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Paper 63
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UNITED STATES PATENT AND TRADEMARK OFFICE

PATENT TRIAL AND APPEAL BOARD

COALITION FOR AFFORDABLE DRUGS V LLC;
HAYMAN CREDES MASTER FUND, L.P.;
HAYMAN ORANGE FUND SPC – PORTFOLIO A;
HAYMAN CAPITAL MASTER FUND, L.P.;
HAYMAN CAPITAL MANAGEMENT, L.P.;
HAYMAN OFFSHORE MANAGEMENT, INC.;
HAYMAN INVESTMENTS, LLC;
NXN PARTNERS, LLC;
IP NAVIGATION GROUP, LLC;
J KYLE BASS, and ERICH SPANGENBERG,
Petitioners,

v.

BIOGEN MA INC.,
Patent Owner.

Case IPR2015-01993
Patent 8,399,514 B2

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

I.

This is a Final Written Decision on the *inter parte* review of Patent 8,399,514. The '514 Patent is assigned to Biogen Ma, Inc. (Biogen). The Coalition for Affordable Drugs V LLC, et al., petitioned for the review seeking cancellation of Claims 1-20, all of the patent claims. Paper 1 (Pet.). In a Decision entered March 22, 2016, a Board panel held that there was a reasonable likelihood that the petitioner would prevail on the claims and grounds raised in the petition and initiated this proceeding. Paper 20 (Dec. Inst.), p. 27. Biogen subsequently filed a response to which Petitioner replied. Papers 38 and 46 (Biogen Res. and Pet. Reply, respectively). An oral argument was held on November 30, 2016. Paper 62.

We have jurisdiction pursuant to 35 U.S.C. § 6(c). This Final Written Decision is issued pursuant to 35 U.S.C. § 318(a) and 37 C.F.R. § 42.73.

For the reason detailed below, we determine that Petitioner has not satisfied its burden of establishing that the subject matter of Claims 1-20 would have been obvious and those claims, therefore, have not been shown to be unpatentable under 35 U.S.C. § 103(a). Specifically, we hold that a preponderance of the evidence shows that the magnitude of the clinical efficacy of treatment of MS patients with 480 mg/day of DMF would have been unexpected to one having ordinary skill in the art.[1]

[1]Biogen was also authorized to file a motion to antedate one of the references (Kappos 2006) relied upon in the Petition. Paper 34. Biogen filed the motion (Paper 40). Petitioner filed an opposition (Paper 45) and Biogen replied (Paper 54). Biogen also argued that another reference (Joshi '999) was not eligible prior art under the provisions of 35 U.S.C. § 103(c). Biogen Res., Paper 38, pp. 17-24. Because post-filing date evidence demonstrates unexpected results, we did not reach the antedation and § 103(c) issues.

A.

Biogen's patent is also involved in pending Interference No. 106,023, captioned *Biogen Ma, Inc. v. Forward Pharma A/S*.

B.

The subject matter claimed in '514 patent is directed to methods of treating patients needing treatment for Multiple Sclerosis or MS. The heart of the treatment, and a requirement of every claim, is administering about 480 milligrams (mg) per day of certain fumarates. The fumarates are limited to dimethyl fumarate (DMF), monomethyl fumarate (MMF), or their combination. Biogen markets dimethyl fumarate under the tradename Tecfidera®. The drug is indicated for the treatment of patients with relapsing forms of MS (RRMS).

C.

The '514 patent has claims 1-20, with claims 1, 11, 15 and 20 being independent. We reproduce illustrative Claim 20, the broadest, below:

> 20. A method of treating a subject in need of treatment for multiple sclerosis comprising
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> treating the subject in need thereof with a therapeutically effective amount of
>
> dimethyl fumarate,
>
> monomethyl fumarate, or
>
> a combination thereof,
>
> wherein the therapeutically effective amount of dimethyl fumarate, monomethyl fumarate, or a combination thereof is about 480 mg per day.

Ex. 1001, 30: 22-28. (paragraphing added). Each remaining independent claim requires *oral* administration of about 480 mg per day of the fumarates. Claim 11 specifies the treatment as "consisting essentially of" the oral administration of about 480 mg/day of the fumarates. Claim 1 requires oral administration of a composition "consisting essentially of" about 480 mg/day of the fumarates along with one or more excipients. Claim 15 specifies the oral administration of a

composition "consisting essentially of" 480 mg/day of DMF and one or more excipients. All remaining claims depend directly or indirectly from the independent claims. Ex. 1001, 28:58 - 30:27.

D.

The following references are relied upon in support of the Petition:

Name	Exhibit No.	Description	Date
Kappos 2006	1003A	*Efficacy of a Novel Oral Single-Agent Fumarate,BG00012, in Patients with Relapsing-Remitting Multiple Sclerosis: Results of a Phase 2 Study*, J. NEUROL (2006) 253 (SUPPL 2); II/1–II/170, page II27	May 2006
Clinical Trials	1022	*Double-Blind, Placebo-Controlled, Dose-Ranging Study to Determine the Effacacy and Safety of BG00012 in Subjects with Relapsing-Remitting Multiple Sclerosis*, CLINICALTRIALS.GOV ARCHIVE	Sept. 14, 2005
Joshi '999	1030	U.S. Patent 7,320,999 B2	Jan. 22, 2008 filed July 17, 2002
ICH	1004	*ICH Harmonised Tripartite Guideline*, DOSE-RESPONSE INFORMATION TO SUPPORT DRUG REGISTRATION E4	Mar. 10, 1994
Joshi '992	1036	U.S. Patent 6,436,992 B1	Aug. 20, 2002
Begleiter	1027	*Dietary Induction of NQOI Increases the Antitumour Activity of Mitomycin C in Human Colon Tumours in vivo*, 91 BRITISH J. CANCER 1624–1631	2004

Pet., Paper 1, pp. 7-8.

E.

The panel instituted inter parte review on the following grounds:

Ground	Statutory Basis	Prior Art	Claims
1	35 U.S.C. § 103(a)	Kappos 2006, Clinical Trials, Joshi '999, and ICH	1–6, 8–16, and 20
2	35 U.S.C. § 103(a)	Kappos 2006, Clinical Trials, Joshi '999, ICH, and Joshi '992	7
3	35 U.S.C. § 103(a)	Kappos 2006, Clinical Trials, Joshi '999, ICH, and Begleiter	17–19

Dec. Inst., Paper 20, pp. 27-28.

II.

A.

The parties disagree on the level of skill of the person ordinarily skilled in the art. Each proposes its own definition. Petitioner, relying on the testimony of Dr. Steven E. Linberg, argues that the person of ordinary skill would have an advanced degree such as an M.D., a D.O., a Pharm D. or a Ph.D. in a life science and would be experienced with clinical trial design and dose selection. Petition, Paper 1, pp. 16-17; Ex. 1005, ¶ 9. Biogen, relying on the testimony of Dr. Rudick, argues it would be someone with at least a medical degree, at least three years of training in neurology and at least three years of clinical experience treating MS. Biogen Opp., Paper 38, p. 4; Ex. ¶ 36.

We recognize that the type of description provided by the parties as to the characteristics of the person having ordinary skill in the art is fairly typical in *inter parte* proceedings. However, in our experience, such descriptions are usually of little practical help in deciding obviousness questions. The person having ordinary skill in the art is a hypothetical person that is presumed to be aware of all the relevant prior art. *Custom Accessories, Inc. v. Jeffrey-Allan Indust., Inc.*, 807 F.2d 955, 962 (Fed. Cir. 1986); *Kimberly-Clarke Corp. v. Johnson & Johnson*, 745 F.2d

1437, 1453 (Fed. Cir. 1984). Generalities that the person of ordinary skill is, for example, an M.D. with three years experience in some field or another, provides little help in establishing what that person knows or doesn't know. It is the relevant references, along with any other evidence specifically identifying knowledge possessed by those working in the art, which substantially informs the level of ordinary skill. As long as the art relied upon is from the same or analogous fields the hypothetical person is presumed to be aware of it. *In re Gorma*n, 933 F2d 982, 986 (Fed. Cir. 1991). Because there is no issue raised that the cited art is not from the same or an analogous field as the claimed invention, the person of ordinary skill is presumed to be aware of the content of the cited references. We hold that the cited references are representative of the level of ordinary skill in the art.

B.

To prevail in this *inter partes* review of the challenged claims, Petitioner must prove unpatentability by a preponderance of the evidence. 35 U.S.C. § 316(e); 37 C.F.R. § 42.1(d). A patent claim is unpatentable under 35 U.S.C. § 103(a) if the differences between the claimed subject matter and the prior art are such that the subject matter, as a whole, would have been obvious at the time the invention was made to a person having ordinary skill in the art to which the subject matter pertains. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying factual determinations, including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of skill in the art; and (4) objective evidence of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966). "All the evidence bearing on the issue of obviousness . . . must be considered and evaluated *before* the required legal

conclusion is reached." *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1555 (Fed. Cir.1983).

As a general rule, "discovery of an optimum value of a result effective variable in a known process is ordinarily within the skill of the art [and obvious.]" *In re Boesch*, 617 F.2d 272, 276 (C.C.P.A. 1980). Accordingly, "where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Applied Materials, Inc.*, 692 F.3d 1289, 1295-96 (Fed. Cir. 2012) *quoting In re Aller*, 220 F.2d 454, 456 (CCPA 1955). The motivation to optimize comes from the natural desire of those skilled in the art to experiment with, and improve upon, known conditions taught in the prior art. *In re Peterson*, 315 F.3d 1325, 1330 (Fed. Cir. 2003). However, there is an exception to the general rule where the results of optimizing the variable are shown to result in a property or benefit that a person of ordinary skill in the relevant art would have found to be unexpected. *In re Antonie*, 559 F.2d 618, 620 (CCPA 1977*), In re Waymouth*, 499 F.2d 1273, 1276 (CCPA 1974). "Objective indicia of non-obviousness 'may often establish that an invention appearing to have been obvious in light of the prior art was not.'" *Institut Pasteur & Universite Pierre et Marie Curie v. Focarino*, 738 F.3d 1337, 1346 (Fed. Cir. 2013), *quoting Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538 (Fed. Cir.1983). Unexpected results need not have been fully recognized at the time the application was filed. *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc*., 655 F.3d 1291, 1307 (Fed. Cir. 2011); *Knoll Pharm. Co. v. Teva Pharms. USA, Inc.*, 367 F.3d 1381, 1385 (Fed.Cir.2004) ("There is no requirement that an invention's properties and advantages were fully known before the patent application was filed, or that the patent application contains all of the work done in studying the invention, in order for that work to be introduced into evidence in response to litigation attack.").

C.

Petitioner asserts that the subject matter of claim 20 is unpatentable under 35 U.S.C. § 103(a) as obvious over the combined teachings of Kappos 2006 (Ex. 1003), Clinical Trials (Ex. 1022), Joshi (Ex. 1030), and ICH Guideline E4 (Ex. 1004). Petition, Paper 1, p. 24. Petitioner also supports its position with the declaration testimony of Dr. Steven E. Linberg (Ex. 1005). Petition, Paper 1, p. 8.

1.

Kappos 2006 describes results of a Phase II trial that treated MS patients with 120, 360 and 720 mg/day of a drug identified as BG00012 (BG12). Ex. 1003, p. 2. It is uncontested that the active ingredient of BG12 was recognized to be DMF. The clinical result of the trial was that administering 720 mg/day of DMF

> significantly reduced the mean number of new Gd+lesions (the primary end point) compared with placebo. In addition, [DMF] reduced the cumulative number of new Gd+lesions, the number of new/enlarging T2-hyperintense lesions, and the number of new T1-hypointense lesions compared with placebo.

Ex. 1003A. p. 2. Gd+ and T2 and T1-hypointense lesions are brain lesions indicative of active inflammation of the type that occurs in patients with RRMS. While the only specific clinical result reported in Kappos 2006 was for the 720 mg/day dose, the study concluded that:

> [DMF] significantly reduces brain lesion activity, *in a dose-dependent manner*, as measured by MRI in patients with RRMS over 24 weeks of treatment.

Ex. 1003A, p. 2 (emphasis added).

With its response Biogen submitted a press release (Press Release, Ex. 2057) that has relevance to the results of the phase II trial described in Kappos 2006. *E.g.*, Biogen Res., Paper 38, p. 43. It was published on the same day as Kappos 2006. Press Release, Ex. 2057. It adds that the "results of the 120 mg and 360 mg

BG-12-treated groups were not statistically significant versus placebo." The press release also noted certain adverse side-effects that occurred during the trial:

> The most common adverse events were flushing, gastrointestinal disorders, headache, and nasopharyngitis.

Press Release, Ex. 2057, p. 2.

2.

We find: (1) that the difference between Kappos 2006 and the subject matter of Claim 20 is the treatment of MS patients with about 480 mg/day of DMF instead of 720 mg/day; (2) that the dosage of DMF in treating MS patients is a result-effective variable with respect to reducing brain lesions of MS patients and (3) the administration of 720 mg/day of DMF resulted in not insignificant adverse side-effects.

3.

Joshi '999 (Ex. 1030) is titled "Dimethyl Fumarate for the Treatment of Multiple Sclerosis." PTO records show that Joshi '999 is assigned to Biogen. The patent issued on January 22, 2008, based on application 10/197,077 filed July 17, 2002. The '077 application was published on January 23, 2003, as patent application publication 2003/0018072. A copy of the published application is of record as Ex. 1031. The technical content of Ex. 1031 appears to be identical to that of the Joshi '999 patent. The content of the published application is 35 U.S.C. § 102(b) prior art with respect to Biogen's earliest possible effective filing date—February 8, 2007.

Joshi '999 (Ex. 1030) relates the therapeutic use of dialkyl fumarates in pharmaceutical preparations for treatment of autoimmune diseases. Ex. 1030, 1:16-20. DMF is a dialkyl fumarate where the "alkyl" is methyl. Joshi '999 teaches providing fumarate preparations in the form of micro-tablets or micro-

pellets containing the dialkyl fumarates. Ex. 1030, 3:6-11. DMF is an "[e]specially preferred" active ingredient in the preparations. Ex. 1030, 4:26-27. The preparations "may be employed for treating autoimmune diseases, particularly . . . [MS] . . . ." Ex. 1030, 2: 2:65 – 3:5. The preferred treatment preparations (i.e., micro-tablets or micro-pellets) include 10 to 300 mg of DMF. Ex. 1030, 4:47-49. Joshi '999 describes formation of micro-tablets including 50 mg, 110 mg, and 120 mg of DMF. Ex. 1030, 5:60 – 7:55. No other examples are presented. Joshi '999 does not teach or exemplify any specific dose of DMF or any other fumarate for treating MS or any other autoimmune disease.

All the claims of the Joshi '999 patent are directed to methods of treating MS by administering an effective amount of DMF. Claim 1 of Joshi '999 provides:

> 1. A method of treating multiple sclerosis comprising
>
> treating a patient in need of treatment for multiple sclerosis with an amount of a pharmaceutical preparation effective for treating said multiple sclerosis,
>
> wherein the only active ingredient for the treatment of multiple sclerosis present in said pharmaceutical preparation is dimethyl fumarate.

Ex. 1030, 8:14-19 (paragraphing added). Joshi gives neither suggestion nor guidance as to the appropriate doses for "treating a patient in need of treatment for multiple sclerosis."

Joshi '999 notes the existence of gastrointestinal irritations and other side effects due to administration of fumarates. The patent teaches that the use of a micro-tablet form of dialkyl fumarates reduces gastrointestinal irritations and side effects vis-à-vis those that occur with conventional fumarate tablets:

> By administration of the dialkyl fumarates in the form of micro-tablets, which is preferred, gastrointestinal irritations and side

> effects, which are reduced already when conventional tablets are administered but is still observed, may be further reduced vis-a-vis fumaric acid derivatives and salts.

Ex. 1030, 5:29-33. Specifically with respect to gastrointestinal irritations, the patent also suggests using enteric-coated microcapsules which reduce the local concentration of the fumarate. Ex. 1030, 5:39-42.

4.

Clinical Trials (Ex. 1022) is a printout from the ClinicalTrials.gov archive, a publically available database of clinical trials information. The document is titled "Double-Blind, Placebo-Controlled, Dose-Ranging Study to Determine the Effacacy [sic] and Safety of BG00012 in Subjects with Relapsing-Remitting Multiple Sclerosis." Ex. 1022, p. 1. It is dated September 14, 2005. *Id.* It identifies DMF as the active ingredient in BG12. *Id*.

The document describes a two-part study. Part 1 describes investigating the effectiveness of the same dosages of DMF tested and reported in Kappos 2006. Ex. 1022, p. 2; Ex. 1003A, p. 2. The study included three treatment groups and a placebo group:

> Treatment Group BG00012 Dosing Regimen BG00012 Total Daily Dose
> 1 120 mg once a day (qd) 120 mg
> 2 120 mg three times a day (tid) 360 mg
> 3 240 mg tid 720 mg
> 4 Placebo

Ex. 1022, p. 2. As part of the study, all subjects were to be evaluated for tolerance to the drug. Ex. 1022, p. 2. Group 3 subjects were to begin with 120 mg three times a day. After Ex. 1022, p. 2. "After 1 week, Group 3 subjects who tolerate 120 mg tid (as determined by the subject's tolerance of flushing episodes and gastrointestinal [GI] disturbances) will have their dose increased to 240 mg tid."

Ex. 1022, p. 2. The study notes that "[d]ose reduction will be allowed for subjects who are unable to tolerate investigational drug." Ex. 1022, p. 2.

5.

ICH is a document issued by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. It is titled "Dose-Response Information to Support Drug Registration E4." It is dated March 10, 1994. Ex. 1004, p. 1.

ICH is not specific as to any particular disease or drug. It presents general guidance to those developing new drugs or drug treatments in determining appropriate and acceptable drug doses. The publication describes general guidelines and techniques relating to determining the dose-response of pharmaceuticals in support of drug approval and registration. Determining the dose-response is significant because "[k]nowledge of the relationships among dose, drug-concentration in blood, and *clinical response (effectiveness and undesirable effects)* is important for the safe and effective use of drugs in individual patients." Ex. 1004, p. 5 (emphasis added). We find that information in the document would have been part of the general knowledge possessed by one having ordinary skill in the art.

ICH notes that the determination of the most appropriate dose for any treatment is not straight forward:

> Historically, drugs have often been initially marketed at what were later recognized as excessive doses (i.e., doses well onto the plateau of the dose-response curve for the desired effect), sometimes with adverse consequences . . . . This situation has been improved by attempts to find the smallest dose with a discernible useful effect or a maximum dose beyond which no further beneficial effects is seen, but practical study designs do not exist to allow for precise determination of these doses. Further, expanding knowledge indicates that the concepts of minimum effective dose and maximum useful dose do not

> adequately account for individual differences and do not allow a comparison, at various doses, of both beneficial and undesirable effects. Any given dose provides a mixture of desirable and undesirable effects, with no single dose necessarily optimal for all patients.

Ex. 1004, p. 5 (emphasis added). We understand the "dose-response curve" to represent the relationship of the effect of the drug—beneficial or undesirable—to the dose of the drug. We understand the "plateau of the dose-response curve" to be the portion of the curve in which the increase in the dose does not significantly change the effect of the drug.

ICH teaches the importance of evaluating both beneficial effects and side effects in determining the dose to be administered:

> What is most helpful in choosing the starting dose of a drug is knowing the shape and location of the population (group) average dose-response curve for both desirable and undesirable effects. Selection of dose is best based on that information, together with a judgement about the relative importance of desirable and undesirable effects.

Ex. 1004, p. 5. Additionally, when evaluating the dose for individual patients the determination of the individual's dose-response curve is also important:

> In adjusting the dose in an individual patient after observing the response to an initial dose, what would be most helpful is knowledge of the shape of individual dose-response curves, which is usually not the same as the population (group) average dose-response curve. Study designs that allow estimation of individual dose-response curves could therefore be useful in guiding titration, although experience with such designs and their analysis is very limited.

Ex. 1004, p. 6 (emphasis added).

ICH describes a number of different trial designs for assessing dose-response. Ex. 1004, pp. 9-12. ICH notes that as a general matter, "useful dose-response information is best obtained from trials specifically designed to compare

several doses." Ex. 1004, p. 9. Additionally, "[i]t is important to choose as wide a range of doses as is compatible with practicality and patient safety to discern clinically meaningful differences." Ex. 1004, p. 10. ICH also identifies exemplary trial designs that can be used:

> A number of specific study designs can be used to assess dose-response. . . . Although not intended to be an exhaustive list, the following approaches have been shown to be useful ways of deriving valid dose-response information. Some designs outlined in this guidance are better established than others, but all are worthy of consideration. These designs can be applied to the study of established clinical endpoints or surrogate endpoints.

Ex. 1004, p. 10. ICH specifically describes four different types of trials: (1) parallel dose-response, (2) cross-over dose-response, (3) forced titration and (4) optional titration (placebo-controlled titration to end-point). Ex. 1004, pp. 10-12. ICH notes that the parallel dose-response trials gives population-average dose-response data and not individual dose-response curves. Ex. 1004, p. 10. Additionally, with respect to parallel dose-response trials, ICH notes that multiple trials may be necessary:

> It is all too common to discover, at the end of a parallel dose-response study, that all doses were too high (on the plateau of the dose-response curve), or that doses did not go high enough. A formally planned interim analysis (or other multi-stage design) might detect such a problem and allow study of the proper dose range.

Ex. 1004, p. 10.

D.

Petitioner argues the difference between the claimed method and that of Kappos 2006 would not have been unobvious. According to petitioner, the person of ordinary skill in the art would have been motivated to conduct further tests to optimize the effective dose: "a POSITA would have been motivated to conduct

routine experiments at a range of doses, including 480 mg/day, by orally administering that dose of a pharmaceutical to subjects in need of treatment for MS." Petition, Paper 1, p. 53. Relying on the testimony of Dr. Linberg, petitioner notes that "side effects are always a concern in drug development." Petition, Paper 1, pp. 52-53; Ex. 1005, ¶ 69. Petitioner directs us to Joshi '999 for the disclosure that it was known that treatments of fumarates, such a DMF, may result in gastrointestinal irritations and undesired side effects. Petition, Paper 1, p. 52; Ex. 1030, 5:29-33. Petitioner also directs us to the teaching in Clinical Trials that if the administration of DMF is not well tolerated due to flushing episodes and gastrointestinal disturbances, the dose may be lowered. Petition, Paper 1, p. 52; Ex. 1022, p. 2. Petitioner also relies on ICH as providing a basis for modifying the trial described in Kappos 2006 to investigate alternative doses to minimize side effects:

> the purpose of the *ICH Guideline E4* was to provide instructions to help identify "an appropriate starting dose, the best way to adjust dosage to the needs of a particular patient, and a dose beyond which increases would be unlikely to provide added benefit or would produce unacceptable side effects."

Petition, Paper 1, p. 53 *quoting* ICH, Ex. 1004, p. 5.

E.

Biogen argues, *inter alia*, that "[t]he magnitude of the clinical efficacy exhibited by administering the 480 mg/day dose was unexpected." Biogen Res., Paper 38, pp. 43-49. Biogen relies on the results of post-filing date Phase III trials for DMF. The results of the Phase III trial are presented in Exs. 2025 and 2026. The documents are referred to as the DEFINE Study and the CONFIRM Study, respectively. The trials treated MS patients with both 480 and 720 mg/day of DMF. Ex. 2025, p. 1; Ex. 2026, p. 2. According to Biogen, DEFINE and

CONFIRM establish "surprisingly—that a 480 mg/day dose of DMF proved to have similar efficacy" to the 720 mg/day taught by Kappos 2006 for almost every end point measured. Biogen Res, Paper 38, p. 43.

1.

Biogen's evidence of unexpected results includes the testimony of Ronald A. Thisted, Ph.D (Thisted Test., Ex. 2038); Richard C. Brundage, Pharm. D., Ph.D (Brundage Test., Ex. 2042) and Richard A. Rudick, M.D. (Rudick Test., Ex. 2044).

a.

Dr. Thisted testifies that he is a Professor and Vice Provost, Academic Affairs, at the University of Chicago and holds faculty appointments in the departments of Statistics, Public Health Sciences, and Anesthesia & Critical Care. He received bachelor's degrees in mathematics and philosophy from Pomona College, and a master's degree and a doctorate of philosophy in statistics from Stanford University. He has more than forty years of research, academic, and practical experience in the area of biostatistics. His research focuses on biostatistics and epidemiology, statistical computation, and the effectiveness of medical intervention from a statistical perspective. He has been on the faculty of the University of Chicago since 1976. His positions included Scientific Director for the Biostatistics Core Facility at the University of Chicago Cancer Research Center from 1999–2014. He has taught courses in biostatistics for over 35 years and also taught courses on statistical methods, epidemiology, and clinical research methods. He is an Elected Fellow of the American Association for the Advancement of Science (1992) and of the American Statistical Association (1988). He has authored over one hundred publications in the area of biostatistics and epidemiology, many in peer-reviewed journals including the *New England Journal of Medicine*, the *Journal of the American Medical Association*, and *The Lancet*. He has acted as a referee for the National Institutes of Health and the

National Science Foundation reviewing grant proposals for potential funding. Since the late 1970s, he has consulted for the pharmaceutical and medical device industries on the design of clinical trials and statistical analysis of clinical trial results. He has consulted regarding the design of Phase I, Phase II, and Phase III clinical trials; designed data collection methods; planned and overseen statistical analysis of results; prepared reports for use by the FDA; and presented statistical aspects of clinical studies to the FDA. He has consulted as the principal biostatistician for studies involving MS patients including as principal biostatistician on two randomized clinical trials for treating specific symptoms in MS patients. Thisted Test., Ex. 2038, ¶¶ 2-11; Ex. 2039.

b.

Dr. Brundage testifies that is Professor of Experimental and Clinical Pharmacology at the College of Pharmacy at the University of Minnesota and has held that position since 2008. He received a Bachelor of Science degree in Pharmacy and a Pharm. D. from the University of Minnesota College of Pharmacy in 1977 and 1985, respectively. He also obtained a Ph.D. in Pharmaceutics from the University of Minnesota in 1996. He was an Assistant Professor of Pharmacy at the Medical University of South Carolina researching clinical pharmacokinetics. His instructional responsibilities included Clinical Pharmacokinetics, Advance Disease Processes and Pharmacotherapeutics: Neurology Module. His current research involves the quantitative modeling of pharmacological systems for better understanding of dose-response relationships. During his tenure at the University of Minnesota, he has taught both professional and graduate courses, including Applied Pharmacokinetics, Pharmacometrics, and Advanced Clinical Pharmacology. He has also taught Clinical Trials Simulations, which involves designing and conducting computer-based clinical trials to explore optimal design elements (e.g., sample size, timing of sample collection, and timing of outcome

measures). Additionally, he has taught numerous lectures, short courses, and workshops on topics including population pharmacokinetics, applications of nonlinear mixed-effects modeling in drug development, and a lecture entitled "Center for Forecasting Drug Response: The Role of Pharmacometrics" at the Institute for Therapeutics Discovery and Development. His research has been funded by grants and contracts, including grants from the National Institutes of Health and several pharmaceutical companies. He has published over 90 papers in peer-reviewed and refereed journals and authored of several book chapters in the field of Pharmacokinetics and Pharmacodynamics. He is a fellow of the International Society of Pharmoacometrics and regularly presents at conferences as an invited speaker. He is a member of and has served on committees of several professional societies, including the International Society of Pharmacometrics, the American College of Clinical Pharmacology, the American Society of Clinical Pharmacology and Therapeutics, and the American Association of Pharmaceutical Scientists. He has served on the editorial boards of the *British Journal of Pharmacology*, the *Journal of Pharmacokinetics and Pharmacodynamics*, and the *International Journal of Clinical Pharmacology and Therapeutics*. He has also been an ad hoc manuscript reviewer for over 20 other journals, including *Clinical Therapeutics*, *Journal of the American Pharmaceutical Association*, and *Pharmaceutical Research*. Brundage Test., Ex. 2042, ¶¶ 2-16, and Ex. 2043.

c.

Dr. Rudick testifies that he is a medical doctor with over thirty-five years of experience in MS related research, teaching, and clinical practice. Since 2014, he has been Vice President of Development Sciences, Value-Based Medicine Group at Biogen which focuses on using new technology to develop innovative programs and tools to better understand, measure, and manage the treatment of MS. He testifies that he earned his M.D. from Case Western Reserve University School of

Medicine in 1975. He also earned a bachelor of science in zoology from Ohio University in 1971. He was a Resident in Medicine at the University of Connecticut School of Medicine From 1975 to 1977, Resident in Neurology at Strong Memorial Hospital in Rochester, New York from 1977 to 1979, and Chief Resident there in Neurology from 1979 to 1980. He testifies that he has over thirty-five years of experience in research related to MS including clinical trials involving MS treatments that are now approved by the U.S. Food and Drug Administration (FDA). He was the co-principal investigator on a National Institutes of Health (NIH)-supported, investigator-initiated clinical trial of intramuscular recombinant interferon beta (rIFNβ) for relapsing MS (1990-1994) which led to registration of the interferon product. He has conducted numerous studies and conducted clinical trials on MS treatment drugs supported by Biogen, the National Institutes of Health and the National MS Society resulting in registration and marketing of those drugs. He has also participated in many other clinical trials, and in clinical research protocols in the general field of MS, translational research, outcome measures, magnetic resonance imaging (MRI), clinical trials, and biomarkers. He has been awarded dozens of research grants and fellowships, including for "Evaluating Selected Monitoring Techniques in MS Clinical Trials" from the National MS Society, "IM Recombinant Beta Interferon as Treatment for MS" from the NIH, "Monitoring Brain Atrophy during the Course of MS" from the NIH, and "Biomarkers of the Therapeutic Response to Interferon in MS" from the NIH. He has also received research grants and fellowships from pharmaceutical companies, including Biogen. He was Director of the Mellen Center for MS Treatment and Research at the Cleveland Clinic from 1987 to 2014 serving as Chairman of the Division of Clinical Research at the Cleveland Clinic (2001-2007), Vice-Chairman of Research and Development at the Neurological Institute at the Cleveland Clinic (2007-2014), and Co-Director of the Cleveland

CTSC (2004-2014). He has over thirty-five years of experience teaching others about MS treatment including teaching at the Rochester University School of Medicine as Instructor in Neurology (1979-1980), Assistant Professor of Neurology (1980-1986), Associate Professor of Neurology (1986-1987), and Adjunct Associate Professor of Neurology (1987-1995). From 1995 to 2014, he was Hazel Prior Hostetler Professor of Neurology at the Cleveland Clinic. He was also Professor in the Department of Medicine at the Cleveland Clinic Lerner College of Medicine (CCLCM) from 2003 to 2014, and Professor in the Department of General Medical Sciences and Center for Clinical Investigation in the Case School of Medicine from 2006 to 2014. He testifies that he has over thirty-five years of clinical experience with MS including diagnosing and treating many thousands of MS patients, including patients who have been referred from physicians all over the world. He diagnosed and treated MS patients as an Associate Neurologist at Strong Memorial Hospital from 1980 to 1987. He also had clinical experience at the Mellen Center, where he diagnosed and treated patients with MS from 1987 to 2014. He also provided consultation to other physicians and supervised a medical staff neurologists specializing in MS treatment and advanced practice clinicians. He was certified by the American Board of Internal Medicine since 1978 and by the American Board of Psychiatry and Neurology in 1981. He has authored over 230 peer-reviewed publications related to MS and has held editorial positions on journals including *Neurotherapeutics*, *Lancet Neurology*, and *Multiple Sclerosis - Clinical Issues*. He has authored ten books and over thirty book chapters, including several editions of the text Multiple Sclerosis Therapeutics. He has given over seventy invited lectures related to MS. He has been engaged as a consulted on MS by pharmaceutical companies, including Biogen. He has served on over a dozen committees and advisory boards, including research peer-review committees for

the National MS Society, the NIH, and the MS International Federation. He has served on and also chaired the National MS Society Research Program Advisory Committee, the NIH Council for the National Council for Research Resources, and the NIH Council of Councils. He is currently the co-director of the MS Outcomes Assessment Consortium (MSOAC), which is sponsored by the National MS Society, a collaboration of eight pharmaceutical companies, MS academic leaders from around the world, the FDA, and European Medicines Agency (EMA). MSOAC has the goal establishing an improved clinical outcome measure for MS disability. He has received many awards for work related to MS, including the Health Care Professional Hall of Fame Award from the National MS Society. Rudick Test., Ex. 2044, ¶¶ 1-17; Ex. 2045.

d.

We find each of Drs. Thisted, Brundage, Rudick are qualified by knowledge, skill, experience, training, and education that is sufficiently related to the claimed invention that they may provide opinion testimony on the subject matter of the invention involved in this proceeding.

2.

In addition to the testimony of Drs. Thisted, Brundage and Rudick, Biogen relies on the phase III trials for DMF to argue unexpected results. Biogen Res, Paper 38, p. 44. The "DEFINE" and "CONFIRM" studies (Exs. 2025 and 2026), report the results of those trials. *Id.*; Rudick Test., Ex. 2044, ¶ 43. DEFINE compares the results of treatment with DMF at 240 mg three times a day (720 mg/day), DMF at 240 mg twice a day (480 mg/day) and placebo. Ex. 2025, p.1. CONFIRM compares the same doses of DMF with placebo and additionally with to an active agent for MS treatment, glatiramer acetater. Ex. 2026, p. 1.

Biogen directs us to its Figure 5 which is said to be based upon data aggregated from DEFINE and CONFIRM. Biogen Res., Paper 38, pp. 46-47;

Rudick Test., Ex. 2044, ¶ 47. Figure 5 graphically compares the relative effects of doses of 480 mg/day (circle), 720 mg/day (triangle) to that of placebo. Biogen Res., Paper 38, pp. 46-47. We reproduce Figure 5 below:

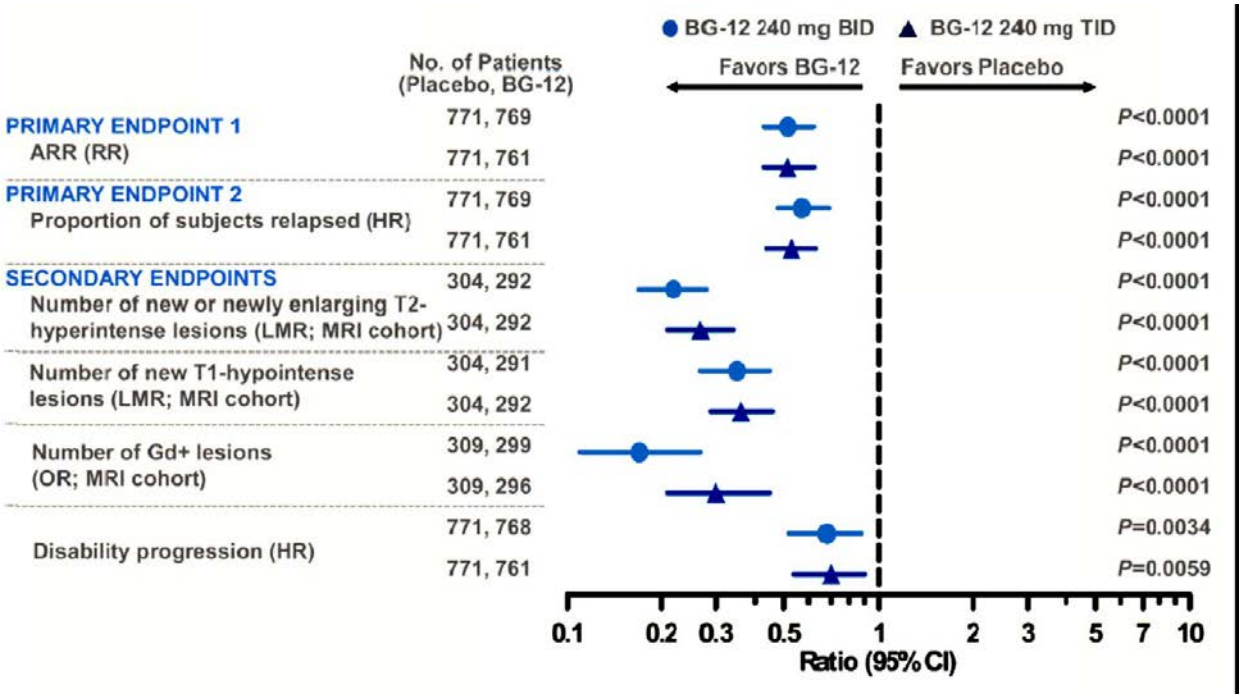

Figure 5, reproduced from Biogen's Response (Paper 38, p. 46) and Dr. Rudick's testimony (Ex. 2044, ¶ 47) depicts the ratio of the effects on MS patients of treatment with 480 mg/day and 720 mg/day to that of placebo.

The figure shows the ratios of the magnitude of the identified outcome to the magnitude resulting from administration of placebo. Rudick Test., Ex. 2044, ¶ 47. The dashed line, showing a value of "1," indicates no difference in effect of the treatment between the tested drug and placebo, i.e. Rudick Test., Ex. 2044, ¶ 47. Values to the left of the dashed line show effects that are better than placebo. Rudick Test., Ex. 2044, ¶ 47. Figure 5 shows that the ratio for most of the effects are very similar for 480 mg/day and 720 mg/day. Dr. Rudick testifies that the figure shows "480 mg/day has similar efficacy to 720 mg on every outcome." Rudick Test., Ex. 2044, ¶ 47.

Dr. Thisted also reviewed the DEFINE and CONFIRM studies. Thisted Test., Ex. 2038, ¶ 34. In his opinion the studies "showed that the therapeutic efficacy of 480 mg/day is essentially the same as that of 720 mg/day. Thisted Test., Ex. 2038, ¶ 42.

3.

It is known to those developing new drugs or treatments that there may be a plateau in the dose-response curve in which the increase in the dose does not significantly change the effect of the drug. ICH, p. 10. However, Drs. Thisted, Brundage and Rudick, testify to the effect that one having ordinary skill in the art would not have expected the 480 and 720 mg/day doses to be on such a plateau. All three experts testify that one skilled in the art would have expected the efficacy of 480 mg/day to be closer to that of 360 mg/day, a dose which did not have a statistically significant effect, than to 720 mg/day dose described in Kappos 2006. Dr. Thisted testifies:

> a person of ordinary skill in the art would not have expected that increasing the dose by an additional 33% (to 480 mg/day) would produce substantial efficacy when the lower dose (360 mg/day) did not. At most, a person of ordinary skill in the art would have expected the effects on brain lesions with 480 mg/day to be closer to those with a 360 mg/day dose than those with a 720 mg/day dose.

Thisted Test., Ex. 2038, ¶ 24. Dr. Brundage similarly testifies:

> Based on Kappos 2006 and Biogen's press release, little or no information was available at that time about the shape of the dose-response curve for DMF in MS between the 360 mg/day and 720 mg/day doses.
>
> 37. I would expect that doses closer to 360 mg/day would have responses more similar to 360 mg/day, and doses closer to 720 mg/day would behave more like the response for 720 mg/day. In other words, I would expect a dose of 480 mg/day of DMF to have a measured response more like 360 mg/day

> than 720 mg/day because 480 mg/day is closer to 360 mg/day than it is to 720 mg/day.
>
> 38. In addition, based on what was known at the time it remained possible that administering an even higher dose of DMF than 720 mg/day would have led to a greater measured response with no increase in adverse drug effects.
>
> 39. In sum, I would expect that 480 mg/day of DMF to show some increase in response compared to 360 mg/day based on the statement in Kappos 2006 that BG00012 (DMF) significantly reduced brain lesion activity in a dose-dependent manner. But because the art lacked a well-defined dose-response curve for DMF in MS, one could not know whether a dose of 480 mg/day of DMF would be statistically significantly different from placebo (efficacious) or not. Any such conclusion would be scientifically unsupported based on the limited scientific information available at the time. As a result, based on the limited disclosure of Kappos 2006, a person of ordinary skill would not have had a reasonable expectation that a dose of 480 mg/day of DMF would be a therapeutically effective daily dose to treat MS, let alone as effective as the tested 720 mg/day dose.

Brundage Test., Ex. 2042, ¶¶ 36-39. Consistently with the other two experts, Dr. Rudick's testifies that one skilled in the art would have expected the efficacy of 480 mg/day to be similar to that of 360 mg/days:

> based on the Phase 2 results, a person of ordinary skill would have at most expected that the efficacy of a 480 mg/day dose would be more like that of the 360 mg/day dose (which was not effective) than that of the 720 mg/day dose (which was effective). This is because a 480 mg/day dose is closer to a 360 mg/day dose than a 720 mg/day dose.

Rudick Test., Rudick Test., Ex. 2044, ¶ 42.

4.

Drs. Thisted and Rudick further testify that the reported similar efficacy for 480 and 720 mg/day would have been unexpected. Thus, Dr. Thisted testifies:

> 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.*

Thisted Test., Thisted Test., Ex. 2038, ¶ 45 (emphasis added). Dr. Rudick testifies that "[a] person of ordinary skill would not have expected 480 mg/day to be similarly efficacious to 720 mg/day." Rudick Test., Ex. 2044, ¶ 48.

5.

Petitioner's Reply does not effectively address Biogen's unexpected results argument and evidence. Petitioner responds only with a single sentence: "As demonstrated above, success was expected, not unexpected." Pet. Reply, Paper 46, p. 24. Biogen's argument, however, is not merely that it would have been unexpected that some lower doses would have been an effective therapeutic treatment. Rather, Biogen's position is that the magnitude of the clinical efficacy at the specifically claimed dose of about 480 mg/day would have been unexpected. Biogen Res., Paper 38, pp. 43-49. Petitioner has not directed us to evidence, or provided a reason, for us to doubt the unrebutted testimony of Biogen's highly qualified and credible experts. Biogen's expert testimony on this point stands unchallenged.

6.

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

E.

Considering the evidence detailed above, we determine that one having ordinary skill in the art would have had ample reason to use routine

experimentation, including appropriate clinical trials, to determine the optimum doses for MS treatment. Kappos 2006 teaches both the effectiveness of the 720 mg/day dose and that DMF is a result-effective variable:

> [DMF] significantly reduces brain lesion activity, *in a dose-dependent manner*, as measured by MRI in patients with RRMS over 24 weeks of treatment.

Ex. 1003A, p. 2 (emphasis added). Because of the reported side-effects from the treatment of with fumarates, (Joshi '999, Ex. 1030, 5:29-42; Press Release, Ex. 2057, p. 1), those working in the art would have had suffient reason to investigate doses between 720 mg/day and 360 mg/day in hopes of identifying effective dose with fewer side-effects. Those working in the art would also have had a reasonable expectation of success in determining additional therapeutically effective doses. As noted by Dr. Brundage: "I would expect that 480 mg/day of DMF to show some increase in response compared to 360 mg/day based on the statement in Kappos 2006 that BG00012 (DMF) significantly reduced brain lesion activity in a dose-dependent manner." Brundage Test., Ex. 2042, ¶ 39.

However, as noted above, the testimony of Biogen's experts, Drs. Thisted, Brundage and Rudick, persuade us that the magnitude of clinical efficacy of the 480 mg/day treatment would have been unexpected by those working in the art. 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 often establish that an invention appearing to have been obvious in light of the prior art was not.'" *Institut Pasteur*, 738 F.3d at 1346. While the proof of the optimization of a result-effective variable is generally sufficient to establish the obviousness of a particular value of that variable, obviousness is not established when the results of optimization are shown to result in a property or benefit that a person of ordinary skill in the relevant art would have found to be unexpected. *See*

Antonie, 559 F.2d at 620. *See also Procter & Gamble Co. v. Teva Pharm. USA, Inc.*, *566 F.3d 989, 994 (Fed. Cir. 2009)*. Because the evidence established unexpected results, we hold that Petitioner has not met its burden to show that the subject matter of Biogen's claim 20 would have been obvious.

F.

Because the treatment with about 480 mg/day is required in each of Biogen's remaining claims, Petitioner has failed to establish that the subject matter of claims 1-19 would have been obvious for the same reasons stated above for claim 20.

III.

Biogen has filed a motion to seal Ex. 2016A and 2017A. Paper 39. We deny the motion and order that Exs. 2016A and 2017A be expunged from the PTO record of this proceeding.

The documents are a license agreement between Biogen, Inc. and Fumapharm AG and a stock purchase agreement for the sale of all registered shares of Fumapharm AG to Biogen Idec MA, Inc. Exs. 2016 and 2017 are redacted versions of the agreements which exclude portions said to include confidential business information.

The motion is unopposed by Petitioner. Neither party has referred to the unredacted versions. A review of the documents shows that the redacted versions (Exs. 2016 and 2017) are sufficient for all issues raised. Therefore, there is no apparent reason to maintain the unredacted versions as part of the official PTO record of this proceeding. We therefore deny the motion and order that Exs. 2016A and 2017A be expunged.

IV.

We conclude that Petitioner has failed to show by a preponderance of the evidence that claims 1-20 of the '514 patent are unpatentable.

ORDER

In consideration of the foregoing, it is hereby:

ORDERED that claims 1-20 of Patent 8,399,514 have not be shown to be unpatentable;

FURTHER ORDERED that Biogen's Motion to Seal is *denied;*

FURTHER ORDERED that Papers 2016A and 2017A be expunged from the record; and

FURTHER ORDERED that, because this is a Final Written Decision, the notice and service requirements of 37 C.F.R. § 90.2 are applicable with respect to any judicial review of this decision.

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