CLINICAL STUDY REPORT

FINAL
Study Number: C-1900

Double-Blind, Placebo-Controlled, Dose-Ranging Study to Determine the Efficacy and Safety of BG00012 in Subjects with Relapsing-Remitting Multiple Sclerosis

Name of Drug:	BG00012
Indication:	Multiple Sclerosis
Drug Development Phase:	2
Sponsor:	Biogen Idec Inc. 14 Cambridge Center Cambridge, MA 02142
Study Dates:	02 November 2004 through 31 March 2006
Coordinating Investigator:	[redacted]
Name of Sponsor Signatory:	[redacted] Vice President Neurology, Chief Medical Officer [redacted]
Study Medical Director:	Kate Dawson, MD (617) 914-6377; FAX (617) 679-3518
Study Medical Director:	Gilmore O'Neill, MB, MRCPI, MMedSc (617) 914-4725; FAX (617) 679-3518
Study Statistician:	Minhua Yang (617) 679-4302; FAX (617) 679-3280
Study Pharmacokineticist:	[redacted]
Report Date:	12 May 2008

To the best of the sponsor's knowledge, this study was conducted in compliance with the requirements of the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP), United States 21 Code of Federal Regulations (CFR) Parts 50, 54, and 56, and other applicable standards for the protection of human subjects and integrity of clinical data. It has been monitored by the sponsor or by the sponsor's representative. There were no deviations from the above-referenced standards that, in the view of the sponsor, were likely to have compromised the integrity or quality of the study, the interpretation of the results, subject safety, or ethical standards. Essential documents, as described in ICH E6, have been archived in Central Clinical Files and in an electronic study file.

6 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

6.1 Investigators

[redacted]

An investigator meeting was held on 14 and 15 September 2004 (in Versailles). The purpose of this meeting was to train Investigators, Study Coordinators, and other team members on the procedures, tests, and evaluations to be used, conducted, or assessed in this study. This meeting was held prior to the first patient being enrolled into the study.

6.2 Study Committees

6.2.1 Advisory Committee

An Advisory Committee (AC) was formed to provide scientific and medical direction for the study and to oversee the administrative progress of the study. The AC was to conduct quarterly reviews of the study to monitor patient accrual and to monitor compliance with the protocol at individual investigational sites. The AC was blinded to patient treatment assignments. The AC was to determine whether the study should be stopped or amended for either efficacy or safety reasons.

The AC was comprised of the Medical Director, Clinical Trial Manager, and Project Statistician from Biogen Idec (and/or their designees), and participating Investigators as well as clinical experts who were not participating as investigators in this study. [redacted], a participating Investigator who was designated as the Coordinating Investigator by Biogen Idec, also chaired the AC. Current curriculum vitae for AC members who were not from Biogen Idec are provided in Appendix 16.1.4.

6.2.2 Clinical Safety Committee

An independent Clinical Safety Committee reviewed all adverse events (AEs), clinical observations, vital signs, and laboratory tests for all patients. The Clinical Safety Committee was comprised of 3 members who were all independent of Biogen Idec. A set of guidelines was established between Biogen Idec and the Clinical Safety Committee to outline the Clinical Safety Committee's responsibilities and procedures. This document is included in Appendix 16.1.13. The first meeting was conducted prior to study onset on 02 November 2004. Members were blinded to patient treatment assignments. Findings and conclusions were to be reported to the Chairman of the AC and Biogen Idec Medical Director.

Investigational sites were to be notified of any relevant safety findings that may have jeopardized patient safety. The Clinical Safety Committee met after 25% of the patients had 3 months exposure to the investigational drug. Subsequent meetings occurred every 3 months throughout the study duration.

6.3 Laboratories

Blood for hematology and blood chemistry and urine for urinalysis were analyzed at [redacted]

Magnetic Resonance Imaging Reading Center

Analysis of all magnetic resonance imaging (MRI) scans conducted in this study was performed at a central facility, [redacted]. Prior to patient enrollment at an investigational site, the MRI reading center verified the investigational site's scanning technique by evaluating a test scan from an MS patient. Original MRI films, as well as tapes or optical disk media, were to be sent by courier to the MRI center for review. MRIs were evaluated by physicians/technicians who are blinded to the patients' treatment assignments. Additional MRI procedures and instructions are provided in Appendix 16.1.10.

6.4 Vendors

6.4.1 Contract Research Organization

[redacted] acted as the Data Coordinating Center (DCC) for all countries and [redacted] for countries in the European Union. [redacted] acted as the CRO for Russia only.

The DCC was responsible for administrative aspects of the study including, but not limited to, study initiation, monitoring, management of AE reports, and data management. Prior to enrollment of the first patient at each investigational site, the DCC was to review study responsibilities with the Investigators and other investigational site personnel, as appropriate.

6.4.2 Centralized Randomization

[redacted] was responsible for patient randomization, patient tracking, and study drug inventory. Before patient

[redacted]

screening or enrollment, the investigational site was provided with appropriate training and a user manual.

6.5 Clinical Study Supply Management

[redacted] manufactured the active pharmaceutical ingredient (API), dimethyl fumarate, of BG00012 for this study.

[redacted]

[redacted] manufactured BG00012 drug product (API plus all additional excipients) and the placebo.

Kits were packaged and labeled at [redacted] and were distributed to clinical sites by [redacted].

Finished product was released by [redacted]

[redacted]

[redacted]

9.1 OVERALL STUDY DESIGN AND PLAN

This study was a Phase 2, double-blind, multicenter, randomized, placebo-controlled, parallel-group, dose-ranging study to determine the efficacy of 3 different BG00012 dose levels on brain lesion activity as measured by MRI in patients with RRMS. Following screening, patients entered a 24-week treatment phase (Part 1) in which they were randomly assigned to receive placebo or one of three dosing regimens of BG00012 (Table 9.1-1). This was followed by a 24-week double-blind, safety extension phase (Part 2). Approximately 260 patients at 42 sites were to be randomized in equal numbers to the 4 treatment groups.

Table 9.1-1: Treatment Groups for Part 1 of Study C-1900

Treatment Group	BG00012 Dosing Regimen	BG00012 Total Daily Dose
1	120 mg QD	120 mg
2	120 mg TID	360 mg
3	240 mg TID	720 mg
4	Placebo	Placebo

Eligible patients were to take 2 oral capsules of study drug (BG00012 or placebo, depending on treatment group and the phase of the study) 3 times a day (TID) for up to 48 weeks.

During the placebo-controlled phase, study drug tolerability was evaluated in all patients after the first week of dosing. Patients randomized to receive the highest dose, 240 mg TID, were initially dosed at 120 mg TID for the first week to determine tolerance to flushing episodes and GI disturbances. If 120 mg TID was tolerated in the first week, the dose was increased to 240 mg TID.

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