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**	

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

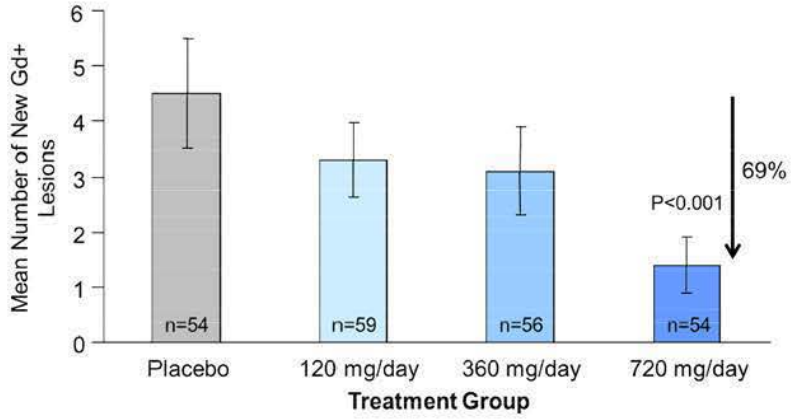
Phase 3 MS clinical studies, to be unexpected (*i.e.*, the 480 mg/day dose was found to be similarly efficacious as the higher dose of 720 mg/day). The observations described below form the basis of my opinion.

(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:

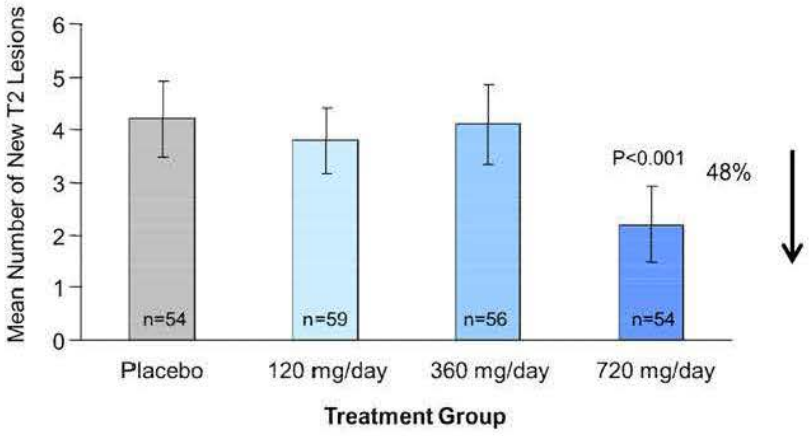
Mean Total Number of Gd+ Lesions at Weeks 12, 16, 20, and 24 Combined in the Phase 2 Trial



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

Figure 2:

Mean Number of New and Enlarging T2-Hyperintense Lesions (Week 24) in the Phase 2 Trial



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

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