109MS311/ NCT02555215

Biogen Idec - BG00012 in MS

Statistical Analysis Plan

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STATISTICAL ANALYSIS PLAN

A Multicenter Extension Study to Determine the Long-Term Safety and Efficacy of BG00012 in Pediatric Subjects With Relapsing-Remitting Multiple Sclerosis

Protocol 109MS311 Statistical Analysis Plan

Study Phase: 3

Product Studied: BG00012

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TABLE OF CONTENTS

List of Abbreviations

AE	adverse event
BID	twice daily
CDT	Clinical Development Team
CI	confidence interval
CRF	case report form
CRO	contract research organization
DMF	dimethyl fumarate
EDC	electronic data capture
GCP	Good Clinical Practice
ICF	informed consent form
ICH	International Council on Harmonisation
IFN	interferon
IgG	immunoglobulin G
IXRS	Interactive Voice/Web Response System
MCV4	meningococcal polysaccharide diphtheria conjugate vaccine (quadrivalent)
MedDRA	Medical Dictionary for Regulatory Activities
MS	multiple sclerosis
PHI	protected health information
PPSV23	23-valent pneumococcal polysaccharide vaccine
RRMS	relapsing-remitting multiple sclerosis
SAE	serious adverse event
SMT	Study Management Team
SUSAR	suspected unexpected serious adverse reaction
Td	tetanus diphtheria toxoids vaccine
US	United States
WHO	World Health Organization

1 STUDY OBJECTIVES AND ENDPOINTS

1.1 Primary Objective and Endpoint

The primary objective of the study is to evaluate the long-term safety of BG00012 in pediatric subjects who completed Study 109MS202.

Primary endpoint:

incidence of AEs, serious AEs (SAEs), and discontinuations of study treatment due to an AE

1.2 Secondary Objectives and Endpoints

The secondary objectives of this study are as follows:

- to evaluate the long-term efficacy of BG00012
- describe the long-term MS outcomes in subjects who completed Study 109MS202

The secondary endpoints are:

- The total number of new or newly enlarging T2 hyperintense lesions on brain MRI scans, the ARR, and the proportion of subjects who experience 1 or more relapses during the study period.
- The degree of disability as measured by the EDSS and disability progression (as measured by at least a 1.0-point increase on the EDSS from baseline EDSS ≥1.0 that is sustained for 24 weeks, or at least a 1.5-point increase on the EDSS from baseline EDSS = 0 that is sustained for 24 weeks).

2 STUDY DESIGN

2.1 Study Overview

This is a multicenter, open-label extension of Study 109MS202 that is designed to evaluate the long-term safety and efficacy of BG00012 in pediatric subjects.

2.2 Overall Study Duration and Follow-Up

The study period will consist of enrollment, treatment, and follow-up. The study duration is approximately 104 weeks, consisting of a 4-week enrollment period (if the Final Study Visit from Study 109MS202 cannot be combined with the Baseline Visit for this study), a 96-week treatment period, and a Safety Follow-Up Visit up to 4 weeks after the last dose of study treatment. Unscheduled Relapse Assessment Visits and Lymphocyte Follow-Up Visits will be performed as necessary.

End of Study for Subjects

The end of the study is the last subject, last visit for final collection of data, which is the Safety Follow-Up Visit. This visit is up to 4 weeks after the last dose of study treatment.

3 STUDY ACTIVITIES

Table 1: Schedule of Activities for 109MS311

Tests and Assessments[1]	Year 1						Year 2					Safety Follow-Up Visit
	Baseline Visit (Day 1)[2]	Visit 1 (Week 12±5d)	Visit 2 (Week 16 ±5d)	Visit 3 (Week 24 ±5d)	Visit 4 (Week 36 ±5d)	Visit 5 (Week 48 ±5d)	Visit 6 (Week 60 ±5d)	Visit 7 (Week 64 ±5d)	Visit 8 (Week 72 ±5d)	Visit 9 (Week 84 ±5d)	Visit 10 (Week 96 ±5d)	
Informed Consent and Assent[3]	X											
Eligibility Criteria	X											
Medical History	X											
MS-Related Medical History[4]	X											
Physical Examination	X											X
Body Weight	X	X		X	X	X	X		X	X	X	X
Height	X			X		X			X		X	X
Vital Signs[5]	X	X		X	X	X	X		X	X	X	X
12-Lead ECG	X										X	X
Hematology	X	X		X	X	X	X		X	X	X	X
Blood Chemistry	X	X		X	X	X			X		X	X
Urine Pregnancy Test[6]	X	X		X	X	X	X		X	X	X	X
Urinalysis [78]	X	X		X	X	X			X		X	X
PTH and Vitamin D Levels	X					X					X	X
Brain MRI Scan[a)910]	X		X	X				X	X			
EDSS	X	X		X	X	X			X		X	
Dispense Study Treatment[b)11]	X	X		X	X	X	X		X	X		
Concomitant Therapy and Procedures Recording	Monitor and record throughout the study											
AE/SAE Reporting	Monitor and record throughout the study											

AE = adverse event; ECG = electrocardiogram; EDSS = Expanded Disability Status Scale; MRI = magnetic resonance imaging; MS = multiple sclerosis; PTH = parathyroid hormone; SAE = serious adverse event.

[1] Tests and assessments must be completed prior to study treatment dispensation.
[2] The Final Study Visit for Study 109MS202 will serve as the Baseline Visit for this extension study. The Final Study Visit from Study 109MS202 can be within 4 weeks of the Baseline Visit for Study 109MS311 if the 2 visits cannot be combined.
[3] Written informed consent from the subject's parents or legal guardians and assent from the subject, if appropriate, must be obtained prior to performing any study-related procedures.
[4] MS-related medical history will include complete MS history of disease, MS diagnostic criteria, MS signs and symptoms, and MS treatment history.
[5] Vital signs include body temperature, pulse rate, and systolic/diastolic blood pressure measurements.
[6] For females of child bearing potential. Results must be known prior to study treatment dispensation.
[7] Urine cytology must be performed at all visits indicated if a subject experiences hematuria (of unknown etiology) at 2 consecutive visits. If urine cytology is positive for malignant cells, the subject must permanently discontinue study treatment.
[8] Study treatment must be temporarily withheld or permanently discontinued if any of the laboratory values meet the criteria defined in the protocol.
[9] MRI must not be performed within 30 days of receiving a course of steroids.
[10] The time between the Week 24 MRI and the Week 16 MRI must be the same as the time between the Day 0 MRI and Week -8 MRI in Study 109MS202 within a window of ±3 days. For example, if the Day 0 and Week -8 MRIs for a particular subject occurred 8 weeks apart in Study 109MS202, then the Week 24 MRI in Study 109MS311 should be 8 weeks ± 3 days after the Week 16 MRI. If necessary, the Week 24 MRI may be conducted separately from the Week 24 clinic visit. Similarly, the time between the Week 72 MRI and the Week 64 MRI must be the same as the time between the Day 0 MRI and Week -8 MRI in Study 109MS202 within a window of ±3 days. If necessary, the Week 72 MRI may be conducted separately from the Week 72 clinic visit.
[11] Initial dispensation of study treatment may require an additional visit on or around Day 7. Laboratory results must be evaluated and eligibility confirmed prior to dispensation of study treatment.

Table 2: Additional Study Activities for Study 109MS311

Tests and Assessments	Unscheduled Relapse Assessment Visit[1] *(within 72 hours after symptom onset)*	Discontinuation/ Withdrawal Visit[2] *(as soon as possible but no later than 4 weeks after last dose of study treatment)*	Lymphocyte Follow-Up Visit[3]
Physical Examination	X	X	X
Body Weight	X	X	X
Height		X	
Vital Signs[4]	X	X	X
12-Lead ECG		X	
Hematology[5,6]	X	X	X
Blood Chemistry[6]	X	X	
Urine Pregnancy Test[7]	X	X	
Urinalysis[6,8]	X	X	
PTH and Vitamin D Levels		X	
EDSS	X	X	
Brain MRI Scan[9]		X[10]	
Relapse Assessment	X		
Concomitant Therapy and Procedures	Monitor and record throughout the study		
AE/SAE Recording	Monitor and record throughout the study		

AE = adverse event; ECG = electrocardiogram; EDSS = Expanded Disability Status Scale; LLN = lower limit of normal; MRI = magnetic resonance imaging; PTH = parathyroid hormone; SAE = serious adverse event.

[1] An Unscheduled Relapse Assessment Visit will be conducted within 72 hours of symptom onset of a suspected relapse (i.e., new or recurrent neurologic symptom[s]).

[2] Discontinuation refers to discontinuation of study treatment. Withdrawal refers to withdrawal of subjects from the study. The Discontinuation/Withdrawal Visit should be conducted as soon as possible and no later than 4 weeks after the last dose of study treatment.

[3] Subjects who complete, temporarily withhold, or permanently discontinue study treatment for any reason and have a lymphocyte count <LLN will continue protocol-required visits and assessments and be followed every 4 weeks for 24 weeks and then every 3 months (unless clinically indicated more often or at the Investigator's discretion) until the lymphocyte count is ≥LLN or for 52 weeks after the last dose (whichever is sooner).

[4] Vital signs include body temperature, pulse rate, and systolic/diastolic blood pressure measurements.

[5] Hematology testing must be performed every 4 weeks in subjects with lymphocyte count <LLN

[6] Study treatment must be temporarily withheld or permanently discontinued if any of the laboratory values meet the criteria defined in the protocol.

[7] For females of childbearing potential.

[8] Urine cytology must be performed if a subject experiences hematuria (of unknown etiology) at 2 consecutive visits or at the Unscheduled Relapse Assessment Visit or the Discontinuation/Withdrawal Visit.

[9] An MRI must not be performed within 30 days of receiving a course of steroids.

[10] A brain MRI scan will be performed unless assessed in the last 30 days.

4 INTERIM ANALYSIS

The data from this study will be summarized periodically to support regulatory submissions, or when further information on the long-term safety and efficacy of BG00012 in the pediatric population is required.

5 SAMPLE SIZE JUSTIFICATION

Because this study is an extension study, the sample size was be determined by the number of eligible subjects who completed Study 109MS202.

6 STATISTICAL ANALYSIS METHODS

The statistical software, SAS® ,will be used for all summaries and statistical analyses.

Statistical analyses will be descriptive in nature with appropriate measures of variation provided where applicable. For continuous endpoints, summary statistics will generally include the following: number of subjects with data, mean, standard deviation, median, and range. For categorical endpoints, summary statistics will generally include the frequency distribution of the analysis population.

6.1 Description of Analytic Methods

As the study contains a single treatment group, descriptive statistics will be the primary approach to analyze the data.

6.1.1 Summary of Baseline Data

Baseline data are defined as data collected prior to the administration of BG00012 on Day 1 on study 109MS311, which should be the final visit in study 109MS202. If the final visit in study 109MS202 cannot be used as baseline, Day 1 on study 109MS311 will be considered baseline. Baseline demographics from study 109MS202 will be summarized using only those subjects that continue into study109MS311. Age will be recalculated based on the date informed consent was signed for study 109MS311.

6.1.2 Accounting of Subjects

Number of subjects who enrolled into 109MS311 from the previous study, number who received at least one dose of BG00012, number completing treatment, number completing the study, number discontinuing prior to Week 96 and reason for early withdrawal, will be summarized.

6.1.3 Protocol Deviations

Major and minor protocol deviations identified in the study will be listed.

6.1.4 Demographic and Baseline Characteristics

Demographic data, including age (in years, at the time of consent to study 109MS311), gender and race category will be summarized for the subjects that enroll into study 109MS311. In addition, baseline height (cm) and weight (kg) will also be presented.

Medical history will be summarized for just those subjects who enrolled in 109MS311 by category using number and percentage of subjects that had experienced certain maladies prior to entering the study. Medical history will include information collected in 109MS202, but for only those subjects who entered 109MS311. Included will be the number of subjects with ongoing or resolved medical/surgical history that have occurred since the subject enrolled in 109MS202.

The MS Pediatric Diagnostic Criteria as defined by Krupp (2013), obtained at screening of study 109MS202, will be summarized for those subjects who enrolled into 109MS311.

MS signs considered typical MS signs and symptoms will be summarized for each area: vision, cognition, coordination/balance, bladder control, bowel, sexual function, and general. In addition, MS signs related to sensory disturbances, motor disturbances, and other will be presented for the population and summarized. Only those subjects who entered 109MS311 will be included in the summaries.

History of MS for the subjects enrolled in 109MS311 will be summarized using information collected prior to study 109MS202. This includes time since first MS diagnosis, time since first symptoms, number of relapses prior to screening in study 109MS202 (prior 12 months, 2 years, and 3 years) and the time since the last relapse prior to 109MS202. In addition, the MS treatment history will be summarized for these subjects in 109MS311 prior to receiving BG00012 in the 109MS202 study.

6.1.5 Concomitant Medications and Non-drug Therapies

Concomitant medication is defined as prescribed or over-the-counter medications used during the study (on or after Day 1 of 109MS311). The World Health Organization (WHO) Drug Dictionary will be used for coding concomitant medications. The Medical Dictionary for Regulatory Activities (MedDRA) will be used for coding concomitant non-drug therapies.

The number and percentage of subjects taking concomitant medication and receiving non-drug treatments will be summarized.

As the study progresses, a listing of all medications will be periodically reviewed by clinical personnel so as to properly classify concomitant medications as allowed or prohibited.

6.1.6 Exposure to study drug

Number of days exposed to BG00012 during study 109MS311, total amount of BG00012 received and overall compliance will be summarized. Compliance for each subject is defined as the total amount of BG00012 received divided by the number of days on treatment.

6.1.7 Visit Windows

If a subject withdraws after receiving at least one dose of BG00012, but prior to the Week 96 scheduled visit, data from the early withdrawal visit will be assigned as the next scheduled visit if it has occurred within a visit window. Scheduled visits have a window of ±5 days.

If more than one observation is within the same window, data closest to the target regular scheduled visit will be used in the summary statistics. If more than one observation falls in the same distance from the target regular scheduled visit day, the later observation will be used in the summary statistics.

6.2 Efficacy Analysis

6.2.1 Analysis Population

The population for the analysis of efficacy endpoints will be all subjects who have received at least 1 dose of BG00012 in this study and who have an evaluation of the efficacy endpoint under analysis.

6.2.2 Analysis Methods

Summary statistics will be presented for MRI data (number of new or newly enlarging T2 hyperintense lesions) over time

ARR will be summarized, along with the proportion of subjects relapsing, the rate of relapses requiring IV steroid use, and the rate of MS-related hospitalizations.

EDSS scores and changes from baseline will be summarized over time along with the proportion of subjects with confirmed disability progression.

6.3 Safety Data

6.3.1 Analysis Population

The analysis population for safety summaries will be all subjects who received at least 1 dose of BG00012.

6.3.2 Analysis Methods

Summaries of safety data will include descriptive statistics for continuous variables and frequency distributions for categorical variables.

6.3.2.1 Definition of Baseline Value and Visit Windows

Baseline values and visit windows for safety summaries are defined in the same way as they are for efficacy analyses (see Section 6.1.1 and 6.1.7, respectively).

6.3.2.2 Clinical Adverse Events

Treatment (BG00012)-emergent AEs are defined as AEs occurring or worsening after beginning study treatment (after the first dose in study 109MS311).

Incidence of AEs will be summarized using frequency distribution tables; overall, by severity, and by relationship to BG00012. The summary tables will include incidences for system organ class as well as for preferred terms within each system organ class. Similar incidence analyses will be summarized for SAEs and for the most common AEs.

AEs will be coded using the MedDRA dictionary (version 20.1). This coding system provides five levels to classify AEs. In general, AEs will be presented by system organ class and preferred term.

The summary tables will include incidence estimates for overall system organ class as well as for preferred terms within each system organ class. AEs will be presented in the order of decreasing incidence of system organ class and then by preferred term within system organ class.

If a subject experiences an event more than once during the study, he/she will be counted only once using the maximum severity if more than one severity is reported, within each system organ class/preferred term.

AEs will be classified by severity (mild, moderate and severe) and by relationship to BG00012.

The incidence of SAEs will be presented by system organ class and preferred term. Details of each SAE will be listed, including subject ID, system organ class/preferred term, date of onset, severity, relationship to BG00012 and action taken. Subject narratives will also be provided.

The incidence of AEs that led to early withdrawal from the study will be presented separately. A listing of the individual subjects with these AEs will also be presented.

The incidence of AEs that led to treatment discontinuation during the study will be presented in a separate table, along with a listing of these individual subjects who experienced AEs leading to treatment discontinuation.

6.3.2.3 Clinical Laboratory Data

The following clinical laboratory parameters are assessed per the protocol:

- Hematology: hemoglobin, hematocrit, red blood cell count, WBC count (with differential) and platelet count.
- Blood chemistry: albumin, sodium, potassium, chloride, total bilirubin, alkaline phosphatase, ALT, AST, GGT, blood urea nitrogen, creatinine, bicarbonate, calcium, magnesium, phosphate, uric acid, and glucose
- Vitamin D and PTH (Day 1 and Week 96 only)
- Urine and serum pregnancy tests

Each laboratory value for each subject will be flagged as 'low', 'normal', or 'high', relative to the parameter's normal range. Each subject's urinalysis values will be flagged as "positive", "negative", or if no value is available, "unknown".

Shifts from baseline to post baseline (Week 4/early withdrawal) high/low status for all hematology and blood chemistry parameters, and shifts from baseline to high/positive status for urinalysis will be presented.

Summary statistics will also be provided for all absolute laboratory values as well as change from baseline. The summaries for laboratory data will be data from baseline to each time point, including early withdrawal. Graphs showing the mean or change from baseline values may be presented as well.

In addition to lymphocyte count data summarized at each timepoint on study treatment, lymphocyte count over time post-treatment and the time to recovery will be descriptively summarized for subjects who develop decreases in lymphocyte count (<LLN).

6.3.2.4 Vital Signs Data

The analysis of vital signs will focus on the incidence of clinically relevant abnormalities. The number of subjects evaluated and the number and percentage of subjects with clinically relevant post-baseline abnormalities will be presented. The criteria for clinically relevant post-baseline abnormalities are shown in the following table (Table 2). Summary statistics for actual values and change from baseline will also be presented.

Table 2 Criteria to Determine Clinically Relevant Abnormalities in Vital Signs

Vital Sign	Criteria for Abnormalities
Temperature	>38ºC or an increase from baseline of at least 1ºC
Pulse	>120 beats per minute (bpm) or an increase from baseline of >20 bpm
	<50 bpm or a decrease from baseline of >20 bpm
Systolic Blood Pressure	>180 mmHg or an increase from baseline of >40 mmHg
	<90 mmHg or a decrease from baseline of >30 mmHg
Diastolic Blood Pressure	>105 mmHg or an increase from baseline of >30 mmHg
	<50 mmHg or a decrease from baseline of >20 mmHg

6.3.2.5 12-Lead ECG

The analysis of ECG will be summarized at each timepoint, presenting only frequencies of Normal, Abnormal – no adverse event, and Abnormal – adverse event.

6.3.2.6 Height and Weight

The analysis of height and weight will be summarized at each timepoint, presenting descriptive statistics for both.