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Paper No. __

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Coalition For Affordable Drugs V LLC
Petitioner
v.

Biogen MA Inc.
Patent Owner

Case IPR2015-01136
Patent 8,399,514
Title: TREATMENT FOR MULTIPLE SCLEROSIS

DECLARATION OF STEVEN E. LINBERG Ph. D.

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Coalition Exhibit 1005A
Coalition v. Biogen
IPR2015-01136

DECLARATION OF STEVEN E. LINBERG PH.D.

I, Steven E. Linberg Ph.D., hereby declare, affirm and state the following:

I. Introduction

1. I have been retained by Neifeld IP Law, PC for this inter partes review proceeding. I understand that this Declaration is being submitted along with a Petition for inter partes review of US Patent No. 8,399,514 ("the '514 patent"). I opine only with respect to certain issues that are discussed in this declaration.

II. RESOURCES CONSULTED

2. I have reviewed the '514 patent (**Exhibit 1001A**) including claims 1-20. I have also reviewed the *Kappos 2005* reference (**Exhibit 1003A**), the *ICH Guideline E4* (**Exhibit 1004A**), the *Werdenberg* reference (**Exhibit 1016A**), the *ClinicalTrials NCT00168701* reference (**Exhibit 1022A**), the *Talalay* reference (**Exhibit 1026A**), and the *Begleiter* reference (**Exhibit 1027A**). I have reviewed other documentation supporting and relevant to this declaration as cited below.

III. BACKGROUND, QUALFICATIONS AND COMPENSATION

3. I received a Ph.D. in Physiology from Pennsylvania State University in 1978. I worked for over 35 years in academic clinical research and commercial drug and biologics development, with particular attention to the overall strategy of drug development programs, to individual clinical trial design, execution, and reporting, and to regulatory interactions with the FDA. Over the course of that time I participated in the design, conduct, reporting or oversight of more than 100

clinical trials. I have held senior positions in companies which were developing drugs, developing biologics, and at contract research organizations. I am the principal editor of, and a contributing author in the text *Expediting Drug and Biologics Development*, now in its 3rd edition. I developed and taught graduate-level courses in Drug and Biologics Development, Clinical Trial Design, and Clinical Trial Operations for the Johns Hopkins University; and An Overview of Clinical Research, for the University of Maryland.

4. From 1978 to 1984, I was a Clinical Physiology Research Associate for the Shock Trauma – Maryland Institute for Emergency Medical Services Systems at the University of Maryland. From 1980 to 1984 I was an Assistant Professor of Pathology, Graduate Faculty at the University of Maryland School of Medicine. From 1985 to 1986 I was a Project Leader and Clinical Research Scientist in the Medical Division of Burroughs Wellcome Co. and from 1986 to 1992 I was an Associate Director of Clinical Research at Boehringer Mannheim Pharmaceuticals. In 1992 I was the Director of Clinical Research at Univax Biologics, Inc.. From 1992 to 1995 I was a consultant at, and owner of, Linberg Research, Inc.. From 1995 to 1996 I was the Vice President of Clinical Development at Collaborative Clinical Research, Inc.. From 1996 to 2001 I was the Vice President of Clinical Development at Cato Research Limited, and from 2001 to 2002 I was promoted to Managing Director and Senior Vice President of Drug Development at the same

company. From 2002 to 2009 I was the Managing Director of Chiesi Pharmaceuticals, Inc. and from 2009 to 2010 I was also Vice President and Treasurer at the same company. From 2011 to 2012 I was the founding President and CEO of Airway Therapeutics, LLC and continue as a Member of Airway Therapeutics, LLC. From 2013 to present I have been a consultant to the pharmaceutical industry, and formed S.E. Linberg Consulting, LLC in 2015 to further that effort.

5. I have published numerous academic papers and have served in various advisory, board and leadership positions for research centers, universities and a charitable foundation. My CV is submitted in this proceeding as **Exhibit 1017A**.

6. I am being compensated for my time at my standard hourly rate for this proceeding. My compensation is in no way contingent upon my performance or the outcome of this case.

IV. LEVEL OF ORDINARY SKILL IN THE ART

7. I have been informed by counsel to regard a person of ordinary skill in the art as being a hypothetical person who is presumed to know all of the relevant art at the time of the invention. Factors that may be considered in determining the level of ordinary skill in the art may include: (1) type of problems encountered in the art; (2) prior art solutions to those problems; (3) rapidity with which innovations are made; (4) sophistication of the technology; and (5) educational

level of active workers in the field. I have been informed by counsel that it is from the viewpoint of a person of ordinary skill in the art that legal issues, such as claim construction and obviousness, are determined.

8. In my opinion and based on my reading of the ‘514 patent, the field of the ‘514 patent is: treating a disease with an orally administered drug.

9. A person of ordinary skill in the art at the time of the alleged invention of the ‘514 patent (“POSITA”) would most likely have held an advanced degree, such as a Ph.D. in one of the life sciences, an M.D., a D.O., or a Pharm.D. Additionally, POSITA would have had some experience with clinical trials.

10. The ‘514 patent was filed on February 13, 2012. For the purposes of this Declaration, I have been asked to assume that the challenged claims may be entitled to the priority date of U.S. provisional application 60/888,921, filed Feb. 8, 2007. I have been advised by counsel that because no inventor of the provisional application was named, the ‘514 patent may not be entitled to the benefit of that 2007 date. At this time I have not investigated or formed any opinions about the contents of provisional application 60/888,921.

11. My opinion regarding the level of ordinary skill in the art for the ‘514 patent is based on my review of the patent and relevant file history, as well as my knowledge of the level of skill of individuals in this field. In forming my opinions, I have also considered the nature of problems that the ‘514 patent was intended to

solve, and the education level of active professionals in the field.

12. According to the description above, I possess at least the ordinary skill in the art, and did so at the time when the inventions in the ‘514 patent were made. I am familiar with the knowledge, experience, and creativity of such a person of ordinary skill in the art of the ‘514 patent during the relevant time period.

V. RELEVANT LEGAL STANDARDS

13. I am not a lawyer and do not purport to offer legal opinions. In forming my opinions, however, I have been asked to apply certain standards regarding patentability that were provided to me by counsel for the Petitioner.

14. I understand that for purposes of this IPR the terms in the claims of the ‘514 patent are to be construed according to their broadest reasonable interpretation in light of the specification of the ‘514 patent, as those terms would have been understood by one of ordinary skill in the art, as of the priority date of the ‘514 patent.

A. Anticipation

15. I have been informed that a patent claim is “anticipated” when a single patent or printed publication describes all of the elements of a claim, either expressly or by inherent disclosure. In this context I have been informed by counsel to assume that inherency means “necessarily,” so that a prior art reference which does not expressly disclose a claim element (or “claim limitation”) may still

inherently disclose that element if the missing description is necessarily present in the disclosure. I have been informed that for this to be true, the disclosure must be such that the natural result flowing from the operation of a system or method described in a reference *necessarily* results in the performance of the claim limitation(s). Standards for "anticipation" as I understand them are reproduced below: (a) the invention was known or used by others in this country (United States), or patented or described in a printed publication in this or a foreign country, before the invention thereof by the application for patent, (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than a year prior to the date of the application for patent in the United States, and (c) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent.

B. Obviousness

16. It is my understanding that a claim is unpatentable for obviousness if two or more prior art references in combination disclose, expressly or inherently, every claim element so as to render the subject matter, as a whole, obvious to a person of ordinary skill in the art. In determining whether a claim would have been obvious at the time it was made, the following factors should be considered: (a) the scope and content of the prior art; (b) the differences between the prior art and the claims

at issue; (c) the level of ordinary skill in the art; and (d) whatever "secondary considerations" may be present, which I have been informed generally take the form of evidence showing that the invention displays a significant and unexpected property. I also understand that if all elements in a claim were known in the prior art, and a person of ordinary skill in the art could have combined the elements by known methods with no change in their respective functions, and the combination yielded no more than the expected results, then such a claim would have been obvious.

VI. Brief overview of the '514 Patent

17. In my opinion, the '514 patent teaches that dimethyl fumarate (DMF) and monomethyl fumarate (MMF) have essentially the same biological activity, "FIG. 1 demonstrates that DMF and MMF are activators of Nrf2 at concentrations within clinical exposure range (cells in culture)." **Ex. 1001A**, 4:65-67. "FIG. 3 shows evidence of Nrf2 activation by DMF and MMF *in vivo*. FIG. 4 shows evidence of Nrf2 activation by DMF and MMF *in vivo*." **Ex. 1001A**, 5:2-5. I find nothing in the '514 patent which defines or explains that the therapeutic properties of MMF are different from the therapeutic properties of DMF.

18. In my opinion, FIG 1 of the '514 patent shows, the expression level of NQO1 is elevated at all concentrations of DMF tested, which expression level is proportional to DMF concentration. The specification of the '514 patent also states

that "[t]he results shown in FIG. 1, demonstrate that DMF and MMF are potent activators of Nrf2 at concentrations within clinical exposure range." **Ex. 1001A**, 2:12-14. The '514 specification teaches that Nrf2 controls the expression level of NQO1 at doses described in the Examples. The '514 patent states that "genes under the control of Nrf2 include…For example, expression levels of endogenous or exogenously introduced NQO1 may be determined as described in the Examples." **Ex. 1001A**, 14:38-44.

19. In my opinion, the '514 patent teaches that the effective amounts of DMF and MMF are the same:

> For DMF or MMF, 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). Effective doses will also vary, as recognized by those skilled in the art, dependent on route of administration, excipient usage, and the possibility of co-usage with other therapeutic treatments including use of other therapeutic agents. For example, an effective dose of DMF or MMR [sic: 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). For example, the 720 mg per day may be administered in separate administrations of 2, 3, 4, or 6 equal doses. The dosage may be determined by a physician and adjusted, as necessary, to suit observed effects of the treatment.

Ex. 1001A, 18:52-67.

20. In my opinion, Example 3 of the '514 patent tested the same dose per body weight (15 mg/kg), twice a day, for both DMF and MMF: "Each treatment group consisted of 8 animals: vehicle alone as a negative control, 5

mg/kg body weight DMF twice a day, 15 mg/kg body weight DMF twice a day, 15 mg/kg body weight MMF twice a day." **Ex. 1001A**, 21:6-10, emphasis added.

VII. CLAIM CONSTRUCTION

A. "Excipients"

21. In my opinion, the '514 patent defines the term "excipient" or "excipients:" "As used herein, the phrase 'pharmaceutically acceptable excipient' refers to any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like, that are compatible with pharmaceutical administration." **Ex. 1001A**, 19:6-10. In my opinion, the term "excipients" means "any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like, that are compatible with pharmaceutical administration."

B. "Consisting essentially of"

22. I have been advised by counsel that for purposes of this declaration to assume that the term "comprising" means "including." Except for claim 20, which uses the phrase "comprising," all other claims in the '514 patent recite compositions "consisting essentially of…[active ingredient(s)]…" such as (claim 1: "consisting essentially of a therapeutically effective amount of dimethyl fumarate, monomethyl fumarate, or a combination thereof") and (claim 7: "consists essentially of monomethyl fumarate") and (claim 6: "consists essentially

of dimethyl fumarate") and (claim 11: "consisting essentially of orally administering to the subject about 480 mg per day of dimethyl fumarate, monomethyl fumarate, or a combination thereof") and (claim 15: "pharmaceutical composition consisting essentially of (a) a therapeutically effective amount of dimethyl fumarate and (b) one or more pharmaceutically acceptable excipients"). I have been advised by counsel to assume for purposes of this declaration that a claim reciting a thing "consisting essentially of" specified ingredients limits the scope of the claim to the specified ingredients plus those ingredients which do not materially affect the basic and novel characteristic(s) of that thing.

VIII. Overview of Prior Art Reviewed by Me

23. In my opinion, once it was known that DMF is therapeutically active for treating RRMS, as taught by *Kappos 2005* or *ClinicalTrials NCT00168701* or '*514 Patent admission of prior art* ("Fumaric acid esters, such as DMF, have been proposed for treatment of MS"), it would have been standard procedure in drug development to determine the appropriate dosing range of DMF or MMF, including its minimum effective dose, in accordance with government guidance: *ICH Guideline E4*.

24. I have also reviewed the document "Drugs R&D, 2005, 6(4):229-30" (**Ex. 1021A**) cited in the '514 patent where it admits that fumaric acid esters, such as DMF, were known to be therapeutically active ("Fumaric acid esters, such as

DMF, have been proposed for treatment of MS…Drugs R&D, 2005,6(4):229-30)." **Ex 1001A**, col. 5:6-8. Drugs R&D reports the following entry in Table II: "Nov 2004 Phase II in Multiple sclerosis in Europe (PO)" **Ex. 1021A**, p2. In my opinion, this table entry indicates to a POSITA that a phase 2 clinical trial using the oral BG00012 composition was conducted on MS patients beginning in 2004. The fact that this was a phase 2 trial indicates that DMF was believed to have therapeutic activity against MS at that time. Also, ClinicalTrials NCT00168701 titled "Effacacy [sic] and Safety of BG00012 in MS" (**Ex. 1022A**) disclosed in 2005 that "DMF, the active ingredient in BG00012, is an immunomodulator demonstrating…possible therapeutic efficacy in MS (Schimrigk *et al*, 2001)." The Drug R&D 2005 (**Ex. 1021A**) article states that "Fumapharm AG has developed a second-generation fumarate (fumaric acid) derivative, BG 12 [BG 00012, FAG-201, BG 12/Oral Fumarate], for the oral treatment of psoriasis" (Abstract).

25. I have also reviewed the document, Fumapharm AG - Galenical Development (**Ex. 1023A**), which is an internet archived webpage of Fumapharm (Aug 3, 2005), indicating development of "enteric coated microtablets in capsules" of a "second-generation product" identified as a fumaric acid derivative "monosubstance." Even though the product BG00012 is not mentioned by name in **Ex. 1023A**, in my opinion it appears that BG00012 is the "second-generation" product discussed on the webpage.

IX. Ground 1: Claims 1-20 would have been obvious over *Kappos 2005* (Ex. 1003A) or *ClinicalTrials NCT00168701* (Ex. 1022A) or '514 Patent admission of prior art in view of *ICH Guideline E4* (Ex. 1004A)

Claim 1: 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.

26. I see that the first element of claim 1 requires, "[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" and defines a method of treating a subject in need of treatment for MS with an oral pharmaceutical composition. In my opinion *Kappos 2005* discloses "A randomized, placebo-controlled phase II trial of a novel oral single agent fumarate therapy, BG00012, in patients with relapsing-remitting multiple sclerosis." **Ex. 1003A**, p2, 1:1-3. *ClinicalTrials NCT00168701* discloses "Double-Blind, Placebo-Controlled, Dose-Ranging Study to Determine the Effacacy [sic] and Safety of BG00012 in Subjects with Relapsing-Remitting Multiple Sclerosis" **Ex. 1022A**, p1.

27. I see that the second element of claim 1 requires, "(a) a therapeutically effective amount of dimethyl fumarate, monomethyl fumarate, or a combination

thereof." In my opinion, *Kappos 2005* discloses a pilot study that orally administered to patients what appears to be a therapeutically effective amount of fumaric acid esters, indicated by a "significantly reduced the number of gadolinium-enhancing (Gd+) lesions in patients with RRMS." **Ex. 1003A**, p2, 1:13-16. *ClinicalTrials NCT00168701* teaches "the efficacy data in the pilot MS study of BG00012 support a proof of concept study in MS." **Ex. 1022A**, p1-2. *ClinicalTrials NCT00168701* also teaches that DMF is the active ingredient in BG00012. **Ex. 1022A**, p1. In my opinion, DMF is an abbreviation for dimethyl fumarate and MMF is an abbreviation for monomethyfumarate. The '514 patent cites to prior art clinical studies on MS patients which indicated that "[f]umaric acid esters, such as DMF have been proposed for treatment of MS." **Ex. 1001A**, 5:6-7. In my opinion, fumaric acid esters refer principally to DMF or MMF. Thus, in my opinion, the '514 Patent admits that a POSITA believed that DMF and MMF were therapeutically active for MS.

28. In my opinion, *Kappos 2005* discloses BG00012

contains a sole active ingredient. The objective is "[t]o determine the efficacy and safety of a novel single-agent oral fumarate therapy, BG00012, in patients with relapsing-remitting multiple sclerosis (RRMS)." **Ex. 1003A**, p2, 1:1-3. *Kappos 2005* discloses that "this phase II study was designed to evaluate the efficacy of three doses of BG00012 on brain lesion activity" in MS patients.

Ex.1003A, p2, 1:17-20 *Kappos 2005* also discloses that this phase II study is a "dose-ranging study." **Ex. 1003A**, p2, 2:16-17. In my opinion, the *Kappos 2005* dose-ranging study would not have been undertaken unless BG00012 had previously been determined to be therapeutically active in treating patients with MS.

29. In my opinion, *ClinicalTrials NCT00168701* discloses: "Effacacy [sic] and Safety of BG00012 in MS." and teaches "the efficacy data in the pilot MS study of BG00012 support a proof of concept study in MS." **Ex. 1022A**, p1-2.

30. Furthermore, DMF is known to be metabolically converted to MMF rapidly by hydrolysis in the intestinal tissue. **Ex. 1016A**, p2, 1:6 - 2:1-12. In my opinion, *Kappos 2005* or *ClinicalTrials NCT00168701* or the '514 patent admissions each teach a POSITA that DMF and MMF are therapeutically active on RRMS.

31. I see the third element of claim 1 requires, "b) one or more pharmaceutically acceptable excipients." In my opinion, DMF is poorly tolerated by patients (**Ex. 1005A** citing to **Ex. 1019A**, p4, 2:6-10, and p5, Table 2) and a POSITA would have been motivated to use excipients to reduce G.I. complaints. Furthermore, in my opinion, MMF is also poorly tolerated in patients and therefore a POSITA would have been motivated to use excipients to reduce G.I. complaints.

32. I see the fourth element of claim 1 requires, "wherein the therapeutically effective amount of dimethyl fumarate, monomethyl fumarate, or a combination thereof is about 480 mg per day." *Kappos 2005* discloses a dose-ranging study in which "[e]ligible patients were randomized to receive BG00012 120 mg PO once daily (120 mg/day), 120 mg PO three times daily (360 mg/day), 240mg PO three times daily (720 mg/day), or placebo." **Ex. 1003A**, p2, 1:28 to 2:1-3. In my opinion, *ClinicalTrials NCT00168701* teaches a dose-ranging study with the same doses of DMF and further acknowledges that if DMF is not well tolerated by patients, lower doses can alleviate the problem. "Dose reduction will be allowed for subjects who are unable to tolerate investigational drug." **Ex. 1022A**, p2, 24-25.

33. In my opinion, the *ICH Guideline E4* would have instructed a POSITA as follows: "Assessment of dose-response should be an integral component of drug development with studies designed to assess dose-response an inherent part of establishing the safety and effectiveness of the drug. If development of dose-response information is built into the development process it can usually be accomplished with no loss of time and minimal extra effort compared to development plans that ignore dose-response." **Ex. 1004A**, p7:27-32. *ICH Guideline E4 also* would have instructed that: **"**It is all too common to discover, at the end of a parallel dose-response study, that all doses were too high (on the plateau of the dose-response curve), or that doses did not go high enough. **Ex.**

1004A, p10:39-41. In my opinion, the *ICH Guideline E4* instructed a POSITA to perform dosing studies as a standard procedure in drug development in order to "allow study of the proper dose range" in phase III. In my opinion, because *Kappos 2005* did not test doses between 360 mg/day and 720 mg/day, because side effects are always a concern in drug development, as they were for DMF, and because doses in multiples of 120 mg and 240 mg were readily available, a POSITA would have conducted clinical trials by administering BG00012 at a total daily dose equivalent to 480 mg/day DMF as well as 600 mg/day, as a standard process of drug development.

34. In my opinion, *Kappos 2005* and *ClinicalTrials NCT00168701* disclose BG00012, which is a composition dosing 120 mg or 240 mg dimethyl fumarate as the sole active ingredient ("patients randomized to receive BG00012 120 mg PO once daily (120 mg/day), 120 mg PO three times daily (360 mg/day), 240mg PO three times daily (720 mg/day), **Ex. 1003A**, p2, 2:1-3. In my opinion, a POSITA would have designed additional dose-ranging studies using doses of 240 mg, 480 mg and 600 mg in multiples of 120 mg or 240 mg, because BG00012 was already conveniently formulated to achieve such doses.

35. In my opinion, a POSITA would have had reason to modify the clinical trial design of *Kappos 2005* or *ClinicalTrials NCT00168701* in view of the *ICH Guideline E4,* as part of a group of dosing studies, because the purpose of the *ICH*

Guideline E4 is to provide instructions to help identify "an appropriate starting dose, the best way to adjust dosage to the needs of a particular patient, and a dose beyond which increases would be unlikely to provide added benefit or would produce unacceptable side effects." **Ex. 1004A**, p5:7-10. In my opinion, a POSITA would have had reason to conduct dose-ranging studies due to the admittedly known therapeutic activity of DMF, in view of the ICH Guideline E4, because the purpose of the *ICH Guideline E4* is to provide instructions to help identify "an appropriate starting dose, the best way to adjust dosage to the needs of a particular patient, and a dose beyond which increases would be unlikely to provide added benefit or would produce unacceptable side effects." **Ex. 1004A**, p5:7-10.

36. In sum, a POSITA would have been motivated to conduct routine experiments at a range of doses, including 480 mg/day, by orally administering that dose and a 600 mg/day dosage strength to subjects in need of treatment for MS. Thus, a POSITA would have been motivated by *Kappos 2005* or *ClinicalTrials NCT00168701* or admitted prior art, in view of *ICH Guideline E4* to treat a subject in need of treatment for multiple sclerosis by 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.

Claim 2: The method of claim 1, wherein the pharmaceutical composition is administered in the form of a tablet, a suspension, or a capsule.

37. I see that claim 2 depends on claim 1 and incorporates all its limitations. Claim 2 further requires, "the pharmaceutical composition is administered in the form of a tablet, a suspension, or a capsule." In my opinion, *Kappos 2005* discloses administering BG00012 orally to MS patients using formulations with dosing strengths of 120 mg or 240 mg DMF. **Ex. 1003A**, p2, 2:1-3. *ClinicalTrials NCT00168701* also discloses the same formulations of DMF: "Effacacy [sic] and Safety of BG00012 in MS," wherein "the efficacy data in the pilot MS study of BG00012 support a proof of concept study in MS. **Ex. 1022A**, p1-2. In my opinion, a POSITA would have been motivated to administer DMF as a tablet or capsule in general, and particularly in view of *Kappos 2005* or *ClinicalTrials NCT00168701*.

38. In sum, in my opinion, a POSITA would have been motivated to, in light of *Kappos 2005 or ClinicalTrials NCT00168701* or admitted prior art in view of *ICH Guideline E4*, to administer DMF as a tablet or capsule.

Claim 3: The method of claim 1, wherein the therapeutically effective amount is administered in separate administrations of 2, 3, 4, or 6 equal doses.

39. I see that claim 3 depends on claim 1 and incorporates all its limitations. Claim 3 further requires, "the therapeutically effective amount is administered in separate administrations of 2, 3, 4, or 6 equal doses." In my opinion, *Kappos 2005* discloses a dose-ranging study in which "[e]ligible patients were randomized to receive BG00012 120 mg PO once daily (120 mg/day), 120 mg PO three times daily (360 mg/day), 240mg PO three times daily (720 mg/day), or placebo." **Ex. 1003A**, p2, 1:28-2:3. *ClinicalTrials NCT00168701* also discloses a dose-ranging study of BG00012 with the same doses. In my opinion, both *Kappos 2005* and *ClinicalTrials NCT00168701* disclose at least one dose or three equal doses. In my opinion, routine dosing experiments would have shown that administration of 2, 4 or 6 equal doses are therapeutically effective.

40. Furthermore, in my opinion, DMF is known to cause gastrointestinal discomfort ("The gastrointestinal complaints, on the other hand, presented a real problem. More than half the patients were troubled by serious stomach complaints, involving gastralgia, but also nausea, vomiting and diarrhea.") **Ex. 1019A**, p4, 2:6-10, and p5, Table 2) and so dividing the daily dose into smaller equal doses taken separately, throughout the day, would have been expected to reduce gastric distress, because smaller doses expose the G. I. tract to less DMF at one time. The *ICH Guideline E4* teaches that "[t]he choice of the size of an individual dose is often intertwined with the frequency of dosing. In general, when the dose interval is long

compared to the half-life of the drug, attention should be directed to the pharmacodynamic basis for the chosen dosing interval. For example, there might be a comparison of the long dose-interval regimen with the same dose in a more divided regimen, looking, where this is feasible, for persistence of desired effect throughout the dose-interval and for adverse effects associated with blood level peaks." **Ex. 1004A**, p7:9-15. In my opinion, attempting to find the optimal individual dose, dosing frequency and total daily dose are a normal part of drug development.

41. In my opinion, administering therapeutically effective amounts of DMF to a subject, in a number of equal doses throughout the day, would necessarily smooth out peak blood levels of the biologically active metabolite, MMF. In my opinion, a POSITA would have known that DMF is therapeutically active for MS, and thus would have been motivated to use multiples of a 120 mg or 240 mg to perform dosing studies, since BG00012 includes both 120 mg and 240 mg dosage strengths of DMF, as disclosed by Kappos 2005. Furthermore, in my opinion, since claim 3 recites every dosing interval from 2 equal doses to 6 equal doses, there is no critical dosing interval.

42. In sum, a POSITA would have been motivated, in light of *Kappos 2005* or *ClinicalTrials NCT00168701* or admitted prior art, in view of *ICH Guideline*

E4, to administer the therapeutically effective amount of about 480 mg/day DMF in separate administrations of 2 or 4 equal doses.

Claim 4: The method of claim 3, wherein the therapeutically effective amount is administered in separate administrations of 2 equal doses.

43. I see that claim 4 depends on claim 3 and incorporates all its limitations. Claim 4 further requires, "the therapeutically effective amount is administered in separate administrations of 2 equal doses." As I have explained with respect to claim 3, a POSITA would have been motivated to administer 480 mg/day in 2 equal doses based on the ready availability of 240 mg BG00012. In my opinion, a POSITA would have been motivated by *ICH Guideline E4*, to administer 480 mg/day in two equal doses, because the alternative of taking 120 mg doses four times per day would be expected to decrease patient compliance. In sum, in my opinion, a POSITA would have been motivated, in light of *Kappos 2005* or *ClinicalTrials NCT00168701* or admitted prior art, in view of *ICH Guideline E4*, to administer 480 mg/day of DMF in separate administrations of 2 equal doses.

Claim 5: The method of claim 3, wherein the therapeutically effective amount is administered in separate administrations of 3 equal doses.

44. I see that claim 5 depends on claim 3 and incorporates all its limitations. Claim 5 further requires, "the therapeutically effective amount is administered in separate administrations of 3 equal doses." *Kappos 2005* discloses a dose-ranging study in which "[e]ligible patients were randomized to receive BG00012 120 mg

PO once daily (120 mg/day), 120 mg PO three times daily (360 mg/day), 240mg PO three times daily (720 mg/day), or placebo." **Ex. 1003A**, p2, 1:28-2:3. *ClinicalTrials NCT00168701* also discloses a dose-ranging study of BG00012 with the same dosing. In my opinion, both of these studies disclose using three equal doses, and if the desired dose is 480 mg a POSITA would have known how to provide equal doses of appropriate strength.

45. In sum, in my opinion, a POSITA would have been motivated by *Kappos 2005* or *ClinicalTrials NCT00168701* or admitted prior art, in view of *ICH Guideline E4* and to administer 480 mg/day of DMF in separate administrations of three equal doses.

Claim 6: The method of claim 1, wherein the pharmaceutical composition consists essentially of dimethyl fumarate and one or more pharmaceutically acceptable excipients.

46. I see that claim 6 depends on claim 1 and incorporates all its limitations. Claim 6 further requires, "the pharmaceutical composition consists essentially of dimethyl fumarate and one or more pharmaceutically acceptable excipients." In my opinion, Kappos 2005 teaches "A randomized, placebo-controlled phase II trial of a novel oral single agent fumarate therapy, BG00012, in patients with relapsing-remitting multiple sclerosis." **Ex. 1003A**, p2, 1:1-3. *ClinicalTrials NCT00168701* discloses "Double-Blind, Placebo-Controlled, Dose-Ranging Study to Determine the Effacacy [sic] and Safety of BG00012 in Subjects with Relapsing-Remitting

Multiple Sclerosis" **Ex. 1022A**, p1. In my opinion, DMF is the only active ingredient in BG00012. Further in my opinion, DMF is poorly tolerated by patients (**Ex. 1019A**, p4, 2:6-10, and p5, Table 2) and a POSITA would have been motivated to use excipients to reduce G.I. complaints.

47. In sum, in my opinion, a POSITA would have been motivated by *Kappos 2005* or *ClinicalTrials NCT00168701* or admitted prior art, in view of *ICH Guideline E4*, to treat a subject in need of treatment for multiple sclerosis by orally administering to the subject in need thereof a pharmaceutical composition consisting essentially of dimethyl fumarate and one or more pharmaceutically acceptable excipients.

Claim 7: The method of claim 1, wherein the pharmaceutical composition consists essentially of monomethyl fumarate and one or more pharmaceutically acceptable excipients.

48. I see that claim 7 depends on claim 1 and incorporates all its limitations. Claim 7 further requires, "the pharmaceutical composition consists essentially of monomethyl fumarate." In my opinion, *Kappos 2005* teaches "A randomized, placebo-controlled phase II trial of a novel oral single agent fumarate therapy, BG00012, in patients with relapsing-remitting multiple sclerosis." **Ex. 1003A**, p2, 1:1-3. *ClinicalTrials NCT00168701* discloses "Double-Blind, Placebo-Controlled, Dose-Ranging Study to Determine the Effacacy [sic] and Safety of BG00012 in Subjects with Relapsing-Remitting Multiple Sclerosis" **Ex. 1022A**, p1. The

therapeutically active compound in BG00012 is dimethyl fumarate, not monomethyl fumarate. However, DMF is known to be metabolically converted to MMF rapidly by hydrolysis in the intestinal tissue. **Ex. 1016A**, p2, 1:6 - 2:1-12. In view of the foregoing, a POSITA would have been motivated to modify the BG00012 of *Kappos,* which contains DMF as the sole active ingredient, and administer a composition in which monomethyl fumarate is the sole active ingredient instead, since the therapeutic efficacy of each is essentially the same.

49. I see that the second element of claim 7 is "one or more pharmaceutically acceptable excipients." DMF is poorly tolerated by patients (**Ex. 1019A**, p4, 2:6-10, and p5, Table 2) and, in my opinion, a POSITA would have been motivated to use excipients to reduce G.I. complaints. In my opinion, MMF is also poorly tolerated in patients and therefore a POSITA would have been motivated to use excipients to reduce G.I. complaints.

50. In sum, in my opinion, a POSITA would have been motivated, in light of *Kappos 2005* or *ClinicalTrials NCT00168701* or admitted prior art in view of *ICH Guideline E4* to treat a subject in need of treatment for multiple sclerosis by orally administering to the subject in need thereof a pharmaceutical composition consisting essentially of monomethyl fumarate and one or more pharmaceutically acceptable excipients.

Claim 8: The method of claim 1, wherein the pharmaceutical composition is administered to the subject for at least 12 weeks.

51. I see that claim 8 depends on claim 1 and incorporates all its limitations. Claim 8 further requires "wherein the pharmaceutical composition is administered to the subject for at least 12 weeks." *Kappos 2005* discloses the following information about its dose-ranging study: "Design: This is a randomized, double-blind, placebo-controlled, phase II study being conducted at 45 clinical centers in Europe…Eligible patients were randomized to receive BG00012 120 mg PO once daily (120 mg/day), 120 mg PO three times daily (360 mg/day), 240mg PO three times daily (720 mg/day), or placebo. The study consists of 2 phases: a 24-week double-blind treatment phase followed by a 24-week, blinded, safety-extension phase in which all patients will receive some level of BG00012." **Ex. 1003A**, p2, 1:21 to 2:5. *ClinicalTrials NCT00168701* discloses the following about its dose-ranging study, "The primary endpoint for the primary objective is the total number of Gd-enhancing lesions over four scans at Weeks 12, 16, 20, and 24 (calculated as the sum of these four MRI scans). **Ex. 1022A**, p3. In my opinion, BG00012 refers to formulations containing DMF as the only active ingredient.

52. In sum, in my opinion, in light of *Kappos 2005* or *ClinicalTrials NCT00168701*, a POSITA would have been motivated to administer DMF to the subject for at least 12 weeks.

Claim 9: The method of claim 6, wherein the therapeutically effective amount is administered to the subject in 2 equal doses.

53. I see that claim 9 depends on claim 6 and incorporates all its limitations. Claim 9 further requires, "the therapeutically effective amount is administered in separate administrations of 2 equal doses." As I have explained above with respect to claim 4, a POSITA would have been motivated to administer 480 mg/day DMF in 2 equal doses based on the ready availability of 240 mg BG00012. In my opinion, a POSITA would have been motivated, in light of *ICH Guideline E4* to administer 480 mg/day in two equal doses, because the alternative of taking 120 mg doses four times per day would be expected to decrease patient compliance.

54. In sum, in my opinion, a POSITA, looking at the teachings of *Kappos 2005* or *ClinicalTrials NCT00168701* or admitted prior art, in view of *ICH Guideline E4*, would have been motivated to administer 480 mg/day of DMF in separate administrations of 2 equal doses.

Claim 10: The method of claim 9, wherein the therapeutically effective amount is administered to the subject for at least 12 weeks.

55. I see that claim 10 depends on claim 9 and incorporates all its limitations. Claim 10 further requires "wherein the pharmaceutical composition is administered to the subject for at least 12 weeks." As I explained above in regard to claim 8, a POSITA would have been motivated to administer DMF to the subject for at least 12 weeks. In sum, in my opinion, a POSITA would have been motivated, in view of the teachings of *Kappos 2005* or *ClinicalTrials*

NCT00168701 or admitted prior art, in view of *ICH Guideline E4*, to administer 480 mg/day of DMF to the subject for at least 12 weeks.

Claim 11: 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.

56. I see that the first element of independent claim 11 requires, "[a] method for treating a subject in need of treatment for multiple sclerosis consisting essentially of orally administering to the subject" and defines a method of treating a subject in need of treatment for MS by administering an oral composition. Claim 11 does not recite "therapeutically effective" but the broadest reasonable interpretation of "treating a subject in need of treatment for multiple sclerosis" requires a therapeutically effective dose.

57. *Kappos 2005* discloses "A randomized, placebo-controlled phase II trial of a novel oral single agent fumarate therapy, BG00012, in patients with relapsing-remitting multiple sclerosis." **Ex. 1003A**, p2, 1:1-3. *ClinicalTrials NCT00168701* discloses "Double-Blind, Placebo-Controlled, Dose-Ranging Study to Determine the Effacacy [sic] and Safety of BG00012 in Subjects with Relapsing-Remitting Multiple Sclerosis" **Ex. 1022A**, p1. In my opinion, the '514 patent cites to prior art clinical studies on MS patients which indicated that "[f]umaric acid esters, such as DMF have been proposed for treatment of MS." **Ex. 1001A**, 5:6-7. In my opinion, fumaric acid esters refers principally to DMF and MMF. Thus, in my opinion, the

‘514 Patent admits a POSITA believed that DMF and MMF were therapeutically active for MS.

58. In my opinion, Kappos 2005 discloses that the “single agent” in BG00012 is DMF. The objective is “[t]o determine the efficacy and safety of a novel single-agent oral fumarate therapy, BG00012, in patients with relapsing-remitting multiple sclerosis (RRMS).” **Ex. 1003A**, p2, 1:1-3. I see that *Kappos 2005* discloses that “this phase II study was designed to evaluate the efficacy of three doses of BG00012 on brain lesion activity” in MS patients. **Ex.1003A**, p2, 1:17-20. I see that *Kappos 2005* also discloses that this phase II study is a “dose-ranging study.” **Ex. 1003A**, p2, 2:16-17. In my opinion, the *Kappos 2005* dose-ranging study would not have been undertaken unless BG00012 had previously been determined to have the potential to be therapeutically active in treating patients with MS, based on the pilot study data mentioned in *Kappos 2005* where “a mixture of fumaric acid esters significantly reduced the number and volume of gadolinium-enhancing (Gd+) lesions in patients with RRMS.” In my opinion, *ClinicalTrials NCT00168701* teaches “the efficacy data in the pilot MS study of BG00012 support a proof of concept study in MS. **Ex. 1022A**, p1-2. The ‘514 patent cites to prior art clinical studies on MS patients which indicated that “[f]umaric acid esters, such as DMF have been proposed for treatment of MS.” **Ex. 1001A**, 5:6-7. In my opinion, fumaric acid esters refers principally to DMF and

MMF. Thus, in my opinion, the '514 Patent admits a POSITA believed that DMF and MMF were therapeutically active for MS. In my opinion, *Kappos 2005* and *ClinicalTrials NCT00168701* and the '514 patent admissions each teach a POSITA that DMF is therapeutically active on RRMS.

59. I see that the second element of claim 11 requires administering to the subject "about 480 mg per day of dimethyl fumarate, monomethyl fumarate, or a combination thereof." In my opinion, *Kappos 2005* discloses a dose-ranging study in which "[e]ligible patients were randomized to receive BG00012 120 mg PO once daily (120 mg/day), 120 mg PO three times daily (360 mg/day), 240mg PO three times daily (720 mg/day), or placebo." **Ex. 1003A**, p2, 1:28 to 2:1-3. In my opinion, *ClinicalTrials NCT00168701* teaches a dose-ranging study with the same doses of DMF. In my opinion, it acknowledges that DMF is not well tolerated by patients, and that lower doses can alleviate the problem. "Dose reduction will be allowed for subjects who are unable to tolerate investigational drug." **Ex. 1022A**, p2.

60. In my opinion, the *ICH Guideline E4* would have instructed a POSITA as follows: "Assessment of dose-response should be an integral component of drug development with studies designed to assess dose-response an inherent part of establishing the safety and effectiveness of the drug. If development of dose-response information is built into the development process it can usually be

accomplished with no loss of time and minimal extra effort compared to development plans that ignore dose-response." **Ex. 1004A**, p7:27-32. *ICH Guideline E4 also* would have instructed that: **"**It is all too common to discover, at the end of a parallel dose-response study, that all doses were too high (on the plateau of the dose-response curve), or that doses did not go high enough. **Ex. 1004A**, p10:39-41. In my opinion, the *ICH Guideline E4* instructed a POSITA to perform dosing studies as a standard procedure in drug development in order to "allow study of the proper dose range" in phase III. In my opinion, because *Kappos 2005* did not test doses between 360 mg/day and 720 mg/day, because side effects are always a concern in drug development, as they were for DMF, and because doses in multiples of 120 mg and 240 mg were readily available, a POSITA would have conducted clinical trials by administering BG00012 at a total daily dose equivalent to 480 mg/day DMF as well as 600 mg/day, as a standard process of drug development.

61. In my opinion, *Kappos 2005* and *ClinicalTrials NCT00168701* disclose BG00012, which is a composition dosing 120 mg or 240 mg dimethylfumarate as the sole active ingredient ("patients randomized to receive BG00012 120 mg PO once daily (120 mg/day), 120 mg PO three times daily (360 mg/day), 240mg PO three times daily (720 mg/day), **Ex. 1003A**, p2, 2:1-3. In my opinion, a POSITA would have designed additional dose-ranging studies using doses between 240 mg

and 600 mg in multiples of 120 mg or 240 mg, because BG00012 is conveniently formulated to achieve such doses.

62. In my opinion, a POSITA would have had reason to modify the clinical trial design of *Kappos 2005* or *ClinicalTrials NCT00168701* in view of the *ICH Guideline E4,* as part of a group of dosing studies, because the purpose of the *ICH Guideline E4* is to provide instructions to help identify "an appropriate starting dose, the best way to adjust dosage to the needs of a particular patient, and a dose beyond which increases would be unlikely to provide added benefit or would produce unacceptable side effects." **Ex. 1004A**, p5:7-10. In my opinion, a POSITA would have had reason to conduct dose-ranging studies due to the admittedly known therapeutic activity of DMF, in view of the *ICH Guideline E4*, because the purpose of the *ICH Guideline E4* is to provide instructions to help identify "an appropriate starting dose, the best way to adjust dosage to the needs of a particular patient, and a dose beyond which increases would be unlikely to provide added benefit or would produce unacceptable side effects." **Ex. 1004A**, p5:7-10.

63. In sum, a POSITA would have been motivated to conduct routine experiments at a range of doses, including 480 mg/day, by orally administering that dose and a 600 mg/day dosage strength to subjects in need of treatment for MS.

Claim 12: The method of claim 11, wherein about 480 mg of dimethyl fumarate per day is administered to the subject.

64. I see that claim 12 depends on claim 11 and incorporates all its limitations. Claim 12 further requires, "wherein about 480 mg of dimethyl fumarate per day is administered to the subject." As I explained above with regard to claim 11, a POSITA would have been motivated to conduct routine experiments to determine the dose-response of DMF, and thereby reveal that 480 mg per day is a therapeutically effective amount.

65. In sum, in my opinion, a POSITA would have been motivated by *Kappos 2005* or *ClinicalTrials NCT00168701* or admitted prior art, in view of *ICH Guideline E4* to administer to the subject about 480 mg of dimethyl fumarate per day.

Claim 13: The method of claim 12, wherein the dimethyl fumarate is administered in separate administrations of 2 equal doses.

66. I see that claim 13 depends on claim 12 and incorporates all its limitations. Claim 13 further requires, "wherein the dimethyl fumarate is administered in separate administrations of 2 equal doses." As I explained above with regard to claim 4, a POSITA would have been motivated to administer 480 mg/day DMF in separate administrations of 2 equal doses.

67. Thus, in my opinion, a POSITA would have been motivated by *Kappos 2005* or *ClinicalTrials NCT00168701* or admitted prior art, in view of *ICH*

Guideline E4 to administer the dimethyl fumarate in separate administrations of 2 equal doses.

Claim 14: The method of claim 12, wherein the dimethyl fumarate is administered in separate administrations of 3 equal doses.

68. I see that claim 14 depends on claim 12 and incorporates all its limitations. Claim 14 further requires, "wherein the dimethyl fumarate is administered in separate administrations of 3 equal doses." As I have explained above in regard to claim 5, a POSITA would have been motivated to administer 480 mg/day DMF in separate administrations of 3 equal doses.

69. Thus, in my opinion, a POSITA would have been motivated by *Kappos 2005* or *ClinicalTrials NCT00168701* or admitted prior art, in view of *ICH Guideline E4* to administer the dimethyl fumarate in separate administrations of 3 equal doses.

Claim 15: A method of treating a subject in need of treatment for multiple sclerosis comprising orally administering to the subject 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.

70. I see that the first element of independent claim 15 requires "[a] method of treating a subject in need of treatment for multiple sclerosis comprising orally administering to the subject pharmaceutical composition consisting essentially of" and defines a method of treating a subject in need of treatment for MS by

administering an oral composition. In my opinion, *Kappos 2005* teaches "A randomized, placebo-controlled phase II trial of a novel oral single agent fumarate therapy, BG00012, in patients with relapsing-remitting multiple sclerosis." **Ex. 1003A**, p2, 1:1-3. *ClinicalTrials NCT00168701* discloses "Double-Blind, Placebo-Controlled, Dose-Ranging Study to Determine the Effacacy [sic] and Safety of BG00012 in Subjects with Relapsing-Remitting Multiple Sclerosis" **Ex. 1022A**, p1.

71. I see that the second element of claim 15 requires, "(a) a therapeutically effective amount of dimethyl fumarate." *Kappos 2005* discloses a pilot study that orally administered to patients a therapeutically active amount of fumaric acid esters, which "significantly reduced the number of gadolinium-enhancing (Gd+) lesions in patients with RRMS." **Ex. 1003A**, p2, 1:13-16. *ClinicalTrials NCT00168701* teaches "the efficacy data in the pilot MS study of BG00012 support a proof of concept study in MS. **Ex. 1022A**, p1-2. In my opinion, DMF is an abbreviation for dimethyl fumarate. The '514 patent cites to prior art clinical studies on MS patients which indicated that "[f]umaric acid esters, such as DMF have been proposed for treatment of MS." **Ex. 1001A**, 5:6-7. In my opinion, fumaric acid esters refers principally to DMF and MMF. Thus, in my opinion, the '514 Patent admits a POSITA believed that DMF and MMF were therapeutically active for MS.

72. In my opinion, the "single agent" in BG00012 disclosed by *Kappos 2005* is DMF. The objective is "[t]o determine the efficacy and safety of a novel single-agent oral fumarate therapy, BG00012, in patients with relapsing-remitting multiple sclerosis (RRMS)." **Ex. 1003A**, p2, 1:1-3. *Kappos 2005* discloses that "this phase II study was designed to evaluate the efficacy of three doses of BG00012 on brain lesion activity" in MS patients. **Ex.1003A**, p2, 1:17-20. *Kappos 2005* discloses that this phase II study is a "dose-ranging study." **Ex. 1003A**, p2, 2:16-17. In my opinion, the *Kappos 2005* dose-ranging study would not have been undertaken unless BG00012 had previously been determined to be therapeutically active in treating patients with MS. *ClinicalTrials NCT00168701* discloses: "Effacacy [sic] and Safety of BG00012 in MS." **Ex. 1022A**, p1. In my opinion, *Kappos 2005* and *ClinicalTrials NCT00168701* and the '514 patent admissions each teach a POSITA that DMF is therapeutically active on RRMS.

73. In my opinion, *Kappos 2005* discloses a dose-ranging study in which "[e]ligible patients were randomized to receive BG00012 120 mg PO once daily (120 mg/day), 120 mg PO three times daily (360 mg/day), 240mg PO three times daily (720 mg/day), or placebo." **Ex. 1003A**, p2, 1:28 to 2:1-3. *ClinicalTrials NCT00168701* teaches a dose-ranging study with the same doses of DMF. In my opinion, it acknowledges that DMF is not well tolerated by patients, and that lower doses can alleviate the problem. "Dose reduction will be allowed for subjects who

are unable to tolerate investigational drug." **Ex. 1022A**, p2. The *ICH Guideline E4* would have instructed a POSITA as follows: "Assessment of dose-response should be an integral component of drug development with studies designed to assess dose-response an inherent part of establishing the safety and effectiveness of the drug. If development of dose-response information is built into the development process it can usually be accomplished with no loss of time and minimal extra effort compared to development plans that ignore dose-response." **Ex. 1004A**, p7:27-32. *ICH Guideline E4 also* would have instructed that: **"**It is all too common to discover, at the end of a parallel dose-response study, that all doses were too high (on the plateau of the dose-response curve), or that doses did not go high enough. **Ex. 1004A**, p10:39-41. In my opinion, the *ICH Guideline E4* instructed a POSITA to perform dosing studies as a standard procedure in drug development in order to "allow study of the proper dose range" in phase III. Further in my opinion, because *Kappos 2005* did not test doses between 360 mg/day and 720 mg/day, because side effects are always a concern in drug development, as they were for DMF, and because doses in multiples of 120 mg and 240 mg were readily available, a POSITA would have conducted clinical trials by administering BG00012 at a total daily dose equivalent to 480 mg/day DMF as well as 600 mg/day, as a standard process of drug development.

74. In my opinion, *Kappos 2005* teaches BG00012, which is a composition containing DMF as the sole active agent ("patients randomized to receive BG00012 120 mg PO once daily (120 mg/day), 120 mg PO three times daily (360 mg/day), 240mg PO three times daily (720 mg/day)"). **Ex. 1003A**, p2, 2:1-3. In my opinion, a POSITA would have designed additional dose-ranging studies using doses between 240 mg and 600 mg in multiples of 120 mg or 240 mg, as disclosed by Kappos 2005. In my opinion, a POSITA would have had reason to modify the clinical trial design of *Kappos 2005* or *ClinicalTrials NCT00168701* in view of the *ICH Guideline E4,* as part of a group of dosing studies, because the purpose of the *ICH Guideline E4* is to provide instructions to help identify "an appropriate starting dose, the best way to adjust dosage to the needs of a particular patient, and a dose beyond which increases would be unlikely to provide added benefit or would produce unacceptable side effects." **Ex. 1004A**, p5:7-10. In my opinion, a POSITA would have had reason to conduct dose-ranging studies due to the admittedly known therapeutic activity of DMF, in view of the *ICH Guideline E4*, because the purpose of the *ICH Guideline E4* is to provide instructions to help identify "an appropriate starting dose, the best way to adjust dosage to the needs of a particular patient, and a dose beyond which increases would be unlikely to provide added benefit or would produce unacceptable side effects." **Ex. 1004A**, p5:7-10.

75. I see that the third element of claim 15 requires, "(b) one or more pharmaceutically acceptable excipients." In my opinion, DMF is poorly tolerated by patients (**Ex. 1019A**, p4, 2:6-10, and p5, Table 2) and a POSITA would have been motivated to use excipients to reduce G.I. complaints. Further in my opinion, MMF is also poorly tolerated in patients and therefore a POSITA would have been motivated to use excipients to reduce G.I. complaints.

76. I see that the fourth element of claim 15 requires, "wherein the therapeutically effective amount of dimethyl fumarate is about 480 mg per day." As shown above with respect to the second element of claim 15, in light of the *ICH Guideline E4* instructions to perform initial dosing studies to "allow study of the proper dose range" and because *Kappos 2005* did not test intermediate dosages, in my opinion, a POSITA would have conducted clinical trials by administering BG00012 at a total daily dose equivalent to 480 mg DMF/per day, as well as 600 mg/day. Thus, in my opinion, a POSITA would have designed additional dose-ranging studies using doses between 240 mg and 600 mg in multiples of 120 mg or 240 mg, as disclosed by *Kappos 2005*. In my opinion, a POSITA would have had reason to consider the clinical trial design of *Kappos 2005* in view of the *ICH Guideline E4,* to be just a part of usual dose ranging studies because the purpose of the *ICH Guideline E4* is to provide instructions to help identify "an appropriate starting dose, the best way to adjust dosage to the needs of a particular patient, and

a dose beyond which increases would be unlikely to provide added benefit or would produce unacceptable side effects." **Ex. 1004A**, p5:7-10.

77. Thus, in my opinion, a POSITA would have been motivated, in view of the teachings of *Kappos 2005* or *ClinicalTrials NCT00168701* or admitted prior art, in view of *ICH Guideline E4* to treat a subject in need of treatment for multiple sclerosis by orally administering to the subject 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.

Claim 16: The method of claim 15, wherein the dimethyl fumarate is administered in separate administrations of 2 equal doses.

78. I see that claim 16 depends on claim 15 and incorporates all its limitations. Claim 16 further requires "wherein the dimethyl fumarate is administered in separate administrations of 2 equal doses." In my opinion, *ICH Guideline E4* teaches "Adjustment of drug exposure levels might be made on the basis of reliable information on drug taking compliance." **Ex. 1004A**, p14:30-31. In my opinion, a POSITA would have been motivated, in light of *ICH Guideline E4*, to administer 480 mg/day DMF in two equal doses because the alternative of taking 120 mg four times per day would be expected to decrease patient compliance.

79. Therefore, in my opinion, a POSITA would have been motivated, in view of the teachings of *Kappos 2005* or *ClinicalTrials NCT00168701* or admitted prior art, in view of *ICH Guideline E4* to administer the DMF in separate administrations of 2 equal doses.

Claim 17: The method of claim 1, 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.

80. Claims 17, 18 and 19 fail to add any narrowing limitations. They recite an intended effect of administering the drug (i.e, the expression level of NQO1 is elevated), but there is only one claimed disease (MS), one claimed dose (about 480 mg/day), and two claimed drugs (DMF or MMF) which both have essentially the same therapeutic properties according the '514 Patent, as explained in the section "Brief overview of the '514 Patent" above. Therefore claims 17, 18, and 19 involve an issue of inherency. In short, administering 480 mg/day of DMF or MMF must elevate NQO1 as claimed.

81. I see that claim 17 depends on claim 1 and incorporates all its limitations. Claim 17 further requires "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."

82. In my opinion, an "elevated" expression of NQO1 is an inherent property of administering 480 mg/day of DMF "to the subject" and that the expression level of NQO1 is necessarily elevated as a result of administering 480 mg/day DMF to the subject. I base my conclusion on the following facts.

83. First, in my opinion, 480 mg is the only amount of "dimethyl fumarate, monomethyl fumarate or a combination thereof" permitted under claim 1, whether it is "therapeutically effective" or not.

84. Second, in my opinion, an "elevated" expression of NQO1 is necessarily present as disclosed in multiple previous studies such as *Talalay* (**Ex. 1026A**) and *Begleiter* (**Ex. 1027A**). *Talalay* teaches that fumaric dimethyl esters, including dimethyl fumarate are moderately potent inducers of QR. **Ex. 1026A**, p3, 1:13-16, Table 3. QR stands for "quinone reductase [NAD(P)H:(quinone-acceptor) oxidoreductase, EC 1.6.99.2]" **Ex. 1026A**, p1, Abstract. In my opinion, the '514 patent teaches that "NAD(P)H:quinone oxidoreductases, now commonly known as nicotinamide quinone oxidoreductase 1 (NQOl; EC 1.6.99.2;" **Ex. 1001A**, 12:10-12. *Begleiter* teaches that NQO1 activity increases after either *in vitro* or *in vivo* treatment with DMF. **Ex. 1027A**, p3, 1:61 – 2:1-3, 2:11-14.

85. Furthermore, in my opinion, the '514 patent admits in claim 18 that "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." (emphasis added).

86. In sum, in my opinion, a POSITA would have been motivated to combine the teachings of *Kappos 2005* or *ClinicalTrials NCT00168701* or admitted prior art in the '514 Patent, and treat a subject in need of treatment for MS by orally administering a composition consisting essentially of 480 mg per day of DMF, and one or more excipients, wherein the expression level of NQO1 in the subject is necessarily elevated after administering to the subject said pharmaceutical composition.

Claim 18: The method of claim 11, 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.

87. I see that claim 18 depends on claim 11 and incorporates all its limitations. Claim 18 further requires, "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." The motivation to administer 480 mg/day is shown above with respect to claim 11 and the increase of expression levels of NQO1 are shown as inherent for the same reasons as set forth above in claim 17.

88. In my opinion, an "elevated" expression of NQO1 is an inherent property of administering 480 mg/day of DMF "to the subject" and that the

expression level of NQO1 is necessarily elevated as a result of administering 480 mg/day DMF to the subject.

89. In sum, in my opinion, a POSITA would have been motivated to combine the teachings of *Kappos2005* or *ClinicalTrials NCT00168701* or admitted prior art in the '514 Patent, and treat a subject in need of treatment for MS by orally administering a composition consisting essentially of 480 mg per day of DMF, and one or more excipients, wherein the expression level of NQO1 in the subject is necessarily elevated after administering to the subject said pharmaceutical composition.

Claim 19: The method of claim 15, wherein the expression level of NQO1 in the subject is elevated after administering to the subject the therapeutically effective amount of dimethyl fumarate.

90. I see that claim 19 depends on claim 15 and incorporates all its limitations. Claim 19 further requires, "wherein the expression level of NQO1 in the subject is elevated after administering to the subject the therapeutically effective amount of dimethyl fumarate." In my opinion, an "elevated" expression of NQO1 is an inherent property of administering 480 mg/day of DMF "to the subject" and the expression level of NQO1 is necessarily elevated as a result of administering 480 mg/day DMF to the subject for the same reasons as set forth above in claim 17.

91. In sum, in my opinion, a POSITA would have been motivated to combine the teachings of *Kappos 2005* or *ClinicalTrials NCT00168701* or admitted prior art in the '514 Patent, and treat a subject in need of treatment for MS by orally administering a composition consisting essentially of 480 mg per day of DMF, and one or more excipients, wherein the expression level of NQO1 in the subject is necessarily elevated after administering to the subject said pharmaceutical composition.

Claim 20: 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.

92. I see that the first element of independent claim 20 requires "A method of treating a subject in need of treatment for multiple sclerosis comprising treating the subject in need thereof" and defines a method of treating a subject in need of treatment for MS by administering an oral pharmaceutical composition. *Kappos 2005* teaches "A randomized, placebo-controlled phase II trial of a novel oral single agent fumarate therapy, BG00012, in patients with relapsing-remitting multiple sclerosis." **Ex. 1003A**, p2, 1:1-3. *ClinicalTrials NCT00168701* discloses "Double-Blind, Placebo-Controlled, Dose-Ranging Study to Determine the Effacacy [sic] and Safety of BG00012 in Subjects with Relapsing-Remitting Multiple Sclerosis" **Ex. 1022A**, p1.

93. I see that the second element of claim 20 requires, "a therapeutically effective amount of dimethyl fumarate, monomethyl fumarate, or a combination thereof." *Kappos 2005* discloses a pilot study that orally administered a therapeutically active amount of fumaric acid esters, which "significantly reduced the number of gadolinium-enhancing (Gd+) lesions in patients with RRMS." **Ex. 1003A**, p2, 1:13-16. In my opinion, *ClinicalTrials NCT00168701* teaches "the efficacy data in the pilot MS study of BG00012 support a proof of concept study in MS. **Ex. 1022A**, p1-2. DMF is an abbreviation for dimethyl fumarate." In my opinion, the '514 patent cites to prior art clinical studies on MS patients which indicated that "[f]umaric acid esters, such as DMF have been proposed for treatment of MS." **Ex. 1001A**, 5:6-7. In my opinion, fumaric acid esters refers principally to DMF or MMF. Thus, in my opinion, the '514 Patent admits a POSITA believed that DMF or MMF were therapeutically active for MS.

94. In my opinion, *Kappos 2005* discloses that the "single agent" in BG00012 is DMF. The objective is "[t]o determine the efficacy and safety of a novel single-agent oral fumarate therapy, BG00012, in patients with relapsing-remitting multiple sclerosis (RRMS)." **Ex. 1003A**, p2, 1:1-3. *Kappos 2005* discloses that "this phase II study was designed to evaluate the efficacy of three doses of BG00012 on brain lesion activity" in MS patients. **Ex.1003A**, p2, 1:17-20 *Kappos 2005* discloses that this phase II study is a "dose-ranging study." **Ex.**

1003A, p2, 2:16-17. In my opinion, the *Kappos 2005* dose-ranging study would not have been undertaken unless BG00012 had previously been determined to be therapeutically active in treating patients with MS. *ClinicalTrials NCT00168701* discloses: "Effacacy [sic] and Safety of BG00012 in MS." **Ex. 1022A**, p1. In my opinion, *Kappos 2005* and *ClinicalTrials NCT00168701* and the '514 patent admissions each teach a POSITA that DMF is therapeutically active on RRMS.

95. I see that the third element of claim 20 requires, "wherein the therapeutically effective amount of dimethyl fumarate, monomethyl fumarate, or a combination thereof is about 480 mg per day." *Kappos 2005* discloses a dose-ranging study in which "[e]ligible patients were randomized to receive BG00012 120 mg PO once daily (120 mg/day), 120 mg PO three times daily (360 mg/day), 240mg PO three times daily (720 mg/day), or placebo." **Ex. 1003A**, p2, 1:28 to 2:1-3. *ClinicalTrials NCT00168701* teaches a dose-ranging study with the same doses of DMF. In my opinion, it acknowledges that DMF is not well tolerated by patients, and that lower doses can alleviate the problem. "Dose reduction will be allowed for subjects who are unable to tolerate investigational drug." **Ex. 1022A**, p2. In my opinion, the *ICH Guideline E4* would have instructed a POSITA as follows: "Assessment of dose-response should be an integral component of drug development with studies designed to assess dose-response an inherent part of establishing the safety and effectiveness of the drug. If development of dose-

response information is built into the development process it can usually be accomplished with no loss of time and minimal extra effort compared to development plans that ignore dose-response." **Ex. 1004A**, p7:27-32. In my opinion, *ICH Guideline E4 also* would have instructed that: **"**It is all too common to discover, at the end of a parallel dose-response study, that all doses were too high (on the plateau of the dose-response curve), or that doses did not go high enough. **Ex. 1004A**, p10:39-41. In my opinion, the *ICH Guideline E4* instructed a POSITA to perform dosing studies as a standard procedure in drug development in order to "allow study of the proper dose range" in phase III. In my opinion, because *Kappos 2005* did not test doses between 360 mg/day and 720 mg/day, because side effects are always a concern in drug development, as they were for DMF, and because doses in multiples of 120 mg and 240 mg were readily available, a POSITA would have conducted clinical trials by administering BG00012 at a total daily dose equivalent to 480 mg/day DMF as well as 600 mg/day, as a standard process of drug development.

96. In my opinion, *Kappos 2005* teaches BG00012, which contains DMF as the sole active agent, and teaches that "patients [were] randomized to receive BG00012 120 mg PO once daily (120 mg/day), 120 mg PO three times daily (360 mg/day), 240mg PO three times daily (720 mg/day)", **Ex. 1003A**, p2, 2:1-3. In my opinion, a POSITA would have designed additional dose-ranging studies using

doses between 240 mg and 600 mg in multiples of 120 mg or 240 mg. In my opinion, a POSITA would have had reason to modify the clinical trial design of *Kappos 2005* in view of the *ICH Guideline E4,* because the purpose of the *ICH Guideline E4* is to provide instructions to help identify "an appropriate starting dose, the best way to adjust dosage to the needs of a particular patient, and a dose beyond which increases would be unlikely to provide added benefit or would produce unacceptable side effects." **Ex. 1004A**, p5:7-10. Further, in my opinion, a POSITA would have had reason to conduct dose-ranging studies due to the admittedly known therapeutic activity of DMF, in view of the *ICH Guideline E4*, because the purpose of the *ICH Guideline E4* is to provide instructions to help identify "an appropriate starting dose, the best way to adjust dosage to the needs of a particular patient, and a dose beyond which increases would be unlikely to provide added benefit or would produce unacceptable side effects." **Ex. 1004A**, p5:7-10.

97. In sum, in my opinion, a POSITA would have been motivated, in view of the teachings of *Kappos 2005* or *ClinicalTrials NCT00168701* or admitted prior art, in view of *ICH Guideline E4*, to treat a subject in need of treatment for multiple sclerosis 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.

98. I declare that all statements made herein are of my own knowledge and 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 are punishable by fine or imprisonment or both pursuant to 18 U.S.C. §1001 and that willful false statements or the like may jeopardize the validity of the patent or any patent issuing thereon.

Respectfully submitted

Signed in _Laytonsville, MD, on_May 26, 2015_

_____/Steven E. Linberg/_____

Steven E. Linberg PhD