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February 14, 2012

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

Confirmation No. 5998
Art Unit To be assigned

Re: U.S. Utility Patent Application
Appl. No. 13/372,426; Filing Date: February 13, 2012
For: **Treatment for Multiple Sclerosis (As Amended)**
Inventors: LUKASHEV *et al.*
Our Ref: 2159.3210002/JMC/MRG/U-S

Sir:

Transmitted herewith for appropriate action are the following documents:

1. Preliminary Amendment Under 37 C.F.R. § 1.115;
2. Exhibit 1 - Declaration of Katherine T. Dawson, M.D. Under 37 C.F.R. § 1.132;
3. Exhibit A to Exhibit 1;
4. Exhibit B to Exhibit 1;
5. Exhibit C to Exhibit 1;
6. Exhibit D to Exhibit 1;
7. Exhibit E to Exhibit 1; and
8. Exhibit 2.

The above-listed documents are filed electronically through EFS-Web.

The Preliminary Amendment submitted herewith is identical to the Preliminary Amendment Under 37 C.F.R. § 1.115 submitted on February 13, 2012, and is being resubmitted with the Exhibits which were inadvertently omitted from the filing on February 13, 2012.

The U.S. Patent and Trademark Office is hereby authorized to charge any fee deficiency, or credit any overpayment, to our Deposit Account No. 19-0036.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

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MRG/U-S:enm
Enclosures

1484850_1.DOCX

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Confirmation No.: *To be assigned*
LUKASHEV *et al.*	Art Unit: *To be assigned*
Appl. No.: *To be assigned*	
(*Continuation of Appl. No. 12/526,296, § 371(c) Date: January 13, 2011*)	Examiner: *To be assigned*
Filing Date: Herewith	Atty. Docket: 2159.3210002/JMC/MRG/U-S
For: **Treatment for Multiple Sclerosis (As Amended)**	

Preliminary Amendment Under 37 C.F.R. § 1.115

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

Sir:

In advance of prosecution, Applicants submit the following amendments and remarks.

Amendments to the Specification begin on page 2 of this paper.

Amendments to the Claims are reflected in the listing of claims which begins on page 3 of this paper.

Remarks and Arguments begin on page 6 of this paper.

It is not believed that extensions of time or fees for net addition of claims are required beyond those that may otherwise be provided for in documents accompanying this paper. However, if additional extensions of time are necessary to prevent abandonment of this application, then such extensions of time are hereby petitioned under 37 C.F.R. § 1.136(a), and any fees required therefor (including fees for net addition of claims) are hereby authorized to be charged to our Deposit Account No. 19-0036.

Amendments to the Specification

Please amend the title as follows:

Treatment for Multiple Sclerosis ~~NRF2 screening assays and related methods and compositions~~

Please amend paragraph [0128], beginning on page 33, line 21, as follows:

[0128] Immunohistochemistry was performed using the Dakoautostainer as follows. Endogenous peroxidase was quenched by a 10 minute incubation in 3% H_2O_2 / Methanol. The rabbit anti Nrf2 antibody C-20 (sc-722, Santa Cruz Biotechnology) was added at a 1:250 dilution in Dako Diluent with Background Reducing Components (Dako # S3022) C-20 antibody was detected using the Envision anti rabbit labeled polymer-HRP (Dako #K4003) and DAB (Vector Labs #SK-4100) was used as the chromogenic substrate. Morphometric analysis of Nrf2 immunostaining was performed using ImageJ software from NIH ~~(http://rsb.info.nih.gov/ij/)~~.

On page 1, below the title of the invention, please add the following new paragraph:

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. Patent Application No. 12/526,296, § 371(c) Date January 13, 2011, now pending, which is the U.S. National Phase of International Application No. PCT/US2008/001602, filed February 7, 2008, which claims the benefit of U.S. Provisional Application 60/888,921, filed February 8, 2007.

Amendments to the Claims

This listing of claims will replace all prior versions, and listings, of claims in the application.

1-17. (Cancelled)

18. (New) A method of treating a subject in need of treatment for multiple sclerosis comprising orally administering to the subject in need thereof a pharmaceutical composition consisting essentially of (a) a therapeutically effective amount of dimethyl fumarate, monomethyl fumarate, or a combination thereof, and (b) one or more pharmaceutically acceptable excipients, wherein the therapeutically effective amount of dimethyl fumarate, monomethyl fumarate, or a combination thereof is about 480 mg per day.

19. (New) The method of claim 18, wherein the pharmaceutical composition is administered in the form of a tablet, a suspension, or a capsule.

20. (New) The method of claim 18, wherein the therapeutically effective amount is administered in separate administrations of 2, 3, 4, or 6 equal doses.

21. (New) The method of claim 20, wherein the therapeutically effective amount is administered in separate administrations of 2 equal doses.

22. (New) The method of claim 20, wherein the therapeutically effective amount is administered in separate administrations of 3 equal doses.

23. (New) The method of claim 18, wherein the pharmaceutical composition consists essentially of dimethyl fumarate and one or more pharmaceutically acceptable excipients.

24. (New) The method of claim 18, wherein the pharmaceutical composition consists essentially of monomethyl fumarate and one or more pharmaceutically acceptable excipients.

25. (New) The method of claim 18, wherein the pharmaceutical composition is administered to the subject for at least 12 weeks.

26. (New) The method of claim 23, wherein the therapeutically effective amount is administered to the subject in 2 equal doses.

27. (New) The method of claim 26, wherein the therapeutically effective amount is administered to the subject for at least 12 weeks.

28. (New) A method of treating a subject in need of treatment for multiple sclerosis consisting essentially of orally administering to the subject about 480 mg per day of dimethyl fumarate, monomethyl fumarate, or a combination thereof.

29. (New) The method of claim 28, wherein about 480 mg of dimethyl fumarate per day is administered to the subject.

30. (New) The method of claim 29, wherein the dimethyl fumarate is administered in separate administrations of 2 equal doses.

31. (New) The method of claim 29, wherein the dimethyl fumarate is administered in separate administrations of 3 equal doses.

32. (New) A method of treating a subject in need of treatment for multiple sclerosis comprising orally administering to the subject a pharmaceutical composition consisting essentially of (a) a therapeutically effective amount of dimethyl fumarate and (b) one or more pharmaceutically acceptable excipients, wherein

the therapeutically effective amount of dimethyl fumarate is about 480 mg per day.

33. (New) The method of claim 32, wherein the dimethyl fumarate is administered in separate administrations of 2 equal doses.

34. (New) The method of claim 18, wherein the expression level of NQO1 in the subject is elevated after administering to the subject the therapeutically effective amount of dimethyl fumarate, monomethyl fumarate, or a combination thereof.

35. (New) The method of claim 28, wherein the expression level of NQO1 in the subject is elevated after administering to the subject about 480 mg per day of dimethyl fumarate, monomethyl fumarate, or a combination thereof.

36. (New) The method of claim 32, wherein the expression level of NQO1 in the subject is elevated after administering to the subject the therapeutically effective amount of dimethyl fumarate.

Remarks

Upon entry of the foregoing amendment, claims 18-36 are pending in the application, with claims 18, 28, and 32 being the independent claims.

Claims 1-17 are sought to be cancelled without prejudice or disclaimer thereof. New claims 18-36 are sought to be added. Support for claims 18-36 is set forth in Section I below.

I. Summary of the Claimed Subject Matter

The claimed invention is generally directed to methods of orally treating multiple sclerosis (MS). MS is a chronic disease for which only a limited number of disease-modifying treatment options are currently available, most of which are administered by injection. Only one disease-modifying oral drug has been approved in the United States and that has only recently been approved. In addition, not all MS drugs are indicated for every MS patient. Furthermore, patients must carefully weigh the risks associated with each drug at a given disease state. It is very clear that additional medications are needed to provide better life quality and reduced risk of disability for MS patients. Oral MS medications with favorable safety profiles are particularly desired. Applicants' invention satisfies this desire.

Applicants disclose a method for treating a neurological disease with at least one fumaric acid derivative, including dimethyl fumarate (DMF) or monomethyl fumarate (MMF), as "method 4" in paragraph [0009], lines 9-11 and paragraphs [0062-0063] of the specification. The application discloses that *"[i]n some embodiments the neurological disease is MS or another demyelinating neurological disease."*

(Specification, p. 4, paragraph [0010]) (emphasis added). Applicants also discussed a MS animal model, Experimental Autoimmune Encephalomyelitis (EAE), in paragraphs [0108] and [0109], as well as Example 3. Therefore, MS is supported in the application.

Additionally, Applicants disclose that DMF and/or MMF are effective in treating MS. For example, DMF and MMF are listed as specific examples of neuroprotective compounds. (Specification, p. 13, paragraph [0063].) Specifically, the specification indicates that

> [i]n some embodiments of method 4, a method of treating a mammal who has or is at risk for a neurological disease is provided. The methods comprises administering to the mammal a therapeutically effective amount of at least one neuroprotective compound which has Formula I, II, III, or IV, e.g., a fumaric acid derivative (e.g., DMF or MMF).

(*Id.*) As such, DMF and MMF are specifically named in the application as compounds effective in treating neurological diseases such as MS. Furthermore, the dosages disclosed in paragraph [0116] of the application refer to the specific compounds "DMF" and "MMF". Accordingly, Applicants teach that DMF and MMF are effective in treating MS.

Applicants also disclose that orally administering 480 mg per day of DMF and/or MMF is effective in treating MS. (Specification, p. 30, paragraph [0116].) Specifically, the specification discloses that

> [a]n effective dose of DMF or MMR [sic] to be administered to a subject orally can be from about 0.1 g to 1 g per pay [sic], 200 mg to about 800 mg per day (e.g.,

> from about 240 mg to about 720 mg per day; or **from about 480 mg to about 720 mg per day**; or about 720 mg per day).

(*Id.*) (emphasis added). Because Applicants teach 480 to 720 mg/day, and further disclose this dosage range as the most narrow range, it is clear that Applicants describe orally administering 480 mg DMF daily to treat MS. *See, e.g., In re Wertheim*, 541 F.2d 257, 191 U.S.P.Q. 90 (C.C.P.A. 1976).

The specification further discloses that the daily dose of DMF and/or MMF can be administered in 2, 3, 4, or 6 equal doses. *See, e.g.*, Specification, pp. 29-30, paragraph [0116] ("[F]or example, the 720 mg per day may be administered in separate administrations of 2, 3, 4, or 6 equal doses.") It is clear from the entire paragraph [0116] that, although the above citation from the specification refers to 720 mg/day as an example, the disclosure of multiple separate administrations equally applies to other dosages, *e.g.*, the 480 mg/day dose.

The specification further discloses that the expression level of NQO1 is elevated in *vivo* after administration of DMF or MMF. *See, e.g.*, original claims 1, 5, and 11; p. 2, paragraph [0006]; pp. 4-5, paragraph [0012]; pp. 22-23, paragraph [0092]; p. 31, paragraph [0122], Example 1, Figure 1; p. 31-32, paragraph [0123], Example 2, Figure 2.

Accordingly, Applicants disclose treating a subject with MS by orally administering 480 mg/day DMF and/or MMF to the subject.

Applicants' claimed method involves the oral administration of a specific daily dose of about 480 mg/day of dimethyl fumarate (DMF) and/or monomethyl fumarate (MMF) (the physiologically active metabolite of DMF). The claimed method has been

proven effective for the treatment of MS in human patients in two large-scale Phase 3 clinical studies (further discussed herein below). Quite surprisingly, it was found in those clinical studies that the 480 mg/day dose is just as effective in treating MS as a higher dose of 720 mg/day DMF. This is especially unexpected given the results of a Phase 2 clinical study in which a dose of 720 mg/day DMF, but not a 360 mg/day DMF dose, was found to be effective.

II. Patentability of the Claimed Invention

The prior art teaches that certain autoimmune diseases (*e.g.*, MS) can be treated with fumarates (*e.g.*, DMF). *See e.g.*, U.S. Patent Publication No. 2003/0018072 to Joshi *et al.* ("Joshi") and Schimrigk *et al.*, *European Journal of Neurology* 2006, 13(6):604-610 ("Schimrigk"). However, the prior art does not teach or suggest a dose consisting essentially of about 480 mg/day of DMF and/or MMF. Needless to say, the prior art does not mention the efficacy of the 480 mg/day dose.

As mentioned above, it is unexpected that the dose of about 480 mg/day DMF was similarly effective compared to the higher dose of about 720 mg/day. The evidence of these unexpected results are provided in a declaration under 37 CFR § 1.132 of Katherine T. Dawson, M.D. ("Declaration") previously filed on October 13, 2011, in U.S. Patent Application No. 12/526,296, submitted herewith as Exhibit 1.

Biogen Idec MA Inc. ("Biogen Idec"), the assignee of the current application, recently completed two pivotal Phase 3 placebo-controlled, double-blind, clinical studies, "the DEFINE study" and "the CONFIRM study", which evaluated the investigational oral drug candidate BG-12 (DMF as the only active ingredient) to treat relapsing-remitting MS (RRMS).

Results of the DEFINE study are depicted in Figures 4-11 and Table 2 of the Declaration. The results of the DEFINE study indicate that the dose of 480 mg/day unexpectedly demonstrated significant efficacy on MS disease activity as measured by the key clinical and MRI disease activity endpoints. (Declaration, pages 11-18, Figures 4-11; and page 20, Table 2.) Even more unexpected was the magnitude of the treatment effect. Given that the dose typically impacts the efficacy, it was quite surprising that the 480 mg/day dose demonstrated similar efficacy to the higher 720 mg/day dose on both clinical and MRI measures of MS disease activity – with a *high level of statistical significance*. (*Id.* at page 19, paragraphs 13-15; and page 20, Table 2.)

Furthermore, the results of the second Phase 3 study (CONFIRM) support the first Phase 3 study. See Exhibit 2, which states "[r]esults of the CONFIRM study showed that 240 mg of BG-12, administered either twice a day (BID) or three times a day (TID), demonstrated significant efficacy and favorable safety and tolerability profiles. Further analyses of the CONFIRM study are ongoing . . . ."

Therefore, the results of the DEFINE and CONFIRM studies indicate that the 480 mg/day DMF dose demonstrates efficacy in the DEFINE study, meeting all measured endpoints with a high level of statistical significance. (*See* Declaration, page 16, paragraph 16; *see* Exhibit 2.) Not only was the 480 mg/day DMF dose efficacious, but the 480 mg/day dose surprisingly demonstrated similar effectiveness on clinical and MRI measures of MS disease activity as 720 mg/day DMF. (*See* Declaration, page 15, paragraph 15.)

III. The Unexpected Results Must Be Given Substantial Weight: There is a Nexus Between the Supported Claims 18-36 and the Unexpected Results of the DEFINE and CONFIRM Studies

Unexpected results of the claimed invention do not need to be included in the specification for an Examiner to consider them. The MPEP at 716.01(b) states that "[t]o be given substantial weight in the determination of obviousness or nonobviousness, evidence of secondary considerations must be relevant to the *subject matter as claimed*, and therefore the examiner must determine whether there is a nexus between the merits of the claimed invention and the evidence of secondary considerations." (emphasis added). Thus, according to the MPEP, the Examiner must consider whether there is a nexus between the ***claimed invention*** and the unexpected results.

As mentioned above, the application teaches and fully supports the claimed invention of treating MS using DMF and/or MMF at a dose of 480 mg/day. Thus, the data from the DEFINE and CONFIRM clinical studies, which flow inherently from the claimed invention, must be given substantial weight when considering the patentability of claims 18-36.

IV. Summary

Based on the reasons set forth above, Applicants respectfully submit that the present claims are patentable.

Conclusion

Prompt and favorable consideration of this Preliminary Amendment is respectfully requested. Applicants believe the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

Marsha A. Rose

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Attorney for Applicants
Registration No. 58,403

Date: 2/14/2012

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1481215_1.DOCX

Exhibit 1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Confirmation No.: 5197
LUKASHEV, Matvey E.	Art Unit: 1649
Appl. No. 12/526,296	Examiner: Ulm, John D.
§ 371(c) Date: January 13, 2011	Atty. Docket: 2159.3210001/JMC/M-R/U-S
For: **Treatment for Multiple Sclerosis** ***(As Amended)***	

Declaration of Katherine T. Dawson, M.D. Under 37 C.F.R. § 1.132

US Patent and Trademark Office
PO Box 1450
Alexandria, Virginia 22313-1450

Dear Sir:

I, the undersigned, Katherine T. Dawson, M.D. residing at 561 Canton Street, Westwood, MA 02090 declare and state as follows:

I. My Background

1. I am a Senior Director of Medical Research at Biogen Idec MA Inc. ("Biogen Idec"), the assignee of the currently pending application. I have seven years of experience in the clinical development of MS drug products. I was involved in the development of Tysabri® and was the medical director of the Avonex® program. Tysabri® and Avonex®, both parenteral therapies, are among the few currently-approved treatment options for MS patients. I am currently responsible for developing BG-12, a new oral MS therapy. A copy of my *curriculum vitae* accompanies this declaration as Exhibit A.

2. I have personal knowledge of the matters in this declaration – knowledge which is either first-hand, or derived from my experience in this field and from interacting with others on the BG-12 development team at Biogen Idec.

II. Long Felt Need for Oral Treatment of Multiple Sclerosis

3. Multiple sclerosis ("MS") is an autoimmune disease characterized by inflammation, myelin destruction, axonal damage and neuronal loss in the central nervous system and affects about 2.5 million people worldwide.

4. Patients with MS are typically treated with injectable medications. Despite the recent approval of one oral MS therapy, a substantial challenge remains to develop efficacious yet safe oral therapies to treat MS patients. As such, there is a high, unmet, long-felt need for oral therapies that are effective in treating MS.

5. In an attempt to address this high, unmet, long-felt need, Biogen Idec has completed Phase 2 and Phase 3 clinical trials to investigate BG-12 as an oral treatment for MS. The only active ingredient of BG-12 is dimethyl fumarate ("DMF").

III. The 480 mg DMF Per Day Dose is Unexpectedly Efficacious

A. Phase 2 Clinical Trial

6. In 2004, Biogen Idec initiated a Phase 2 six-month placebo controlled clinical trial of BG-12 in 10 countries and enrolled 257 patients with relapsing remitting MS (RRMS). The clinical trial included an additional six-month safety extension. Overall, ninety-one percent of the patients completed the placebo-controlled part of the Phase 2 clinical trial.

a. 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 (a well-known measure of the disabilities suffered by MS patients) between 0.0 and 5.0. Additionally, the patients had to have had at least 1 relapse within 12 months prior to randomization or gadolinium-enhancing (Gd+) lesions (Gd+ lesions in the brain are a well-known marker of MS) on brain MRI within six weeks of randomization.

b. The patients were randomly assigned to one of four treatment groups for 24 weeks: (a) 120 mg BG-12 once daily (120 mg/day); (b) 120 mg BG-12 three times daily (360 mg/day); (c) 240 mg BG-12 three times daily (720 mg/day); and (d) placebo.

c. The primary end point of the Phase 2 clinical trial was the sum of all new Gd+ lesions from four brain MRI scans obtained at Weeks 12, 16, 20, and 24. The number of Gd+ lesions is considered a surrogate end point for clinical efficacy and as such is accepted as a primary end point for a proof of concept study.

d. The secondary end points of the Phase 2 clinical trial included the cumulative number of new Gd+ lesions on scans from Weeks 4 and 24, the number of new or newly enlargingT2-hyperintense lesions at Week 24, and the number of new T1 hypointense lesions at week 24.

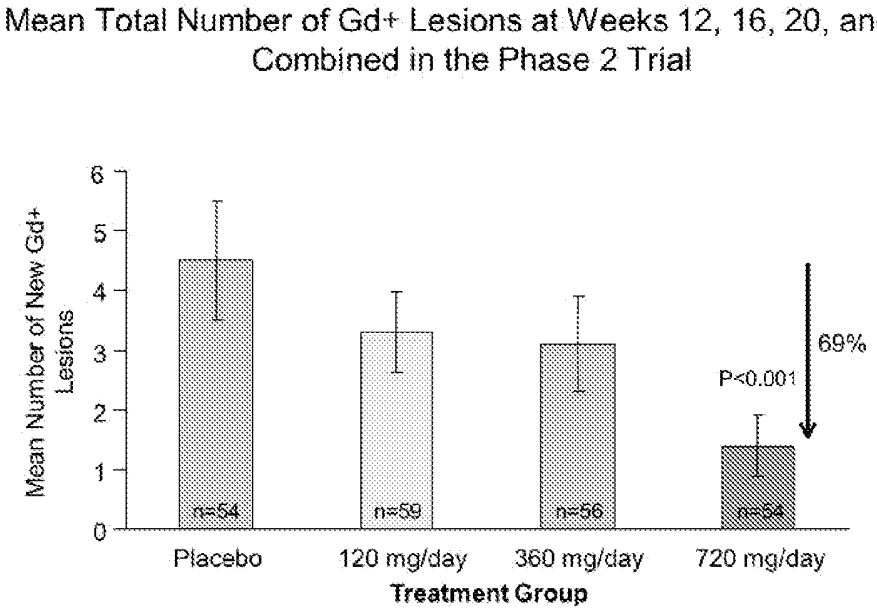
e. Additional end points included annualized relapse rate ("ARR") and disability progression as measured by EDSS.

7. The results of the Phase 2 clinical trial are reported in the peer-reviewed publication of Kappos, L., *et al.*, "Efficacy and safety of oral fumarate in patients with relapsing-remitting multiple sclerosis: a multicentre, randomised, double-blind, placebo-controlled phase IIb study,"

Lancet 372:1463-72 (2008) (Exhibit B); as well as in Kappos, L., *et al.*, "Efficacy of a novel oral single-agent fumarate, BG00012, in patients with relapsing-remitting multiple sclerosis: results of a phase 2 study," 16th Meeting of the European Neurological Society (presentation given on May 30, 2006) (Exhibit C); Kappos, L., *et al.*, "Efficacy of a novel oral single-agent Fumarate, BG00012, in patients with relapsing-remitting multiple sclerosis: results of a phase II study," 16th Meeting of the European Neurological Society (abstract to presentation given on May 30, 2006) (Exhibit D); and "Oral Compound BG-12 Achieves Primary Endpoint in Phase II Study of Relapsing-Remitting MS with BG-12 Led to Statistically Significant Reductions in MRI Measures," Biogen Idec News Release (May 30, 2006) (Exhibit E).

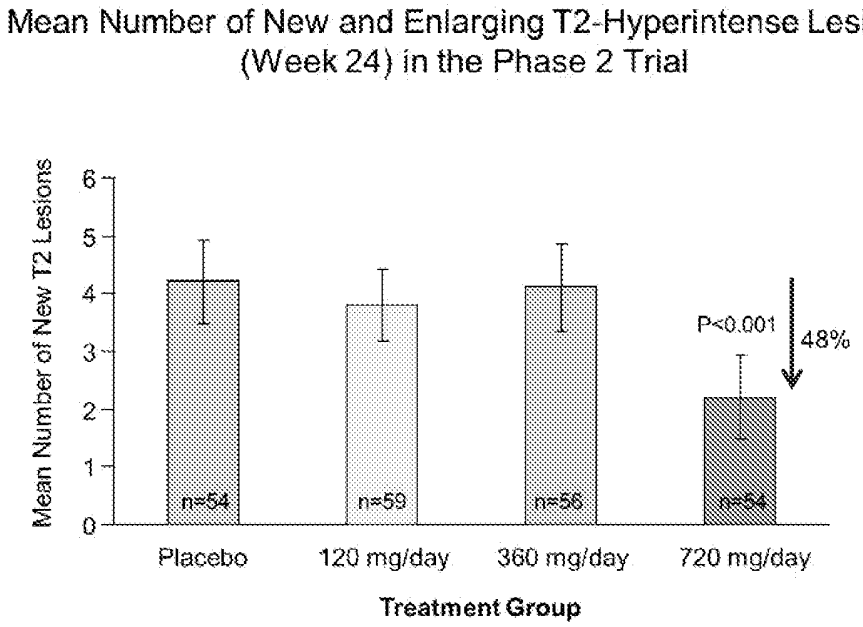
a. Only the patients who were administered 720 mg/day DMF exhibited a statistically significant effect on the primary endpoint vs. placebo. Patients in this dose group showed a 69% decrease ($P<0.001$) in the mean number of new Gd+ lesions over MRI scans Weeks 12 to 24 as shown in Figure 1 below.

Figure 1:


Mean Total Number of Gd+ Lesions at Weeks 12, 16, 20, and 24 Combined in the Phase 2 Trial
Mean Number of New Gd+ Lesions
0
1
2
3
4
5
6
n=54
n=59
n=56
n=54
P<0.001
69%
Placebo
120 mg/day
360 mg/day
720 mg/day
Treatment Group

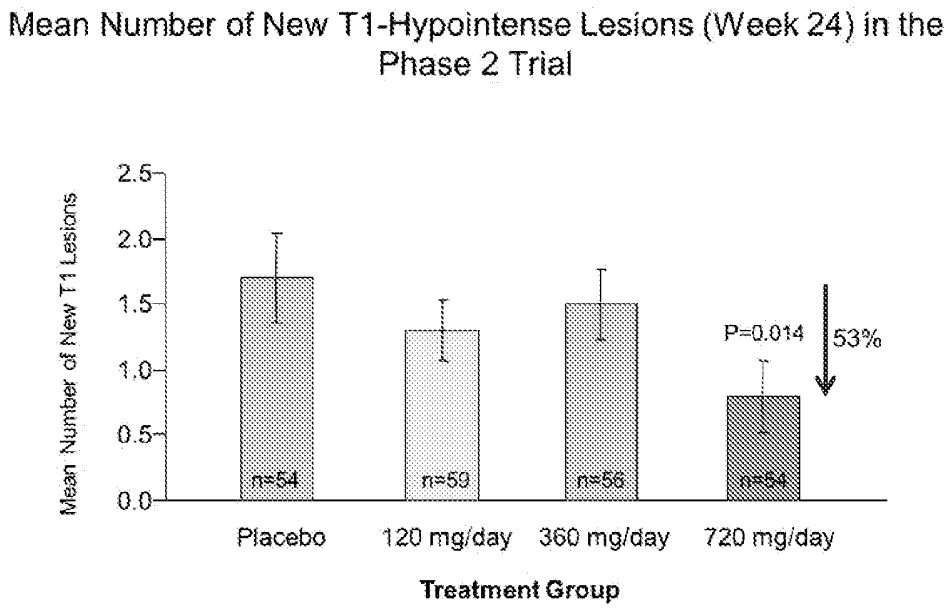
b. Additionally, patients administered 720 mg/day DMF exhibited a 48% decrease ($p<0.001$) in the mean number of new and enlarging T2-hyperintense lesions at Week 24, compared to placebo as shown in Figure 2 below.

Figure 2:



c. Patients administered 720 mg/day DMF also exhibited a 53% decrease (p=0.014) in the mean number of new T1-hypointense lesions at Week 24 vs. placebo as shown in Figure 3 below.

Figure 3:



d. Finally, patients administered 720 mg/day DMF exhibited an ARR of 0.44, as compared to an ARR of 0.65 in patients administered placebo as shown in Table 1 below, resulting in a clinically meaningful 32% reduction in ARR, which is similar to the treatment effect on ARR of the approved interferon-*beta* and glatiramer acetate treatments for MS. The reduction in ARR was not statistically significant[1] and has to be viewed in the context of the study being powered to achieve statistical significance for MRI endpoints and not for an evaluation of ARR.

Table 1:

	Treatment Group			
	Placebo N=65	120 mg /day N=64	360 mg/day N=64	720 mg/day N=63
Annualized relapse rate (95% CI)*	0.65 (0.43, 1.01)	0.42 (0.24, 0.71)	0.78 (0.52, 1.16)	0.44 (0.26, 0.76)

CI = confidence interval

8. In comparison, treatment with 120 mg/day and 360 mg/day DMF did not provide results that were statistically significant versus placebo on any endpoint. (*See, e.g.*, Exhibit E).

9. The Phase 2 clinical trials results indicated 720 mg/day DMF significantly reduced the cumulative number of new Gd+ lesions, the number of new or enlarging T2-hyperintense lesions, and the number of new T1-hypointense lesions compared with placebo. (*See, e.g.*, Exhibit C).

[1] One could attempt to draw a conclusion that the relapse efficacy endpoint of the Phase 2 clinical trial suggests that patients administered 120 mg/day DMF exhibit essentially the same annualized relapse rate as patients administered 720 mg/day DMF. However, the study was not designed to achieve statistical significance for this endpoint. (*See, e.g.*, Exhibit E).

10. Therefore, the results of the Phase 2 clinical trial demonstrated that 720 mg/day DMF was an efficacious dose for treating patients with MS. Additionally, because the 120 mg/day DMF and the 360 mg/day DMF groups were not statistically significant compared to placebo and the magnitude of effect on MRI lesions was not dose proportional, the results of the Phase 2 study did not suggest that DMF exhibited a linear dose response.

B. Phase 3 DEFINE Clinical Trial Results[2]

11. The BG-12 Phase 3 placebo-controlled, double-blind clinical trial, named the "DEFINE" trial, was completed earlier this year and its top-line results were announced in April 2011. The trial included over 1200 patients, in 28 different countries, on 5 different continents. Seventy-seven percent of the patients completed the clinical trial.

a. Men and women 18 to 55 years of age were eligible for the study if they had a diagnosis of RRMS and EDSS score between 0.0 and 5.0. Additionally, the patients must have had at least one clinically confirmed relapse within 12 months prior to randomization and a brain MRI scan at any time that was consistent with MS or that showed evidence of at least one Gd+ enhancing lesion within 6 weeks of randomization.

b. Patients were randomly assigned to one of three treatment groups: (a) 240 mg BG-12 twice daily (480 mg/day); (b) 240 mg BG-12 three times daily (720 mg/day); and (c) placebo.

c. The primary end point of the Phase 3 clinical trial was the proportion of relapsing patients at 2 years. A relapse was defined as new or recurrent neurologic

[2] DEFINE is one of the two Phase 3 clinical trials conducted by Biogen Idec. The results of the other Phase 3

symptoms lasting for at least 24 hours that were not associated with fever or infection but were accompanied by new, objective neurological findings.

d. Secondary end points of the Phase 3 clinical trial included the number of Gd+ lesions, new or newly enlarging T2-hyperintense lesions, ARR, and sustained 12-week disability progression. Disability progression was defined as an increase in EDSS of (a) at least 1.0 point in patients with a baseline EDSS of $\geq$ 1.0 or (b) at least 1.5 point increase in patients with a baseline EDSS of 0.0, sustained for 12 weeks and confirmed by an independent neurologic evaluation committee (INEC). Additional MRI endpoints included the number of new T1 hypointense lesions, and the mean-percentage change from baseline in Gd+, T2 hyperintense and T1 hypointense lesion volumes.

12. As shown below, the results at 2 years of the Phase 3 clinical trial demonstrated that both the 480 mg/day dose and the 720 mg/day dose regimens versus placebo met all primary and secondary endpoints with a high level of statistical significance and that both doses demonstrate efficacy in the DEFINE trial.

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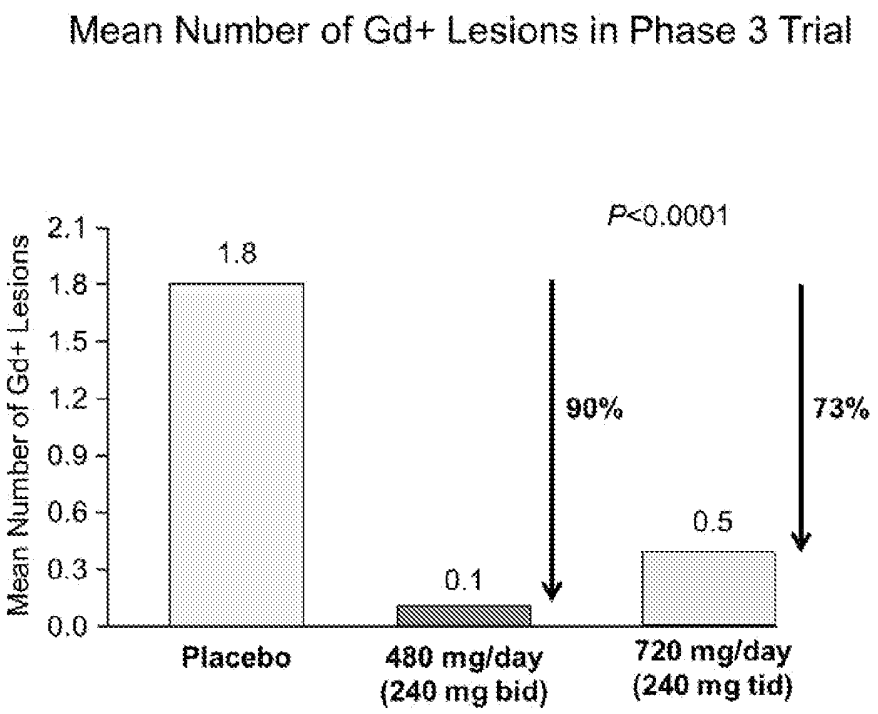
clinical trial, CONFIRM, are expected to be released by the end of 2011.

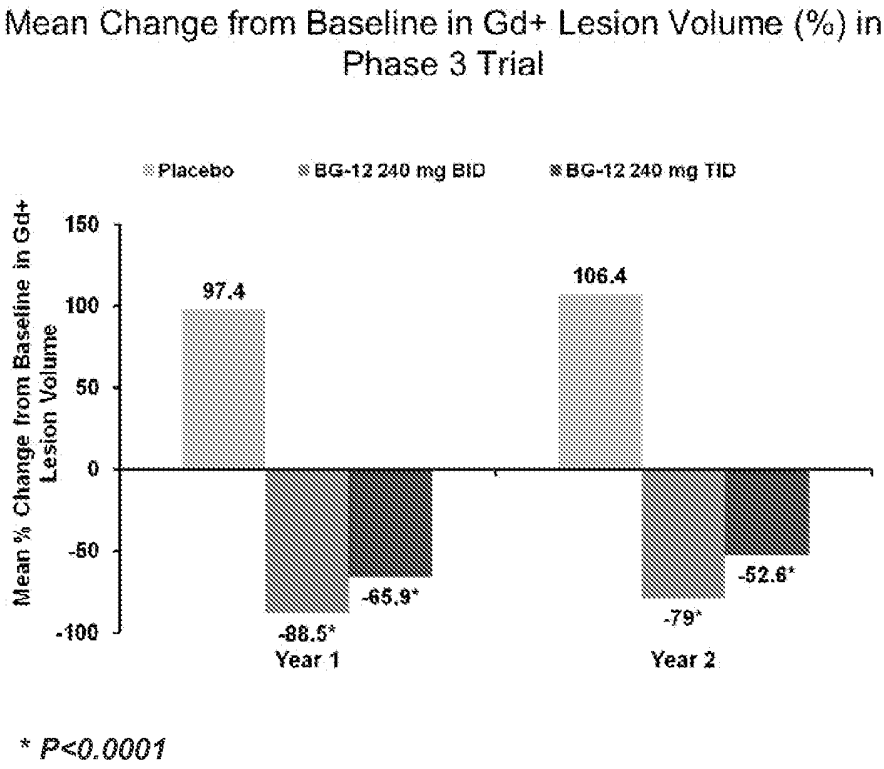
a. Compared to placebo (n=165), patients administered 480 mg/day (n=152) or 720 mg/day DMF (n=152) exhibited a 90% or 73% ($p<0.0001$ for both), respectively, decrease in the number of new Gd+ lesions at 2 years as shown in Figure 4 below.

Figure 4:



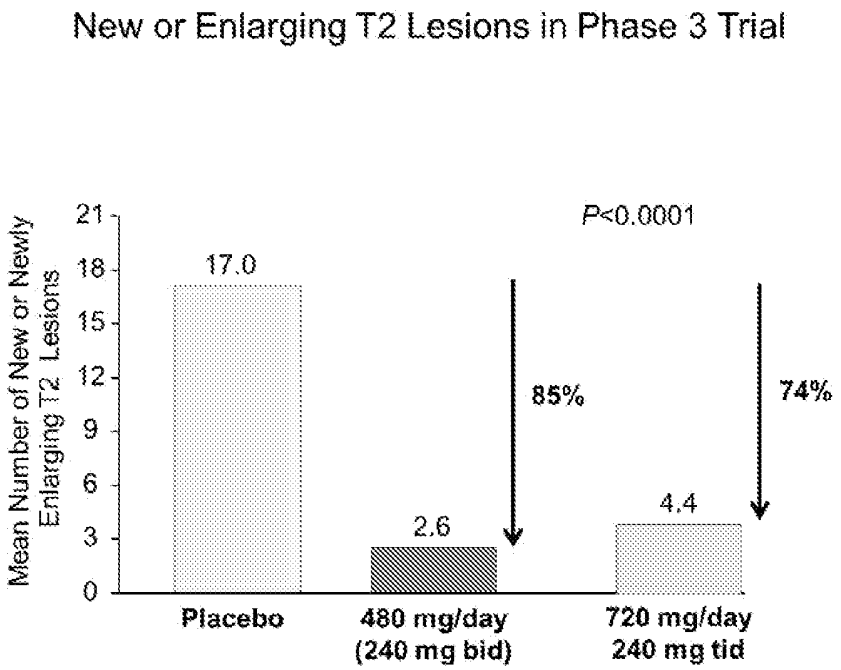
b. Patients administered 480 mg/day (240 mg BID) DMF or 720 mg/day (240 TID) DMF also exhibited a decrease in Gd+ lesion volume as shown in Figure 5 below (n=69 for placebo, n=49 for BG-12 480 mg/day, and n=52 for BG-12 720 mg/day).

Figure 5:



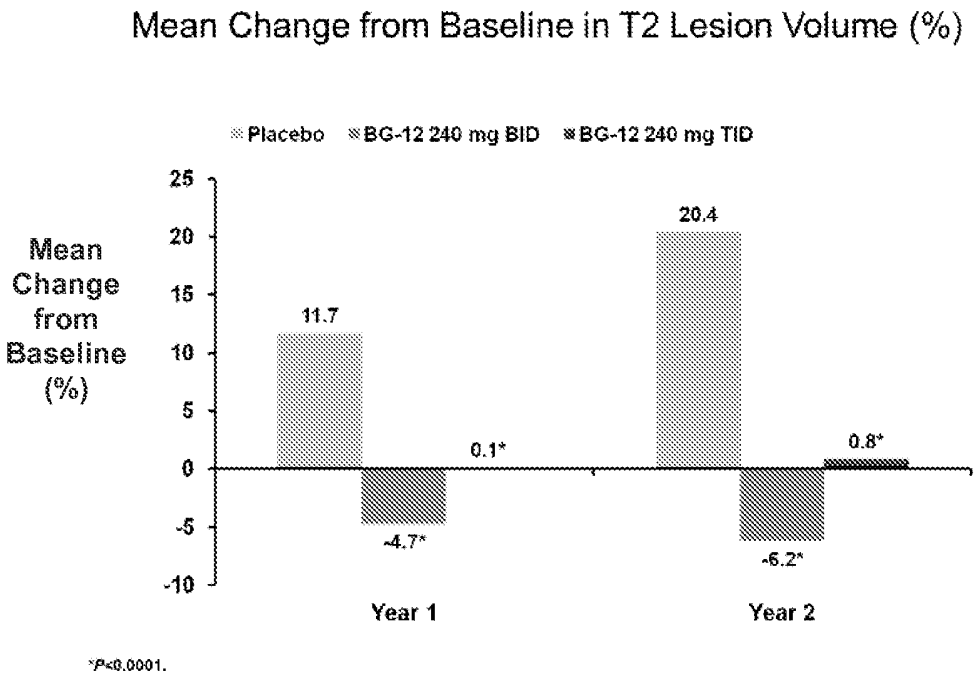
c. Furthermore, patients administered 480 mg/day DMF or 720 mg/day DMF exhibited an 85% or 74%, ($p<0.0001$ for both) respectively, decrease in the mean number of new and enlarging T2-hyperintense lesions developed over 2 years as shown in Figure 6 below (n=165 for placebo, n=152 for BG-12 480 mg/day, and n=152 for BG-12 720 mg/day).

Figure 6:



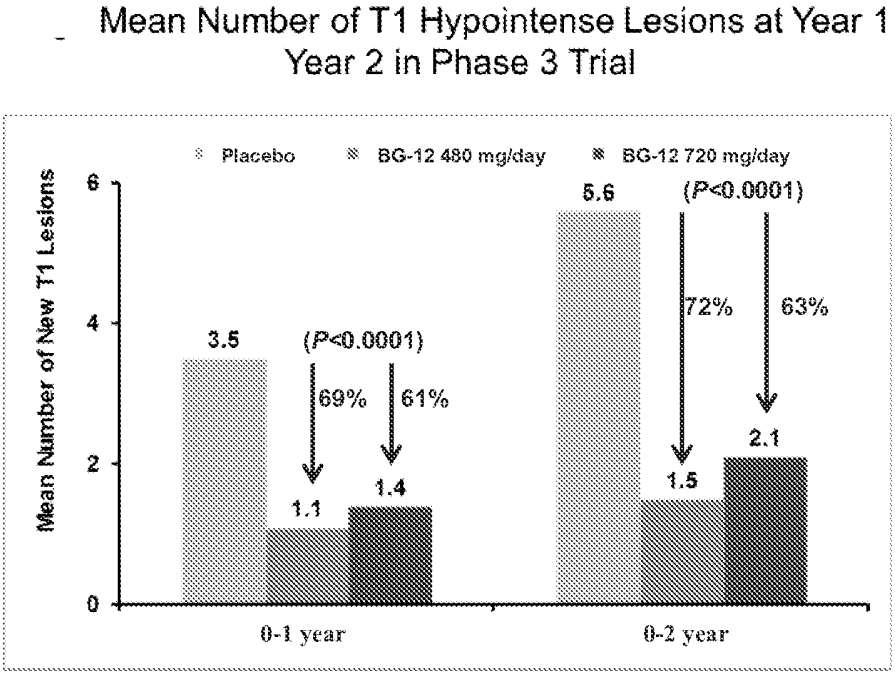
d. Also, patients administered 480 mg/day DMF or 720 mg/day DMF exhibited a decrease in T2 lesion volume as shown in Figure 7 below (n=164 for placebo, n=152 for BG-12 480 mg/day, and n=152 for BG-12 720 mg/day).

Figure 7:



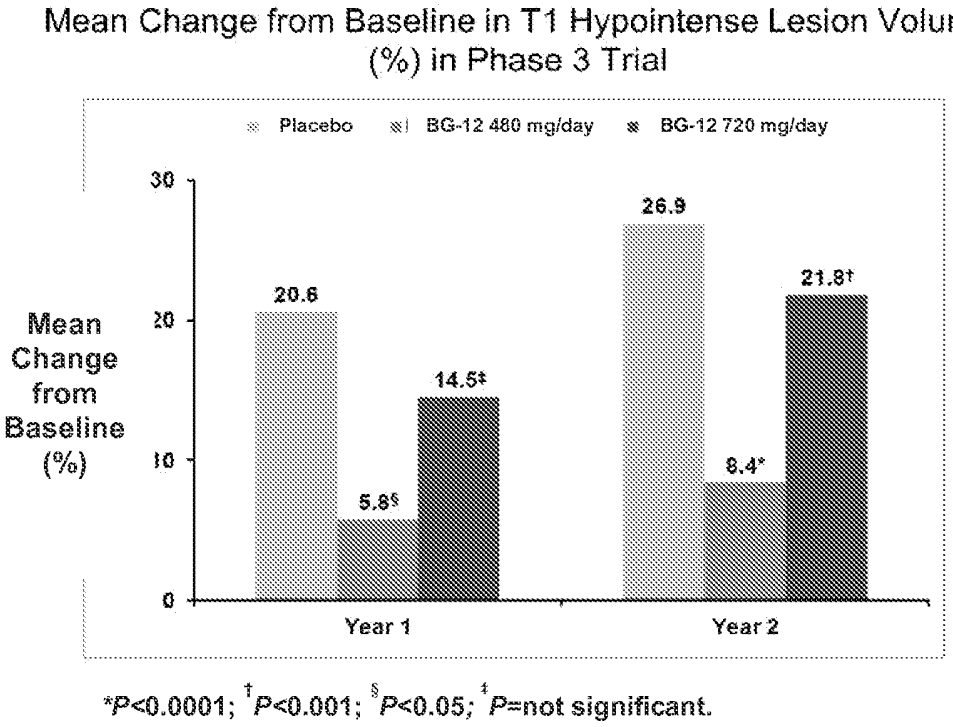
e. Patients administered 480 mg/day DMF and 720 mg/day DMF exhibited a decrease in the mean number of new T1 hypointense lesions as shown in Figure 8 below (n=165 for placebo, n=151 for BG-12 480 mg/day, and n=152 for BG-12 720 mg/day).

Figure 8:



f. Patients administered 480 mg/day DMF or 720 mg/day DMF also exhibited a decrease in T1 hypointense lesion volume as shown in Figure 9 below (n=160 for placebo, n=150 for BG-12 480 mg/day, and n=150 for BG-12 720 mg/day).

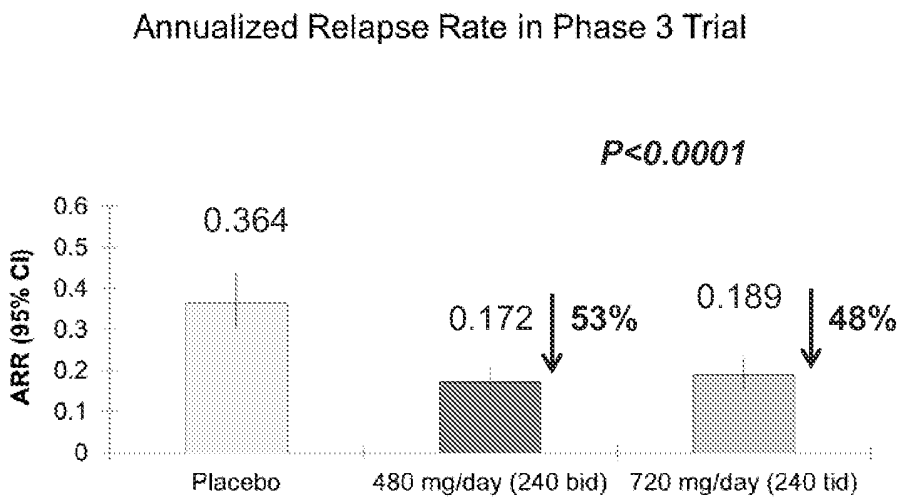
Figure 9:



*P<0.0001; †P<0.001; §P<0.05; ‡P=not significant.

g. Patients administered 480 mg/day DMF (n=410) or 720 mg/day DMF (n=416) also exhibited a statistically significant decrease (P<0.0001 for both) in the annualized relapse rate at 2 years compared to placebo (n=408) as shown in Figure 10 below.

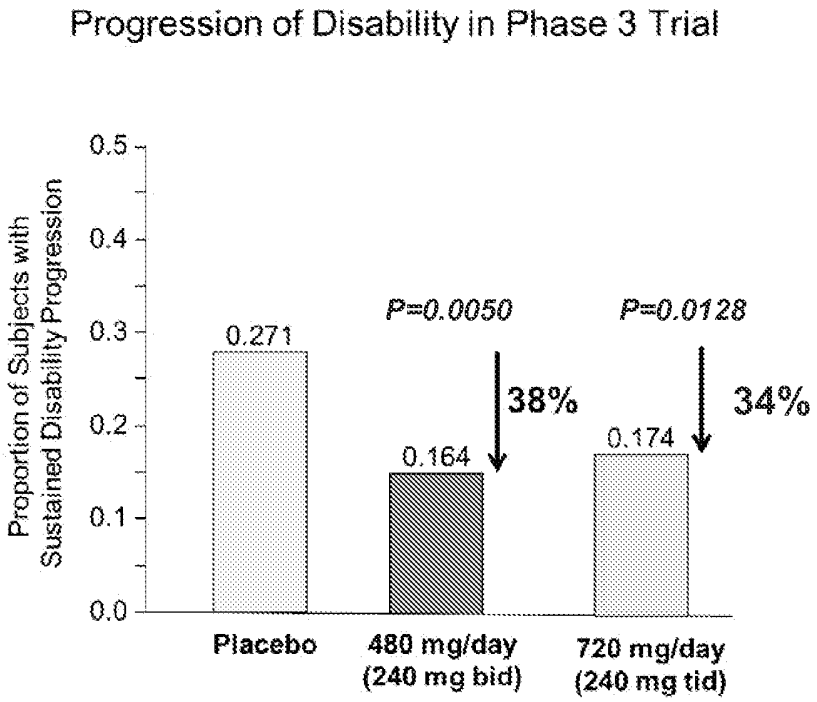
Figure 10:



h. BG-12 480 mg/day (n=410) and 720 mg/day (n=416) reduced the risk of relapse at 2 years by 49% and 50%, respectively, (P<0.0001 for both) compared to placebo (n=408).

i. Finally, patients administered 480 mg/day DMF and 720 mg/day DMF exhibited a statistically significant (P=0.0050 and P=0.0128, respectively) decrease in the progression of confirmed disability sustained at 12 weeks as compared with patients administered placebo as shown in Figure 11 below.

Figure 11:



C. Summary

13. As discussed above, the Phase 2 clinical trial results demonstrated that 720 mg/day DMF was efficacious in treating MS while 120 mg/day and 360 mg/day DMF dosing regimens were statistically indistinct from placebo. Additionally, the Phase 3 DEFINE study results demonstrated that 480 mg/day of DMF was efficacious in treating MS.

14. The positive and clinically meaningful results obtained with the 480 mg per day dose of DMF were unexpected to me given (1) that the Phase 2 clinical trial indicated that both the 120 mg/day and 360 mg/day doses of BG-12 were not efficacious and (2) that there was no apparent linear dose response.

15. Even more unexpected, in my opinion, was the magnitude of the treatment effect of the DEFINE study – the 480 mg/day dose demonstrated similar efficacy to the 720 mg/day dose on both clinical and MRI measures of MS disease activity – with a *high level of statistical significance*. Table 2 below compares key endpoints for the 480 mg/day dose and the 720 mg/day dose in the DEFINE study.

Table 2: DEFINE study results

	96 weeks treatment with 480 mg/day	**96 weeks treatment with 720 mg/day**
Reduction in number of Gd+ lesions	90%[1]	73%[1]
Reduction of mean number of new/newly enlarging T2 lesions	85%[1]	74%[1]
Reduction of mean number of New T1 hypointense lesions	73%[1]	63%[1]
ARR Reduction	53%[1]	48%[1]
Disability progression	38%[3]	34%[4]
Proportion of subjects relapsed	49%[1]	50%[1]

[1] $p<0.0001$ vs. placebo; [2] $p<0.001$ vs. placebo; [3] $p=0.0050$ vs. placebo; [4] $p=0.0128$ vs. placebo

16. In view of the foregoing and based on my personal knowledge and experience, as well as comments from others in the MS field that I have received since the top-line results from the DEFINE study were released, I conclude that a person of ordinary skill in the art would not have a reasonable expectation that the 480 mg/day dose would provide statistically significant and clinically meaningful effectiveness for treating MS. I further conclude that a person of ordinary skill in the art would have been very surprised that the treatment effect of the 480 mg/day dose was similar to the 720 mg/day dose.

17. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the present patent application or any patent issued thereon.

Respectfully submitted,

Katherine T. Dawson

Date: Oct 13, 2011

1431835_1.DOC

Appendix A

Exhibit A	Curriculum Vitae for Katherine T. Dawson
Exhibit B	Kappos, L., *et al.*, "Efficacy and safety of oral fumarate in patients with relapsing-remitting multiple sclerosis: a multicenter, randomised, double-blind, placebo-controlled phase IIIb study," *Lancet 372*: 1463-72 (2008)
Exhibit C	Kappos, L., *et al.*, "Efficacy of a novel oral single-agent fumarate, BG00012, in patients with relapsing-remitting multiple sclerosis: results of a phase 2 study," 16th Meeting of the European Neurological Society (May 30, 2006) (Slide Presentation)
Exhibit D	Kappos, L., *et al.*, "Efficacy of a novel oral single-agent Fumarate, BG00012, in patients with relapsing-remitting multiple sclerosis: results of a phase II study," 16th Meeting of the European Neurological Society (May 30, 2006) (Abstract to the Presentation)
Exhibit E	"Oral Compound BG-12 Achieves Primary Endpoint in Phase II Study of Relapsing-Remitting MS with BG-12 Led to Statistically Significant Reductions in MRI Measures," Biogen Idec News Release (May 30, 2006)

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/372,426	02/13/2012	Matvey E. LUKASHEV	2159.3210002/JMC/MRG/U-S	5998

53644 7590 05/03/2012

STERNE, KESSLER, GOLDSTEIN & FOX, P.L.L.C.
1100 NEW YORK AVE., N.W.
WASHINGTON, DC 20005

EXAMINER	
ULM, JOHN D	
ART UNIT	PAPER NUMBER
1649	

MAIL DATE	DELIVERY MODE
05/03/2012	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	13/372,426	LUKASHEV ET AL.	
	Examiner	Art Unit	
	JOHN ULM	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 February 2012*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *18-36* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *18-36* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

12)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *02/13/12 x 6*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1) Claims 18 to 36 are pending in the instant application. Claims 1 to 17 have been canceled and claims 18 to 36 added as requested by Applicant in the preliminary amendment filed concurrently with the instant application.

Information Disclosure Statement

2) The six information disclosure statements (IDS) submitted on 14 February of 2012 are in compliance with the provisions of 37 CFR 1.97 and have been considered by the examiner.

3) Applicant is advised that M.P.E.P. 609.02(A)(2) states that "[t]he examiner will consider information which has been considered by the Office in a parent application when examining: (A) a continuation application filed under 37 CFR 1.53(b), (B) a divisional application filed under 37 CFR 1.53(b), or (C) a continuation- in-part application filed under 37 CFR 1.53(b). A listing of the information need not be resubmitted in the continuing application unless the applicant desires the information to be printed on the patent". Therefore, Applicant is hereby assured that information which has been considered by the Office in any parent of the instant application has been considered by the examiner in the instant application. However, if applicant desires the information to be printed on the patent they must submit an information disclosure statement in accordance with 37 CFR 1.98.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented 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 said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

4) Claims 18 to 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over the Joshi et al. patent publication (US 2003/0018072 A1). These claims are drawn to a method of treating multiple sclerosis in an individual suffering therefrom by the daily oral administration thereto of dimethyl fumarate or diethyl fumarate at a rate of 480 mg per day.

The Joshi et al. patent publication has been cited because it fairly taught the oral administration of dialkyl fumarates to a subject suffering from an auto immune disease. The text in paragraph [024] therein expressly identified dimethyl fumarate, methyl ethyl fumarate and diethyl fumarate as preferred embodiments of the dialkyl fumarates discussed therein. Further, the text in paragraphs [003], [014] and [030] specifically identified multiple sclerosis as one of the autoimmune diseases to be treated by the oral administration of dialkyl fumarates. The Joshi et al. patent publication does not anticipate the instant claims because it did not disclose the specific treatment protocol recited therein.

However, given the disclosure by Joshi et al. that multiple sclerosis can be effectively treated by the oral administration of dimethyl fumarate or diethyl fumarate to an individual suffering therefrom, one of ordinary skill in the art would have found it *prima facie* obvious to have engaged in that routine experimentation needed to determine the optimal effective protocol for such treatment. Merely determining the optimal conditions for practicing a prior art process, in the absence of unexpected results, does not constitute a patentable inventive contribution. See M.P.E.P. 2144.05 II.

In addition, the only *in vivo* method of treatment that is described in the specification involves the mouse experimental autoimmune encephalitis (EAE) model, which is an entirely artificial condition that mimics only certain pathological manifestations of MS and is causally unrelated thereto. In discussing a primate-based EAE system, the abstract of the 't Hart et al. publication (The Lancet Neurology 3(10):588-597, Oct. 2004, cited by Applicant) states that "[t]he many, highly specific, biological therapies for immune-based diseases create a need for valid preclinical animal models", and that "[t]he wide immunological gap between human beings and laboratory mouse and rat models makes many disease models in these species invalid". The concluding paragraph on page 569 of t' Hart et al. further advises that "[a]lthough many features of the MS immunopathogenesis have been elegantly modeled in inbred strains of rats and mice, successful therapeutic interventions in these models have shown limited predictive value for clinical success". This reference shows that one of ordinary skill in this art would not reasonably conclude that the *in vivo* treatment

protocols described in the working examples of the instant specification, which employ a mouse EAE model system and from which the parameters of the claims method have been derived, can be expected to be predictive of the optimal conditions for the treatment of MS in humans by the oral administration of dimethyl fumarate or diethyl fumarate thereto.

5) Claims 18 to 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over the Schimrigh et al. publication (Euro. J. Neurol. 13(6):604-610, Jun. 2006, cited by Applicant). As indicated above, these claims are drawn to a method of treating multiple sclerosis in an individual suffering therefrom by the daily oral administration thereto of dimethyl fumarate or diethyl fumarate at a rate of 480 mg per day. The Schimrigh et al. publication is cited because it described the successful clinical treatment of human subjects suffering from multiple sclerosis by the administration of fumaric acid esters, which include dimethyl fumarate, methyl ethyl fumarate and diethyl fumarate, to those subjects. The Schimrigh et al. publication does not anticipate the instant claims because it did not disclose the specific treatment protocol recited therein. However, as indicated above, one of ordinary skill in the art would have found it *prima facie* obvious to have engaged in that routine experimentation needed to determine the optimal effective protocol for such treatment. Merely determining the optimal conditions for practicing a prior art process, in the absence of unexpected results, does not constitute a patentable inventive contribution.

6) In a preliminary amendment filed of 14 February of 2012 in the instant application, Applicant has extensively traversed the above rejections as they have been

applied to identical claims 18 to 36 in application number 12/526,296 essentially on the premise that the claimed method produces particularly advantageous and unexpected results as applied to individuals suffering from relapsing-remitting multiple sclerosis (RRMS). The unexpected and advantageous results demonstrated for the claimed method relative to the other embodiments that are disclosed in the instant specification are not in dispute. However, neither those unexpected and allegedly advantageous results nor the particular combination now claimed are described in the specification as filed. In fact, the demonstration that the now claimed combination is operable in not unexpected. It is Applicant's discovery, subsequent to the filing of the instant application, that the majority of embodiments described in the specification are inoperative that is unexpected. The fact that dimethyl fumarate, methyl ethyl fumarate and diethyl fumarate can be successfully employed to treat MS was not unexpected as of the filing date of the instant application.

The instant specification teaches the treatment of a plurality of neurological diseases including those listed in paragraphs [0104] to [0106] therein, which states that "neurological diseases suitable for the methods described herein include neurodegenerative diseases such as amyotrophic lateral sclerosis (ALS), Parkinson's disease, Alzheimer's disease, and Huntington's disease", "MS", "acute haemorrhagic leucoencephalomyelitis, Hurst's disease, acute disseminated encephalomyelitis, optic neuritis, Devic's disease, spinal cord lesions, acute necrotizing myelitis, transverse myelitis, chronic progressive myelopathy, progressive multifocal leukoencephalopathy (PML), radiation myelopathy, HTLV-1 associated myelopathy, monophasic isolated

demyelination, central pontine myelinolysis, and leucodystrophy (e.g., adrenoleucodystrophy, metachromatic leucodystrophy, Krabbe's disease, Canavan's disease, Alexander's disease, Pelizaeus-Merbacher disease, vanishing white matter disease, oculodentodigital syndrome, Zellweger's syndrome), chronic inflammatory demyelinating polyneuropathy (CIDP), acute inflammatory demyelinating polyneuropathy (AIDP), Leber's optic atrophy," "Charcot-Marie-Tooth disease", "polyneuritis and mitochondrial disorders with demyelination". Nowhere does the instant specification, as filed, disclose a particular advantage to applying the method described therein to RRMS.

In addition, with respect to dimethyl fumarate (DMF) or monomethyl fumarate (MMF), the text in paragraph [0116] of the specification taught that "an effective amount can range from 1 mg/kg to 50 mg/kg (e.g., from 2.5 mg/kg to 20 mg/kg or from 2.5 mg/kg to 15 mg/kg)" and that "an effective dose of DMF or MMF to be administered to a subject orally can be from about 0.1 g to 1 g per pay, 200 mg to about 800 mg per day (e.g., from about 240 mg to about 720 mg per day; or from about 480 mg to about 720 mg per day; or about 720 mg per day)". Again, the specification, as filed, fails to demonstrate any particular advantage to be realized from the administration of a dosage of 480 mg per day of DMF or methyl ethyl fumarate (MEF) to an individual suffering from RRMS. Applicant's subsequent discovery that the vast majority of dosages described in the specification are inoperative is the only unexpected result that is supported by the evidence of record, and those embodiments are not the subject of the instant claims.

It is a matter of law that a claimed invention must be patentable as of the effective filing date of the application containing that claim. Applicant may not rely upon subsequent discoveries made by themselves or others to complete the claimed invention. In the decision *In re Lundberg*, 117 USPQ 190, 1958, the CCPA held that "advantages which are not disclosed in application cannot be urged as basis for allowing claims". This rejection is not in conflict with the decision in *in re Chu*, 66 F.3d 292, 298-99, 36 USPQ2d 1089, 1094-95 (Fed. Cir. 1995). The claimed subject matter at issue in *in re Chu* (US Patent 5,567,394, Chu et al.) was distinguished from the most closely related prior art by the placement of a catalyst at a particular position in an apparatus for controlling emissions of a fossil fuel fired boiler. Evidence provided by Applicant demonstrated addition undisclosed advantages that inherently result from that placement. Whereas the Chu et al. application did not disclose certain unexpected results obtained thereby, it clearly disclosed the criticality of placing the catalyst at the particular position recited in the claims and the subsequently demonstrated advantages were inherent to that element. In the present case, the instant specification does not disclose the criticality of the limitations of the now claimed treatment protocol nor does it identify the claimed combination as being particularly advantageous, which distinguishes the current fact pattern from that which was addressed by the court in *in re Chu*. Applicant's discovery that the majority of embodiments disclosed in the specification are inoperative hardly supports the patentability of those few embodiments that have been subsequently discovered by Applicant to be operable.

Response to Arguments

7) Applicant's arguments filed 14 February of 2012, as well as the declaration by Katherine Dawson under 37 CFR 1.132 that was executed on 13 October of 2011, have been fully considered but they are not persuasive essentially for those reasons given above.

Double Patenting

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

8) Claims 18 to 36 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 18 to 36 of copending Application No. 12/526,296. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JOHN ULM whose telephone number is (571)272-0880. The examiner can normally be reached on 9:00AM to 5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker can be reached on (571) 272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/John D. Ulm/
Primary Examiner, Art Unit 1649

MARSHA ROSE GILLENTINE
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Sterne Kessler Goldstein Fox
ATTORNEYS AT LAW

August 3, 2012

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

Confirmation No. 5998
Art Unit 1649
Attn: Mail Stop Amendment

Re: U.S. Utility Patent Application
Appl. No. 13/372,426; Filing Date: February 13, 2012
For: **Treatment for Multiple Sclerosis**
Inventors: LUKASHEV *et al.*
Our Ref: 2159.3210002/JMC/MRG/U-S

Commissioner:

Transmitted herewith for appropriate action are the following documents:

1. Online Credit Card Payment Authorization in the amount of $430.00 to cover
   $180.00 Information Disclosure Statement Fee;
   $250.00 Excess Claim Fee (1 extra independent claim);
2. A copy of an original Power of Attorney to Prosecute Applications Before the USPTO;
3. A copy of an original Statement Under 37 C.F.R. § 3.73(b);
4. Amendment and Reply Under 37 C.F.R. § 1.111;
5. Exhibit 1 - Declaration of Richard A. Rudick, M.D. Under 37 C.F.R. § 1.132;
6. Exhibits A through Q to Exhibit 1;
7. Exhibit 2 - Declaration of Katherine T. Dawson, M.D. Under 37 C.F.R. § 1.132;
8. Exhibits A through E to Exhibit 2;
9. Exhibit 3;
10. Fourth Supplemental Information Disclosure Statement;
11. Form PTO/SB/08a (1 sheet) listing 9 documents (**US41-US48** and **FP54**);
12. Form PTO/SB/08b (1 sheet) listing 5 documents (**NPL337-NPL341**); and
13. Copies of cited documents (**FP54** and **NPL337-NPL340**).

The above-listed documents are filed electronically through EFS-Web.

In the event that extensions of time are necessary to prevent abandonment of this patent application, then such extensions of time are hereby petitioned.

Fee payment is provided through online credit card payment. The U.S. Patent and Trademark Office is hereby authorized to charge any fee deficiency, or credit any overpayment, to our Deposit Account No. 19-0036.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

Marsha Rose Gillentine
Attorney for Applicants
Registration No. 58,403

MRG/U-S/lam
Enclosures

1566797_1.DOCX

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Confirmation No.: 5998
LUKASHEV *et al.*	Art Unit: 1649
Appl. No. 13/372,426	Examiner: Ulm, John D.
Filing Date: February 13, 2012	Atty. Docket: 2159.3210002/JMC/MRG/U-S
For: **Treatment for Multiple Sclerosis**	

Amendment and Reply Under 37 C.F.R. § 1.111

Mail Stop Amendment

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

Sir:

In reply to the Office Action dated May 3, 2012, Applicants submit the following Amendments and Remarks.

The Claims are listed beginning on page 2 of this paper.

Remarks and Arguments begin on page 6 of this paper.

It is not believed that extensions of time or fees for net addition of claims are required beyond those that may otherwise be provided for in documents accompanying this paper. However, if additional extensions of time are necessary to prevent abandonment of this application, then such extensions of time are hereby petitioned under 37 C.F.R. § 1.136(a), and any fees required therefor (including fees for net addition of claims) are hereby authorized to be charged to our Deposit Account No. 19-0036.

Listing of the Claims

The claims are listed below for the Examiner's convenience.

1-17. (Cancelled)

18. (Previously Presented) A method of treating a subject in need of treatment for multiple sclerosis comprising orally administering to the subject in need thereof a pharmaceutical composition consisting essentially of (a) a therapeutically effective amount of dimethyl fumarate, monomethyl fumarate, or a combination thereof, and (b) one or more pharmaceutically acceptable excipients, wherein the therapeutically effective amount of dimethyl fumarate, monomethyl fumarate, or a combination thereof is about 480 mg per day.

19. (Previously Presented) The method of claim 18, wherein the pharmaceutical composition is administered in the form of a tablet, a suspension, or a capsule.

20. (Previously Presented) The method of claim 18, wherein the therapeutically effective amount is administered in separate administrations of 2, 3, 4, or 6 equal doses.

21. (Previously Presented) The method of claim 20, wherein the therapeutically effective amount is administered in separate administrations of 2 equal doses.

22. (Previously Presented) The method of claim 20, wherein the therapeutically effective amount is administered in separate administrations of 3 equal doses.

23. (Previously Presented) The method of claim 18, wherein the pharmaceutical composition consists essentially of dimethyl fumarate and one or more pharmaceutically acceptable excipients.

24. (Previously Presented) The method of claim 18, wherein the pharmaceutical composition consists essentially of monomethyl fumarate and one or more pharmaceutically acceptable excipients.

25. (Previously Presented) The method of claim 18, wherein the pharmaceutical composition is administered to the subject for at least 12 weeks.

26. (Previously Presented) The method of claim 23, wherein the therapeutically effective amount is administered to the subject in 2 equal doses.

27. (Previously Presented) The method of claim 26, wherein the therapeutically effective amount is administered to the subject for at least 12 weeks.

28. (Previously Presented) A method of treating a subject in need of treatment for multiple sclerosis consisting essentially of orally administering to the subject about 480 mg per day of dimethyl fumarate, monomethyl fumarate, or a combination thereof.

29. (Previously Presented) The method of claim 28, wherein about 480 mg of dimethyl fumarate per day is administered to the subject.

30. (Previously Presented) The method of claim 29, wherein the dimethyl fumarate is administered in separate administrations of 2 equal doses.

31. (Previously Presented) The method of claim 29, wherein the dimethyl fumarate is administered in separate administrations of 3 equal doses.

32. (Previously Presented) A method of treating a subject in need of treatment for multiple sclerosis comprising orally administering to the subject a pharmaceutical composition consisting essentially of (a) a therapeutically effective amount of dimethyl fumarate and (b) one or more pharmaceutically acceptable excipients, wherein the therapeutically effective amount of dimethyl fumarate is about 480 mg per day.

33. (Previously Presented) The method of claim 32, wherein the dimethyl fumarate is administered in separate administrations of 2 equal doses.

34. (Previously Presented) The method of claim 18, wherein the expression level of NQO1 in the subject is elevated after administering to the subject the therapeutically effective amount of dimethyl fumarate, monomethyl fumarate, or a combination thereof.

35. (Previously Presented) The method of claim 28, wherein the expression level of NQO1 in the subject is elevated after administering to the subject about 480 mg per day of dimethyl fumarate, monomethyl fumarate, or a combination thereof.

36. (Previously Presented) The method of claim 32, wherein the expression level of NQO1 in the subject is elevated after administering to the subject the therapeutically effective amount of dimethyl fumarate.

37. (New) A method of treating a subject in need of treatment for multiple sclerosis comprising 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.

Remarks

Reconsideration of this Application is respectfully requested.

Claims 18-37 are pending in the application, with claims 18, 28, 32, and 37 being the independent claims. Support for new claim 37 can be found at least in paragraphs [0009], [0010], [0062-0063], and [0116] of the specification. Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

I. Summary of the Claimed Subject Matter

The claimed invention is generally directed to methods of treating multiple sclerosis ("MS") which involve the administration of, or treatment of a subject with, a specific daily dose of about 480 mg/day of dimethyl fumarate ("DMF") and/or monomethyl fumarate ("MMF") (a biologically active metabolite of DMF).

The claimed method demonstrated surprising efficacy in two large-scale Phase 3 MS clinical studies (further discussed herein below). These clinical studies demonstrated that 480 mg/day of DMF was unexpectedly just as efficacious in treating MS as 720 mg/day of DMF. This result was especially unexpected given the results of an earlier Phase 2 clinical study in which 720 mg/day of DMF was the only dose found to be efficacious, while the other tested doses, *i.e.*, 120 mg/day and 360 mg/day of DMF did not show any statistically significant efficacy when compared to placebo. Since the dose response was not linear, the magnitude of the efficacy demonstrated by the 480 mg/day dose (that it is just as efficacious

as the 720 mg/day dose) is surprising and unexpected. Moreover, knowledge available to a person or ordinary skill in the art as of the priority date of the instant application (*i.e.*, February 8, 2007) (referred to "at the time of the invention" here) would have led the person of ordinary skill in the art to use a higher dose to treat MS, effectively teaching away from the claimed invention of using the 480 mg/day dose of DMF.

As will be discussed in more detail below, the 480 mg/day DMF dose is preferred over the 720 mg/day or an even higher dose. One reason 480 mg/day DMF is preferred is because side effects associated with chronic, lifelong treatment are generally dose-related, so the 480 mg/day dose naturally would be expected to have fewer side effects in the long run.

II. No *Prima Facie* Case of Obviousness

Claims 18 to 36 are rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent Publication No. US 2003/0018072 to Joshi *et al.* ("Joshi"). Claims 18 to 36 are further rejected under 35 U.S.C. § 103(a) as being unpatentable over Schimrigk *et al.*, *European Journal of Neurology* 2006, 13(6):604-610 ("Schimrigk"). Applicants respectfully traverse both rejections.

The Examiner acknowledges that neither Joshi nor Schimrigk anticipate the pending claims because neither reference teaches the specific treatment protocol recited in the claims. (Office Action of May 3, 2012, page 3, last sentence, and page 5, lines 14-16). However, the Examiner alleges that "merely determining the optimal conditions for practicing a prior art process, in the absence of unexpected results, does not constitute a

patentable inventive contribution." (*Id.* at page 4, lines 5-7 and page 5, lines 18-20 (emphasis added)).

The current claims are not *prima facie* obvious over the cited art because neither Joshi nor Schimrigk teaches or suggests the treatment of MS with a pharmaceutical composition consisting essentially of about 480 mg/day of DMF and/or MMF. Moreover, the cited references, especially Schimrigk, together with the knowledge available at the time of the invention, direct a person of ordinary skill in the art toward using higher doses of MS to treat MS than the claimed 480 mg/day dose.

A. Joshi does not teach or suggest using a 480 mg/day dose of DMF and/or MMF to treat MS

Joshi teaches oral administration of dialkyl fumarates (*e.g.*, DMF) to treat MS. However, as appreciated by the Examiner, Joshi does not teach or suggest a 480 mg/day dose of DMF and/or MMF. Furthermore, there is nothing in Joshi that would motivate a person of ordinary skill in the art to select the particular dosing regimen involving 480 mg/day of DMF and/or MMF to effectively treat MS as required in the claims.

Still, it is the Examiner's view that the skilled person would have engaged in routine experimentation needed to determine the optimal effective dose. *See* the Office Action, page 4, lines 1-5. Applicants disagree because a person of ordinary skill in the art at the time of the invention would have been aware of the results of the Phase 2 clinical study described herein that involved the use of BG-12 (DMF). In light of those results, a person of

ordinary skill in the art would have been motivated to treat a patient having MS by administering 720 mg/day DMF, not a DMF dose less than 720 mg/day (*e.g.*, 480 mg/day).

In 2006, Biogen Idec completed a six-month Phase 2 placebo controlled clinical study of BG-12 (DMF), which enrolled 257 patients with relapsing-remitting MS ("RRMS"). Three doses, 120 mg, 360 mg, and 720 mg/day of DMF, were tested and compared to placebo. The Phase 2 endpoints included MRI endpoints such as the number of Gd+ lesions (primary endpoint), the number of new or newly enlarging T2-hyperintense lesions, and the number of new T1 hypointense lesions, endpoints commonly used in MS clinical studies. The results of the Phase 2 clinical study, which were available as of June 2006, showed that only the 720 mg/day DMF dose had a statistically significant effect compared to placebo and the 120 mg/day dose and the 360 mg/day dose both failed to achieve statistically significant results.[1] Thus, the results of the Phase 2 clinical study would have led one of ordinary skill in the art to use a different, higher dose (*i.e.*, 720 mg/day) rather than the dose required by the claimed invention (*i.e.*, 480 mg/day). Because the results of the Phase 2 clinical study were available before the priority date of the present application, the skilled person would have used the 720 mg/day dose rather than engaging in experimentation as suggested by the Examiner. Thus, Applicants respectfully submit that the claimed invention is not *prima facie* obvious over Joshi.

[1] *See, e.g.*, Kappos, L., *et al.*, 16th Meeting of the European Neurological Society (May 30, 2006) (Abstract); Kappos, L., *et al.*, 16th Meeting of the European Neurological Society (May 30, 2006) (presentation given on May 30, 2006); and Biogen Idec News Release of May 30, 2006 (submitted herewith as Exhibits B, C, and D to Exhibit 1 – the Rudick Declaration (discussed below), respectively), as well as Kappos, L., *et al.*, *Lancet 372*:1463-72 (2008), submitted as Exhibit B to the Dawson Declaration.

B. Schimrigk does not teach or suggest using a pharmaceutical composition consisting essentially of DMF and/or MMF to treat MS, let alone a dose of about 480 mg/day of DMF and/or MMF

Schimrigk teaches the administration of Fumaderm forte®, a pharmaceutical preparation which contains a mixture of DMF and monoethyl fumarate ("MEF") salts (also known as ethylhydrogen salts). One tablet of Fumaderm forte® contains 120 mg of DMF plus 87 mg of MEF-Ca salt, 5 mg of MEF-Mg salt, and 3 mg of MEF-Zn salt.[2] *See* Schimrigk, page 605, right column, paragraph entitled "Study drug." Specifically, in Schimrigk, patients were administered six tablets of Fumaderm forte® during the 18-week main treatment phase. Six tablets of Fumaderm forte® correspond to 720 mg of DMF and 570 mg of MEF salts, a total of 1,290 mg of fumarates per day, a dose that is much higher than the 480 mg/day required in the present claims. Subsequent to the main treatment phase, the patients in Schimrigk were administered three tablets of Fumaderm forte® during a 48-week second treatment phase (a total of 645 mg/day of fumarates). *See* Schimrigk, page 605, "Study design and assessments" and "Study drug." According to Schimrigk, this high dosing regimen showed promise with respect to certain MS parameters, such as reduction of the mean number of Gd+ lesions, and the positive effects from the first treatment phase were maintained in the second treatment phase. *See, e.g.,* Schimrigk at page 607, third paragraph "Clinical outcomes", Figures 1 and 2, and page 608, last paragraph "Discussion." As a whole, Schimrigk teaches the use of a dosing regimen that uses high doses of fumarates (*i.e.*, 1,290 mg/day followed by 645 mg/day).

[2] Fumaderm initial®, which contains 67 mg of MEF-Ca salt, 5 mg of MEF-Mg salt, 30 mg of DMF, and 3 mg of MEF-Zn salt, was administered to patients during up-titration, which lasted 9 weeks, and the final dose was reached after the up-titration period.

However, nothing in Schimrigk teaches or suggests replacing Fumaderm Forte®, *i.e.*, a mixture of four active ingredients, with a pharmaceutical composition consisting essentially of DMF and/or MMF or that such a composition could be efficacious for treating MS. Furthermore, even if Schimrigk had suggested a pharmaceutical composition consisting essentially of DMF and/or MMF, which it did not, one would still not arrive at the instantly claimed invention because Schimrigk does not teach or suggest the specific dose as required in the present claims, *i.e.*, about 480 mg/day of DMF and/or MMF, to treat MS.

In fact, Schimrigk directs a person of ordinary skill in the art toward using much higher doses of fumarates than the claimed invention, which uses 480 mg/day of DMF, effectively teaching away from the claimed invention. Based on the teaching of Schimrigk, a person of ordinary skill in the art would have expected a dose that is much higher than 480 mg/day to be required to effectively treat MS. After all, the promising results described in Schimrigk were generated by using the dosing regimen of 1,290 mg/day followed by a dose of 645 mg/day. In contrast to the claimed invention which requires the use of DMF and/or MMF, Schimrigk teaches the use of a mixture of four fumarates (*i.e.*, DMF and three MEF salts). Taking together the teaching of high fumarate doses and the use of the four fumarates, Schimrigk clearly leads a person of ordinary skill in the art away from the claimed invention of using a dose of 480 mg/day of DMF.

In summary, neither Joshi nor Schimrigk teaches or suggests administering about 480 mg/day of DMF and/or MMF to effectively treat MS. With the knowledge of the Phase

2 clinical study, one would not have engaged in routine experimentation to arrive at the claimed invention in view of either reference. Applicants respectfully submit that the present claims are not *prima facie* obvious in view of the cited references. However, even assuming *arguendo* that *prima facie* obviousness has been established, Applicants submit that it is rebutted by (1) the unexpected results obtained from practicing the claimed invention and (2) evidence that the claimed invention satisfies a long-felt but unsolved need as set forth below.

III. Unexpected Results Overcome the Alleged *Prima Facie* Case of Obviousness

A. The claimed invention demonstrates unexpected results

The unexpected results, which flow inherently from the claimed invention, are based on results of two large-scale Phase 3 MS clinical studies.

1. Results of the Phase 3 clinical studies

Biogen Idec MA Inc. ("Biogen Idec"), the assignee of the current application, recently completed two pivotal Phase 3 placebo-controlled, double-blind, clinical studies (DEFINE and CONFIRM) ("the Phase 3 clinical studies"). The Phase 3 clinical studies evaluated the investigational oral drug candidate BG-12, which contains DMF as substantially the only active ingredient, at two doses, 480 mg/day and 720 mg/day, for the treatment of RRMS. As mentioned above, MMF is the active metabolite of DMF.

In both Phase 3 clinical studies, the magnitude of the efficacy demonstrated by the 480 mg/day dose was quite surprising. Specifically, the lower 480 mg/day dose of DMF was shown to be just as efficacious as the higher 720 mg/day dose of DMF in almost every

endpoint of the Phase 3 clinical studies including annualized relapse rate, proportion of subjects relapsed, number of Gd+ lesions, and disability progression at two years. These endpoints are standard endpoints, commonly used in MS clinical studies. The unexpected results from the DEFINE study were previously presented in the form of a declaration under 37 CFR § 1.132 by Katherine T. Dawson, M.D. ("the Dawson Declaration") in U.S. Patent Application No. 12/526,296, and submitted herewith as Exhibit 2. The unexpected results from both Phase 3 clinical studies are presented in a separate declaration under 37 CFR § 1.132 by Richard A. Rudick, M.D.,[3] which is submitted herewith as Exhibit 1 ("the Rudick Declaration").[4]

Graphical representations of the Phase 3 clinical study results related to the Annualized Relapse Rate ("ARR") and disability progression, and a summary of the pooled DEFINE and CONFIRM data are shown in Figures 3-5 of the Rudick Declaration. Table 1 below summarizes some of the results of the Phase 3 clinical studies.

[3] Richard A. Rudick, M.D., is a physician, professor and clinical investigator who focuses on treating patients with neurological diseases. During the last 30 years, much of his clinical research has focused on MS. He is the Director of the Mellen Center for Multiple Sclerosis Treatment and Research at the Cleveland Clinic, the Vice Chairman for Research and Development at Cleveland Clinic's Neurological Institute, and a Professor of Medicine in the Cleveland Clinic Lerner College of Medicine at Case Western Reserve University. As a physician and an expert in the MS field, and further as a clinical investigator, Dr. Rudick is qualified to provide an opinion as to what a person of ordinary skill in the art would have known and concluded at the time of the invention.

[4] Results of the Phase 3 clinical studies (DEFINE and CONFIRM) are summarized in Biogen Idec press releases of April 11, 2011 and October 26, 2011, respectively (submitted herewith as Exhibits E and F to the Rudick Declaration).

Table 1

Comparison of BG-12 at 480 mg/day and 720 mg/day[5]

	DEFINE		CONFIRM	
	480 mg/day	**720** mg/day	**480** mg/day	**720** mg/day
Reduction of Annualized Relapse Rate	53%	48%	44%	51%
Disability Progression at 2 Years	38%	34%	21%	24%
Reduction of Mean Number of New/Newly Enlarging T2 Lesions	85%	74%	71%	73%
Reduction of Mean Number of New T1 Hypointense Lesions	73%[a]	63%[b]	57%[c]	65%[d]
Reduction in Number of Gd+ Lesions	90%	73%	74%	65%

The 480 mg/day DMF dose and the 720 mg/day DMF dose similarly reduced ARR compared to placebo by 53% and 48%, respectively, in the DEFINE trial, and by 44% and 51%, respectively, in the CONFIRM trial with high statistical significance ($p<0.0001$ vs. placebo). Disability progression was also similarly reduced compared to placebo by the 480 mg/day and 720 mg/day doses (38% and 34%, respectively for the DEFINE trial and 21% and 24% for the CONFIRM trial). *See, e.g.*, Rudick Declaration, Figures 3 and 4. The similarity of the efficacy obtained with the 480 mg/day and 720 mg/day doses of DMF is further demonstrated by the largely overlapping "activity ratios" depicted in Figure 5 of the Rudick Declaration.

[5] Except for disability progression ([a] $p=0.0050$; [b] $p=0.0128$; [c] $p=0.2536$; [d] $p=0.2041$), all data points are statistically significant versus placebo ($p<0.0001$ vs. placebo).

Given what was known about the use of DMF to treat MS at the time of the invention (see discussion below), the person of ordinary skill in the art would have been quite surprised by the unexpected results demonstrated by the DEFINE and CONFIRM studies (*i.e.*, the 480 mg/day dose was just as effective as the 720 mg/day dose in treating MS), not to mention that the skilled person would have been taught away from using the 480 mg/day dose based on the knowledge available at the time of the invention.

(a) The 480 mg/day dose having similar efficacy as the 720 mg/day dose is unexpected based on results from a Phase 2 study

As mentioned above, Biogen Idec completed the six-month Phase 2 clinical study involving the use of BG-12 (DMF) in 2006. The results, which were available as of June 2006, found that the 720 mg/day DMF dose was the only dose tested that was clinically effective, whereas both 120 mg/day dose and the 360 mg/day failed to show clinical effectiveness when compared to placebo.[6] Accordingly, the Phase 2 results did not indicate a dose-proportional relationship for the three DMF doses investigated. *See, e.g.*, Rudick Declaration, paragraph 9: "*the effects seen for the different doses of BG-12 were not clearly dose-proportional*" (emphasis added). Similarly, Dr. Dawson notes in her Declaration at page 19, paragraph 14: "*the Phase 2 results do not demonstrate a linear dose response between the DMF dose and the efficacy*" (emphasis added). Thus, there is no expectation as to whether the 480 mg/day dose would be efficacious when compared to placebo (and

[6] *See, e.g.*, Rudick Declaration page 4, paragraph 8, and Figures 1 and 2, and Dawson Declaration, page 9, paragraph 10, Figures 1-3).

certainly no expectation the 480 mg/day dose would have similar efficacy as the 720 mg/day dose). Indeed, Dr. Rudick states that

> based on the Phase 2 clinical study results, . . . a person of ordinary skill in the art at the time of the invention would not have reasonably expected a 480 mg/day dose of DMF to have similar efficacy as the 720 mg/day dose of DMF for the treatment of MS.

Rudick Declaration, page 6, paragraph 9. In other words, the level of efficacy demonstrated by the 480 mg/day dose is unexpected and quite surprising.

If a person of ordinary skill in the art had any expectation, the person would have expected a lower dose (*i.e.*, 480 mg/day) to have lower efficacy when compared to a higher dose (*i.e.,* a 720 mg/day). *See, e.g.*, Rudick Declaration, page 6, paragraph 9:

> The person of ordinary skill would have expected that the efficacy of the of the 480 mg/day dose to be less than that of the 720 mg/day dose. The fact that the 480 mg/day dose and the 720 mg/day dose, as tested in the Phase 3 clinical studies (see below), are found to be similarly efficacious is surprising.

To reiterate, based on the earlier phase 2 clinical study results, the results of the phase 3 clinical studies demonstrated quite unexpectedly that the 480 mg/day dose was just as efficacious as the 720 mg/day dose.

(b) The 720 mg/day dose was expected to be required for clinical effectiveness

As discussed above, the Phase 2 clinical study results teach a person of ordinary skill in the art to orally administer the only dose effective in the study, namely 720 mg/day of DMF, to treat patients with MS.

At the time of the invention, Schimrigk was the only other clinical study (other than the Phase 2 clinical study) known to a person of ordinary skill in the art that disclosed using fumarates to treat MS. Schimrigk administered 1,290 mg/day of a mixture of four fumarates (six tablets of Fumaderm Forte®) to MS patients in the main treatment phase to achieve positive clinical results. Based on the high fumarate dose taught by Schimrigk (and its teaching that three other MEF salts were required), a person of ordinary skill in the art would not have reasonably expected that 480 mg/day of DMF alone would be as efficacious as seen in the Phase 3 clinical studies.

Taking the Phase 2 clinical study results and the teaching of Schimrigk together, the 720 mg/day dose of DMF (or an even higher dose of fumarates) was clearly expected to be required for clinical effectiveness. As Dr. Rudick concluded:

> In summary, given that Schimrigk does not provide any teaching or expectation with regard to DMF dosing and that the results of the Phase 2 clinical study provides the expectation that 720 mg/day of DMF is the effective dose for MS treatment, it would have been highly unexpected by a person of ordinary skill in the art that 480 mg/day of DMF is as effective for the treatment of MS as 720 mg/day of DMF.

Rudick Declaration, page 9, paragraph 12.

Importantly, considering the Phase 2 clinical study results and Schimrigk as a whole, the references both teach or suggest a dose higher than 480 mg/day DMF is required to effectively treat MS. In other words, the references effectively teach away from the claimed invention. Because Applicants proceeded contrary to the accepted wisdom to arrive at the

claimed invention, which demonstrated the unexpected results (that the 480 mg/day dose of DMF met all measured endpoints with a high level of statistical significance and that this dose was shown to be just as efficacious as the 720 mg/day dose), Applicants submit that a *prima facie* case of obviousness, had one been established, has been overcome.

IV. The Unexpected Results, Which Inherently Flow From the Claimed Invention, Must Be Given Substantial Weight

It is well settled that unexpected results or advantages of the claimed invention (in this case, Applicants' clinical study results) do not need to be included in the specification for an Examiner to consider them. MPEP 716.02(f) states that:

> [t]he totality of the record must be considered when determining whether a claimed invention would have been obvious to one of ordinary skill in the art at the time the invention was made. Therefore, evidence and arguments directed to advantages not disclosed in the specification cannot be disregarded.

(emphasis added). So long as the undisclosed property would inherently flow from the claimed invention, which is well supported by the specification, such property must be given substantial weight in determining obviousness. As discussed below, the claimed invention is fully supported in the specification.

A. Every claimed limitation is described in the specification

Each of the independent claims (*i.e.*, claims 18, 28, 32, and 37) contains the following key claim limitations:

(i) A method of **treating** ... **multiple sclerosis**

(ii) Orally administering (or treating...with)... **dimethyl fumarate, monomethyl fumarate, or a combination thereof,**[7] ...

(iii)The therapeutically effective amount ...is **about 480 mg per day**.

For "treating MS," Applicants disclose in the specification a method for treating a neurological disease with at least one fumaric acid derivative, including dimethyl fumarate (DMF) or monomethyl fumarate (MMF), as "method 4" in paragraph [0009], lines 9-11 and paragraphs [0062-0063] of the specification. The application discloses that *"[i]n some embodiments the neurological disease is MS or another demyelinating neurological disease*." Specification, p. 4, paragraph [0010] (emphasis added). Applicants also discussed a MS animal model, Experimental Autoimmune Encephalomyelitis (EAE), in paragraphs [0108] and [0109], as well as Example 3. Therefore, MS is supported in the application.

For using "DMF and/or MMF," Applicants disclose in the specification that DMF and/or MMF are effective in treating MS. For example, DMF and MMF are listed as specific examples of neuroprotective compounds. Specification, p. 13, paragraph [0063]. Specifically, the specification indicates that

> [i]n some embodiments of method 4, a method of treating a mammal who has or is at risk for a neurological disease is provided. The methods comprises administering to the mammal a therapeutically effective amount of at least one neuroprotective compound which has Formula I, II, III, or IV, e.g., a fumaric acid derivative (e.g., DMF or MMF).

[7] Claim 32 covers the use of a pharmaceutical composition consisting essentially of DMF (and not DMF, MMF, or combination thereof).

(*Id.*) As such, DMF and MMF are specifically named in the application as compounds effective in treating neurological diseases such as MS. Furthermore, the dosages disclosed in paragraph [0116] of the application refer to the specific compounds "DMF" and "MMF". Accordingly, Applicants teach that DMF and MMF are effective in treating MS.

For the dose "480 mg per day," Applicants disclose in the specification that orally administering 480 mg per day of DMF and/or MMF is effective in treating MS. Specification, p. 30, paragraph [0116]. Specifically, the specification discloses that

> [a]n effective dose of DMF or MMR [sic] to be administered to a subject orally can be from about 0.1 g to 1 g per pay [sic], 200 mg to about 800 mg per day (e.g., from about 240 mg to about 720 mg per day; or **from about 480 mg to about 720 mg per day**; or about 720 mg per day).

(*Id.*) (emphasis added). Because Applicants teach 480 to 720 mg/day, and further disclose this dosage range as the most narrow range, it is clear that Applicants describe administering 480 mg DMF and/or MMF daily to treat MS (or treating an MS patient with 480 mg/day DMF and/or MMF). *See, e.g., In re Wertheim*, 541 F.2d 257, 191 U.S.P.Q. 90 (C.C.P.A. 1976).

Based on the discussion above, each of the limitations (treating a subject with MS by using 480 mg/day DMF and/or MMF) is described in the specification.

B. The law does not require the unexpected results to be disclosed in the specification for the results to be considered

Courts have repeatedly addressed the issue of unexpected results. As mentioned above, MPEP 716.02(f) explains the importance of considering the totality of the record in

determining obviousness and evidence and arguments associated with advantages not disclosed in the specification must therefore also be considered. The case law discussed therein and in the Office Action supports this position.

For example, in *In re Lundberg*, 253 F.2d 244, 117 U.S.P.Q. 190 (C.C.P.A. 1958), the applicant argued that a claimed valve was different from the prior art because the claimed valve could be opened by movement in either direction, thereby producing the unexpected result of avoiding obstruction when it is moved in one direction. *In re Lundberg*, 253 F.2d at 247. However, according to the C.C.P.A., "that advantage is not disclosed in appellant's application and he is, therefore, not in a favorable position to urge it as a basis for the allowance of claims." *Id.* (internal citations omitted). The C.C.P.A. could not consider this "advantage" or unexpected result not because the result was not described in the application, but rather, it was because the feature (two-direction opening) producing the result was not described in the application. Indeed, the C.C.P.A. went on to state that "appellant's valve has a scale which is readable only in one direction, and a stop which permits it to move in only one direction for opening. Accordingly, . . . the reversible operation now proposed by appellant would require modifications which are not disclosed in the application." *Id.* Stated differently, in *Lundberg*, the applicant was relying upon a physical feature of a claimed apparatus that was not described in the specification. In contrast, the present Applicants disclosed all features of the claimed invention that produce the unexpected results, namely the administration of 480 mg/day of DMF and/or MMF to effectively treat MS (see discussion above). Thus, the present situation is distinguishable

from *Lundberg* as the unexpected results inherently flow from the 480 mg/day dose, which was disclosed in the present specification.

The Federal Circuit distinguished *Lundberg* in *In re Chu*, 66 F.3d 292, 36 U.S.P.Q.2d 1089 (Fed. Cir. 1995), for similar reasons. In *Chu*, the applicant argued the advantage of placing a catalyst in his bag retainer to overcome an obviousness rejection over a reference disclosing all elements of the claimed device except that it "fails to disclose a baghouse filters [sic] having a catalyst located within the filter . . . ." *Chu*, 66 F.3d at 295. Applicant's argument was not considered by the PTO, which reasoned "Chu's 'specification is virtually silent on the matter of any purported advantage to locating the catalyst within the bag retainer . . . .'" *Id.* at 298. The Federal Circuit reversed the PTO and stated that:

> [w]e have found no cases supporting the position that a patent applicant's evidence and/or arguments traversing a § 103 rejection must be contained within the specification.

Id. at 299.

The Examiner attempted to distinguish *Chu* from the case at hand, stating that *Chu* "clearly disclosed the criticality of placing the catalyst at the particular position recited in the claims" whereas "the instant specification does not disclose the criticality of the limitations of the now claimed treatment protocol nor does it identify the claimed combination as being particularly advantageous . . . ." Office Action, page 8, lines 12-17. According to the *Chu* case, the applicants did argue the significance of the placement in response to the obviousness rejection, but it is not clear whether the original specification

teaches the criticality of such placement. Regardless, it is clearly stated in the same section of the MPEP that

> [t]he specification need not disclose proportions or values as critical for applicants to present evidence showing the proportions or values to be critical. *In re Saunders*, 444 F.2d 599, 607, 170 USPQ 213, 220 (CCPA 1971).

MPEP 716.02(f), last paragraph. Thus, the unexpected results which flow inherently from the present Applicants' claimed invention, which is described in the specification, must be given significant weight.

Additional Federal Circuit cases not mentioned in the Office Action but which further support Applicants' position are set forth below.

In *In re Dillon*, 919 F.2d 688, 16 U.S.P.Q.2d 1897 (Fed. Cir. 1990), the Federal Circuit indicated that the unexpected results cannot be simply discovery of an unknown property of a structure already known in the prior art. *In re Dillon*, 919 F.2d at 693. *Dillon* does not apply to the facts at hand because the dose of 480 mg/day was not a "structure already known in the prior art." As discussed above, neither Joshi nor Schimrigk discloses or suggests the 480 mg/day DMF dose. It follows that the unexpected results, namely the established clinical efficacy of the 480 mg/day dose of DMF, are not merely an unknown property of a known structure.

Recently, the Federal Circuit in *Genetics Institute, LLC v. Novartis Vaccines & Diagnostics, Inc.*, 2011 WL 672474 (Fed. Cir. 2011) (provided as Exhibit 3) discussed the court's history regarding submitting evidence of unexpected results obtained after the filing

date. According to the Federal Circuit, "[o]ur law is . . . clear that every property of a claimed compound need not be fully recognized as of the filing date of the patent application to be relevant to nonobviousness." *Id.* at 14 (citing *Knoll Pharm. Co. v. Teva Pharms. USA, Inc.*, 367 F.3d 1381, 1385 (Fed. Cir. 2004)). The Federal Circuit had indicated in *Knoll* that

> [t]here 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 . . . . Nor is it improper to conduct additional experiments and provide later-obtained data in support of patent validity.

Knoll, 367 F.3d at 1385. In addition to *Knoll*, the Federal Circuit also referred to *In re Khelghatian*, 364 F.2d 870 (CCPA 1966), *Eli Lilly & Co. v. Zenith Goldline Pharms., Inc.*, 471 F.3d 1369 (Fed. Cir. 2006), and *In re Chu*, 66 F.3d 292, 299 (Fed. Cir. 1995) to highlight that unexpected results obtained and submitted after the filing date must be considered when determining the patentability of the claims.

The Examiner stated that the MS animal model (the EAE model) disclosed in the specification does not have predictive value for clinical success and one of ordinary skill in the art would not have reasonably relied on the results from such an animal model. *See* the Office Action, page 4, line 9 to page 5, line 5. The EAE model is a useful research tool that provides insights into the effectiveness of a test compound to treat MS. Regardless of whether or not the EAE results disclosed in the specification are predictive, Applicants are relying on the unexpected results from two Phase 3 human clinical studies presented here to support patentability of the claimed invention. Because the present application teaches and

fully supports the claimed invention of treating MS using DMF and/or MMF at a dose of 480 mg/day (*i.e.*, every claimed limitation is described in the specification), the results from the DEFINE and CONFIRM Phase 3 clinical studies obtained after the filing date, which flow inherently from the claimed invention, must be given substantial weight when considering the patentability of the claimed invention.

As such, Applicants respectfully request the unexpected results presented here and in the Rudick and Dawson Declarations be considered in determining whether or not the current claims are obvious over the cited references.

C. Unexpected results, and not operability, is the issue in the present case

The Examiner states in the Office Action of May 3, 2012, at page 6, lines 4-11 that "[t]he unexpected and advantageous results demonstrated for the claimed method relative to the other embodiments that are disclosed in the instant specification are not in dispute . . . . [T]he demonstration that the now claimed combination is operable is not unexpected. It is Applicant's [*sic*] discovery, subsequent to the filing of the instant application, that the majority of embodiments described in the specification are inoperative that is unexpected." (emphasis added). Applicants submit the Examiner's basis for not giving significant weight to the unexpected results presented here are misplaced for the following reasons.

First, the Examiner alleged that the claimed combination (treating MS with a dose of about 480 mg/day of DMF and/or MMF) is operable is not unexpected. As mentioned above, it would have been difficult at the time of the invention to predict which doses would produce clinically meaningful efficacy based on the teachings of Schimrigk and the Phase 2

clinical study. Importantly, the surprising result Applicants presented is the magnitude of the efficacy of the 480 mg/day dose (that it is similarly efficacious as the 720 mg/day dose), which the Examiner does not seem to appreciate.

Second, only the 120 mg/day and 360 mg/day doses in the 6-month Phase 2 clinical study did not exhibit statistically significant clinical efficacy as compared with placebo. Applicants are puzzled as to how the Examiner arrived at the conclusion that the majority of embodiments described in the specification are inoperable.

Third, Applicants submit that, even if the specification discloses an inoperable embodiment, this would be irrelevant for the patentability of the instant claims as Applicants are not claiming an inoperable embodiment.[8] Because Applicants claim only an operable embodiment here (as demonstrated by two large-scale Phase 3 clinical studies), the patentability of the instant claims cannot be affected by the operability or inoperability of other embodiments that are disclosed but unclaimed in the specification.

The issue at hand is not operability but whether the claimed invention is *prima facie* obvious in view of the cited references and if so, whether the unexpected results, which inherently flow from the claimed invention, overcome the obviousness. For the reasons set forth above, Applicants submit the claims are not *prima facie* obvious in view of the cited references but, even assuming for arguments sake they were, the unexpected results presented, overcome the obviousness.

[8] Even if Applicants' were to claim an inoperable embodiment, the Federal Circuit has held that such an inoperable embodiment does not render a claim invalid as long as the majority of the embodiments encompassed by the claims are operable. *See Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1576-77, 224 U.S.P.Q. 409, 414 (Fed. Cir. 1984).

V. Other Secondary Consideration of Patentability – 480 mg/day of DMF Effectively Treats MS Satisfies a Long-Felt But Unsolved Need

The MS medical field has long recognized a high unmet need for, and a substantial challenge associated with, the development of efficacious, yet safe oral MS therapies. *See, e.g.*, Rudick Declaration, paragraphs 13-16:

> [A] long-felt but unmet need for disease-modifying oral MS medications has existed for decades . . . . A heightened anticipation for disease-modifying oral MS therapies has existed among health care professionals and patients alike since the first disease-modifying MS treatment entered the market (*e.g.*, about 15 years prior to the Applicants' priority date).

Rudick Declaration page 11, paragraph 15; Dawson Declaration at page 2, paragraphs 3-5.

A. There is currently no cure for MS – the goal has long been to find an effective and safe oral lifelong treatment

MS is a chronic autoimmune disease for which only a limited number of disease-modifying treatment options are currently available and which requires lifelong therapy. "Not only is MS treatable by only a handful of MS drugs, but all but one of the current disease-modifying drugs for MS require regular injections or monthly parenteral infusions. Administration of these medications is often associated with injection anxiety and/or injection-related adverse effects and limited long-term adherence to treatment." Rudick Declaration, page 10, paragraph 14[9]. Dr. Rudick further notes that

[9] *See e.g.*, Klauer T. and Zettl, U.K., "Compliance, adherence, and the treatment of multiple sclerosis," *J. Neurol.*, 255 Suppl 6: 87-92 (2008) (submitted herewith as Exhibit I to the Rudick Declaration); Devonshire V., *et al.*, "The Global Adherence Project (GAP): a multicenter observational study on adherence to disease-modifying therapies in patients with relapsing-remitting multiple sclerosis," *Eur. J. Neurol.*, 18(1): 69-77 (2011) (submitted herewith as Exhibit J to the Rudick Declaration); Miller A.E. and Rhoades R.W.,

> [m]aintaining adherence to the treatment regimens is a challenge when providing care for MS patients. Oral MS medications not only bring significant convenience for patients, but are also expected to greatly enhance patient compliance and thus are expected to improve long-term treatment benefits compared to injectable MS medications.

Rudick Declaration, page 10, paragraph 14.

A long-felt but unmet need for effective and safe disease-modifying oral MS medications has existed for decades, as recognized by a person of ordinary skill in the art. "However, at the time of the invention not a single oral drug for the treatment of MS was available. . . ." Rudick Declaration, page 10, paragraph 15. *See, e.g.*, Gold, R. "Oral therapies for multiple sclerosis: a review of agents in phase III development or recently approved," *CNS Drugs* 2011, 25(1): 37-52 ("Gold"):

> [t]here is a desire among patients for an oral therapy, which neurologists are also anticipating to help improve patient satisfaction and treatment adherence.

Gold at page 38.

One disease-modifying oral drug, Gilenya®, has recently been approved in the United States. *See e.g.*, Food and Drug Administration News Release of September 22, 2010. "FDA approves first oral drug to reduce MS relapses" (submitted herewith as Exhibit M to the Rudick Declaration). While providing the advantages of an oral treatment, Gilenya® can cause serious side effects such as "serious infections, transient reductions in heart rate, vision problems, and respiratory and liver complications." Sheridan C., *Nat*

"Treatment of relapsing-remitting multiple sclerosis: current approaches and unmet needs," *Curr. Opin. Neurol.*, 25 (suppl 1):S4-S10 (2012) (submitted herewith as Exhibit K to the Rudick Declaration).

Biotechnol. 2012, 30(1): 6-8 ("Sheridan") (submitted herewith as Exhibit N to the Rudick declaration). Consequently, not every patient can take Gilenya®, leaving many patients having to rely on injectable drugs. S*ee, e.g.*, Exhibit K to the Rudick declaration. "Indeed, the US prescribing information for Gilenya® was recently updated to include patient selection parameters as a result of FDA's review of a reported death upon administration of the drug." Rudick Declaration, page 11, paragraph 16.

It is very clear that additional medications are needed to achieve the long-felt but unmet goal and provide better life quality and reduced risk of disability for MS patients. Oral MS medications with favorable safety profiles are particularly desired. *See, e.g.*, Gold; Killestein, J., *et al.*, *Lancet Neurology* 2011, 10:1026-34 (submitted herewith as Exhibit H to the Rudick Declaration). As will be discussed below, Applicants' invention (*i.e.*, MS treatment using 480 mg/day of DMF) satisfies the above described long-felt need.

B. BG-12 (DMF) satisfies the long-felt but unsolved need

"BG-12 is an oral pharmaceutical formulation, which demonstrated significant efficacy for the treatment of MS coupled with favorable safety and tolerability in two pivotal Phase 3 clinical studies." Rudick Declaration, page 11, paragraph 17; *see*, *e.g.*, Exhibits E and F to the Rudick Declaration. In the first Phase 3 clinical study (DEFINE), "[r]esults showed that 240 mg of BG-12, administered either twice or three times a day, met the primary study endpoint, demonstrating a highly statistically significant reduction ($p<0.0001$) in the proportion of patients with RRMS who relapsed at two years compared with placebo." Exhibit E to the Rudick Declaration. Note that 240 mg of BG-12, when administered twice

a day, is a dose of 480 mg/day of DMF. For the second Phase 3 clinical study, "BG-12 met the CONFIRM study's primary endpoint by significantly reducing annualized relapse rate (ARR) by 44 percent for BID ($p< 0.0001$) and by 51 percent for TID ($p< 0.0001$) versus placebo at two years." Exhibit F to the Rudick Declaration.

1. The 480 mg/day DMF dose satisfies the unmet need particularly well

As Dr. Rudick explains, the claimed 480 mg/day dose of DMF satisfies the above described unmet need for an oral MS drug particularly well because this dose promotes patient compliance by only requiring patients to take the drug twice a day as opposed to three time a day for the 720 mg/day dose and because it is expected to provide a long-term safety advantage compared to the 720 mg/day dose without sacrificing the efficacy.

(a) Two times per day (BID) treatment regimen is superior to three times per day dosing regimen (TID)

The claimed 480 mg/day dose of DMF satisfies the unmet need particularly well because the dose "provides a superior regimen when compared with the 720 mg/day DMF dose." Rudick Declaration, page 13, paragraph 23. BG-12 at a dose of 480 mg/day DMF is administered using a twice a day dosing regimen (BID) of two doses of 240 mg each, whereas the other Phase 3 dose, the 720 mg/day dose, was administered using a thrice a day dosing regimen (TID) of three doses of 240 mg each. "BID administration provides a significant advantage over TID administration because such dosing regimen significantly increases convenience, which means increased patient compliance. Increased patient

compliance typically translates into greater patient benefit from the drug." Rudick Declaration, page 13, paragraph 24.

(b) 480 mg/day DMF may provide a safety advantage for long-term treatment

Furthermore, the claimed 480 mg/day dose is expected to provide a better long-term safety profile than the 720 mg/day DMF dose. "Safety concerns are on the forefront of the scientific discussion for additional long-term treatment options for MS. Oral drugs that are not only efficacious, but are characterized by a favorable long-term safety profile have the best chances of providing long-term benefits to MS patients and are particularly desirable." Rudick Declaration, page 13, paragraph 25; *see, e.g.*, Gold and Sheridan.

Dr. Rudick declares that "the Phase 3 clinical studies demonstrate an extraordinary safety/adverse event profile for BG-12." Rudick Declaration, page 14, paragraph 26. This view is shared by others in the field, including pharmaceutical analysts. For example, Bloomberg discloses:

> "[t]he most important thing is safety, and the safety profile looks exceptional," Eric Schmidt, an analyst with Cowen & Co. in New York, said in a telephone interview today. "This will position BG-12 as a front-line drug. It's hard to imagine this won't be a blockbuster."

Id. (emphasis added).

Additionally, Sheridan indicates that "some highlight Biogen Idec's oral small molecule BG-12 as the pipeline drug with the greatest potential to reconcile the twin goals of efficacy and safety." Sheridan at page 6. This would be particularly true for the claimed

DMF dose of 480 mg/day. Even though both the 480 mg/day and the 720 mg/day doses demonstrated similarly good safety profile in the Phase 3 clinical studies, Dr. Rudick notes that physicians (as well as the FDA and other regulatory agencies) will prefer the 480 mg/day dose of DMF over the 720 mg/day dose given the similar clinical effectiveness. The lower 480 mg/day DMF dose is the safer choice as it is expected to offer fewer side effects/adverse events upon administration over a prolonged period of time (*e.g.*, more than the 2-year period designated in each of the Phase 3 studies) than the 720 mg/day dose. Rudick Declaration, page 14, paragraph 26; *see*, *e.g.*, Exhibits E and F to the Rudick Declaration. In this sense, 480 mg/day DMF satisfies the above discussed long-felt need for a safe and efficacious oral MS treatment particularly well.

2. Publication of the Phase 3 clinical trial results have created excitement among physicians and pharmaceutical analysts

The publication of the results of the DEFINE and CONFIRM clinical studies in 2011 have created a great interest in BG-12 in the MS medical community as well as among observers of the pharmaceutical industry. Dr. Rudick notes that "[t]he results of the Phase 3 studies have created much excitement for . . . physicians in this field, as well as analysts of the pharmaceutical industry for this promising MS treatment." Rudick Declaration, page 12, paragraph 18; *see*, *e.g.*, Bloomberg.com article of October 26, 2011, "Biogen MS Pill With $3 Billion Potential Hits Study Goals," in response to the Biogen Idec press release regarding the CONFIRM data ("Bloomberg", submitted herewith as Exhibit O to the Rudick Declaration):

> "These data generally 'confirm' BG-12's efficacy . . . ," Mark Schoenebaum, an analyst with ISI Group in New York, wrote in a note to clients today. "On a scale of 1-10, with '10' being absolute best case, we would put these data at perhaps 8 or 9."

Id. (emphasis added).

Given the positive response to the Phase 3 clinical study results, it has become clear that BG-12 satisfies the above described long-felt but unsolved need for an oral MS drug. Dr. Rudick notes that "[t]here is no question in my mind that once BG-12 becomes available, it will make a significant difference in the lives of many MS patients." Rudick Declaration, page 12, paragraph 20. This view is shared by others in the field. For example, a Decision Resources article of June 25, 2012 (submitted herewith as Exhibit Q to the Rudick Declaration) discloses:

> [N]inety-five percent of all surveyed neurologists in the EU5[France, Germany, Italy, Spain, United Kingdom] expect to prescribe BG-12 . . . .

As such, BG-12 at 480 mg daily dose of DMF satisfies the above discussed long felt but unmet need for a safe and efficacious oral MS therapy.

The U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) both recently accepted Biogen Idec's New Drug Applications for BG-12 (with a prescribed dose of 480 mg/day of DMF as described in the instant claims) for the treatment of MS. *See, e.g.*, Biogen Idec press release dated May 9, 2012, submitted herewith as Exhibit P to the Rudick Declaration.

In conclusion, Dr. Rudick states that "at the time of the invention, there had been a long-felt need for oral therapies for MS, not met for several decades prior to the invention.

A need for safe and efficacious oral MS therapies persists to this current day. 480 mg/day of DMF meets this long-felt but unmet need while providing additional advantages over the similarly effective, higher dose of 720 mg/day." Rudick Declaration, page 14, paragraph 28.

Because it would not have been obvious for a person of ordinary skill in the art at the time of the invention to engage in experimentation with a dose of about 480 mg/day of DMF and/or MMF for the treatment of MS; because a dose of about 480 mg/kg of DMF produced unexpected results; and because treating MS with a dose of about 480 mg/kg of DMF satisfies a long-felt but unmet need, Applicants respectfully submit that the present claims would not have been obvious to a person of ordinary skill in the art at the time of the invention. In view of the foregoing, Applicants respectfully request that the obviousness rejections be withdrawn.

VI. Double Patenting

The Examiner has provisionally rejected claims 18-36 under 35 U.S.C. 101 as claiming the same invention as that of claims 18-36 of copending Application No. 12/526,296. Applicants submit that Application No. 12/526,296 is no longer pending and respectfully request that this rejection be withdrawn.

VII. Summary

Based on the reasons set forth above, Applicants respectfully submit that the present claims are patentable.

Conclusion

Prompt and favorable consideration of this Preliminary Amendment is respectfully requested. Applicants believe the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

Marsha Rose Gillentine

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EXHIBIT 1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Confirmation No.: 5998
LUKASHEV *et al.*	Art Unit: 1649
Appl. No. 13/372,426	Examiner: Ulm, John D.
Filing Date: February 13, 2012	Atty. Docket: 2159.321002/JMC/MRG/U-S
For: **Treatment for Multiple Sclerosis**	

Declaration of Richard A. Rudick, M.D. Under 37 C.F.R. § 1.132

US Patent and Trademark Office
PO Box 1450
Alexandria, Virginia 22313-1450

Dear Sir:

I, the undersigned, Richard A. Rudick, M.D., residing at 5067 Boulder Creek Drive, Solon, Ohio 44139-1379, declare and state as follows:

I. My Background

1. I am a physician (neurologist), professor and clinical investigator with a focus on treating patients with neurological diseases. During the last 30 years, much of my clinical research has focused on multiple sclerosis ("MS"). I am Director of the Mellen Center for Multiple Sclerosis Treatment and Research at the Cleveland Clinic (since 1987), the Vice Chairman for Research and Development at the Neurological Institute at the Cleveland Clinic (since 2007), and a Professor of Medicine in the Cleveland Clinic Lerner College of Medicine at Case Western Reserve University (since 2003). I served on the Editorial Board of the journal

Multiple Sclerosis – Clinical Issues from 1992 to 2010, and as a member of the Research Program Advisory Committee at the National Multiple Sclerosis Society since 2006 (chair of the committee since 2009). I am an author or co-author of about 200 peer-reviewed scientific articles, nine (9) books, and more than 40 book chapters related to MS. A copy of my *curriculum vitae* accompanies this declaration as **Exhibit A**.

2. I have extensive educational and research experience in the field of neurologic disorders. I currently focus on therapeutic aspects of MS, including clinical and MRI outcome measures for MS patient care and research. I conducted pivotal clinical trials involving MS treatments that are now approved by the Food and Drug Administration. For example, I was an investigator for the Phase 3 clinical trials involving interferon beta (IFNβ-1a), now marketed as Avonex®. I conducted MS clinical trials on behalf of Biogen Idec Inc. ("Biogen Idec") in connection with natalizumab, a parenteral therapy for relapsing-remitting MS ("RRMS"), now marketed as Tysabri®.

3. I am familiar with U.S. Patent Application No. 13/372,426 (filed February 13, 2012) entitled "Treatment for Multiple Sclerosis" and the current claims in that application, which are directed to methods of treating MS by administering 480 mg/day of dimethyl fumarate ("DMF") and/or monomethyl fumarate ("MMF"). I am also familiar with the two references cited by the Examiner: U.S. Patent Publication No. US 2003/0018072 to Joshi *et al.* ("Joshi"), and Schimrigk *et al.*, "Oral fumaric acid esters for the treatment of active multiple sclerosis: an open-label baseline-controlled pilot study," *European Journal of Neurology* 2006, 13(6):604-610 ("Schimrigk").

4. The Cleveland Clinic (my employer) is being compensated by Biogen Idec for my services related to this declaration at a rate in accordance with my standard consultation fee. In the past, the Cleveland Clinic (my employer) received two research grants from Biogen Idec for research studies for which I served as principal investigator (**Exhibit A**).

5. As a physician and an expert in the field of MS, and further as a clinical investigator, I am qualified to provide an opinion as to what a person of ordinary skill in the art would have known and concluded as of February 8, 2007, the priority date for U.S. Patent Application No. 13/372,426 ("the time of the invention").

6. I have been asked by Applicants' attorneys to comment on two areas of interest in connection with Biogen Idec's investigational drug BG-12, which contains dimethyl fumarate ("DMF") as the only active ingredient. First, I was asked to comment on whether or not a person of ordinary skill in the art at the time of the invention would have reasonably expected a 480 mg/day dose of DMF to be as efficacious as a 720 mg/day dose of DMF. Second, I was asked to comment on whether there was a long-felt, but unmet need for oral MS therapies at the time of the invention.

II. It is unexpected that 480 mg/day of DMF is as efficacious as 720 mg/day of DMF in treating MS

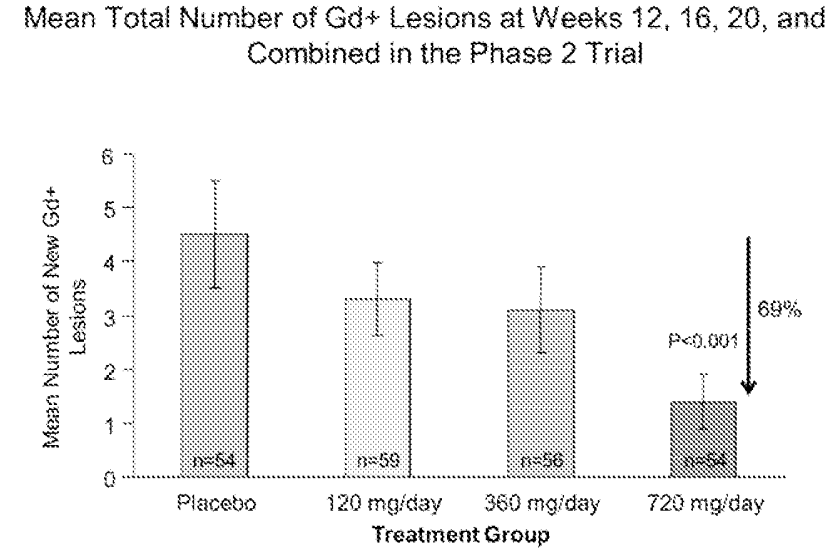
7. In view of what was publicly known about treating MS with fumarates at the time of the invention (*e.g.*, the teaching in Schimrigk and the DMF doses used in the Phase 2 BG-12 clinical study), based on my knowledge and experience, I believe that a person of ordinary skill in the art would have found the magnitude of the efficacy of the 480 mg/day dose of DMF, as observed in two recently completed

Phase 3 MS clinical studies, to be unexpected (*i.e.*, the 480 mg/day dose was found to be similarly efficacious as the higher dose of 720 mg/day). The observations described below form the basis of my opinion.

(a) The 480 mg/day dose was unexpectedly efficacious based on results from the Phase 2 clinical study

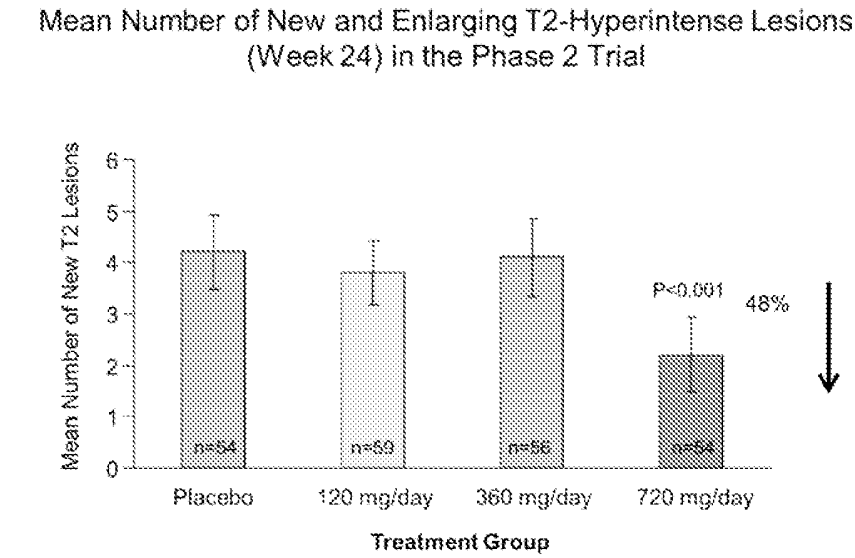
8. In 2004, Biogen Idec initiated a Phase 2 placebo controlled clinical study of BG-12 (DMF), which enrolled 257 patients with RRMS ("the Phase 2 clinical study"). Three doses, 120 mg, 360 mg, and 720 mg/day of DMF, were tested. *See, e.g.*, Kappos, L., *et al.*, "Efficacy of a novel oral single-agent fumarate, BG00012, in patients with relapsing-remitting multiple sclerosis: results of a phase 2 study," 16th Meeting of the European Neurological Society (May 30, 2006) (Abstract) (**Exhibit B**); Kappos, L., *et al.*, "Efficacy of a novel oral single-agent Fumarate, BG00012, in patients with relapsing-remitting multiple sclerosis: results of a phase II study," 16th Meeting of the European Neurological Society (May 30, 2006) (Slide Presentation) (**Exhibit C**); and "Oral Compound BG-12 Achieves Primary Endpoint in Phase II Study of Relapsing-Remitting MS with BG-12 Led to Statistically Significant Reductions in MRI Measures," Biogen Idec News Release (May 30, 2006) (**Exhibit D**). I am familiar with the results of the Phase 2 study. The study results show that the 120 mg/day and 360 mg/day doses did not exhibit a statistically significant difference compared to placebo with respect to the clinical endpoints measured in the trial (*i.e.*, the mean total number of Gd+ lesions, and the number of new and enlarging T-2 hyperintense lesions). The 720 mg/day dose was the only dose found to have a statistically significant effect compared to placebo. See figures below which are reproduced from the slide presentation of May 30, 2006 (**Exhibit C**):

Figure 1:



Note: The mean number of new Gd+ lesions was measured in comparison to the placebo.

Figure 2:



Note: The mean number of new and enlarging T2-hyperintense lesions was measured in comparison to the placebo.

9. As one can tell from the figures above, the effects seen for different doses of BG-12 were not clearly dose-proportional (*i.e.*, no suggestion of linear

response). Based on the Phase 2 clinical study results, I believe a person of ordinary skill in the art at the time of the invention would not have reasonably expected a 480 mg/day dose of DMF to have similar efficacy as the 720 mg/day dose of DMF for the treatment of MS. The person of ordinary skill would have expected that the efficacy of the 480 mg/day dose to be less than that of the 720 mg/day dose. The fact that the 480 mg/day dose and the 720 mg/day dose, as tested in the Phase 3 clinical studies (see below), were found to be similarly efficacious is surprising.

10. BG-12 was subsequently evaluated in two placebo-controlled, double-blind Phase 3 clinical studies (DEFINE and CONFIRM) ("the Phase 3 clinical studies"). In both of these Phase 3 clinical studies, it was unexpectedly found that the 480 mg/day dose of DMF has similar efficacy as the 720 mg/day dose of DMF in treating MS in almost every endpoint measured (*i.e.*, annualized relapse rate, proportion of subjects relapsed, number of Gd+ lesions, and progression of disability at two years). *See, e.g.*, results of the DEFINE study summarized in a Biogen Idec press release of April 11, 2011 (**Exhibit E**), results of the CONFIRM study summarized in a Biogen Idec press release of October 26, 2011 (**Exhibit F**), and a recent Biogen Idec slide presentation (**Exhibit G**). See figures 3-5 below which are reproduced from **Exhibit G**.

Figure 3:

Annualized Relapse Rate (ARR)[a)]

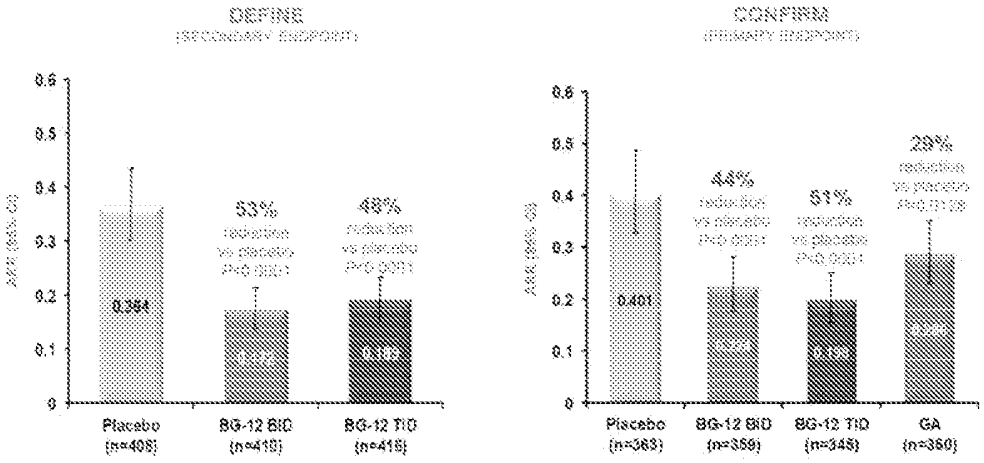
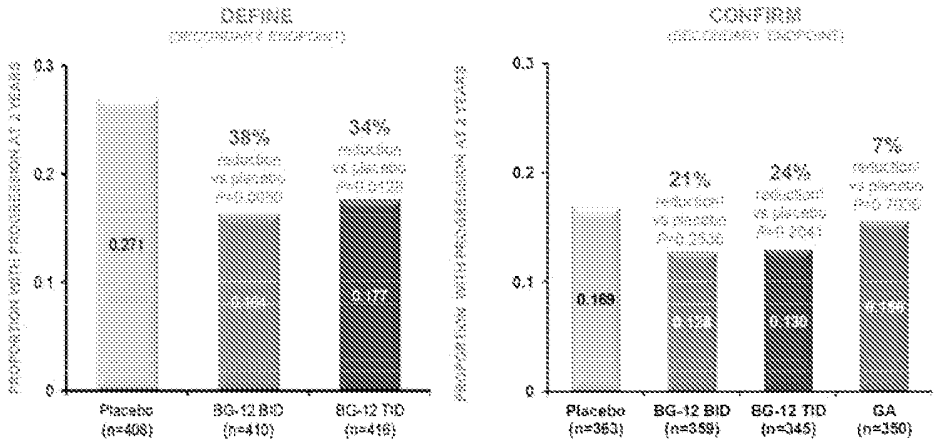


Figure 4:

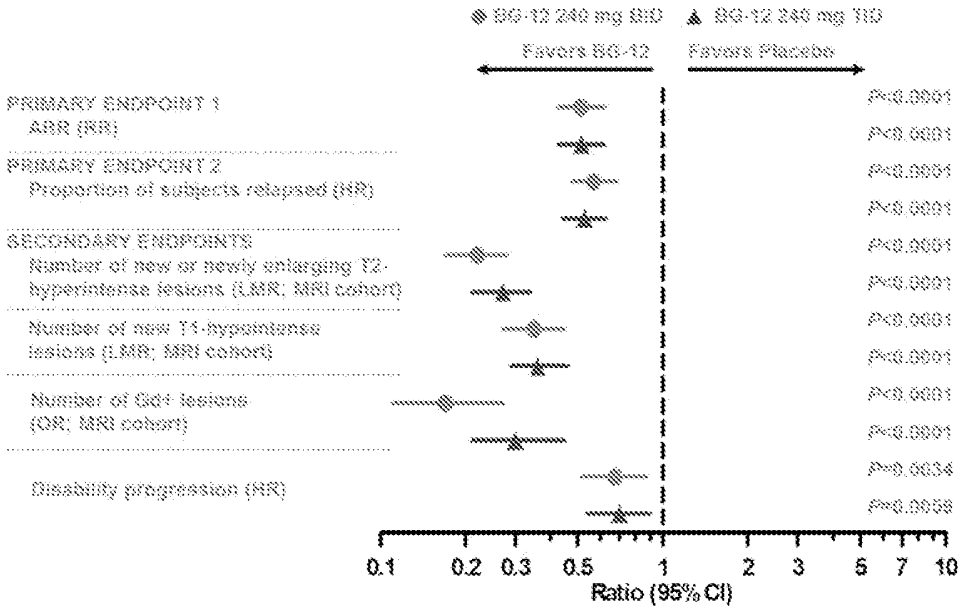
Disability Progression at Two (2) Years[a)]



a) BID = 480 mg/day of DMF; TID = 720 mg/day of DMF; GA = glatiramer acetate
† = not statistically significant against placebo

Figure 5:

Summary of Key Efficacy Endpoints (Ratio and 95% CI)
DEFINE and CONFIRM (Pooled)



Key: CI (Confidence Interval), RR (Rate Ratio), HR (Hazard Ratio), LMR (Lesion Mean Ratio), and OR (Odds Ratio)

(b) Based on past clinical studies, 720 mg/day of DMF was expected to be required dose for efficacy

11. Results from an earlier MS clinical study were reported by Schimrigk. In Schimrigk, investigators administered 1,290 mg/day of a mixture of four fumarates (six tablets of Fumaderm Forte®) to MS patients in the main treatment phase.[1] According to Schimrigk, the administered fumarate mixture at this dose was associated with promising results with respect to certain MS parameters. Even though DMF is one of the four fumarates in the mixture, the remaining three fumarates are each an active ingredient. Thus, in my opinion, a person of ordinary skill in the art would not have reasonably expected DMF by itself to have similar efficacy in treating MS as four active fumarates (including DMF) together. The

[1] Schimrigk also disclosed administration of three tablets of Fumaderm forte® during a second treatment phase (a total of 645 mg/day of fumarates) and that the effects from the first treatment phase were maintained.

person of ordinary skill would have even less expectation that 480 mg/day of DMF would have similar efficacy as 1,290 mg/day of a mixture of fumarates.

12. In summary, given that Schimrigk does not provide any teaching or expectation with regard to DMF dosing and that the results of the Phase 2 clinical study provides the expectation that 720 mg/day of DMF is the effective dose for MS treatment, it would have been highly unexpected by a person of ordinary skill in the art that 480 mg/day of DMF is as effective for the treatment of MS as 720 mg/day of DMF.

III. BG-12 satisfies a long felt but unsolved need for oral treatment of MS

13. Over the many years I have been treating MS patients and conducting clinical research on MS, I have seen the devastation the disease can bring. MS is a chronic autoimmune disease requiring lifelong therapy. The disease affects about 2.5 million people worldwide and has a prevalence that ranges between 2 and 150 per 100,000 people (*see e.g.*, Rosati, G., *Neurol. Sci.* 2001, 22(2): 117-39; Nicholas, R. *et al.*, *Drug Design, Development and Therapy* 2011, 5:255-274). MS is characterized by inflammation, myelin destruction, axonal damage and neuronal loss in the central nervous system. *See, e.g.*, Killestein, J., *et al.*, "Oral treatment for multiple sclerosis." *Lancet Neurology* 2011, 10:1026-34 ("Killestein") (**Exhibit H**). Physical and cognitive impairments of varying degrees are common in MS. The disease is one of the primary causes for neurological disability in young adults.

A. There is currently no cure for MS – lifelong treatment is required

14. Not only is MS treatable by only a handful of MS drugs, but all but one of the current disease-modifying drugs for MS require regular injections or monthly parenteral infusions. I have observed in my patients that administration of

these medications is often associated with injection anxiety and/or injection-related adverse effects and limited long-term adherence to treatment. *See, e.g.*, Klauer T., and Zettl, U.K., "Compliance, adherence, and the treatment of multiple sclerosis," *J. Neurol.* 2008, 255 Suppl 6: 87-92 (**Exhibit I**); Devonshire, V. *et al.*, "The Global Adherence Project (GAP): a multicenter observational study on adherence to disease-modifying therapies in patients with relapsing-remitting multiple sclerosis," *Eur. J. Neurol.* 2011, 18(1): 69-77 (**Exhibit J**); Miller, A.E. and Rhoades, R.W., "Treatment of relapsing-remitting multiple sclerosis: current approaches and unmet needs," *Curr. Opin. Neurol.* 2012, 25 (suppl 1):S4-S10 (**Exhibit K**) , Gold, R., "Oral therapies for multiple scleroris: a review of agents in phase III development or recently approved," *CNS Drugs* 2011, 25(1): 37-52 (**Exhibit L**), and **Exhibit H**. From my personal experience over many years, it is clear that maintaining adherence to the treatment regimens is a challenge when providing care for MS patients. Oral MS medications not only bring significant convenience for patients, but are also expected to greatly enhance patient compliance and thus are expected to improve long-term treatment benefits compared to injectable MS medications.

15. A long-felt but unmet need for disease-modifying oral MS medications has existed for decades. However, at the time of the invention not a single oral drug for the treatment of MS was available. *See, e.g.*, "FDA approves first oral drug to reduce MS relapses," Food and Drug Administration News Release (September 22, 2010) (**Exhibit M**). A heightened anticipation for disease-modifying oral MS therapies has existed among health care professionals and patients alike since the first disease-modifying MS treatment entered the market (*e.g.*, about 15 years prior to the Applicants' priority date). As indicated in Killestein, "[t]he need for oral drugs for

patients with MS is obvious . . . . Compliance is poor in many patients because of the low effi cacy and frequent injections." (Killestein, page 1026).

16. Recently, the first (and currently, the only) oral MS therapy, Gilenya®, was approved. *See, e.g.*, **Exhibit M**. However, while providing the advantages of an oral treatment, Gilenya® can cause serious side effects such as "serious infections, transient reductions in heart rate, vision problems, and respiratory and liver complications." *See, e.g.*, Sheridan C. Safety profiles come to fore as more drugs approach MS market. *Nat Biotechnol.* 2012, 30(1): 6-8 ("Sheridan") (**Exhibit N**, page 7). For these and other reasons, not every patient can take Gilenya®, leaving many patients having to rely on injectable drugs. (**Exhibit K**). Indeed, the US prescribing information for Gilenya® was recently updated to include patient selection parameters as a result of FDA's review of a reported death upon administration of the drug. Thus, additional oral drugs that are safe, effective, appropriate for patients with comorbidities, and suitable for long-term treatment, are still needed.

B. BG-12 (DMF) satisfies the long-felt but unsolved need

17. BG-12 is an oral pharmaceutical formulation, which demonstrated significant efficacy for the treatment of MS coupled with favorable safety and tolerability in two pivotal Phase 3 clinical studies. *See, e.g.*, **Exhibit E** and **Exhibit F.** "Results showed that 240 mg of BG-12, administered either twice or three times a day, met the primary study endpoint, demonstrating a highly statistically significant reduction ($p<0.0001$) in the proportion of patients with RRMS who relapsed at two years compared with placebo." (**Exhibit E**) "BG-12 met the CONFIRM study's primary endpoint by significantly reducing annualized relapse rate (ARR) by 44

percent for BID ($p < 0.0001$) and by 51 percent for TID ($p < 0.0001$) versus placebo at two years." (**Exhibit F**).

18. The results of the Phase 3 studies have created much excitement for me and other physicians in this field, as well as analysts of the pharmaceutical industry for this promising MS treatment. *See, e.g.*, Bloomberg article in response to CONFIRM data of Oct 26, 2011 ("Bloomberg article") (**Exhibit O**).

> *"These data generally 'confirm' BG-12's efficacy . . . ," Mark Schoenebaum, an analyst with ISI Group in New York, wrote in a note to clients today. "On a scale of 1-10, with '10' being absolute best case, we would put these data at perhaps 8 or 9."*

Id. (emphasis added).

19. Furthermore, the Food and Drug Administration (FDA) recently accepted Biogen Idec's New Drug Application (NDA) for BG-12 for the treatment of MS (*see, e.g.*, Biogen Idec press release dated May 9, 2012, **Exhibit P**).

20. There is no question in my mind that once BG-12 becomes available, it will make a significant difference in the lives of many MS patients. This view is shared by others in the field. For example, a Decision Resources article of June 25, 2012 (**Exhibit Q**) discloses:

> *[N]inety-five percent of all surveyed neurologists in the EU5[France, Germany, Italy, Spain, United Kingdom] expect to prescribe BG-12 . . . .*

(emphasis added).

21. As such, BG-12 at 480 mg/day of DMF will contribute significantly toward meeting the above discussed long-felt but unmet need for a safe and efficacious oral MS therapy.

22. In addition to satisfying the unmet need, there are, in my view, two additional advantages of the 480 mg/day dose of DMF as compared with the 720 mg/day DMF dose.

(a) Two times per day (BID) treatment regimen is superior to three times per day dosing regimen (TID)

23. BG-12 at a dose of 480 mg/day DMF is administered using a twice a day dosing regimen – 240 mg DMF each administration (BID), whereas the other Phase 3 dose, the 720 mg/day dose, was administered in three doses of 240 mg each (TID).

24. BID administration provides a significant advantage over TID administration because such dosing regimen significantly increases patient convenience and is expected to increase patient compliance with the treatment schedule. Increased patient compliance is crucial to achieving maximal benefit from the drug.

(b) 480 mg/day DMF may provide a safety advantage for long-term treatment

25. Safety concerns are on the forefront of the scientific discussion for additional long-term treatment options for MS. Oral drugs that are not only efficacious, but are characterized by a favorable long-term safety profile have the best chances of providing long-term benefits to MS patients and are particularly desirable. *See, e.g.*, **Exhibit L** and **Exhibit N**.

26. In my opinion, the Phase 3 clinical studies demonstrate an extraordinary safety/adverse event profile for BG-12 (*see, e.g.*, slide 9 of **Exhibit G**). My opinion is shared by others in the field, including pharmaceutical analysts. For example, the Bloomberg article discloses

> *"[t]he most important thing is safety, and the safety profile looks exceptional," Eric Schmidt, an analyst with Cowen & Co. in New York, said in a telephone interview today. "This will position BG-12 as a front-line drug. It's hard to imagine this won't be a blockbuster."*

Id. (emphasis added). Additionally, Sheridan indicates that "some highlight Biogen Idec's oral small molecule BG-12 as the pipeline drug with the greatest potential to reconcile the twin goals of efficacy and safety." (Sheridan at page 6.)

27. Furthermore, physicians (as well as the FDA and other regulatory agencies) will prefer the 480 mg/day dose of DMF given the similar safety/efficacy profile compared to the 720 mg/day dose. The lower 480 mg/day DMF dose is expected to offer fewer side effects/adverse events upon administration over a prolonged period of time (*e.g.*, more than the 2-year period designated in each of the Phase 3 studies) than the similarly effective higher dose of 720 mg/day of DMF (although the BG-12 clinical studies did not indicate a difference between the safety profiles of the 480 mg/day and the 720 mg/day dose over two years; *see, e.g.*, **Exhibit E**, **Exhibit F**, and slide 9 of **Exhibit G**). In this sense, 480 mg/day DMF satisfies the above discussed long-felt need for a safe and efficacious oral MS treatment particularly well.

28. In summary, at the time of the invention, there had been a long-felt need for oral therapies for MS, not met for several decades prior to the invention. A need for safe and efficacious oral MS therapies persists to this current day. 480 mg/day of DMF contributes to meeting this long-felt but unmet need while providing additional advantages over the similarly effective, higher dose of 720 mg/day.

IV. Conclusion

29. In view of the foregoing, I conclude that it would have been unexpected to a person of ordinary skill at the time of the invention that a 480 mg/day DMF dose is similarly effective in treating MS than a 720 mg/day DMF dose. Furthermore, it is my opinion that 480 mg/day (240 mg BID) DMF satisfies a long-felt, but unmet need for an oral MS therapy.

30. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the present patent application or any patent issued thereon.

Respectfully submitted,

Richard A Rudick

Richard A. Rudick, M.D.

Date: 7/30/12

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Appendix A

Exhibit A	Curriculum Vitae for Richard A. Rudick, M.D.
Exhibit B	Kappos, L., *et al.*, "Efficacy of a novel oral single-agent fumarate, BG00012, in patients with relapsing-remitting multiple sclerosis: results of a phase 2 study," 16th Meeting of the European Neurological Society (May 30, 2006) (Abstract)
Exhibit C	Kappos, L., *et al.*, "Efficacy of a novel oral single-agent Fumarate, BG00012, in patients with relapsing-remitting multiple sclerosis: results of a phase II study," 16th Meeting of the European Neurological Society (May 30, 2006) (Slide Presentation)
Exhibit D	"Oral Compound BG-12 Achieves Primary Endpoint in Phase II Study of Relapsing-Remitting MS with BG-12 Led to Statistically Significant Reductions in MRI Measures," Biogen Idec News Release (May 30, 2006)
Exhibit E	Biogen Idec Press Release (April 11, 2011)
Exhibit F	Biogen Idec Press Release (October 26, 2011)
Exhibit G	Biogen Idec Slide Presentation "BG-12 for RRMS – Registration Submitted"
Exhibit H	Killestein, J., *et al.*, "Oral treatment for multiple sclerosis." *Lancet Neurology* 2011, 10:1026-34
Exhibit I	Klauer, T. and Zettl, U.K., "Compliance, adherence, and the treatment of multiple sclerosis," *J. Neurol.* 2008, 255 Suppl 6: 87-92
Exhibit J	Devonshire, V., *et al.*, "The Global Adherence Project (GAP): a multicenter observational study on adherence to disease-modifying therapies in patients with relapsing-remitting multiple sclerosis," *Eur. J. Neurol.* 2011, 18(1): 69
Exhibit K	Miller, A.E. and Rhoades, R.W., "Treatment of relapsing-remitting multiple sclerosis: current approaches and unmet needs," *Curr. Opin. Neurol.* 2012, 25 (suppl 1):S4-S10
Exhibit L	Gold R. Oral therapies for multiple sclerosis: a review of agents in phase III development or recently approved. *CNS Drugs* 2011, 25(1): 37-52
Exhibit M	"FDA approves first oral drug to reduce MS relapses," Food and Drug Administration News Release (September 22, 2010)

Exhibit N	Sheridan, C., "Safety profiles come to fore as more drugs approach MS market," *Nat Biotechnol.* 2012, 30(1): 6-8
Exhibit O	"Biogen MS Pill With $3 Billion Potential Hits Study Goals," Bloomberg.com (October 26, 2011)
Exhibit P	Biogen Idec Press Release (May 9, 2012)
Exhibit Q	"For the treatment of Multiple Sclerosis, More than 85 Percent of Surveyed Neurologists in the EU5 Expect to Prescribe Biogen Idec's BG-12, Sanofi/Genzyme's Aubagio and Sanofi/Genzyme/Bayer HealthCare's Lemtrada" (Decision Resources, June 25, 2012)

EXHIBIT 2

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Confirmation No.: 5197
LUKASHEV, Matvey E.	Art Unit: 1649
Appl. No. 12/526,296	Examiner: Ulm, John D.
§ 371(c) Date: January 13, 2011	Atty. Docket: 2159.3210001/JMC/M-R/U-S
For: **Treatment for Multiple Sclerosis** ***(As Amended)***	

Declaration of Katherine T. Dawson, M.D. Under 37 C.F.R. § 1.132

US Patent and Trademark Office
PO Box 1450
Alexandria, Virginia 22313-1450

Dear Sir:

I, the undersigned, Katherine T. Dawson, M.D. residing at 561 Canton Street, Westwood, MA 02090 declare and state as follows:

I. My Background

1. I am a Senior Director of Medical Research at Biogen Idec MA Inc. ("Biogen Idec"), the assignee of the currently pending application. I have seven years of experience in the clinical development of MS drug products. I was involved in the development of Tysabri® and was the medical director of the Avonex® program. Tysabri® and Avonex®, both parenteral therapies, are among the few currently-approved treatment options for MS patients. I am currently responsible for developing BG-12, a new oral MS therapy. A copy of my *curriculum vitae* accompanies this declaration as Exhibit A.

2. I have personal knowledge of the matters in this declaration – knowledge which is either first-hand, or derived from my experience in this field and from interacting with others on the BG-12 development team at Biogen Idec.

II. Long Felt Need for Oral Treatment of Multiple Sclerosis

3. Multiple sclerosis ("MS") is an autoimmune disease characterized by inflammation, myelin destruction, axonal damage and neuronal loss in the central nervous system and affects about 2.5 million people worldwide.

4. Patients with MS are typically treated with injectable medications. Despite the recent approval of one oral MS therapy, a substantial challenge remains to develop efficacious yet safe oral therapies to treat MS patients. As such, there is a high, unmet, long-felt need for oral therapies that are effective in treating MS.

5. In an attempt to address this high, unmet, long-felt need, Biogen Idec has completed Phase 2 and Phase 3 clinical trials to investigate BG-12 as an oral treatment for MS. The only active ingredient of BG-12 is dimethyl fumarate ("DMF").

III. The 480 mg DMF Per Day Dose is Unexpectedly Efficacious

A. Phase 2 Clinical Trial

6. In 2004, Biogen Idec initiated a Phase 2 six-month placebo controlled clinical trial of BG-12 in 10 countries and enrolled 257 patients with relapsing remitting MS (RRMS). The clinical trial included an additional six-month safety extension. Overall, ninety-one percent of the patients completed the placebo-controlled part of the Phase 2 clinical trial.

a. 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 (a well-known measure of the disabilities suffered by MS patients) between 0.0 and 5.0. Additionally, the patients had to have had at least 1 relapse within 12 months prior to randomization or gadolinium-enhancing (Gd+) lesions (Gd+ lesions in the brain are a well-known marker of MS) on brain MRI within six weeks of randomization.

b. The patients were randomly assigned to one of four treatment groups for 24 weeks: (a) 120 mg BG-12 once daily (120 mg/day); (b) 120 mg BG-12 three times daily (360 mg/day); (c) 240 mg BG-12 three times daily (720 mg/day); and (d) placebo.

c. The primary end point of the Phase 2 clinical trial was the sum of all new Gd+ lesions from four brain MRI scans obtained at Weeks 12, 16, 20, and 24. The number of Gd+ lesions is considered a surrogate end point for clinical efficacy and as such is accepted as a primary end point for a proof of concept study.

d. The secondary end points of the Phase 2 clinical trial included the cumulative number of new Gd+ lesions on scans from Weeks 4 and 24, the number of new or newly enlargingT2-hyperintense lesions at Week 24, and the number of new T1 hypointense lesions at week 24.

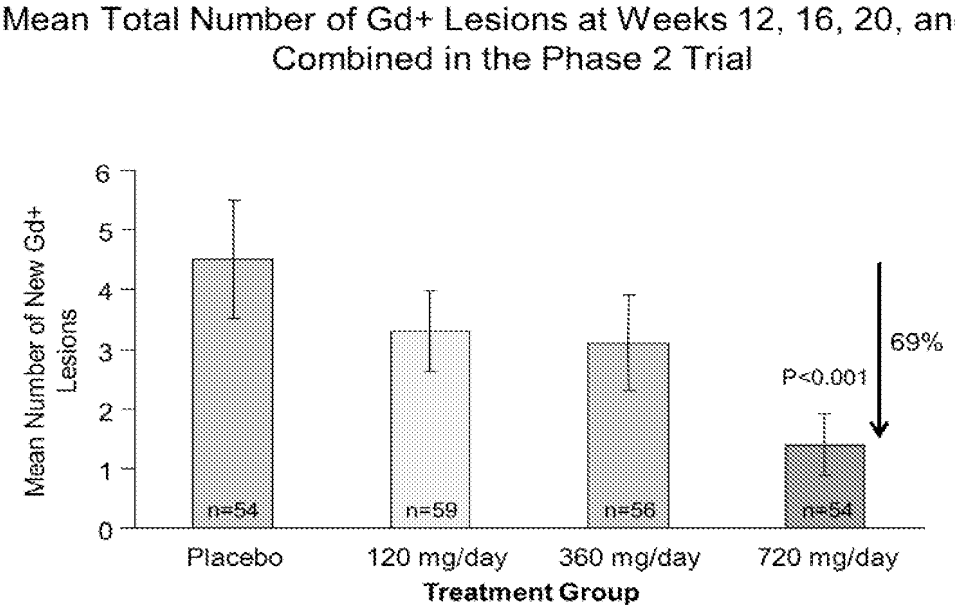
e. Additional end points included annualized relapse rate ("ARR") and disability progression as measured by EDSS.

7. The results of the Phase 2 clinical trial are reported in the peer-reviewed publication of Kappos, L., *et al*., "Efficacy and safety of oral fumarate in patients with relapsing-remitting multiple sclerosis: a multicentre, randomised, double-blind, placebo-controlled phase IIb study,"

Lancet 372:1463-72 (2008) (Exhibit B); as well as in Kappos, L., *et al*., "Efficacy of a novel oral single-agent fumarate, BG00012, in patients with relapsing-remitting multiple sclerosis: results of a phase 2 study," 16th Meeting of the European Neurological Society (presentation given on May 30, 2006) (Exhibit C); Kappos, L., *et al*., "Efficacy of a novel oral single-agent Fumarate, BG00012, in patients with relapsing-remitting multiple sclerosis: results of a phase II study," 16th Meeting of the European Neurological Society (abstract to presentation given on May 30, 2006) (Exhibit D); and "Oral Compound BG-12 Achieves Primary Endpoint in Phase II Study of Relapsing-Remitting MS with BG-12 Led to Statistically Significant Reductions in MRI Measures," Biogen Idec News Release (May 30, 2006) (Exhibit E).

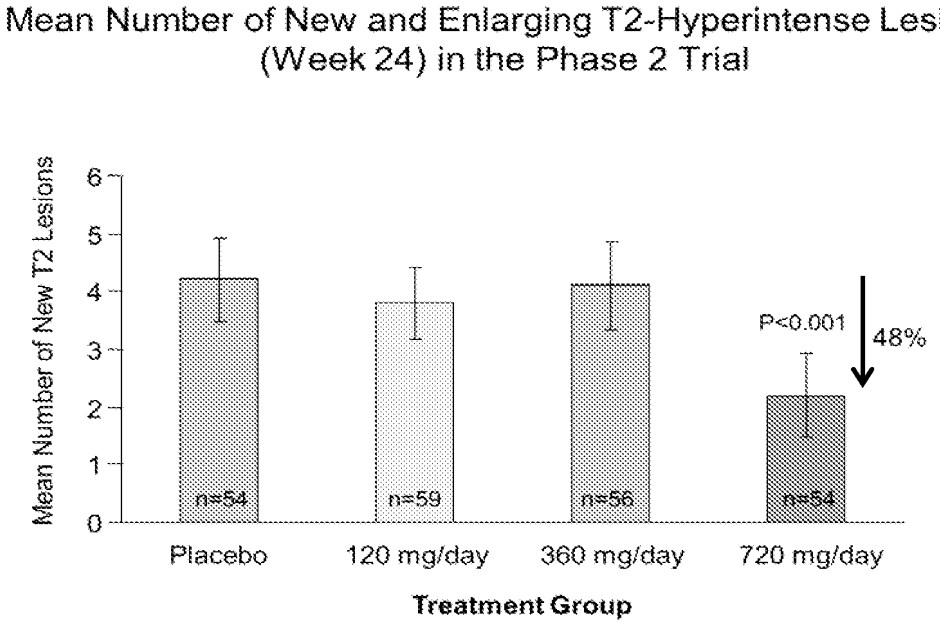
a. Only the patients who were administered 720 mg/day DMF exhibited a statistically significant effect on the primary endpoint vs. placebo. Patients in this dose group showed a 69% decrease ($P<0.001$) in the mean number of new Gd+ lesions over MRI scans Weeks 12 to 24 as shown in Figure 1 below.

Figure 1:


Mean Total Number of Gd+ Lesions at Weeks 12, 16, 20, and 24 Combined in the Phase 2 Trial
Mean Number of New Gd+ Lesions
0
1
2
3
4
5
6
n=54
n=59
n=56
n=54
P<0.001
69%
Placebo
120 mg/day
360 mg/day
720 mg/day
Treatment Group

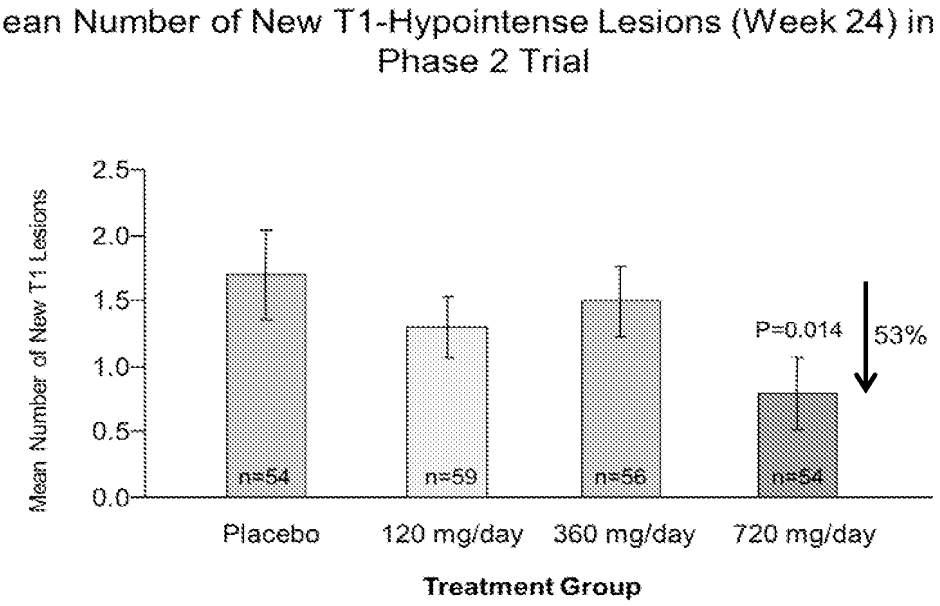
b. Additionally, patients administered 720 mg/day DMF exhibited a 48% decrease ($p<0.001$) in the mean number of new and enlarging T2-hyperintense lesions at Week 24, compared to placebo as shown in Figure 2 below.

Figure 2:



c. Patients administered 720 mg/day DMF also exhibited a 53% decrease (p=0.014) in the mean number of new T1-hypointense lesions at Week 24 vs. placebo as shown in Figure 3 below.

Figure 3:



d. Finally, patients administered 720 mg/day DMF exhibited an ARR of 0.44, as compared to an ARR of 0.65 in patients administered placebo as shown in Table 1 below, resulting in a clinically meaningful 32% reduction in ARR, which is similar to the treatment effect on ARR of the approved interferon-*beta* and glatiramer acetate treatments for MS. The reduction in ARR was not statistically significant[1] and has to be viewed in the context of the study being powered to achieve statistical significance for MRI endpoints and not for an evaluation of ARR.

Table 1:

	Treatment Group			
	Placebo N=65	120 mg /day N=64	360 mg/day N=64	720 mg/day N=63
Annualized relapse rate (95% CI)*	0.65 (0.43, 1.01)	0.42 (0.24, 0.71)	0.78 (0.52, 1.16)	0.44 (0.26, 0.76)

CI = confidence interval

8. In comparison, treatment with 120 mg/day and 360 mg/day DMF did not provide results that were statistically significant versus placebo on any endpoint. (*See, e.g.*, Exhibit E).

9. The Phase 2 clinical trials results indicated 720 mg/day DMF significantly reduced the cumulative number of new Gd+ lesions, the number of new or enlarging T2-hyperintense lesions, and the number of new T1-hypointense lesions compared with placebo. (*See, e.g.*, Exhibit C).

[1] One could attempt to draw a conclusion that the relapse efficacy endpoint of the Phase 2 clinical trial suggests that patients administered 120 mg/day DMF exhibit essentially the same annualized relapse rate as patients administered 720 mg/day DMF. However, the study was not designed to achieve statistical significance for this endpoint. (*See, e.g.*, Exhibit E).

10. Therefore, the results of the Phase 2 clinical trial demonstrated that 720 mg/day DMF was an efficacious dose for treating patients with MS. Additionally, because the 120 mg/day DMF and the 360 mg/day DMF groups were not statistically significant compared to placebo and the magnitude of effect on MRI lesions was not dose proportional, the results of the Phase 2 study did not suggest that DMF exhibited a linear dose response.

B. Phase 3 DEFINE Clinical Trial Results[2]

11. The BG-12 Phase 3 placebo-controlled, double-blind clinical trial, named the "DEFINE" trial, was completed earlier this year and its top-line results were announced in April 2011. The trial included over 1200 patients, in 28 different countries, on 5 different continents. Seventy-seven percent of the patients completed the clinical trial.

a. Men and women 18 to 55 years of age were eligible for the study if they had a diagnosis of RRMS and EDSS score between 0.0 and 5.0. Additionally, the patients must have had at least one clinically confirmed relapse within 12 months prior to randomization and a brain MRI scan at any time that was consistent with MS or that showed evidence of at least one Gd+ enhancing lesion within 6 weeks of randomization.

b. Patients were randomly assigned to one of three treatment groups: (a) 240 mg BG-12 twice daily (480 mg/day); (b) 240 mg BG-12 three times daily (720 mg/day); and (c) placebo.

c. The primary end point of the Phase 3 clinical trial was the proportion of relapsing patients at 2 years. A relapse was defined as new or recurrent neurologic

[2] DEFINE is one of the two Phase 3 clinical trials conducted by Biogen Idec. The results of the other Phase 3

symptoms lasting for at least 24 hours that were not associated with fever or infection but were accompanied by new, objective neurological findings.

d. Secondary end points of the Phase 3 clinical trial included the number of Gd+ lesions, new or newly enlarging T2-hyperintense lesions, ARR, and sustained 12-week disability progression. Disability progression was defined as an increase in EDSS of (a) at least 1.0 point in patients with a baseline EDSS of $\geq$ 1.0 or (b) at least 1.5 point increase in patients with a baseline EDSS of 0.0, sustained for 12 weeks and confirmed by an independent neurologic evaluation committee (INEC). Additional MRI endpoints included the number of new T1 hypointense lesions, and the mean-percentage change from baseline in Gd+, T2 hyperintense and T1 hypointense lesion volumes.

12. As shown below, the results at 2 years of the Phase 3 clinical trial demonstrated that both the 480 mg/day dose and the 720 mg/day dose regimens versus placebo met all primary and secondary endpoints with a high level of statistical significance and that both doses demonstrate efficacy in the DEFINE trial.

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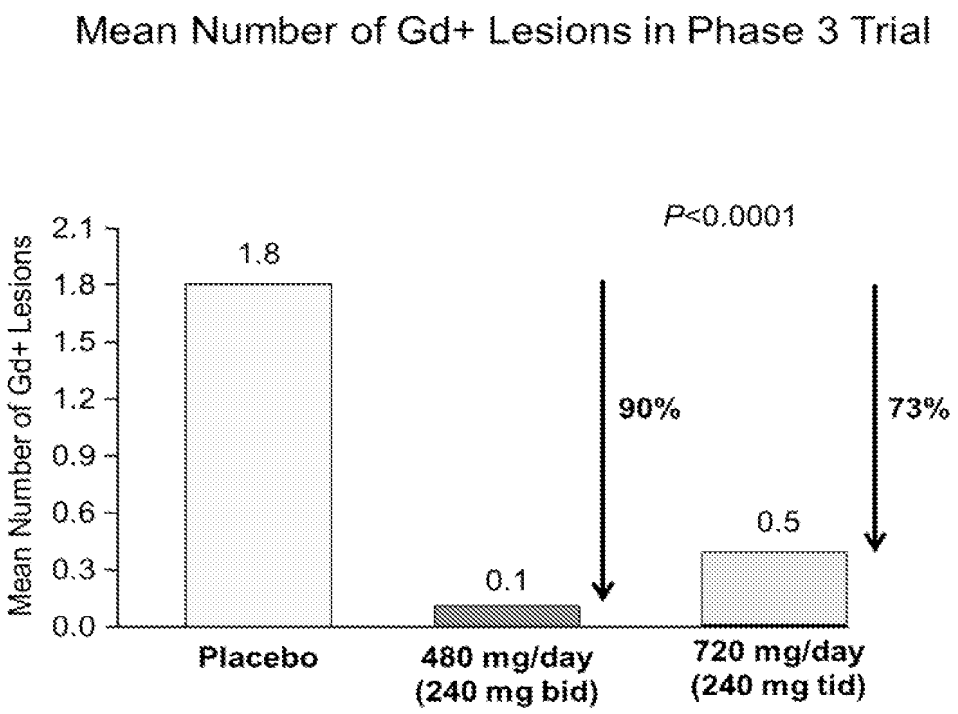
clinical trial, CONFIRM, are expected to be released by the end of 2011.

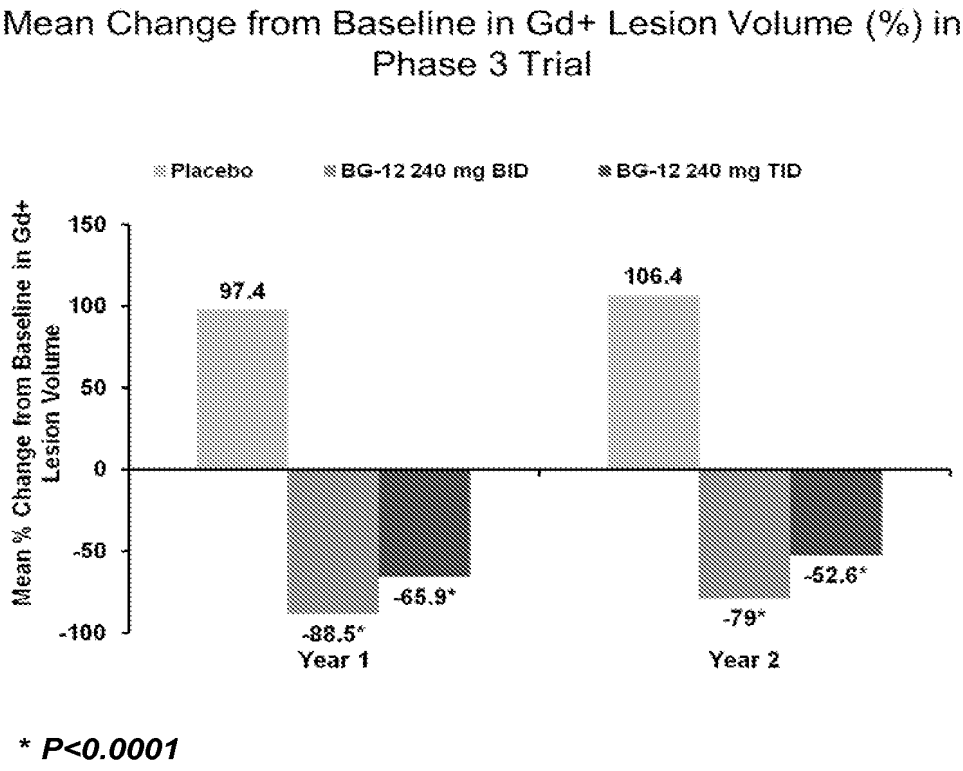
a. Compared to placebo (n=165), patients administered 480 mg/day (n=152) or 720 mg/day DMF (n=152) exhibited a 90% or 73% ($p<0.0001$ for both), respectively, decrease in the number of new Gd+ lesions at 2 years as shown in Figure 4 below.

Figure 4:



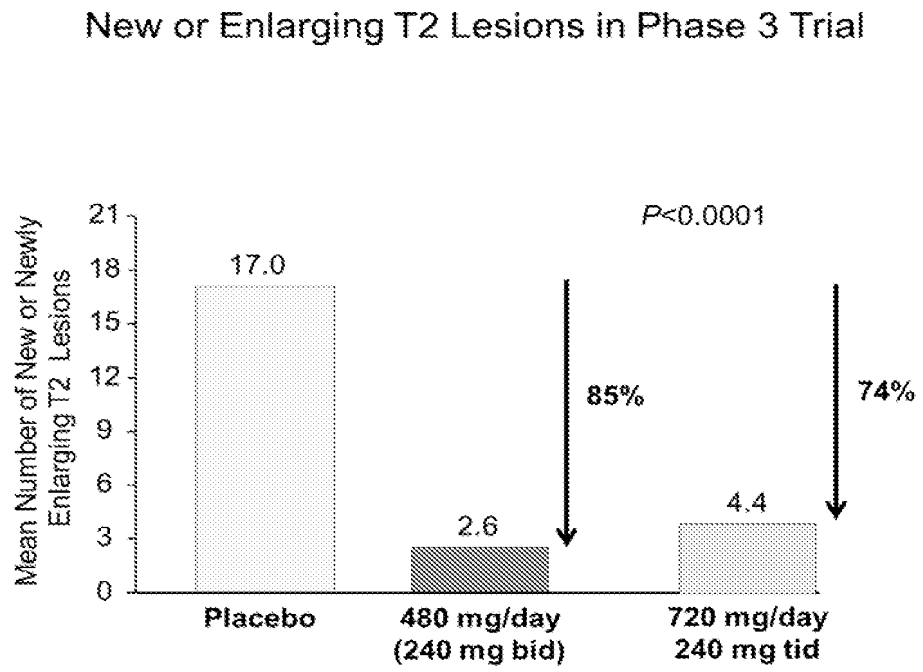
b. Patients administered 480 mg/day (240 mg BID) DMF or 720 mg/day (240 TID) DMF also exhibited a decrease in Gd+ lesion volume as shown in Figure 5 below (n=69 for placebo, n=49 for BG-12 480 mg/day, and n=52 for BG-12 720 mg/day).

Figure 5:



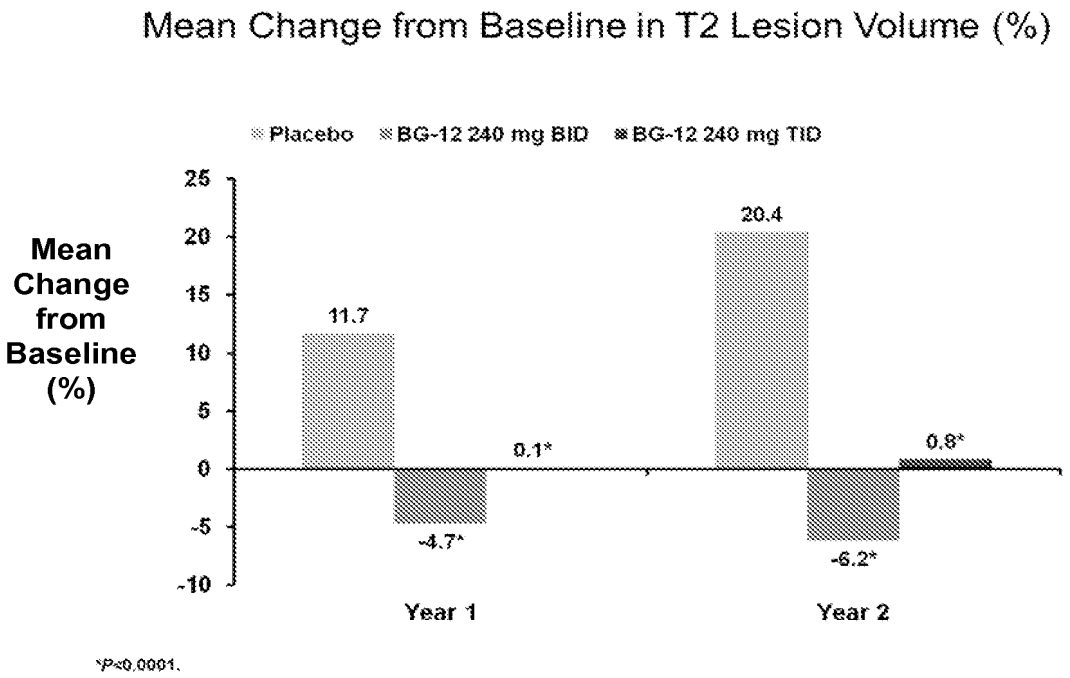
c. Furthermore, patients administered 480 mg/day DMF or 720 mg/day DMF exhibited an 85% or 74%, ($p<0.0001$ for both) respectively, decrease in the mean number of new and enlarging T2-hyperintense lesions developed over 2 years as shown in Figure 6 below (n=165 for placebo, n=152 for BG-12 480 mg/day, and n=152 for BG-12 720 mg/day).

Figure 6:



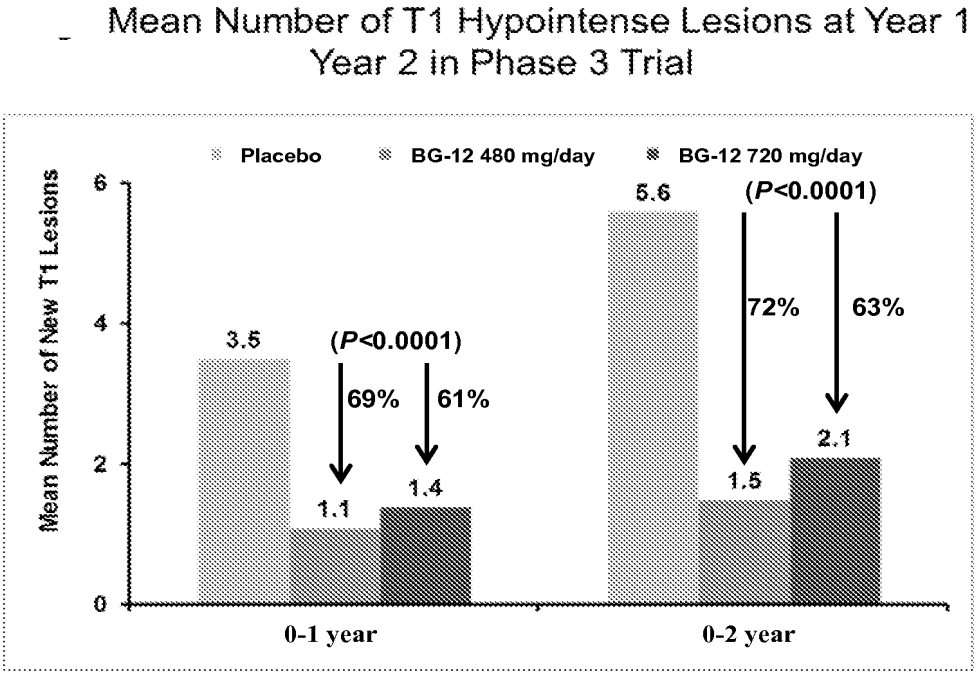
d. Also, patients administered 480 mg/day DMF or 720 mg/day DMF exhibited a decrease in T2 lesion volume as shown in Figure 7 below (n=164 for placebo, n=152 for BG-12 480 mg/day, and n=152 for BG-12 720 mg/day).

Figure 7:



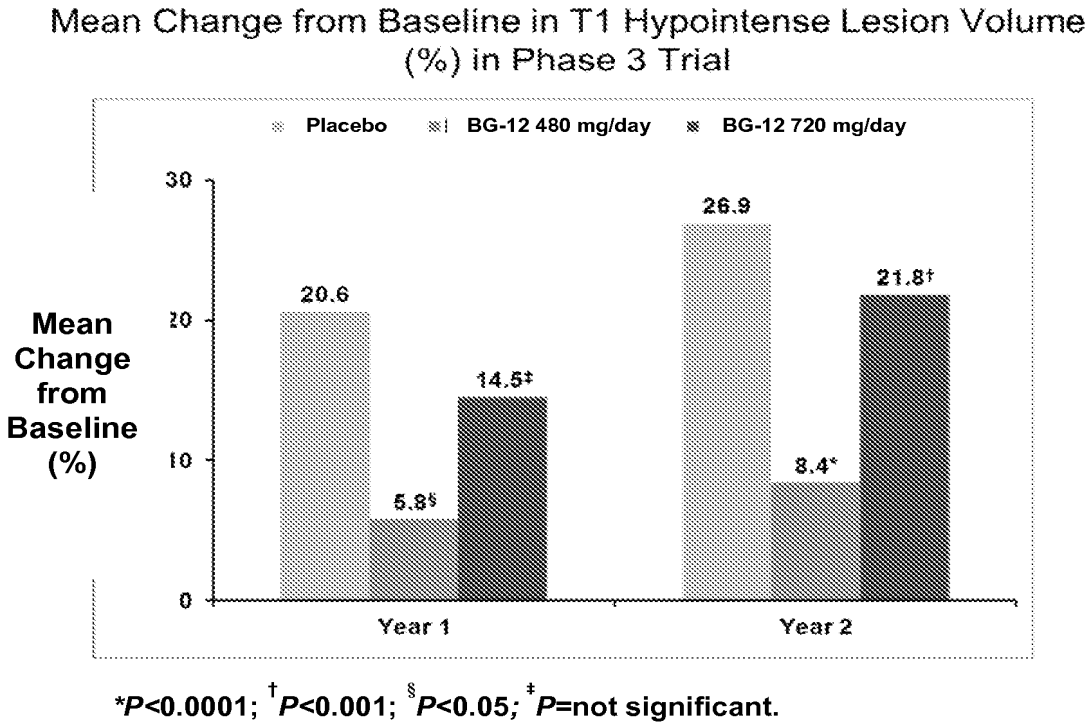
e. Patients administered 480 mg/day DMF and 720 mg/day DMF exhibited a decrease in the mean number of new T1 hypointense lesions as shown in Figure 8 below (n=165 for placebo, n=151 for BG-12 480 mg/day, and n=152 for BG-12 720 mg/day).

Figure 8:



f. Patients administered 480 mg/day DMF or 720 mg/day DMF also exhibited a decrease in T1 hypointense lesion volume as shown in Figure 9 below (n=160 for placebo, n=150 for BG-12 480 mg/day, and n=150 for BG-12 720 mg/day).

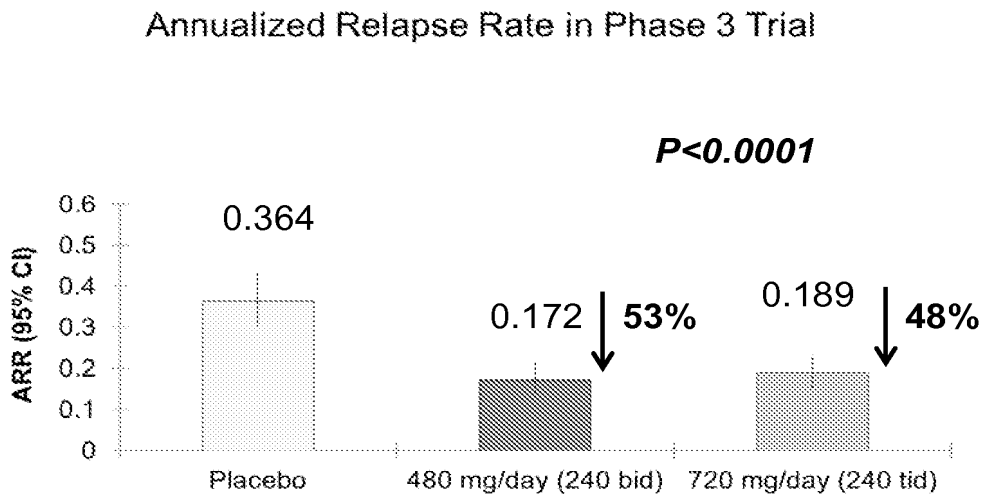
Figure 9:



*P<0.0001; †P<0.001; §P<0.05; ‡P=not significant.

g. Patients administered 480 mg/day DMF (n=410) or 720 mg/day DMF (n=416) also exhibited a statistically significant decrease (P<0.0001 for both) in the annualized relapse rate at 2 years compared to placebo (n=408) as shown in Figure 10 below.

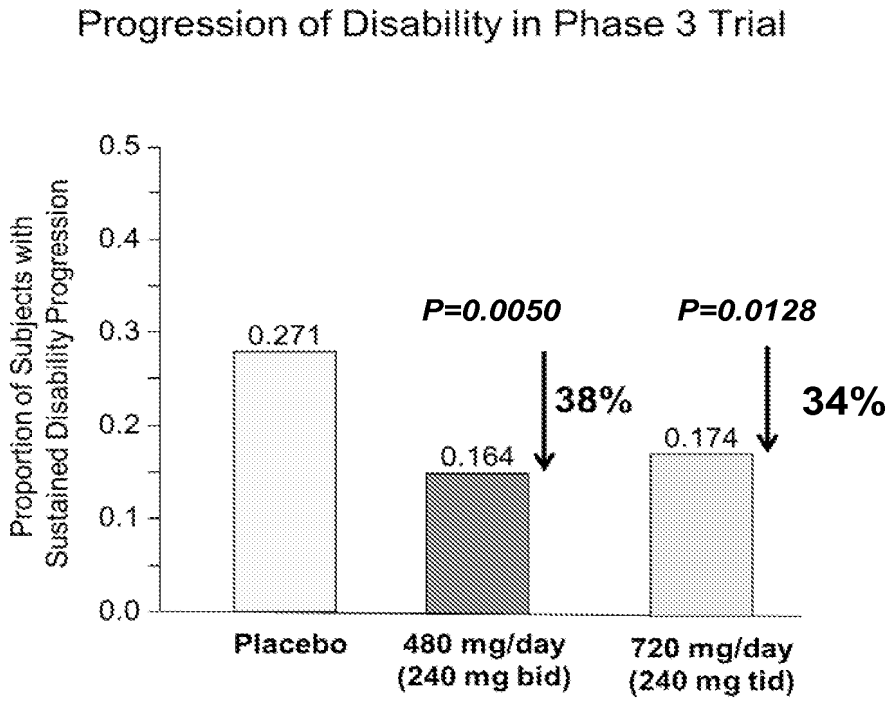
Figure 10:



h. BG-12 480 mg/day (n=410) and 720 mg/day (n=416) reduced the risk of relapse at 2 years by 49% and 50%, respectively, (P<0.0001 for both) compared to placebo (n=408).

i. Finally, patients administered 480 mg/day DMF and 720 mg/day DMF exhibited a statistically significant (P=0.0050 and P=0.0128, respectively) decrease in the progression of confirmed disability sustained at 12 weeks as compared with patients administered placebo as shown in Figure 11 below.

Figure 11:



C. Summary

13. As discussed above, the Phase 2 clinical trial results demonstrated that 720 mg/day DMF was efficacious in treating MS while 120 mg/day and 360 mg/day DMF dosing regimens were statistically indistinct from placebo. Additionally, the Phase 3 DEFINE study results demonstrated that 480 mg/day of DMF was efficacious in treating MS.

14. The positive and clinically meaningful results obtained with the 480 mg per day dose of DMF were unexpected to me given (1) that the Phase 2 clinical trial indicated that both the 120 mg/day and 360 mg/day doses of BG-12 were not efficacious and (2) that there was no apparent linear dose response.

15. Even more unexpected, in my opinion, was the magnitude of the treatment effect of the DEFINE study – the 480 mg/day dose demonstrated similar efficacy to the 720 mg/day dose on both clinical and MRI measures of MS disease activity – with a *high level of statistical significance*. Table 2 below compares key endpoints for the 480 mg/day dose and the 720 mg/day dose in the DEFINE study.

Table 2: DEFINE study results

	96 weeks treatment with 480 mg/day	**96 weeks treatment with 720 mg/day**
Reduction in number of Gd+ lesions	90%[1]	73%[1]
Reduction of mean number of new/newly enlarging T2 lesions	85%[1]	74%[1]
Reduction of mean number of New T1 hypointense lesions	73%[1]	63%[1]
ARR Reduction	53%[1]	48%[1]
Disability progression	38%[3]	34%[4]
Proportion of subjects relapsed	49%[1]	50%[1]

[1] $p<0.0001$ vs. placebo; [2] $p<0.001$ vs. placebo; [3] $p=0.0050$ vs. placebo; [4] $p=0.0128$ vs. placebo

16. In view of the foregoing and based on my personal knowledge and experience, as well as comments from others in the MS field that I have received since the top-line results from the DEFINE study were released, I conclude that a person of ordinary skill in the art would not have a reasonable expectation that the 480 mg/day dose would provide statistically significant and clinically meaningful effectiveness for treating MS. I further conclude that a person of ordinary skill in the art would have been very surprised that the treatment effect of the 480 mg/day dose was similar to the 720 mg/day dose.

17. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the present patent application or any patent issued thereon.

Respectfully submitted,

Katherine T. Dawson

Date: Oct 13, 2011

1431835_1.DOC

Appendix A

Exhibit A	Curriculum Vitae for Katherine T. Dawson
Exhibit B	Kappos, L., *et al.*, "Efficacy and safety of oral fumarate in patients with relapsing-remitting multiple sclerosis: a multicenter, randomised, double-blind, placebo-controlled phase IIIb study," *Lancet 372*: 1463-72 (2008)
Exhibit C	Kappos, L., *et al.*, "Efficacy of a novel oral single-agent fumarate, BG00012, in patients with relapsing-remitting multiple sclerosis: results of a phase 2 study," 16th Meeting of the European Neurological Society (May 30, 2006) (Slide Presentation)
Exhibit D	Kappos, L., *et al.*, "Efficacy of a novel oral single-agent Fumarate, BG00012, in patients with relapsing-remitting multiple sclerosis: results of a phase II study," 16th Meeting of the European Neurological Society (May 30, 2006) (Abstract to the Presentation)
Exhibit E	"Oral Compound BG-12 Achieves Primary Endpoint in Phase II Study of Relapsing-Remitting MS with BG-12 Led to Statistically Significant Reductions in MRI Measures," Biogen Idec News Release (May 30, 2006)

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/372,426	02/13/2012	Matvey E. LUKASHEV	2159.3210002/JMC/MRG/U-S	5998

53644 7590 10/12/2012

STERNE, KESSLER, GOLDSTEIN & FOX, P.L.L.C.
1100 NEW YORK AVE., N.W.
WASHINGTON, DC 20005

EXAMINER	
ULM, JOHN D	
ART UNIT	PAPER NUMBER
1649	

MAIL DATE	DELIVERY MODE
10/12/2012	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	13/372,426	LUKASHEV ET AL.	
	Examiner	Art Unit	
	JOHN ULM	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 August 2012*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *18-37* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *18-37* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

12)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/3/12*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

DETAILED ACTION

1) Claims 18 to 37 are pending in the instant application. Claim 37 has been added as requested by Applicant in the amendment filed 03 August of 2012.

2) Any objection or rejection of record that is not expressly repeated in this action has been overcome by Applicant's response and withdrawn.

3) The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 103

4) Claims 18 to 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over the Joshi et al. patent publication (US 2003/0018072 A1) for those reasons of record as applied to claims 1 to 36 in section 4 of the office action mailed 03 May of 2012. As stated therein, these claims are drawn to a method of treating multiple sclerosis (MS) in an individual suffering therefrom by the daily oral administration thereto of dimethyl fumarate or diethyl fumarate at a rate of 480 mg per day, which is *prima facie* obvious in view of the Joshi et al. patent publication because Joshi et al. fairly taught the treatment of MS by the administration to an individual suffering therefrom an effective amount of dimethyl fumarate, methyl ethyl fumarate and diethyl fumarate. Whereas Joshi et al. does not anticipate the instant claims because it did not disclose the specific treatment protocol recited therein, one of ordinary skill in the art would have found it *prima facie* obvious to have engaged in that routine experimentation needed to determine the optimal effective protocol for such treatment.

Applicant has extensively traversed this rejection essentially on the premise that the claimed method produces particularly advantageous and unexpected results as applied to individuals suffering from multiple sclerosis (MS). The unexpected and advantageous results demonstrated for the claimed method relative to the other embodiments that are disclosed in the instant specification are not in dispute. However, neither those unexpected and allegedly advantageous results ***nor the particular combination now claimed*** are described in the specification as filed. In fact, the demonstration that the now claimed combination is operable in not unexpected. It is Applicant's discovery, subsequent to the filing of the instant application, that the majority of embodiments described in the specification are inoperative that is unexpected. The fact that dimethyl fumarate, methyl ethyl fumarate and diethyl fumarate can be successfully employed to treat MS was not unexpected as of the filing date of the instant application. The only aspect of the claimed invention that is absent from the prior art is daily dosage, and the instant specification, as filed, disclosed no particular advantage to the dosage of fumarate derivative recited in the instant claims.

The instant specification teaches the treatment of a plurality of neurological diseases including those listed in paragraphs [0104] to [0106] therein, which states that "neurological diseases suitable for the methods described herein include neurodegenerative diseases such as amyotrophic lateral sclerosis (ALS), Parkinson's disease, Alzheimer's disease, and Huntington's disease", "MS", "acute haemorrhagic leucoencephalomyelitis, Hurst's disease, acute disseminated encephalomyelitis, optic neuritis, Devic's disease, spinal cord lesions, acute necrotizing myelitis, transverse

myelitis, chronic progressive myelopathy, progressive multifocal leukoencephalopathy (PML), radiation myelopathy, HTLV-1 associated myelopathy, monophasic isolated demyelination, central pontine myelinolysis, and leucodystrophy (e.g., adrenoleucodystrophy, metachromatic leucodystrophy, Krabbe's disease, Canavan's disease, Alexander's disease, Pelizaeus-Merbacher disease, vanishing white matter disease, oculodentodigital syndrome, Zellweger's syndrome), chronic inflammatory demyelinating polyneuropathy (CIDP), acute inflammatory demyelinating polyneuropathy (AIDP), Leber's optic atrophy," "Charcot-Marie-Tooth disease", "polyneuritis and mitochondrial disorders with demyelination". Nowhere does the instant specification, as filed, disclose a particular advantage to applying the method described therein to MS.

In addition, with respect to dimethyl fumarate (DMF) or monomethyl fumarate (MMF), the text in paragraph [0116] of the specification taught that "an effective amount can range from 1 mg/kg to 50 mg/kg (e.g., from 2.5 mg/kg to 20 mg/kg or from 2.5 mg/kg to 15 mg/kg)" and that "an effective dose of DMF or MMF to be administered to a subject orally can be from about 0.1 g to 1 g per day, 200 mg to about 800 mg per day (e.g., from about 240 mg to about 720 mg per day; or from about 480 mg to about 720 mg per day; or about 720 mg per day)". Again, the specification, as filed, fails to demonstrate, or even predict, any particular advantage to be realized from the administration of a dosage of 480 mg per day of DMF or methyl ethyl fumarate (MEF) to an individual suffering from MS. Applicant's subsequent discovery that the vast majority of dosages described in the specification are inoperative is the only unexpected result

that is supported by the evidence of record, and those embodiments are not the subject of the instant claims.

Applicant's assertion on page 9 of the response filed 03 August of 2012 that "the results of the Phase 2 clinical study would have led one of ordinary skill in the art to use a different, higher dose (i.e., 720 mg/day) rather than the dose required by the claimed invention (i.e., 480 mg/day)" is not consistent with the express teachings of the instant specification as cited above. If one of ordinary skill was aware of these results then Applicant was certainly aware of them, and yet, as discussed above, the specification expressly teaches the daily administration of DMF or MMF "from about 0.1 g to 1 g per day, 200 mg to about 800 mg per day (e.g., from about 240 mg to about 720 mg per day; or from about 480 mg to about 720 mg per day; or about 720 mg per day". In addition, the instant specification, as filed, fails to suggest any specific daily dosage of DMF or MMF that had been shown or could reasonably be predicted to be effective in the treatment of MS, in particular. The only dosages described in the specification were identified therein as being applicable to the treatment of the whole variety of neurological diseases recited in paragraphs [0104] to [0106].

It is a matter of law that a claimed invention must be patentable as of the effective filing date of the application containing that claim. Applicant may not rely upon subsequent discoveries made by themselves or others to complete the claimed invention. In the decision *In re Lundberg*, 117 USPQ 190, 1958, the CCPA held that "advantages which are not disclosed in application cannot be urged as basis for allowing claims". This rejection is not in conflict with the decision in *in re Chu*, 66 F.3d

292, 298-99, 36 USPQ2d 1089, 1094-95 (Fed. Cir. 1995). The claimed subject matter at issue in *in re Chu* (US Patent 5,567,394, Chu et al.) was distinguished from the most closely related prior art by the placement of a catalyst at a particular position in an apparatus for controlling emissions of a fossil fuel fired boiler. Evidence provided by Applicant demonstrated addition undisclosed advantages that inherently result from that placement. Whereas the Chu et al. application did not disclose certain unexpected results obtained thereby, it clearly disclosed the criticality of placing the catalyst at the particular position recited in the claims and the subsequently demonstrated advantages were inherent to that element. In the present case, the instant specification does not disclose the criticality of the limitations of the now claimed treatment protocol nor does it identify the claimed combination as being particularly advantageous, which distinguishes the current fact pattern from that which was addressed by the court in *in re Chu*. Applicant's discovery that the majority of embodiments disclosed in the specification are inoperative hardly supports the patentability of those few embodiments that have been subsequently discovered by Applicant to be operable.

5) Claims 18 to 37 are are rejected under 35 U.S.C. 103(a) as being unpatentable over the Schimrigh et al. publication (Euro. J. Neurol. 13(6):604-610, Jun. 2006) for those reasons of record as applied to claims 1 to 36 in section 5 of the office action mailed 03 May of 2012. As indicated above, these claims are drawn to a method of treating multiple sclerosis in an individual suffering therefrom by the daily oral administration thereto of dimethyl fumarate or diethyl fumarate at a rate of 480 mg per day.

The Schimrigh et al. publication has been relied upon because it described the successful clinical treatment of human subjects suffering from multiple sclerosis by the administration of fumaric acid esters, which include dimethyl fumarate, methyl ethyl fumarate and diethyl fumarate, to those subjects. The Schimrigh et al. publication does not anticipate the instant claims because it did not disclose the specific treatment protocol recited therein. However, as indicated above, one of ordinary skill in the art would have found it *prima facie* obvious to have engaged in that routine experimentation needed to determine the optimal effective protocol for such treatment. Merely determining the optimal conditions for practicing a prior art process, in the absence of unexpected results, does not constitute a patentable inventive contribution. The discovery that not all of the possible treatment protocols encompassed by the prior art are operable is not unexpected. One of ordinary skill would not reasonably expect the administration of dimethyl fumarate, methyl ethyl fumarate or diethyl fumarate to an individual suffering from MS at any and all dosage regimens to be operable. However, identifying an optimal treatment protocol, including the identification of inoperable regimens, requires nothing more than the routine practice of the art.

Applicant has traversed this rejection essentially on the premise that Schimrigh et al. taught the administration of 1290 mg of fumarates a day. No effort has been made to review Applicant's mathematical analysis of Schimrigh et al. since, with respect to the fumaric acid esters employed therein, the abstract of that publication expressly stated that "[t]he study consisted of the following four phases: 6-week baseline, 18-week treatment (**target dose of 720 mg/day**), 4-week washout, and a second 48-week

treatment phase (**target dose of 360 mg/day**)" (emphasis added). The Schimrigh et al. abstract further expressly identified the treatment protocol described therein as an "exploratory, prospective, open-label study". As indicated by the text in the paragraph entitled "Study Drug" on page 605 of that reference, the predominant active ingredient in Fumaderm is the same dimethylfumarate recited in the instant claims. Therefore, Applicant's position that the Schimrigh et al. taught away from a dosage of 480 mg/day of fumarate derivatives is not supported by the facts of record.

Response to Arguments

6) Applicant's arguments filed 03 August of 2012, as well as the declarations by Richard A. Rudick and Katherine Dawson under 37 CFR 1.132 that were filed 03 August of 2012, have been fully considered but they are not persuasive essentially for those reasons given above.

Conclusion

7) **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JOHN ULM whose telephone number is (571)272-0880. The examiner can normally be reached on 9:00AM to 5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker can be reached on (571) 272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/John D. Ulm/
Primary Examiner, Art Unit 1649

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OK TO ENTER: /J.U./

Reply Under 37 C.F.R. § 1.116
Prioritized Examination (Track 1) – Art Unit 1649

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Confirmation No.: 5998
LUKASHEV *et al.*	Art Unit: 1649
Appl. No.: 13/372,426	Examiner: ULM, John D.
Filed: February 13, 2012	Atty. Docket: 2159.3210002/JMC/MRG/U-S
For: **Treatment for Multiple Sclerosis**	

Reply to Final Office Action Under 37 C.F.R. § 1.116

Mail Stop AF

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

Commissioner:

In reply to the Final Office Action dated October 12, 2012 ("the Final Office Action"), Applicants submit the following Remarks.

The Claims are listed beginning on page 2 of this paper.

Remarks and Arguments begin on page 6 of this paper.

It is not believed that extensions of time or fees for net addition of claims are required beyond those that may otherwise be provided for in documents accompanying this paper. However, if additional extensions of time are necessary to prevent abandonment of this application, then such extensions of time are hereby petitioned under 37 C.F.R. § 1.136(a), and any fees required therefor (including fees for net addition of claims) are hereby authorized to be charged to our Deposit Account No. 19-0036.

Reply Under 37 C.F.R. § 1.116
Prioritized Examination (Track 1) – Art Unit 1649

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Confirmation No.: 5998
LUKASHEV *et al.*	Art Unit: 1649
Appl. No.: 13/372,426	Examiner: ULM, John D.
Filed: February 13, 2012	Atty. Docket: 2159.3210002/JMC/MRG/U-S
For: **Treatment for Multiple Sclerosis**	

Reply to Final Office Action Under 37 C.F.R. § 1.116

Mail Stop AF

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

Commissioner:

In reply to the Final Office Action dated October 12, 2012 ("the Final Office Action"), Applicants submit the following Remarks.

The Claims are listed beginning on page 2 of this paper.

Remarks and Arguments begin on page 6 of this paper.

It is not believed that extensions of time or fees for net addition of claims are required beyond those that may otherwise be provided for in documents accompanying this paper. However, if additional extensions of time are necessary to prevent abandonment of this application, then such extensions of time are hereby petitioned under 37 C.F.R. § 1.136(a), and any fees required therefor (including fees for net addition of claims) are hereby authorized to be charged to our Deposit Account No. 19-0036.

Listing of the Claims

The claims are listed below for the Examiner's convenience.

1-17. (Cancelled)

18. (Previously Presented) A method of treating a subject in need of treatment for multiple sclerosis comprising orally administering to the subject in need thereof a pharmaceutical composition consisting essentially of (a) a therapeutically effective amount of dimethyl fumarate, monomethyl fumarate, or a combination thereof, and (b) one or more pharmaceutically acceptable excipients, wherein the therapeutically effective amount of dimethyl fumarate, monomethyl fumarate, or a combination thereof is about 480 mg per day.

19. (Previously Presented) The method of claim 18, wherein the pharmaceutical composition is administered in the form of a tablet, a suspension, or a capsule.

20. (Previously Presented) The method of claim 18, wherein the therapeutically effective amount is administered in separate administrations of 2, 3, 4, or 6 equal doses.

21. (Previously Presented) The method of claim 20, wherein the therapeutically effective amount is administered in separate administrations of 2 equal doses.

22. (Previously Presented) The method of claim 20, wherein the therapeutically effective amount is administered in separate administrations of 3 equal doses.

23. (Previously Presented) The method of claim 18, wherein the pharmaceutical composition consists essentially of dimethyl fumarate and one or more pharmaceutically acceptable excipients.

24. (Previously Presented) The method of claim 18, wherein the pharmaceutical composition consists essentially of monomethyl fumarate and one or more pharmaceutically acceptable excipients.

25. (Previously Presented) The method of claim 18, wherein the pharmaceutical composition is administered to the subject for at least 12 weeks.

26. (Previously Presented) The method of claim 23, wherein the therapeutically effective amount is administered to the subject in 2 equal doses.

27. (Previously Presented) The method of claim 26, wherein the therapeutically effective amount is administered to the subject for at least 12 weeks.

28. (Previously Presented) A method of treating a subject in need of treatment for multiple sclerosis consisting essentially of orally administering to the subject about 480 mg per day of dimethyl fumarate, monomethyl fumarate, or a combination thereof.

29. (Previously Presented) The method of claim 28, wherein about 480 mg of dimethyl fumarate per day is administered to the subject.

30. (Previously Presented) The method of claim 29, wherein the dimethyl fumarate is administered in separate administrations of 2 equal doses.

31. (Previously Presented) The method of claim 29, wherein the dimethyl fumarate is administered in separate administrations of 3 equal doses.

32. (Previously Presented) A method of treating a subject in need of treatment for multiple sclerosis comprising orally administering to the subject a pharmaceutical composition consisting essentially of (a) a therapeutically effective amount of dimethyl fumarate and (b) one or more pharmaceutically acceptable excipients, wherein the therapeutically effective amount of dimethyl fumarate is about 480 mg per day.

33. (Previously Presented) The method of claim 32, wherein the dimethyl fumarate is administered in separate administrations of 2 equal doses.

34. (Previously Presented) The method of claim 18, wherein the expression level of NQO1 in the subject is elevated after administering to the subject the therapeutically effective amount of dimethyl fumarate, monomethyl fumarate, or a combination thereof.

35. (Previously Presented) The method of claim 28, wherein the expression level of NQO1 in the subject is elevated after administering to the subject about 480 mg per day of dimethyl fumarate, monomethyl fumarate, or a combination thereof.

36. (Previously Presented) The method of claim 32, wherein the expression level of NQO1 in the subject is elevated after administering to the subject the therapeutically effective amount of dimethyl fumarate.

37. (Previously Presented) A method of treating a subject in need of treatment for multiple sclerosis comprising 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.

Remarks

Claims 18-37 are pending in the application, with claims 18, 28, 32, and 37 being the independent claims. Based on the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

I. Summary of the Claimed Subject Matter

The claimed invention is directed to methods of treating multiple sclerosis ("MS") which involve the administration of, or treatment of a subject with, a specific daily dose of about 480 mg/day of dimethyl fumarate ("DMF") and/or monomethyl fumarate ("MMF") (a biologically active metabolite of DMF).

As demonstrated in two phase 3 MS clinical studies, the claimed methods produced unexpectedly high efficacy, i.e., 480 mg/day DMF showed very similar efficacy in treating MS as 720 mg/day of DMF. The magnitude of the efficacy demonstrated for the 480 mg/day dose was especially unexpected and quite surprising given the results of an earlier Phase 2 clinical study in which 720 mg/day of DMF showed statistically significant efficacy when compared to placebo while 120 mg/day and 360 mg/day of DMF did not exhibit statistically significant efficacy versus placebo. See Applicants' prior responses in connection with U.S. Patent Application No. 12/526,296, and the response to the first Office Action filed August 3, 2012 in the instant application (collectively "the prior responses").

II. A *Prima Facie* Case of Obviousness Has Not Been Established

The Examiner maintains his obviousness rejections of claims 18-37 over U.S. Patent Publication No. US 2003/0018072 to Joshi *et al.* ("Joshi") and over Schimrigk *et al.*, *European Journal of Neurology*13:604-610 (2006) ("Schimrigk"). Applicants respectfully traverse both rejections on the grounds that a *prima facie* case of obviousness has not been adequately established. See Applicants' prior responses (see, in particular, response dated August 3, 2012, page 7, line 10 to page 12, line 7).

As appreciated by the Examiner, neither Joshi nor Schimrigk teaches or suggests using a 480 mg/day dose to treat MS. It is the Examiner's position that a skilled person in the art, based on either Joshi or Schimrigk, would have engaged in routine experimentation to arrive at the 480 mg/day dose as claimed, thus rendering it *prima facie* obviousness. It is well established that obviousness cannot be based on selectively picking and choosing from diverse teachings of references, but must be based on the teachings of the prior art as a whole. *See In re Dow Chemical Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988) ("In determining whether such a suggestion can fairly be gleaned from the prior art, the full field of the invention must be considered; for the person of ordinary skill is charged with knowledge of the entire body of technological literature, including that which might lead away from the claimed invention.") However, considering the total knowledge available to the skilled person as of the filing date of the present application, the results of the Phase 2 clinical study would not have motivated the skilled person to use the 480 mg/day dose since the 720 mg/day was the dose a skilled person would have expected to be most effective. In light of the lack of prior art

teachings directing a skilled person to the claimed dosage (and indeed directing to a higher dosage), a *prima facie* case of obviousness has not been established.

In addition, Applicants would like to address the Examiner's understanding of Schimrigk. In the Final Office Action (the paragraph bridging pages 7 and 8), the Examiner justifies disregarding Applicants' remarks concerning Schimrigk's teaching of using 1290 mg/day of fumaric acid esters (FAE) because the abstract recites a "target dose of 720 mg/day" in connection with the main treatment phase and a "target dose of 360 mg/day" in connection with the second treatment phase. The abstract does not reveal to what the term "target dose" refers. The Examiner seems to be under the impression that the term "target dose" refers to the total daily amount of FAEs administered to the MS patients. However, this conclusion is incorrect.

In the Schimrigk study, scientists used Fumaderm®, a medication that contains DMF as well as three different monoethyl fumarate ("MEF") salts, also referred to as ethylhydrogen fumarates in the study. This is clearly stated in the paragraph under "Study Drug" on page 605 with Fumaderm forte® containing 120 mg of DMF and 95 mg of MEF. Schimrigk further states that patients were administered up to 6 tablets of Fumaderm forte® in the main treatment phase and up to 3 tablets of Fumaderm forte® in the second treatment phase. See page 605, left column, last sentence of the last full paragraph. Simple additions of the FAE amounts in 6 tablets of Fumaderm forte® lead to 720 mg/day of DMF and 570 mg/day of MEF - a total of 1290 mg/day of FAE. Schimrigk may have referred to the DMF dose in the abstract as "the target dose" as a short hand notation since there was more DMF (120 mg) than MEF (95 mg) in a

Fumaderm® tablet. But a skilled person in the art reading the entire Schimrigk reference would have realized that the reference taught administration of 1290 mg/day FAE. Indeed, a skilled person in the art would have been aware that Fumaderm® contains four active ingredients, i.e., DMF + 3 MEF salts. *See, e.g.* "Summary of Product Characteristics" for Fumaderm® (also referred to herein as Fumaderm forte®, "Fumaderm") and Fumaderm® Initial, which is submitted herewith as Exhibit A. The Examiner clearly acknowledges that Schimrigk teaches the use of a mixture of fumaric acid esters. See, e.g., Final Office Action, page 7, lines 1-4.[1] Importantly, Schimrigk does not teach that the MEF salts were inert in this study. The Examiner's conclusion that the predominant active ingredient in Fumaderm is DMF appears to be unsupported based on the teaching of Schimrigk alone.[2] See Final Office Action, page 8, lines 3-5. No evidence was presented as to why a skilled person in the art would have ignored the presence of MEF in the Fumaderm tablets and used only DMF.

In summary, the Examiner has provided no rationale as to why a person of ordinary skill in the art, based on Schimrigk in its entirety, would have made the changes necessary to arrive at the instant invention, i.e., (1) DMF+MEF to DMF only and (2) 1290 mg/day fumarates to 480 mg/day of DMF or MMF.

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[1]Applicants would like to point out that Fumaderm (as used in the study described in Schimrigk) contains DMF and 3 different MEF (monoethylfumarate) salts, and not "methyl ethyl fumarate and diethyl fumarate" as stated in the Final Office Action, page 7, lines 3-4.

[2]The two most abundant active ingredients in Fumaderm are DMF and MEF, Ca salt. The ratio of the amount of DMF vs. MEF, Ca salt is 58% (120 mg) vs. 40% (87 mg). Applicants disagree that DMF can be considered the predominant active ingredient in a Fumaderm tablet.

Contrary to the Examiner's position and for at least the reasons stated here, as well as those set forth in the prior responses, the claimed method is not *prima facie* obvious in view of either Joshi or Schimrigk.

III. Even if A *Prima Facie* Case Of Obviousness Had Been Established, Applicants' Evidence of Unexpected Results Would Overcome it

The Examiner acknowledges "[t]he unexpected and advantageous results demonstrated for the claimed method relative to the other embodiments that are disclosed in the instant specification are not in dispute." See Final Office Action, page 3, lines 3-5. However, the Examiner continues to maintain that because "neither those unexpected and allegedly advantageous results ***nor the particular combination now claimed*** are described in the specification as filed" (see Final Office Action, page 3, lines 5-7; emphasis original), the unexpected results cannot be used to overcome the obviousness rejection. Thus, it appears that the following two issues must be addressed in determining whether the unexpected results must be considered for overcoming the *prima facie* obviousness rejections (assuming they have been established, which Applicants disagree): (1) does the specification describe or reasonably convey the claimed invention to a skilled person in the art? and (2) do the unexpected results have to be described in the specification as filed for them to be considered?

A. The Claimed Invention Is Described In The Specification As Filed – The Specification Directs a Person Of Ordinary Skill To The Claimed Invention

As summarized below, the specification contains ample teachings directing a person of ordinary skill in the art to the claimed invention (treating MS with DMF/MMF using a 480 mg/day dose). It is well settled that when considering whether a claimed

invention is described in the specification, the totality of the teaching of the application must be considered (*see, e.g., In re Dow Chemical Co., supra*).

1. The Specification Focuses On Treating MS with DMF and/or MMF

The Examiner indicates that MS is disclosed in the description only in the context of a long list of neurological diseases and that the description does not disclose "a particular advantage to applying the method described therein to MS." See Final Office Action, the paragraph bridging pages 3-4. Contrary to the Examiner's assertion, MS is singled out throughout the specification and is clearly not just one of many diseases in a long laundry list of diseases.

In fact, paragraphs [0001] to [0004] of the background section are explicitly directed to MS, as well as treatments of MS available as of the filing date. Additionally, the abstract lists MS as the sole exemplary disease to be treated. The application also specifically discloses that the neurological disease can be MS. *See, e.g.*, page 4, paragraph [0010] and page 25, paragraph [0104]. Furthermore, paragraph [0032] explains DMF's neuroprotective nature and activation of Nrf2 pathway help form the rationale for its effective treatment of neurological disorders such as MS. Additionally, the one animal disease model disclosed in the specification to test the effect of DMF and MMF is a generally accepted mouse model of MS, known as Experimental Autoimmune Encephalomyelitis (EAE). See, e.g., pages 26-27, paragraphs [108]-[0110] and Example 3.

There is well-established case law holding that guidance or so-called "blaze marks" contained in the originally filed disclosure, which direct the skilled artisan to the

claimed invention, are sufficient to describe the claimed invention and to reasonably convey to a person of skill in the art that Applicants had possession of the invention. *See, e.g., In re Ruschig*, 379 F.2d 990, 154 U.S.P.Q. 118 (C.C.P.A. 1967) and *Purdue Pharma L.P. v. Faulding Inc.*, 230 F.3d 1320, 56 U.S.P.Q. 2d 1481 (Fed. Cir. 2000). The Court in *Purdue* notes that "[t]he blaze marks directing the skilled artisan to [the claimed invention] must be in the originally filed disclosure." *Purdue*, 230 F.3d at 1326-1327.

There are a number of blaze marks in the instant specification which clearly direct a person of ordinary skill in the art to use DMF and/or MMF in treating MS. For example, Applicants disclose (i) a method (method 4) comprising administering to a mammal a therapeutically effective amount of at least one neuroprotective compound, e.g., DMF or MMF (see, page 13, paragraph [0063]) and (ii) a specific embodiment of neurological disease being MS (see, page 4, paragraph [0010]).

Therefore, Applicants respectfully submit that, contrary to the Examiner's contention, treatment of MS with DMF and/or MMF is specifically singled out and described in the present application.

2. The Specification Teaches The Claimed Dose of 480 mg/day DMF and/or MMF

The Examiner asserts that "the specification, as filed, fails to demonstrate, or even predict, any particular advantage to be realized from the administration of a dosage of 480 mg/day of DMF . . . to an individual suffering from MS." See Final Office Action, page 4, lines 18-21. The Examiner further states that "the instant specification, as filed, fails to suggest any specific daily dosage of DMF or MMF that had been shown

or could reasonably be predicted to be effective in the treatment of MS in particular. *Id.* at page 5, lines 12-14. Applicants respectfully disagree with the Examiner and submit that the specific dose of 480 mg/day is clearly conveyed in the specification to a skilled person in the art.

The specification discloses a limited number of progressively narrowing effective dose ranges of DMF or MMF and discloses the 480 to 720 mg/day dosage range as the narrowest range for the treatment of a patient with a neurodegenerative disease (see page 30, paragraph [0116]). As set forth above, MS is a neurodegenerative disease that is specifically singled out in the specification. Therefore, for at least these reasons and those discussed above, it is clear that the specification describes and directs a skilled person in the art to the claimed combination (i.e., using 480 mg/day DMF and/or MMF to treat MS). See, e.g., *In re Wertheim*, 541 F.2d 257, 191 U.S.P.Q. 90 (C.C.P.A. 1976).

B. Unexpected Results or Advantages That Inherently Flow From A Claimed Invention Must Be Given Significant Weight

As mentioned above, even though the Examiner acknowledges the unexpected and advantageous results demonstrated for the claimed method, he nevertheless maintains the obviousness rejections on the basis that such unexpected results are not described in the specification as filed (see Final Office Action, page 3, lines 3-5). Contrary to the Examiner's position, the law is clear that unexpected results or advantages need not be disclosed in the specification as filed. So long as the advantages or unexpected results inherently flow from the claimed invention described in the

specification, substantial weight must be given to them in the obviousness determination.

In support of his position, the Examiner relied on two cases, *In re Lundberg*, 253 F.2d 244, 117 U.S.P.Q. 190 (C.C.P.A. 1958) and *In re Chu*, 66 F.3d 292, 36 U.S.P.Q.2d 1089 (Fed. Cir. 1995). However, neither case supports the Examiner's position that unexpected results or advantages of a claimed invention must be found in the specification to be considered.

In the *Lundberg* case, while it is true that the asserted advantages or unexpected results were not disclosed in the specification and they were not given weight, the reason they were not given weight was that they did not flow from the claimed invention as disclosed in the specification. Rather, they flowed from a feature of an invention that was not described in the specification. *In re Lundberg*, 253 F.2d at 247. In marked contrast, the unexpected results or advantages of the instant invention inherently flow from an invention that was disclosed in the specification as filed, i.e., 480 mg/day DMF to treat MS. As such, the unexpected results or advantages presented in the instant case must be considered. The *Lundberg* case is clearly distinguishable from the present case.

The Examiner's reliance on the *Chu* case is equally misplaced. In *Chu*, to overcome an obviousness rejection, the applicant presented advantages that had not been disclosed in the specification that were based on the location of the catalyst. The Board in *Chu*, like the Examiner in the present case, justified its rejection by stating Chu's "specification is virtually silent on the matter of any purported advantage to locating the catalyst within the bag retainer" and "does not state that the claimed location of the

catalyst 'inside the bag retainer' solves any particular problem or produces any unexpected result." While the location of the catalyst in *In re Chu* was disclosed, its "criticality" was not disclosed. Both the examiner and Board in that case found the location to be a "design choice." The Board concluded that the specification was "virtually silent on the matter of any purported advantage" of the location. *In re Chu*, 66 F.3d 292, 298 (Fed. Cir. 1995). The Federal Circuit, however, rejected the Board's holding that advantages must be contained within the specification in order for them to be considered.

In the instant case, the Examiner distinguishes the present case and justifies not giving weight to the unexpected results submitted by the Applicants post-filing by stating that "the instant specification does not disclose the criticality of the limitations...nor does it identify the claimed combination as being particularly advantageous..." (see Final Office Action, page 6, lines 9-13). First, nowhere in *Chu* did the Court state that criticality of a claimed feature must be contained in the specification. In fact, the Court in *Chu* simply stated that evidence and/or arguments to rebut an obviousness rejection do not need to be disclosed in the specification. *Id.* at 299. Further, the Court explicitly rejected the Board's requirement that the specification must disclose an advantage of the claimed feature to be considered. Thus, the Examiner's justification for requiring the specification to disclose criticality or to identify advantageous features of the claimed invention is unsupported. In fact, Applicants emphasize the guidance outlined in the MPEP 716.02(f): "[t]he specification need not disclose proportions or values as critical for applicants to present evidence

showing the proportions or values to be critical. *In re Saunders*, 444 F.2d 599, 607, 170 USPQ 213, 220 (CCPA 1971)" (emphasis added).

Based on the relevant section in the MPEP and the case law discussed above, it is clear that unexpected results or advantages or criticality of a claimed feature do not need to be disclosed in the specification to be considered. The Examiner must therefore give substantial weight to the unexpected results, which flow inherently from the claimed invention of using the 480 mg/day of DMF to treat MS.

IV. Addressing the Examiner's Remaining Reasons For Maintaining The Obviousness Rejection

In the Final Office Action, the Examiner states that in his view the true unexpectedness of the instant rejection resides in the inoperability of a majority of embodiments disclosed in the specification. See Final Office Action, page 3, lines 3-10. As discussed in the Applicants' response to the Office Action filed August 3, 2012, the Examiner's position is unsupported and no evidence or argument was presented in the Final Office Action to address Applicants' rebuttal. As pointed out in Applicants previous response, the unexpectedness of the instant invention is the magnitude of the effect of the 480 mg/day dose and not simply that the dose is efficacious as expressed by the Examiner (see Final Office Action, page 3, lines 7-8). Further, no reason was given as to why the operability of an unclaimed species would be relevant to the patentability of the claimed invention. In the instant case, the unexpected results flow inherently from the claimed invention, and that should be the focal point in determining whether the obviousness rejection has been overcome.

V. Summary

Based on the reasons set forth above and those presented in Applicants' prior responses, Applicants submit that the present claims are patentable over the art of record. Applicants respectfully request the Examiner reconsider the rejections in the Final Office Action.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

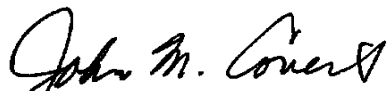

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EXHIBIT A

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	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

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 the start-up phase.

Fumaderm:
Indicated for the treatment of severe forms of plaque psoriasis (*Psoriasis vulgaris*), in cases where previous, externally applied, stand-alone treatments have failed. Prior to administration, patient tolerability must firstly be reinforced by treatment with Fumaderm Initial (q.v.).

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 escalation should be gradual. During the first week of treatment, 1 gastro-resistant Fumaderm Initial tablet should be taken once daily (evenings). During Week 2, this daily dose should be increased to 2 gastro-resistant Fumaderm Initial tablets (1 x mornings and 1 x evenings). During Week 3 (daily dose = 3 gastro-resistant

Fumaderm Initial tablets), as soon as the course of Fumaderm Initial tablets has finished, treatment should be immediately switched over to Fumaderm, viz. at an initial daily dose of 1 gastro-resistant Fumaderm tablet once daily (evenings).

Week	Dosage		
	Mornings	Lunchtimes	Evenings
1	-	-	1
2	1	-	1
3	1	1	1

Fumaderm:
Unless otherwise prescribed, dosage instructions are as follows:
Following pre-treatment with Fumaderm Initial to increase tolerability, treatment should be switched over to Fumaderm during the third week of treatment.
During the first week of treatment with Fumaderm, 1 gastro-resistant Fumaderm tablet should be taken once daily (evenings). Depending on individual tolerability, this daily dosage should be increased in weekly increments (i.e. by one gastro-resistant Fumaderm tablet per week), according to the following chart:

Week	Dosage		
	Mornings	Lunchtimes	Evenings
1	-	-	1
2	1	-	1
3	1	1	1
4	1	1	2
5	2	1	2
6	2	2	2

The maximum daily dosage of 3 x 2 gastro-resistant Fumaderm tablets must not be exceeded. However, in most cases, administration of this maximum daily dosage is not needed. Clinical experience has shown that the initial therapeutic effects are noticed within 4 – 6 weeks of treatment.
When skin reactions subside, daily dosage should be reduced gradually until the individual maintenance dose is reached. Fumaderm gastro-resistant tablets should be swallowed whole (not chewed) with plenty of liquid during or immediately after a meal. Patients should be advised to drink sufficient amounts of water during the day (1½ - 2 litres). Duration of treatment is left up to the discretion of the treating physician. Adequate experience gained during clinical trials would suggest a treatment period of four months. However, clinical experience exists of treatment periods of up to 36 months, recorded within the framework of post-marketing observational studies.

4.3 Contraindications
Fumaderm Initial and Fumaderm are contraindicated in the following cases:
- Known hypersensitivity to the active ingredients (dimethyl fumarate; ethyl hydrogen fumarate calcium/ magnesium and/or zinc salt) or any of the excipients used in Fumaderm Initial/ Fumaderm;
- Severe gastrointestinal disease, such as gastric and/or duodenal ulcers;
- Severe hepatic and renal disease;
- Due to the therapeutic risk involved (risk/ benefit ratio), mild cases of *Psoriasis vulgaris*, e.g. circumscribed plaque psoriasis or chronic stationary plaque psoriasis covering less than 10% of total body surface;
- Due to insufficient clinical experience, cases of pustular psoriasis– although isolated case reports would seem to indicate some degree of therapeutic efficacy;
- In patients below 18 years of age;

– During pregnancy and lactation.

4.4 Special warnings and special precautions for use
Prior to initiation of treatment with Fumaderm Initial and Fumaderm, a full blood count (including a differential count and platelets) should be performed. In the presence of values outside the normal range, treatment with Fumaderm Initial and Fumaderm must not be instituted. During the course of treatment, full blood counts (leukocyte count and differential count) must be monitored on a regular basis. Tests should be performed no earlier than 14 days following treatment initiation and within the first three months of therapy. If results from these tests reveal no anomalies, a full blood count (performed on a monthly basis thereafter) is sufficient. Treatment with Fumaderm Initial or Fumaderm should be suspended immediately in the presence of a significant reduction in leukocyte levels – particularly if values should fall below 3000/mm3 — or if there are any other pathologic changes in the blood count. In such events, blood count levels should be monitored until normalisation is achieved. Similarly, prior to and during treatment, the following parameters should be tested (no earlier than 14 days following treatment initiation and within the first four weeks; and every four weeks thereafter) to identify any possible adverse effects on liver and kidney function: SGOT (ASAT) and SGPT (ASAT) activity; Gamma GT; AP; serum creatinine concentrations; proteinuria; urinary sediment. Furthermore, caution should be exercised in the presence of haematological disorders. Therapy should be discontinued in the case of increased creatinine levels above the normal range.

4.5 Interaction with other medicinal products and other forms of interaction
Whilst receiving Fumaderm Initial/ Fumaderm therapy, concomitant use of the following is not permitted: methotrexate, retinoids, psoralens, cyclosporine, immunosuppressants, cytostatics and drugs known to impair renal function. During treatment with Fumaderm Initial/ Fumaderm, concomitant topical application of fumaric acid derivatives (e.g. in the form of ointments and/or baths) should be avoided, as the additional uptake of these derivatives, found in certain ointments and bath formulations, may lead to an overdose as a result of exceeding the maximal tolerable dose.

4.6 Pregnancy and lactation
Although, on the basis of animal experiments, there are no indications of any teratogenic effect, Fumaderm Initial and Fumaderm should not be used during either pregnancy or lactation, as there is a lack of clinical experience regarding use during human pregnancy, and it is not known whether their active substances are excreted in human milk.

4.7 Effects on ability to drive and use machines
When used at recommended doses, it can be expected that Fumaderm Initial and Fumaderm have no effect on the ability to drive or operate machinery.

4.8 Undesirable effects
Undesirable effects have been evaluated in accordance with the following frequency convention:

Very common: (> 1/ 10 of patients treated)	Common: (> 1/ 100 of patients treated)
Uncommon: (1/ 1,000 of patients treated)	Rare: (1/ 10,000 of patients treated)
Very rare: (≤ 1/ 10,000 patients; including isolated cases)	

Undesirable effects and counter-measures

***Skin and subcutaneous disorders*:**
Very common:
– Facial redness and hot flushes
These disorders occur very frequently at initiation of therapy and usually subside during the course of treatment. However, severe manifestations of this kind may necessitate the discontinuation of treatment with either product.

Rare:
– Allergic skin reactions
These disorders are reversible upon discontinuation of treatment.

***Gastrointestinal disorders*:**
Very common:
– Diarrhoea

Common:
– Feelings of bloatedness
– Upper abdominal cramps
– Flatulence

Uncommon:
– Nausea

These undesirable effects are very common at initiation of therapy and usually subside during the course of treatment. In most cases, reduced dosage is sufficient to alleviate these disorders. However, should these effects persist, the treating physician should consider the possibility of discontinuing therapy.

***Nervous system disorders*:**
Uncommon:
– Tiredness
– Dizziness
– Headaches
These side effects usually subside during the course of treatment. In most cases, reduced dosage is sufficient to alleviate these disorders. However, should these effects persist, the treating physician should consider the possibility of discontinuing therapy.

***Blood and lymphatic system disorders*:**
Changes in blood count levels, such as leuko/ lymphopenia and varying degrees of eosinophilia, have been reported (cf. section 4.4: "Special warnings and special precautions for use"):

Very common:
– mild forms of lymphopenia (approx. 50% of patients)
– mild leukopenia (approx. 11% of patients)

Common:
– More severe forms of lymphopenia (approx. 3% of patients)
Signs of lymphopenia and leukopenia may regress. However, they may also repeatedly reoccur during treatment or even progress over the longer term.

Common:
– Transient eosinophilia

Very rare:
– Persistent eosinophilia

There are no indications to suggest that these changes in blood count values might lead to opportunistic infections. The above-mentioned blood count changes are reversible upon discontinuation of therapy.

Very rare:
– Acute lymphatic leukaemia (ALL)
Isolated case:
– Irreversible pancytopenia

Renal and urinary disorders:
Uncommon:
– Proteinuria
– Increased serum creatinine concentrations

Therapy should be discontinued in the case of increased creatinine levels above the normal range (cf. section 4.4: "Special warnings and special precautions for use").

Hepatobiliary disorders:
Uncommon:
– Increased liver values (SGOT [ASAT], SGPT [ALAT], Gamma GT)

Other undesirable effects:
Very rare:
– Occurrence of non-specific bone pains and increased alkaline phosphatase accompanied by decreased inorganic phosphate levels. This phenomenon may be linked to bone disease. These disorders and abnormal levels are reversible upon discontinuation of therapy.

4.9 Overdose
In cases of overdose, in addition to general measures to eliminate toxins and reduce gastrointestinal absorption, appropriate symptomatic treatment is indicated. There is no known specific antidote.

5. Pharmacological properties

5.1 Pharmacodynamic properties
Fumaderm Initial and FUMADERM contain fumaric acid esters.
Pharmacotherapeutic group: systemic anti-psoriasis products.
ATC code: D05BX51

Preclinical studies are lacking due to the absence of suitable animal models. The current state of knowledge on the mechanism of action for fumaric acid esters is based on the following scientific results:
Fumaric acid esters influence the regulatory site of succinate dehydrogenase within the citric acid cycle.
Dimethyl fumarate, monomethyl fumarate (the main metabolite of dimethyl fumarate) and monoethyl fumarate inhibit the proliferation of ceratinocytes, possibly due to a transient increase in intracellular Ca^{2+} concentrations. Therapy with Fumaderm Initial/ Fumaderm reduces intraepidermal infiltration of the skin with granulocytes and t-helper cells, bringing about a reduction in acanthosis and hyperkeratosis.
Monomethyl fumarate is known to affect the cytokine secretion pattern of T-helper cells, which results in increased secretion of the anti-inflammatory cytokines IL 4, IL 5 and IL10.

In pharmacological safety studies involving Fumaderm Initial and Fumaderm (blend of active ingredients) a hypotensive effect was observed at a high doses in narcotised dogs. In one acute study on rats, increased saluresis was observed, whilst in reproductive toxicological studies, increased diuresis was reported. However, in clinical studies, these findings (i.e. reduction in blood pressure, increased saluresis and diuresis) were not reproduced at therapeutic dosage regimens within humans.

5.2 Pharmacokinetic properties
Pharmacokinetic studies have been performed both *in vitro* and *in vivo*. Studies on rats and dogs reveal that, following oral administration of the Fumaderm active ingredient blend, individual substances were almost completely absorbed (approx. 30 minutes – 2 hours). It has been shown that, in the intestines, hydrolysation of dimethyl fumarate to monomethyl fumarate is very rapid. Peak serum levels were reached 15 mins and 1 h respectively after administration. Studies on rats were performed after oral administration, using labelled dimethyl fumarate. Results from these studies clearly demonstrate that excretion mainly occurs via the respiratory tract, with only relatively small amounts being excreted via the stools or urine. Furthermore, metabolisation studies involving human serum (*in vitro*) have also revealed that dimethyl fumarate is rapidly yet completely hydrolysed to methyl hydrogen fumarate (with a half-life of 11.6 minutes). Conversely, the processes involved in breaking down methyl hydrogen fumarate in the serum are very slow (half-life = approx. 36 hours). Both dimethyl fumarate and fumaric acid have been shown not to be protein-bound. On the other hand, protein binding for methyl hydrogen fumarate and ethyl hydrogen fumarate stands at around 50% and 60% respectively.

During *in vivo* tests, it was not possible to detect any increase in fumaric acid (metabolite). Fumaric acid concentration levels remained constant throughout all the tests performed.
In human subject studies, it was revealed that dimethyl fumarate - unlike its main metabolite methyl hydrogen fumarate - is not detectable in the blood, which can be attributed to its rapid hydrolysis. The peak serum concentration of methyl hydrogen fumarate (2.4 mg/l) is reached after 5 – 6 hours. The mean *in vivo* lag-time of 313 minutes (5 – 6 hours) confirms the efficacy of the tablet's gastro-resistant properties. The mean elimination half-life is around 80 minutes.

5.3 Preclinical safety data
Acute toxicity studies have revealed that the compounds used in Fumaderm Initial/ Fumaderm gastro-resistant tablets are more toxic on their own than when combined (LTD, LD50).

Chronic toxicity studies on rats and dogs, involving oral administration of the product, have yielded the following results:
In rats, within the first few weeks of treatment, repeat-dose oral administration of Fumaderm Initial/ Fumaderm induced leukocytosis and lymphopenia, as well as increased liver weight.
At toxic dose levels, the main effect observed was gastric damage, which manifested itself merely as clinical signs (in dogs: vomiting) or as pathological/anatomical changes (in rats: pachyderma of the stomach, hyperplasia and hyperkeratosis of the cutaneous rumen mucosa, which in some cases developed into papillomas and carcinomas). In all probability, these effects were as a result of the acidity of the product's active ingredients. In assessing this phenomenon, it should be borne in mind that human therapeutic use of Fumaderm Initial/ Fumaderm involves tablets with a gastro-resistant coating, which should prevent similar damage from occurring in humans. Moreover, fumaric acid esters were administered to rats and dogs over a 52-week period, which induced dose-dependent renal toxicity in both species. This toxicity manifested itself in increased serum urea values and pathomorphological changes. Furthermore, in male rats exposed to levels 10 times higher than the maximum allowed in human clinical use, benign Leydig cell tumours appeared. After a 26-week treatment period, no renal or testicular changes were observed. Studies on rats and rabbits, exposed to doses approaching levels causing maternal toxicity, yielded no evidence of any teratogenic effect. In fact, embryo-foetal toxicity (growth retardation, mortality) was only observed at doses known to cause maternal toxicity. In one reproduction study on rats, there was no evidence to indicate any effect on fertility. Human data on use of the product during pregnancy and lactation are lacking. It is not known whether the individual compounds making up this blend of active ingredients are excreted in human milk. However, on the basis of results obtained from *in vitro* and *in vivo* mutagenicity studies, any mutagenic risk for humans can be ruled out. This applies for the active ingredient blend, as well as its individual compounds. Carcinogenicity studies are lacking. No effect on the immune system could be observed during subacute and chronic studies on systemic use of fumaric acid esters (active ingredient blend). However, targeted sensitisation studies on guinea pigs revealed that fumaric acid esters (active ingredient blend) and monoethyl fumarate have a sensitising effect, following dermal application.

6. Pharmaceutical particulars

6.1 List of excipients
Fumaderm Initial:
Croscarmellose sodium, talc, magnesium stearate, pigments (E 171), methacrylic acid-methyl methacrylate copolymer (1:1), methacrylic acid-ethyl acrylate copolymer (1:1), macrogol 6000, simethicone, povidon, dibutyl phthalate, microcrystalline cellulose, colloidal anhydrous silica.

Fumaderm:
Croscarmellose sodium, talc, magnesium stearate, pigments E 171 and E 132), methacrylic acid-methyl methacrylate copolymer (1:1), methacrylic acid-ethyl acrylate copolymer (1:1), macrogol 6000, simethicone, povidon, dibutyl phthalate, microcrystalline cellulose, colloidal anhydrous silica.

6.2 Incompatibilities
Not applicable

6.3 Shelf life
3 years

6.4 Special precautions for storage
No special requirements for storage

6.5 Nature and contents of container
Fumaderm Initial:
40 gastro-resistant tablets N 2
Each pack contains 4 blister strips, each strip containing 10 gastro-resistant tablets:
The film-coated tablets are packed in blister strips (alfoil T250/30/90 polymer film-aluminium foil).

Fumaderm:
70 gastro-resistant tablets N 3
Each pack contains 7 blister strips, each strip containing 10 gastro-resistant tablets:
The film-coated tablets are packed in blister strips (alfoil T250/30/90 polymer film-aluminium foil).

100 gastro-resistant tablets N 3
Each pack contains 10 blister strips, each strip containing 10 gastro-resistant tablets:
The film-coated tablets are packed in blister strips (alfoil T250/30/90 polymer film-aluminium foil).

200 gastro-resistant tablets*
Each pack contains 20 blister strips, each strip containing 10 gastro-resistant tablets:
The film-coated tablets are packed in blister strips (alfoil T250/30/90 polymer film-aluminium foil).

200 gastro-resistant tablets*
Hospital pack size
Each pack contains 20 blister strips, each strip containing 10 gastro-resistant tablets:
The film-coated tablets are packed in blister strips (alfoil T250/30/90 polymer film-aluminium foil).

*These package sizes are currently not being marketed.

6.6 Instructions for use, handling and disposal
No special requirements

7. Marketing authorisation holder
FUMEDICA Arzneimittel GmbH
Industriestraße 40

D-44628 Herne
Germany
Tel.: 0049 (0) 2323/ 1496 0
Fax: 0049 (0) 2323/ 1496 20

Co-distributor:
HERMAL KURT HERRMANN GmbH & Co OHG
Scholtzstraße 3
D-21465 Reinbek
Germany
Tel.: 0049 (0) 40/ 727 04 0
Fax: 0049 (0) 40/ 722 92 96

Under licence from:
Fumapharm AG Schweiz
CH-6006 Lucerne
Switzerland

8. Marketing authorisation number/s
Fumaderm Initial, gastro-resistant tablets:
27561.00.00

Fumaderm, gastro-resistant tablets:
27561.01.00

9. Date of first authorisation/ renewal of the authorisation
Date of authorisation for Fumaderm Initial/ Fumaderm:
09. 08. 1994

10. Date of revision of the text
April 2005

11. Prescription status/ Availability
Available on prescription only
Please send all inquiries to:
BPI Service GmbH
FachInfo-Service
PO Box 12 55
D-88322 Aulendorf
Germany

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

53644 7590 12/26/2012

STERNE, KESSLER, GOLDSTEIN & FOX, P.L.L.C.
1100 NEW YORK AVE., N.W.
WASHINGTON, DC 20005

EXAMINER
ULM, JOHN D

ART UNIT	PAPER NUMBER
1649	

DATE MAILED: 12/26/2012

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/372,426	02/13/2012	Matvey E. LUKASHEV	2159.3210002/JMC/MRG/U-S	5998

TITLE OF INVENTION: Treatment for Multiple Sclerosis

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1770	$0	$0	$1770	03/26/2013

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the SMALL ENTITY status shown above.

If the SMALL ENTITY is shown as YES, verify your current SMALL ENTITY status:

A. If the status is the same, pay the TOTAL FEE(S) DUE shown above.

B. If the status above is to be removed, check box 5b on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and twice the amount of the ISSUE FEE shown above, or

If the SMALL ENTITY is shown as NO:

A. Pay TOTAL FEE(S) DUE shown above, or

B. If applicant claimed SMALL ENTITY status before, or is now claiming SMALL ENTITY status, check box 5a on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and 1/2 the ISSUE FEE shown above.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

53644 7590 12/26/2012

STERNE, KESSLER, GOLDSTEIN & FOX, P.L.L.C.
1100 NEW YORK AVE., N.W.
WASHINGTON, DC 20005

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/372,426	02/13/2012	Matvey E. LUKASHEV	2159.3210002/JMC/MRG/U-S	5998

TITLE OF INVENTION: Treatment for Multiple Sclerosis

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1770	$0	$0	$1770	03/26/2013

EXAMINER	ART UNIT	CLASS-SUBCLASS
ULM, JOHN D	1649	514-549000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list

(1) the names of up to 3 registered patent attorneys or agents OR, alternatively, 1_____

(2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed. 2_____ 3_____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. The following fee(s) are submitted:

❑ Issue Fee

❑ Publication Fee (No small entity discount permitted)

❑ Advance Order - # of Copies _____

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**

❑ A check is enclosed.

❑ Payment by credit card. Form PTO-2038 is attached.

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)

❑ a. Applicant claims SMALL ENTITY status. See 37 CFR 1.27.

❑ b. Applicant is no longer claiming SMALL ENTITY status. See 37 CFR 1.27(g)(2).

NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

This collection of information is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/372,426	02/13/2012	Matvey E. LUKASHEV	2159.3210002/JMC/MRG/U-S	5998

53644 7590 12/26/2012

STERNE, KESSLER, GOLDSTEIN & FOX, P.L.L.C.
1100 NEW YORK AVE., N.W.
WASHINGTON, DC 20005

EXAMINER	
ULM, JOHN D	
ART UNIT	PAPER NUMBER
1649	

DATE MAILED: 12/26/2012

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment to date is 0 day(s). If the issue fee is paid on the date that is three months after the mailing date of this notice and the patent issues on the Tuesday before the date that is 28 weeks (six and a half months) after the mailing date of this notice, the Patent Term Adjustment will be 0 day(s).

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Notice of Allowability	Application No.	Applicant(s)	
	13/372,426	LUKASHEV ET AL.	
	Examiner	Art Unit	
	JOHN ULM	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *the correspondence filed 12 December 2012*.

2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

3. ☒ The allowed claim(s) is/are *18-37*. As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☐ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____.
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☒ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date 12/12/12
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____.
5. ☐ Examiner's Amendment/Comment
6. ☐ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/John D. Ulm/
Primary Examiner, Art Unit 1649