At least 1 relapse within the 12 months immediately prior to study entry with a prior cranial MRI scan demonstrating lesions consistent with MS OR evidence of Gd+ lesions of the brain on an MRI performed within the 6 weeks prior to study entry

Willingness to use appropriate contraceptive measures during the study

clusion Criteria

A progressive form of MS

Treatment with IFNβ (3 months), glatiramer acetate (3 months), or intravenous immunoglobulin (6 months), or natalizumab (6 months) within the 6 months prior to randomization

Corticosteroid treatment within 30 days of randomization

An MS relapse within 50 days prior to randomization and/or not stabized from a previous relapse

A history of malignancy, severe allergic or anaphylactic reaction, or known drug hypersensitivity

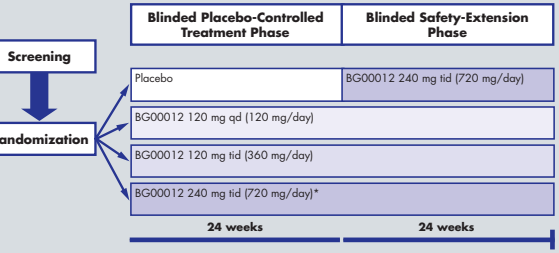
A history of abnormal laboratory results, HIV infection, drug or alcohol abuse

udy Design

Randomized, double-blind, placebo-controlled, parallel-group, dose-anging study conducted at 42 clinical centers in Europe

The study consisted of a 24-week double-blind, placebo-controlled reatment phase followed by a 24-week, blinded, safety-extension hase (*Figure 2*).

gure 2. Study Design



atients received 120 mg tid during the first week to determine tolerability.

Patients were equally randomized to one of four treatment groups:

- Placebo
- BG00012 120 mg once daily (qd) (120 mg/day)
- BG00012 120 mg three times daily (tid) (360 mg/day)
- BG00012 240 mg tid (720 mg/day)

120 mg tid for the first week to determine tolerability.

Table 1. Schedule for Study Drug Administration

Treatment Group	Morning	Midday	Evening
Placebo	2P	2P	2P
120 mg of BG00012 (1 capsule)	1A + 1P	2P	2P
360 mg of BG00012 (3 capsules)	1A + 1P	1A + 1P	1A + 1P
720 mg of BG00012 (6 capsules)	2A	2A	2A

P=placebo; A=active (BG00012, 120 mg of fumaric acid ester per capsule).

- In the blinded safety-extension phase, the three BG00012 treatment groups continue at the dosage assigned in the placebo-controlled treatment phase, and the placebo group receives BG00012 720 mg/day (120 mg tid was given the first week).

Study Endpoints

- The primary endpoint is the total number of new Gd+ lesions on MRI scans performed at Weeks 12, 16, 20, and 24 (calculated as the sum of these 4 MRI scans).
- Secondary MRI endpoints include:
  - Cumulative number of new Gd+ lesions from baseline to Week 24
  - Number of new or newly enlarging T2-hyperintense lesions at Week 24 compared to baseline
- Other endpoints include:
  - Number of new T1-hypointense lesions at Week 24
  - Annualized relapse rate
  - Proportion of relapse-free patients
  - Disability progression as measured by EDSS
  - Safety/tolerability

RESULTS

- A total of 257 patients were enrolled in the study.
- The patient population was 63% females and the mean age of patients enrolled was 36 years (*Table 2*).
- The mean (±SD) disease duration of patients was 4.6 (±4.9) years, the mean EDSS score was 2.6 (±1.2), and the mean number of relapses during the 3 years prior to enrollment was 2.5 (±1.3) (*Table 2*).

	All Patients (N=257)
Age, mean years (±SD)	36.0 (±9.3)
Women, %	63
Caucasian, %	98
Time since onset of symptoms	
Mean years (±SD)	7.8 (±6.0)
Time since diagnosis	
Mean years (±SD)	4.6 (±4.9)
EDSS score, n (%)	
≤3.5	203 (79)
4.0-5.0	54 (21)
≥5.0	0 (0)
Mean (±SD)	2.63 (±1.2)
Median	2.5
Min, max	0.0, 5.0
Relapses,* n (%)	
0	1 (<1)
1	50 (19)
2	87 (34)
3	78 (30)
≥4	41 (16)
Mean (±SD)	2.5 (±1.3)
Median	2.0
Min, max	0, 10

SD=standard deviation; EDSS=Expanded Disability Status Scale.
*During the 3 years prior to study enrollment.

CONCLUSIONS

- BG00012 represents a potentially important therapeutic option for patients with MS.
- This study will provide the first double-blind, placebo-controlled data to evaluate the efficacy and safety of BG00012 in patients with MS.

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Study sponsored by Biogen Idec, Inc. and Fumapharm AG

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BIOGEN MA INC.,
Patent Owner.

Case IPR2015-01993
Patent 8,399,514 B2

DECLARATION OF GILMORE O'NEILL, M.D.

Personal Background and Introduction

1. I am currently Senior Vice President, Drug Innovation Units at Biogen and have held this position since October 2015. In this position, I am responsible for leading multi-disciplinary groups accountable for research and development in Pain, Immunology, Hemophilia and Rare Diseases, and Gene and Cell therapeutics.

2. I received my medical degree from University College Dublin in 1988 and completed residencies and fellowship training in internal medicine, pulmonology and neuropathology in 1993 at Beaumont Hospital, Dublin. I completed my residency in Neurology at Massachusetts General Hospital in 1997 and was Chief Resident from 1996 to 1997 during that time. I also received a Master of Medical Science degree from Harvard Medical School in 1999. I am a Clinical Instructor in Neurology at Harvard Medical School and a Neurologist at Massachusetts General Hospital and have held those positions since 1997. I joined Biogen in 2003 as Associate Director, Medical Research and, through my work at the company over approximately the past 12 years, am now Senior Vice President, Drug Innovation Units.

on my contribution to the claimed subject matter.

4. I understand that Biogen submitted **Ex. 2005**, a poster entitled "A Randomized, Placebo-Controlled Phase 2 Trial of a Novel Oral Fumarate, BG00012, in Patients With Relapsing-Remitting Multiple Sclerosis" presented at the 15th Meeting of the European Neurological Society on June 18-22, 2005, in support of its Patent Owner Preliminary Response. I am a co-author on that poster (**Ex. 2005**), which I have reviewed.

5. I provide this declaration based on my personal knowledge of **Ex. 2005**. I am not being compensated to provide this declaration, nor will I receive any compensation based on a favorable outcome for Biogen in this proceeding.

II. Ex. 2005 is a True Copy of the Poster Presentation Made in June 2005

6. I attended the 15th Meeting of the European Neurological Society held in Vienna, Austria from June 18-22, 2005. I believe that **Ex. 2005** is a true and accurate copy of the poster that was presented at that meeting.

7. At Biogen, I led the MS Clinical Development Team's ("CDT") efforts to design a Clinical Development Plan for the MS indication and to design a Phase 2 proof-of-concept clinical trial using BG-00012, an orally administered

8. I was the principal lead on Biogen's Phase 2 study, the clinical design of which is summarized in **Ex. 2005**. I confirm, based on my personal knowledge, that the active dosage units of DMF used in that study contained 120 mg of DMF per capsule. The study did not use capsules containing 240 mg of DMF. Thus, for example, patients in the 720 mg/day group took two 120 mg DMF capsules three times a day as shown in Table 1 of **Ex. 2005**.

III. Conclusion

9. I 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 are made with knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and may jeopardize the patentability of Biogen's U.S. Patent No. 8,399,514.

10. In signing this declaration, I understand that the declaration may be filed as evidence in a contested case before the Patent Trial and Appeal Board of the United States Patent and Trademark Office. I acknowledge that I may be subject to cross-examination in the case and that cross-examination will take place

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