U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 204063
Drug Name:	BG00012 (Dimethyl Fumarate) delayed release capsules
Indication(s):	Relapsing multiple sclerosis
Applicant:	Biogen Idec Inc.
Date(s):	Submission date: 02/27/2012
	PDUFA Date: 12/27/12
Review Priority:	Standard
Biometrics Division:	Division of Biometrics I
Statistical Reviewer:	Xiang Ling, Ph.D.
Concurring Reviewers:	Kun Jin, Ph.D., Team Leader
	James Hung, Ph.D., Director
Medical Division:	Division of Neuropharmacological Drug Products, HFD-120
Clinical Team:	Heather Fitter, M.D., Clinical reviewer
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1 EXECUTIVE SUMMARY

The data overall provided adequate evidence to support for the efficacy of BG00012 as treatment of patients with relapsing multiple sclerosis.

In both pivotal studies, treatment with BG00012 BID and TID resulted in a statistically significant effect on relapses and MRI lesion accumulation. Study 301 also yielded a statistically significant effect of BG00012 on disability progression, and in Study 302 BG00012 groups had numerically fewer subjects with disability progression compared to the placebo group. The effect of BG00012 was generally consistent across a variety of subgroups defined by demographic and baseline disease characteristics.

Since flushing is a known side effect of BG00012 and occurred to high percentage of subjects, the agency was concerned about perceived unblinding of subjects' treatment assignments by observing flushing related events. To assess the robustness of the primary analysis result against potentially biased relapse assessment in case of perceived unblinding, this reviewer conducted worst case scenario analyses, in which all relapses prior to and after alternative MS medications were included for subjects in BG00012 groups but only relapses that met objective criteria as assessed by sites, confirmed by a blinded Independent Neurology Evaluation Committee (INEC), and occurred prior to alternative MS medications, were included for placebo subjects. The results of the worst case analysis still reached statistical significance.

The treatment discontinuation rate was high in both studies, partly because the studies allowed subjects to cross over to alternative MS treatments. However, as shown in a series of sensitivity analyses including analyses of the worst case scenario, treatment discontinuation or the switch to alternative MS medications did not appear to have a significant effect on the efficacy results or conclusions.

2 INTRODUCTION

2.1 Overview

BG00012 is an oral formulation containing the single active ingredient dimethyl fumarate (DMF) for the intended treatment of subjects with relapsing multiple sclerosis (MS). BG00012 was developed under IND 73061. SPA was submitted for pivotal Studies 109MS301 and 109MS302 (hereafter referred to as "Study 301" and "Study 302," respectively) without reaching Agency agreement. However, advices from the Agency were incorporated into the study protocols before the studies were initiated, such as inclusion of the 240 mg BID dose group, changing the primary endpoint in one study from proportion relapsed to annualized relapse rate, and requiring subjects to remain on study treatment for 1 year before being eligible for rescue treatment with an approved therapy due to relapse. Statistical analysis plan (SAP) was submitted for Agency review (SN143) and revised according to the agency's comments.

Studies 301 and 302 were Phase 3, randomized, placebo-controlled studies that evaluated the efficacy and safety of 2 dosing regimens of BG00012 (240 mg BID and 240 mg TID) versus placebo. Study 302 also included an active reference comparator (GA). A total of 1237 RRMS subjects were enrolled into Study 301 and 1430 subjects into Study 302. Subjects were required to have an EDSS between 0 and 5 at randomization and must have experienced a least 1 relapse within the year prior to randomization or have had a Gd-enhancing lesion on MRI scan obtained within 6 weeks prior to randomization. The only difference between the eligibility criteria of the 2 studies was in exposure to GA. In Study 302, no prior exposure to GA was allowed, whereas in Study 301, subjects could have received prior treatment with GA but had to have discontinued for at least 3 months prior to randomization.

2.2 Data Sources

Materials reviewed for this application include the clinical study reports, raw and derived datasets, SAS codes used to generate the derived datasets and tables, protocols, statistical analysis plans, and documents of regulatory communications, which are located in the following directory: \\cdsesub5\EVSPROD\NDA204063\0000.

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