo) group, indicating that one would not have expected to improve on side effects by lowering the dose below 720 mg/day at all. (Ex. 1046 at 24.)"

Ex. 2058 (Dr. Duddy), ¶97

Serious Adverse Events

	Treatment Group			
	Placebo n=65	120 mg qd n=64	120 mg tid n=64	240 mg tid n=63
Total SAE	8 (12)	4 (6)	7 (11)	7 (11)
Infections	0	0	1 (2)	0
Neoplasm	1 (2)	0	0	0
CNS (MS)	5 (8)	4 (6)	6 (9)	5 (8)
Ear	1 (2)	0	0	0
Vascular	0	0	1(2)	0
GI	0	0	0	1 (2)
Renal	0	0	0	1 (2)
Injury	1 (2)	0	0	0

Ex. 1046, 24

Similar Side Effects Across All Doses

Declaration of Biogen's Expert Dr. Duddy:

"… Indeed, the Kappos presentation indicates that there were no greater adverse event-related drop-outs in the 720 mg/day dose group compared to the 360 mg/day dose group. (Ex. 1046 at 18.)"

Ex. 2058 (Dr. Duddy), ¶97

Discontinuations

	Treatment Group			
	Placebo n=65	120 mg qd n=64	120 mg tid n=64	240 mg tid n=63
Discontinuations, n (%)	6 (9)	6 (9)	8 (13)	10 (16)
Due to AEs	0 (0)	4 (6)	6 (9)	6 (9)

AEs=adverse events; qd=once daily; tid=three times daily

Ex. 1046, 18

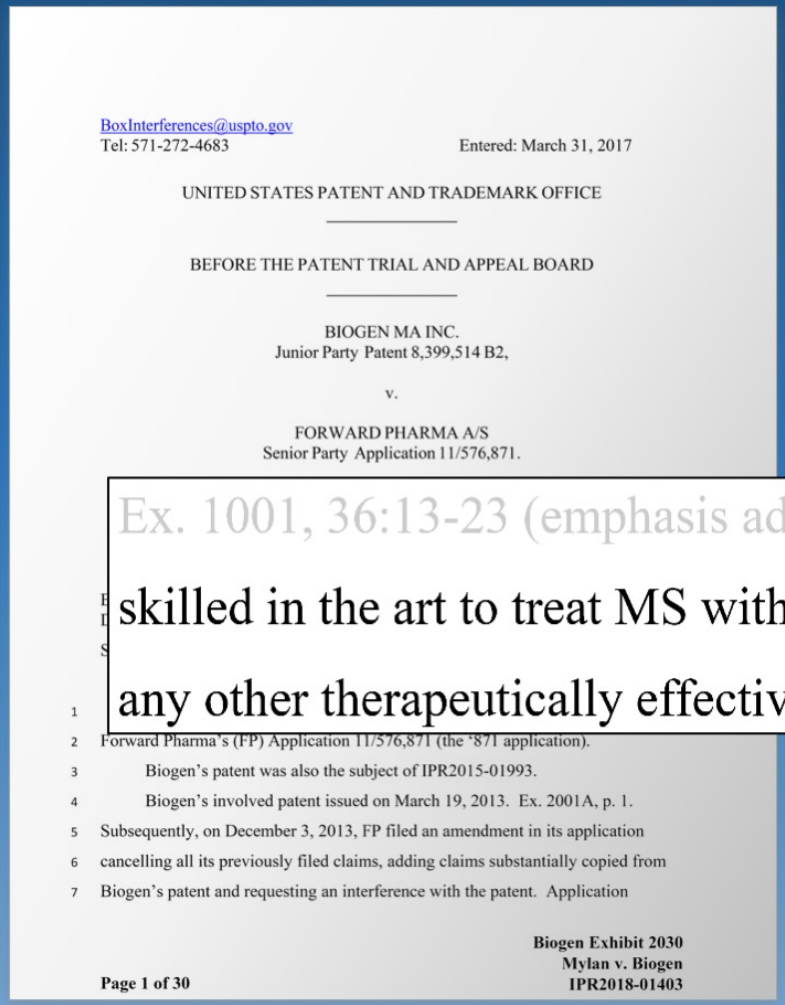
Dr. Duddy's Testimony – WO '342

Testimony of Biogen's Expert Dr. Duddy:

A: With [the knowledge that DMF monotherapy effectively treated MS from Biogen's Phase II studies] that in my head, I come to '342, and I find a long list of diseases with nothing pointing me towards multiple sclerosis. I find a long list of fumarates, none of which is specifically linked to multiple sclerosis, and I find a massive dose range, none of which is linked to any fumarate or multiple sclerosis.

Ex. 1125 (Dr. Duddy), 174:14-175:10

WO '342 - *Biogen MA Inc. v. Forward Pharma A/S* (PTAB 2017)



BoxInterferences@uspto.gov
Tel: 571-272-4683 Entered: March 31, 2017

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

BIOGEN MA INC.
Junior Party Patent 8,399,514 B2,

v.

FORWARD PHARMA A/S
Senior Party Application 11/576,871.

Forward Pharma's (FP) Application 11/576,871 (the '871 application).
Biogen's patent was also the subject of IPR2015-01993.
Biogen's involved patent issued on March 19, 2013. Ex. 2001A, p. 1.
Subsequently, on December 3, 2013, FP filed an amendment in its application cancelling all its previously filed claims, adding claims substantially copied from Biogen's patent and requesting an interference with the patent. Application

Biogen Exhibit 2030
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IPR2018-01403

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Ex. 1001, 36:13-23 (emphasis added). There is no discussion that would guide one skilled in the art to treat MS with a therapeutically effective dose of 480 mg/day, or any other therapeutically effective doses within the ranges disclosed. None of the

Ex. 2030, 22

***Aff'd, FWP IP ApS v. Biogen MA Inc.*, 749 F. Appx. 969, 976 (Fed. Cir. 2018)**

Psoriasis vs. Multiple Sclerosis

Declaration of Biogen's Expert Dr. Wynn:

"Second, **MS and psoriasis are very different diseases**. Psoriasis manifests itself in the skin and can be treated intermittently. As a result, the dose for psoriasis can easily be titrated based on an observed improvement in skin lesions. In contrast, **MS is largely a clinically silent disease, and once there are clinical manifestations, damage has already been done**. Given the course of MS and the grave consequence of undertreatment, the dose for disease modifying therapies cannot be titrated to effect such as in blood pressure or psoriasis, and such therapies are not given intermittently. **Moreover, a person of ordinary skill in the art would not have thought that a dose of one active ingredient to treat psoriasis would necessarily be effective given the different pathophysiologies**."

Ex. 2061 (Dr. Wynn), ¶83

Psoriasis vs. Multiple Sclerosis

Admissions of Petitioner's Dr. Benet:

Q: The concentration at different sites within the body, the brain, the heart, the skin, they could be different for the same plasma concentration; is that correct?

A: They are usually different.

Q: And how variable can they be between different sites within the body even given a common plasma concentration?

A: **Hugely different.**

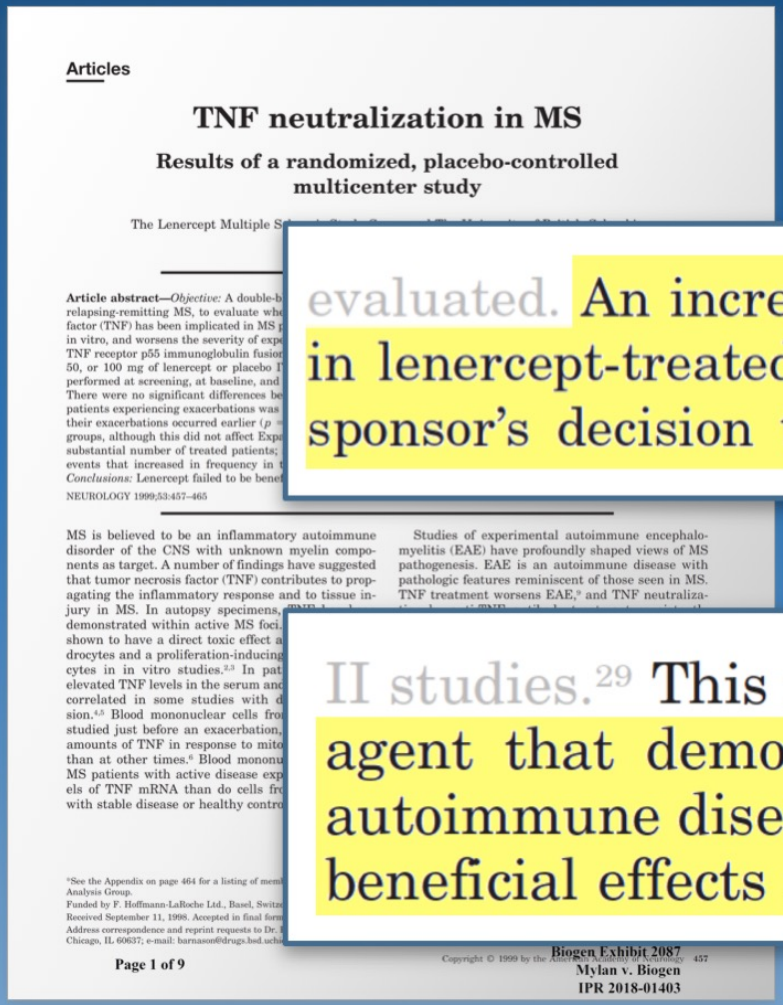
***

Q: And could it also be a function of the disease state?

A: Could be a function of disease state, also, yes.

Ex. 2062 (Dr. Benet), 36:15-24, 37:9-12

Psoriasis Drug Lenercept Made MS Worse



Articles

TNF neutralization in MS

Results of a randomized, placebo-controlled multicenter study

The Lenercept Multiple S

Article abstract—*Objective:* A double-b
relapsing-remitting MS, to evaluate wh
factor (TNF) has been implicated in MS p
in vitro, and worsens the severity of exp
TNF receptor p55 immunoglobulin fusio
50, or 100 mg of lenercept or placebo
performed at screening, at baseline, and
There were no significant differences be
patients experiencing exacerbations was
their exacerbations occurred earlier (p
groups, although this did not affect Exp
substantial number of treated patients;
events that increased in frequency in
Conclusions: Lenercept failed to be benef

NEUROLOGY 1999;53:457–465

MS is believed to be an inflammatory autoimmune disorder of the CNS with unknown myelin components as target. A number of findings have suggested that tumor necrosis factor (TNF) contributes to propagating the inflammatory response and to tissue injury in MS. In autopsy specimens,
demonstrated within active MS foci.
shown to have a direct toxic effect a
drocytes and a proliferation-inducing
cytes in in vitro studies.[2,3] In pat
elevated TNF levels in the serum and
correlated in some studies with d
sion.[4,5] Blood mononuclear cells fro
studied just before an exacerbation,
amounts of TNF in response to mito
than at other times.[6] Blood mononu
MS patients with active disease exp
els of TNF mRNA than do cells fr
with stable disease or healthy contr

Studies of experimental autoimmune encephalomyelitis (EAE) have profoundly shaped views of MS pathogenesis. EAE is an autoimmune disease with pathologic features reminiscent of those seen in MS. TNF treatment worsens EAE,[9] and TNF neutraliza-

*See the Appendix on page 464 for a listing of mem
Analysis Group.
Funded by F. Hoffmann-LaRoche Ltd., Basel, Switz
Received September 11, 1998. Accepted in final form
Address correspondence and reprint requests to Dr.
Chicago, IL 60637; e-mail: barnason@drugs.bsd.uch

Page 1 of 9

457

evaluated. An increase in the exacerbation rate was noted in lenercept-treated patients. This finding resulted in the sponsor's decision to terminate the study and to release

Ex. 2087, 459

II studies.[29] This finding suggests a final caution. An agent that demonstrates a beneficial effect in one autoimmune disease should not be presumed to have beneficial effects in another.

Ex. 2087, 464

Psoriasis vs. Multiple Sclerosis - Lenercept

Declaration of Biogen's Expert Dr. Duddy:

"In fact, it was known in the art that drugs meant to shift the Th1/Th2 balance away from Th1 or Th1-type cytokines in favor of Th2 cytokines **actually exacerbated or even caused MS**. In contrast, some of these drugs had a **favorable efficacy profile in psoriasis**."

Ex. 2058, ¶83

"The results of reported clinical studies in human patients, however, demonstrated that **targeting TNF-α, a Th1-type cytokine, actually exacerbated and even caused MS**."

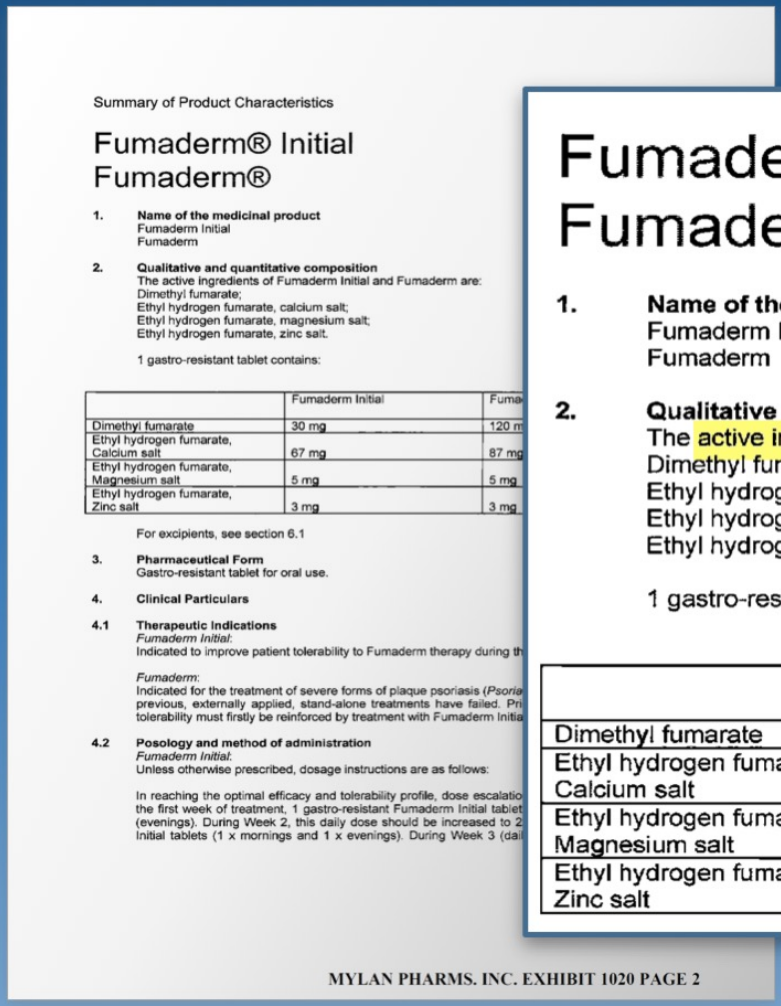
Ex. 2058, ¶85

"Based on this collection of data, a person of ordinary skill in the art would have recognized that statements such as those in Schimrigk 2004 and ClinicalTrials regarding the **hypothetical link between psoriasis and MS** to be just that—**speculative** and potentially interesting for future investigation. **But certainly at the time that Biogen filed its earliest application, such statements would not have provided a person of ordinary skill in the art with an expectation that a drug used for psoriasis would necessarily treat MS, let alone at the same dose**."

Ex. 2058, ¶89

POR, 41-42

Fumaderm® Is a Combination of Four Active Fumarates



Summary of Product Characteristics

Fumaderm® Initial
Fumaderm®

1. **Name of the medicinal product**
Fumaderm Initial
Fumaderm

2. **Qualitative and quantitative composition**
The active ingredients of Fumaderm Initial and Fumaderm are:
Dimethyl fumarate;
Ethyl hydrogen fumarate, calcium salt;
Ethyl hydrogen fumarate, magnesium salt;
Ethyl hydrogen fumarate, zinc salt.

1 gastro-resistant tablet contains:

	Fumaderm Initial	Fuma
Dimethyl fumarate	30 mg	120 m
Ethyl hydrogen fumarate, Calcium salt	67 mg	87 mg
Ethyl hydrogen fumarate, Magnesium salt	5 mg	5 mg
Ethyl hydrogen fumarate, Zinc salt	3 mg	3 mg

For excipients, see section 6.1

3. **Pharmaceutical Form**
Gastro-resistant tablet for oral use.

4. **Clinical Particulars**

4.1 **Therapeutic Indications**
Fumaderm Initial:
Indicated to improve patient tolerability to Fumaderm therapy during th

Fumaderm:
Indicated for the treatment of severe forms of plaque psoriasis (*Psoria*
previous, externally applied, stand-alone treatments have failed. Pri
tolerability must firstly be reinforced by treatment with Fumaderm Initia

4.2 **Posology and method of administration**
Fumaderm Initial:
Unless otherwise prescribed, dosage instructions are as follows:

In reaching the optimal efficacy and tolerability profile, dose escalatio
the first week of treatment, 1 gastro-resistant Fumaderm Initial tablet
(evenings). During Week 2, this daily dose should be increased to 2
Initial tablets (1 x mornings and 1 x evenings). During Week 3 (dai

MYLAN PHARMS. INC. EXHIBIT 1020 PAGE 2

Fumaderm® Initial
Fumaderm®

1. **Name of the medicinal product**
Fumaderm Initial
Fumaderm

2. **Qualitative and quantitative composition**
The active ingredients of Fumaderm Initial and Fumaderm are:
Dimethyl fumarate;
Ethyl hydrogen fumarate, calcium salt;
Ethyl hydrogen fumarate, magnesium salt;
Ethyl hydrogen fumarate, zinc salt.

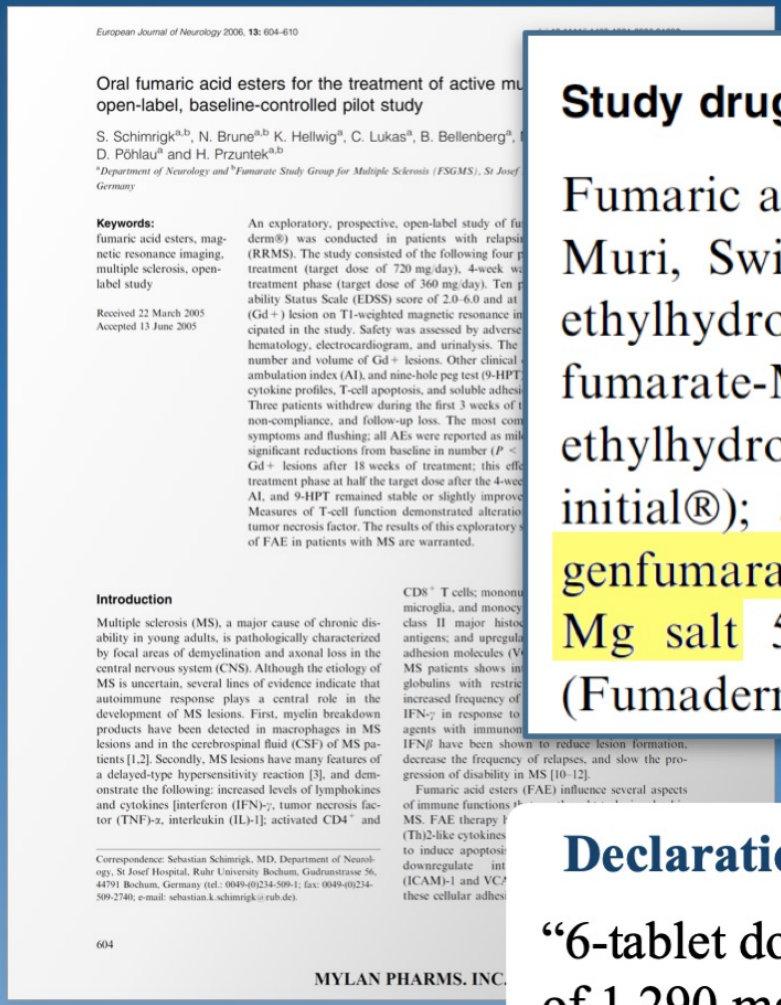
1 gastro-resistant tablet contains:

	Fumaderm Initial	Fumaderm
Dimethyl fumarate	30 mg	120 mg
Ethyl hydrogen fumarate, Calcium salt	67 mg	87 mg
Ethyl hydrogen fumarate, Magnesium salt	5 mg	5 mg
Ethyl hydrogen fumarate, Zinc salt	3 mg	3 mg

Ex. 1020, 2

Fumaderm® Is a Combination of Four Active Fumarates

Schimrigk 2006:



European Journal of Neurology 2006, 13: 604–610

Oral fumaric acid esters for the treatment of active mu
open-label, baseline-controlled pilot study

S. Schimrigk[a,b], N. Brune[a,b] K. Hellwig[a], C. Lukas[a], B. Bellenberg[a], [illegible]
D. Pöhlau[a] and H. Przuntek[a,b]
[a]Department of Neurology and [b]Fumarate Study Group for Multiple Sclerosis (FSGMS), St Josef
Germany

Keywords:
fumaric acid esters, magnetic resonance imaging, multiple sclerosis, open-label study

Received 22 March 2005
Accepted 13 June 2005

An exploratory, prospective, open-label study of fu
derm®) was conducted in patients with relapsi
(RRMS). The study consisted of the following four p
treatment (target dose of 720 mg/day), 4-week w
treatment phase (target dose of 360 mg/day). Ten p
ability Status Scale (EDSS) score of 2.0–6.0 and at
(Gd+) lesion on T1-weighted magnetic resonance in
cipated in the study. Safety was assessed by adverse
hematology, electrocardiogram, and urinalysis. The
number and volume of Gd+ lesions. Other clinical
ambulation index (AI), and nine-hole peg test (9-HPT
cytokine profiles, T-cell apoptosis, and soluble adhesi
Three patients withdrew during the first 3 weeks of t
non-compliance, and follow-up loss. The most com
symptoms and flushing; all AEs were reported as mil
significant reductions from baseline in number ($P <$
Gd+ lesions after 18 weeks of treatment; this effe
treatment phase at half the target dose after the 4-wee
AI, and 9-HPT remained stable or slightly improve
Measures of T-cell function demonstrated alteratio
tumor necrosis factor. The results of this exploratory
of FAE in patients with MS are warranted.

Introduction

Multiple sclerosis (MS), a major cause of chronic disability in young adults, is pathologically characterized by focal areas of demyelination and axonal loss in the central nervous system (CNS). Although the etiology of MS is uncertain, several lines of evidence indicate that autoimmune response plays a central role in the development of MS lesions. First, myelin breakdown products have been detected in macrophages in MS lesions and in the cerebrospinal fluid (CSF) of MS patients [1,2]. Secondly, MS lesions have many features of a delayed-type hypersensitivity reaction [3], and demonstrate the following: increased levels of lymphokines and cytokines [interferon (IFN)-γ, tumor necrosis factor (TNF)-α, interleukin (IL)-1]; activated $CD4^+$ and $CD8^+$ T cells; mononu
microglia, and monocy
class II major histo
antigens; and upregula
adhesion molecules (V
MS patients shows in
globulins with restric
increased frequency of
IFN-γ in response to
agents with immunon
IFNβ have been shown to reduce lesion formation,
decrease the frequency of relapses, and slow the progression of disability in MS [10–12].

Fumaric acid esters (FAE) influence several aspects of immune functions
MS. FAE therapy
(Th)2-like cytokines
to induce apoptosis
downregulate int
(ICAM)-1 and VC
these cellular adhesi

Correspondence: Sebastian Schimrigk, MD, Department of Neurology, St Josef Hospital, Ruhr University Bochum, Gudrunstrasse 56, 44791 Bochum, Germany (tel.: 0049-(0)234-509-1; fax: 0049-(0)234-509-2740; e-mail: sebastian.k.schimrigk@rub.de).

604

MYLAN PHARMS. INC.

Study drug

Fumaric acid ester tablets (Fumaderm®, Fumapharm, Muri, Switzerland) were composed of the following: ethylhydrogenfumarate-Ca salt 67 mg, ethylhydrogenfumarate-Mg salt 5 mg, dimethylfumarate 30 mg, ethylhydrogenfumarate-Zn salt 3 mg (Fumaderm initial®); and dimethylfumarate 120 mg, ethylhydrogenfumarate-Ca salt 87 mg, ethylhydrogenfumarate-Mg salt 5 mg, ethylhydrogenfumarate-Zn salt 3 mg (Fumaderm forte®).

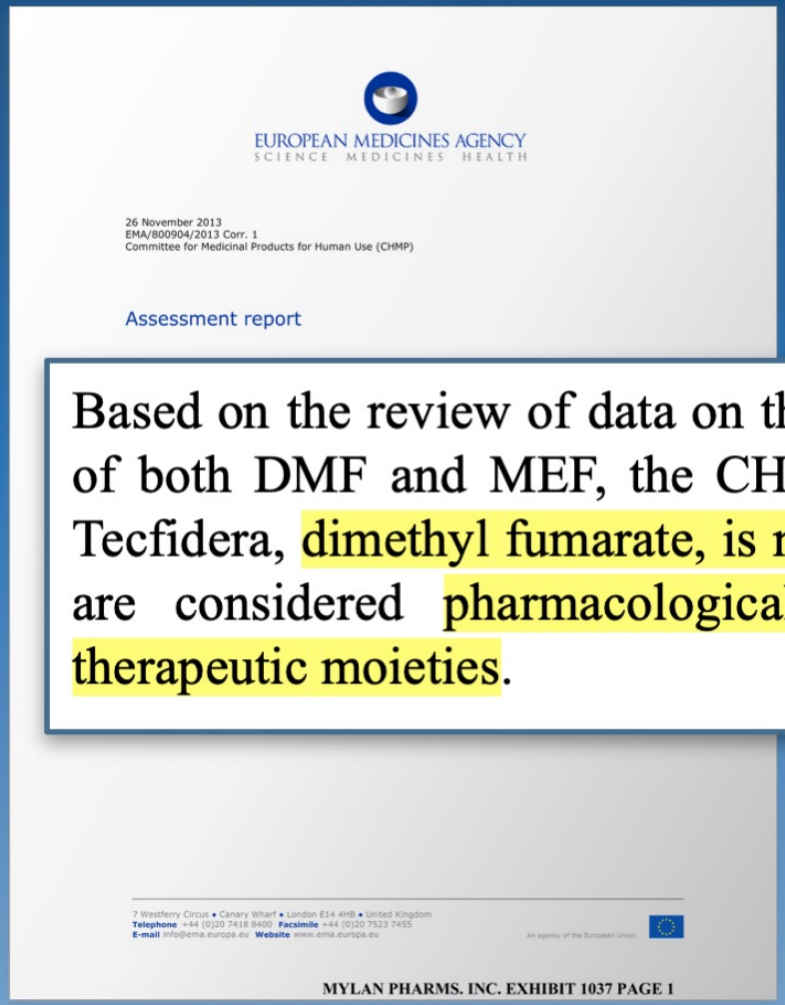
Ex. 1018, 2

Declaration of Biogen's Expert Dr. Duddy:

"6-tablet dose of Fumaderm® . . . contains a total dose of 1,290 mg active fumarates"

Ex. 2058 (Dr. Duddy), ¶60
POR, 20; Sur-reply, 5

Fumaderm® Is a Combination of Four Active Fumarates



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

26 November 2013
EMA/800904/2013 Corr. 1
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

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An agency of the European Union

MYLAN PHARMS. INC. EXHIBIT 1037 PAGE 1

Based on the review of data on the quality, non-clinical and clinical properties of both DMF and MEF, the CHMP considered that, the active substance of Tecfidera, dimethyl fumarate, is not the same as Fumaderm as MEF and DMF are considered pharmacologically active agents which contain different therapeutic moieties.

Ex. 1037, 120

Schimrigk's Atypical Non-Placebo Controlled Design

Declaration of Biogen's Expert Dr. Duddy:

"**The trial design of Schimrigk 2004 does not lend itself to determining whether the 3-tablet dose of Fumaderm® (645 mg total fumarates) is effective to treat MS**. Specifically, the patients in the study first received a 6-tablet dose of Fumaderm® (1,290 mg total fumarates). (Ex. 1006 at 5; Ex. 1020 at 2.) During this treatment phase, after 12 weeks, with the 6-tablet Fumaderm® dose, Schimrigk 2004 reports a statistically significant reduction in Gd+ lesions and volume but without providing any underlying numerical data. Following 18 weeks of treatment on the 6-tablet regimen and after only a 4-week washout period, the patients were then maintained on a 3-tablet daily dose of Fumaderm® (645 mg total fumarates). (Ex. 1006 at 5; Ex. 1020 at 2.) Schimrigk 2004 offers no data on the magnitude or trajectory of treatment response following the first observation of response at 12 weeks on the 6-tablet dose. **It is thus impossible to determine the contribution, if any, of the 3-tablet dose to the reported conclusion**."

Ex. 2058 (Dr. Duddy), ¶52

Schimrigk's Atypical Non-Placebo Controlled Design

Admissions of Petitioner's Dr. Benet:

Q: And **what about a study where the doses start high and then move low**; if the effects of the high dose don't dissipate rapidly, does that affect the interpretation of what the low dose is doing?

A: **So you just don't do those kinds of studies**. I mean, that will would not be a dose response I do.

Ex. 2062 (Dr. Benet), 58:9-17

Inventor Dr. O'Neill's Work Under 35 U.S.C. § 102(a)

In re Katz, 687 F.2d 450 (CCPA 1982)

"[O]ne's own invention, whatever the form of disclosure to the public, may not be prior art against oneself, absent a statutory bar."

Id. at 454 (quoting In re Facius, 56 CCPA 1348, 1358 (CCPA 1969))

"What is required is a reasonable showing supporting the basis for the applicant's position."

Id. at 455.

Petitioner's Burden

Varian Med. Sys., Inc. v. William Beaumont Hosp., IPR2016-00160, Paper 82 (PTAB May 4, 2017)

"[W]e are not persuaded that **Petitioner has met its burden of persuasion** by showing sufficiently that the portions of Jaffray 1999 SPIE and Jaffray 1999 JRO on which it relies are the work of 'others'."

Id. at 22.

Coal. for Affordable Drugs (ADROCA) LLC v. Acorda Therapeutics, IPR2015-01850, Paper 72 (PTAB Mar. 9, 2017)

"We find that **Petitioner's evidence that allegedly casts doubt** on the authorship of the relevant portions of S-1 **is not sufficient** to overcome the ample, unequivocal evidence presented by Patent Owner that supports our finding that the relevant portions of S-1 are the original work of Drs. Blight and Cohen alone."

Id. at 42.

Ex. 1007: Dr. O'Neill Original Draft and Publication

Dr. O'Neill Draft (Jan. 31, 2006)

Efficacy of a Novel Oral Single-Agent Fumarate, BG00012, in Patients With Relapsing-Remitting Multiple Sclerosis: Results of a Phase 2 Study

<<Please enter authors and affiliations>>

<<Character limit: 2500; Character count: 2145>>

Objective: To determine the efficacy of three dose levels of BG00012, a novel single-agent oral fumarate, on brain lesion activity as measured by magnetic resonance imaging (MRI) in patients with relapsing-remitting multiple sclerosis (RRMS).
Methods: This was a randomized, double-blind, placebo-controlled clinical trial of BG00012 in patients with RRMS. Men and women 18 to 55 years of age were eligible for the study if they had a diagnosis of RRMS and an Expanded Disability Status Scale (EDSS) score between 0.0 and 5.0. In addition, patients must have had either ≥1 relapse within 12 months prior to randomization or gadolinium-enhancing (Gd+) lesions on cranial MRI at screening. Patients received BG00012 120 mg by mouth (PO) once daily (120 mg/day), 120 mg PO three times daily (360 mg/day), 240 mg PO three times daily (720 mg/day), or placebo for 24 weeks. The treatment period was followed by a 24-week dose-blinded safety-extension period during which all patients received BG00012. The prima… 16, 2… the c… new/… numb… progr…

Results: A total of 257 patients were enrolled in the study; 64 patients each were randomly assigned to receive one of the three BG00012 doses and 65 patients to placebo. Approximately 90% of patients completed the 24-week treatment period. BG00012 (720 mg/day) significantly reduced the mean number of new Gd+ lesions (the primary end point) compared with placebo. In addition, BG00012 reduced the cumulative number of

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Conclusion: BG00012 significantly reduces brain lesion activity as measured by MRI in patients with RRMS over 24 weeks of treatment.

Ex. 2093, 2

Published Abstract (May 30, 2006)

O108
Efficacy of a novel oral single-agent fumarate, BG00012, in patients with relapsing-remitting multiple sclerosis: results of a phase 2 study
L. Kappos, D. H. Miller, D. G. MacManus, R. Gold, E. Havrdova, V. Limmroth, C. Polman, K. Schmierer, T. Yousry, M. Yang, M. Eraksoy, E. Meluzinova, I. Rektor, G. N. O'Neill
Universitätsspital Basel (Basel, CH); University College London (London, UK); University Gottingen and Gemeinnützige Hertie-Stiftung (Gottingen, D); General Teaching Hospital (Prague, CZ); City Hospital of Cologne (Cologne, D); VU Medical Centre (Amsterdam, NL); Biogen Idec (Cambridge, USA); University of Istanbul (Istanbul, TR); Faculty Hospital V Motole (Prague, CZ); Masaryk University (Brno, CZ)

Objective: To determine the efficacy of three dose levels of BG00012, a novel oral fumarate preparation, on brain lesion activity as measured by magnetic resonance imaging (MRI) in patients with relapsing-remitting multiple sclerosis (RRMS).

Methods: This was a randomised, double-blind, placebo-controlled clinical trial of BG00012 in patients with RRMS. Men and women 18 to 55 years of age were eligible for the study if they had a diagnosis of RRMS and an Expanded Disability Status Scale (EDSS) score between 0.0 and 5.0. In addition, patients must have had either ≥1 relapse within 12 months prior to randomisation or gadolinium-enhancing (Gd+) lesions on cranial MRI at

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Conclusion: BG00012 significantly reduces brain lesion activity, in a dose-dependent manner, as measured by MRI in patients with RRMS over 24 weeks of treatment.

This study was sponsored by Biogen Idec and Fumapharm AG.

Ex. 1007, 27
POR, 9; Sur-reply, 22

Ex. 1007 - Emails Between Dr. O'Neill and Dr. Kappos

Dr. O'Neill – Original Draft

Efficacy of a Novel Oral Single-Agent Fumarate, BG00012, in Patients With Relapsing-Remitting Multiple Sclerosis: Results of a Phase 2 Study

<<Please enter authors and affiliations>>

<<Character limit: 2500; Character count: 2145>>

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Results: A total of 257 patients were enrolled in the study; 64 patients each were randomly assigned to receive one of the three BG00012 doses and 65 patients to placebo. Approximately 90% of patients completed the 24-week treatment period. BG00012 (720 mg/day) significantly reduced the mean number of new Gd+ lesions (the primary end point) compared with placebo. In addition, BG00012 reduced the cumulative number of new Gd+ lesions, the number of new/enlarging T2-hyperintense lesions, and the number of new T1-hyperintense lesions, compared with placebo.
Conclusion: BG00012 significantly reduces brain lesion activity as measured by MRI in patients with RRMS over 24 weeks of treatment.

Ex. 2093, 2

Dr. Kappos – Return Draft to Dr. O'Neill

Efficacy of a Novel Oral Single-Agent Fumarate, BG00012, in Patients with Relapsing-Remitting Multiple Sclerosis: Results of a Phase 2 Study

<<Please enter authors and affiliations>>

<<Character limit: 2500; Character count: 2169>>

Objective: To determine the efficacy of three dose levels of BG00012, a novel oral fumarate preparation, on brain lesion activity as measured by magnetic resonance imaging (MRI) in patients with relapsing-remitting multiple sclerosis (RRMS).
Methods: This was a randomized, double-blind, placebo-controlled clinical trial of BG00012 in patients with RRMS. Men and women 18 to 55 years of age were eligible for the study if they had a diagnosis of RRMS and an Expanded Disability Status Scale (EDSS) score between 0.0 and 5.0. In addition, patients must have had either ≥1 relapse within 12 months prior to randomization or gadolinium-enhancing (Gd+) lesions on cranial MRI at screening. Patients received BG00012 120 mg by mouth (PO) once daily (120 mg/day), 120 mg three times daily (360 mg/day), 240 mg three times daily (720 mg/day), or placebo for 24 weeks. The treatment period was followed by a 24-week dose-blinded safety-extension period during which all patients received BG00012. The primary end point was the total number of Gd+ lesions over four MRI scans at weeks 12, 16, 20, and 24 (calculated as the sum of the four scans). Secondary end points included the cumulative number of new Gd+ lesions from week 4 to week 24 and the number of new/enlarging T2-hyperintense lesions at week 24. Additional end points included the number of new T1-hypointense lesions at week 24, relapse rate, and disability progression as measured by EDSS.
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Conclusion: BG00012 significantly reduces brain lesion activity as measured by MRI in patients with RRMS over 24 weeks of treatment.

Ex. 2093, 5

Ex. 1007 - Emails Between Dr. O'Neill and Dr. Kappos

Dr. O'Neill – Original Draft

Efficacy of a Novel Oral Single-Agent Fumarate, BG00012, in Patients With Relapsing-Remitting Multiple Sclerosis: Results of a Phase 2 Study

<<Please enter authors and affiliations>>

<<Character limit: 2500; Character count: 2145>>

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Ex. 2093, 2

Dr. Kappos – Return Draft to Dr. O'Neill

Efficacy of a Novel Oral Single-Agent Fumarate, BG00012, in Patients with Relapsing-Remitting Multiple Sclerosis: Results of a Phase 2 Study

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Conclusion: BG00012 significantly reduces brain lesion activity as measured by MRI in patients with RRMS over 24 weeks of treatment.

Ex. 2093, 5

Phase II Clinical Trial Unblinding Plan

Presentation of the grouped results to C-1900 Advisory Committee by GON

GON = Dr. Gilmore O'Neill

Flow Diagram of C-1900 Unblinding Process

Database lock for the Treatment phase study C-1900 02 Nov 05

Transfer of responsibilities to a second blinded set of statisticians and programmers that assume routine stats responsibilities for the extension phase (SMC, SMT)

Initial unblinding and analysis of C-1900 Treatment phase – Mon 21 Nov 05 – Week 47 -

2 statistician (Minhua Yang, Frances Lynn and 3 programmers (Sarah McLaughlin, Huijuan Xu and Tim Tian) are unblinded.

Review of analysis by 2 Medical Directors (Alfred Sandrock, Gilmore O'Neill) – Wed 23rd Nov– Week 47 GON to grouped results ONLY.

Presentation of analysis to members of senior management committee (Whaijen Soo, Laura Meyerson, Carmen Bozic, Glyn Belcher, Dale Spriggs) Mon 28 Nov -Week 48 - By Gilmore O'Neill

Approximately 12 individuals unblinded to data results

Presentation of analysis to Neurology SBU Bob Hamm, HP Hasler by GON – Tues 29 Nov -

Ex. 2090, 2

Presentation of the grouped results to C-1900 Advisory Committee (Efficacy only) and to the C-1900 SMC (Safety data only) by GON – Wed 30 Nov -

Approximately 23 individuals unblinded to data results

Presentation of the grouped results (Efficacy only) to the Program Team By Gilmore O'Neill - Thu 01st Dec -

Presentation of the grouped results to 2 individuals from Regulatory Affairs and 1 Medical writer for German MAA update and MS IND Filing, and IB update, respectively – by GON – Thu 01st Dec

Presentation of the grouped results to Fumapharm By Gilmore O'Neill - Week 49 -

DOC 's GO/ No GO Meeting – Mon 12 Dec –

Presentation of the grouped results (Efficacy only) to C-1900 Investigators by teleconference – Week 50 – ONLY in case of a press release.

1

Tue Oct 25 2005

Inventor Dr. O'Neill's Work Under 35 U.S.C. § 102(a)

In re Katz, 687 F.2d 450 (CCPA 1982)

"[W]e hold that authorship of an article by itself does not raise a presumption of inventorship with respect to the subject matter disclosed in the article .... The content and nature of the printed publication, as well as the circumstances surrounding its publication, not merely its authorship, must be considered."

Testimony of Ms. Conaghan (Phase II Clinical Trial Manager):

Q: What does the coordinating investigator -- what does that title convey?

A: Well, first of all, **they are one of the investigators like everybody else**. And then he was also the coordinating investigator, meaning he sat on the advisory committee.

Ex. 1129, (Ms. Conaghan), 30:11-16

Testimony of Dr. Havrdova (Phase II Investigator and SAC Member):

Q: What was Dr. Kappos's role in the Phase II study?

A: He was -- his job was the coordinator of the clinical trial.

Q: What does the job of coordinator entail in a Phase II clinical trial?

A: If the person -- **if people from other countries could not come to an agreement with their country coordinator, they could contact him**.

Ex. 1130, (Dr. Havrdova) 16:13-21
POR, 9; Sur-reply, 22-23

Inventor Dr. O'Neill's Work Under 35 U.S.C. § 102(a)

Efficacy and safety of oral fumarate in patients with
relapsing-remitting multiple sclerosis: a multicentr
randomised, double-blind, placebo-controlled phas

Summary

Introduction

Methods

Ex. 1048

Testimony of Biogen Inventor Dr. O'Neill:

Q: And so Dr. Kappos was involved in drafting and amending the study protocol and statistical analysis plan, correct?

A: **As I said, I designed the study. I drafted the study protocol. And my team -- and the team under my direction created the statistical analysis plan.** Professor Kappos and other members of the Scientific Advisory Committee had the opportunity after we had completed the protocol to actually review it and give advice and were also able to and did look at the data accorded the unblinding process that I've outlined in Exhibit 2090 and then were able to input the manuscript that was written up under my direction. And in order to enable Professor Kappos to be corresponding author, he had full access to the tables, listings, and figures that were generated by the analysis plan that my team generated under my direction.

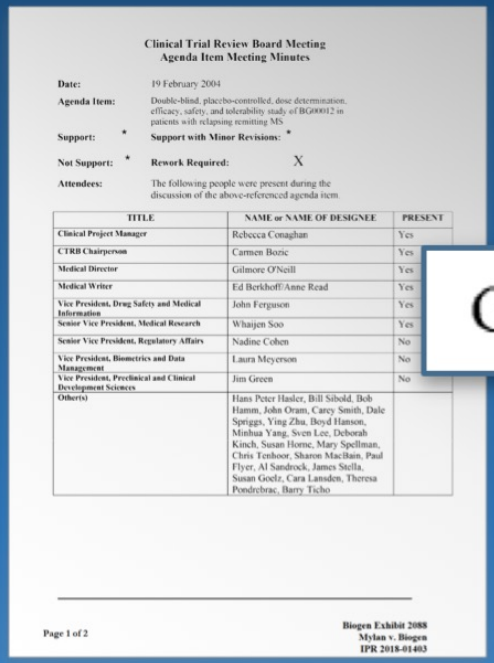
***

Q: Well, it doesn't say that GNO was involved in drafting and amending the study protocol and statistical analysis plan, does it?

A: What is written there is not incompatible with what I've said, which is that I conceived of the study design, drafted the original protocol, amended, oversaw the execution of the entire study, the analysis, and the conclusions.

Ex. 1127, (Dr. O'Neill), 154:21-155:21, 162:20-163:6

Inventor Dr. O'Neill's Work Under 35 U.S.C. § 102(a)



Clinical Trial Review Board Meeting
Agenda Item Meeting Minutes

Date: 19 February 2004

Agenda Item: Double-blind, placebo-controlled, dose determination, efficacy, safety, and tolerability study of BG00012 in patients with relapsing remitting MS

Support: * **Support with Minor Revisions:** *

Not Support: * **Rework Required:** X

Attendees: The following people were present during the discussion of the above-referenced agenda item.

TITLE	NAME or NAME OF DESIGNEE	PRESENT
Clinical Project Manager	Rebecca Conaghan	Yes
CTRB Chairperson	Carmen Bozic	Yes
Medical Director	Gilmore O'Neill	Yes
Medical Writer	Ed Berkhoff/Anne Read	Yes
Vice President, Drug Safety and Medical Information	John Ferguson	Yes
Senior Vice President, Medical Research	Whaijen Soo	Yes
Senior Vice President, Regulatory Affairs	Nadine Cohen	No
Vice President, Biometrics and Data Management	Laura Meyerson	No
Vice President, Preclinical and Clinical Development Sciences	Jim Green	No
Other(s)	Hans Peter Hasler, Bill Sibold, Bob Hamm, John Oram, Carey Smith, Dale Spriggs, Ying Zhu, Boyd Hanson, Minhua Yang, Sven Lee, Deborah Kinch, Susan Horne, Mary Spellman, Chris Tenhoor, Sharon MacBain, Paul Flyer, Al Sandrock, James Stella, Susan Goelz, Cara Lansden, Theresa Pondrebrac, Barry Ticho	

Page 1 of 2

Biogen Exhibit 2088
Mylan v. Biogen
IPR 2018-01403

CTRB Meeting Minutes (Ex. 2088)

> Gilmore O'Neill presented the concept to the CTRB.

Ex. 2088, 2

Testimony of Biogen Inventor Dr. O'Neill:

Q: And what was the role of the CTRB?

A: **The CTRB's role was to review and approve the proposed designs of clinical trials.**

Ex. 1127 (Dr. O'Neill), 47:6-8

Inventor Dr. O'Neill's Work Under 35 U.S.C. § 102(a)

Testimony of Dr. Havrdova (Phase II Investigator and SAC Member):

Q: Doctor, if you could turn to your declaration and paragraph 11. And if you could look at the second sentence. And you reference the three exhibits and state that they are solely the work of Dr. O'Neill and those working under his direction and supervision.
Do you see that?

A: Yes.

Q: **Who were you referring to when you said "those working under his direction and supervision"?**

A: Each study is a work of many people, and in any pharmaceutical company, it's not only one person that is responsible for the study.

Ex. 1130 (Dr. Havrdova), 25:11-26:1