COVER PAGE

Official Title:	Open-Label, Randomized, Multicenter, Multiple-Dose,Active-Controlled, Parallel-Group, Efficacy and Safety Study of BG00012 in Children From 10 to Less Than 18 Years of Age With Relapsing-Remitting Multiple Sclerosis, With Optional Open-Label Extension
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109MS306

Biogen - BG00012 in MS

Statistical Analysis Plan

BIOGEN

STATISTICAL ANALYSIS PLAN

Open-Label, Randomized, Multicenter, Multiple-Dose, Active-Controlled, Parallel-Group, Efficacy and Safety Study of BG00012 in Children From 10 to Less Than 18 Years of Age With Relapsing-Remitting Multiple Sclerosis, With Optional Open-Label Extension

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Note: On 30 April 2021 an administrative update was produced for this document, specifically to correct the Table of Contents on pages 3 and 4.

Protocol 109MS306: Phase 3 Study

Product Studied: BG00012

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List of Abbreviations

AE	adverse event
ALT	alanine transaminase
ANCOVA	analysis of covariance
ARR	annualized relapse rate
AST	aspartate transaminase
BID	twice daily
BUN	blood urea nitrogen
BVMT-R	Brief Visuospatial Memory Test - Revised
CI	confidence interval
CNS	central nervous system
CRO	contract research organization
CSR	clinical study report
DHA	Directions for Handling and Administration
DMF	dimethyl fumarate
DSMB	Data Safety Monitoring Board
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
EDSS	Expanded Disability Status Scale
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
Gd	gadolinium
GGT	gamma-glutamyl-transferase
GI	gastrointestinal
HbcAb	hepatitis B core antibody
HbsAb	hepatitis B surface antibody
HbsAg	Hepatitis B surface antigen
ICF	informed consent form
ICH	International Conference on Harmonisation
IFN β	interferon β
IFN β-1a	interferon β-1a
IM	intramuscular
ITT	Intent-to-Treat
IV	intravenous
IVMP	intravenous methylprednisolone
IXRS	Interactive Voice/Web Response System
LH	luteinizing hormone
LLN	lower limit of normal
MMF	monomethyl fumarate
MRI	magnetic resonance imaging
MS	multiple sclerosis
PedsQL	Pediatric Quality of Life Inventory
PHI	protected health information
RDC	remote data capture

RRMS	relapsing-remitting multiple sclerosis
SABR	Safety and Benefit-Risk Management
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SDMT	Symbol Digit Modalities Test
SUSAR	suspected unexpected serious adverse reaction
TID	3 times daily
ULN	upper limit of normal
US	United States
WBC	white blood cell

1. STUDY OBJECTIVES AND ENDPOINTS

1.1. Primary Objective and Endpoint

- The primary objective of the study is to evaluate the safety, tolerability, and efficacy of BG00012 in pediatric subjects with relapsing-remitting multiple sclerosis (RRMS), as compared with a disease-modifying treatment

Primary endpoint:

- The proportion of subjects free of new or newly enlarging T2 hyperintense lesions on brain MRI scans at Week 96

1.2. Secondary Objectives and Endpoints

The secondary objective of this study are as follows:

- to assess health outcomes and evolution of disability

The secondary endpoints are:

- Number of new or newly enlarging T2 hyperintense lesions on brain MRI scans at Weeks 24 and 96
- Proportion of subjects free of new or newly enlarging T2 hyperintense lesions on brain MRI scans at Weeks 24 and 48
- Proportion of subjects free of new MRI activity (i.e., free of Gd-enhancing and free of new or newly enlarging T2 MRI lesions on brain MRI scans) at Weeks 24, 48, and 96
- Time to first relapse
- Proportion of subjects free of relapse up to Week 96
- Annualized relapse rate (ARR) at Weeks 48 and 96
- Incidence of AEs and serious adverse events (SAEs), including prospective follow-up of flushing, nausea, abdominal pain, and diarrhea
- Vital signs, electrocardiograms (ECGs), and changes in clinical laboratory data, including liver function, renal function, hematologic, and coagulation parameters
- Fatigue as measured by the PedsQL Multidimensional Fatigue Scale scores
- Quality of Life as measured by the PedsQL
- Change from baseline to Week 96 in the EDSS score

1.3. Exploratory Endpoints

The exploratory endpoints of Part 1 are as follows:

- Number of new or newly enlarging T2 hyperintense lesions on brain MRI scans at Weeks 48 and 72
- Proportion of subjects free of new or newly enlarging T2 hyperintense lesions on brain MRI scans at Week 72
- Proportion of subjects free of new MRI activity (i.e., free of Gd-enhancing and free of new or newly enlarging T2 MRI lesions on brain MRI scans) at Week 72
- Number of new T1 hypointense lesions on brain MRI scans at Weeks 24, 48, 72, and 96
- Number of Gd-enhancing lesions on brain MRI scans at Weeks 24, 48, 72, and 96
- Time to progression of disability at 96 weeks as measured by at least a 1.0 point increase on the EDSS from baseline EDSS ≥1.0 that is sustained for 12 weeks, or at least a 1.5 point increase on the EDSS from baseline EDSS = 0 that is sustained for 12 weeks
- BVMT-R scores (to assess learning/memory) and SDMT scores (to assess processing speed), and school progression query at Weeks 48 and 96

2. STUDY DESIGN

2.1. Study Overview

Part 1 will be an open-label, randomized, multicenter, multiple dose, active controlled, parallel group phase to evaluate the safety, tolerability, and efficacy of daily oral BG00012 administered for 96 weeks, compared with disease modifying treatment for pediatric MS, in male and female pediatric subjects with RRMS (aged from 10 to less than 18 years old at the time of informed consent or assent). Only subjects who have agreed (through parents or legal guardians, according to local regulations) with their treating physician to be involved in the study will be enrolled. Subjects will be screened over a maximum of 6 weeks prior to first dose.

Eligible subjects will be randomly assigned in a 1:1 ratio to treatment with BG00012, administered orally at a dose of 240 mg BID, or IFN β1a (Avonex), administered at a dose of 30 μg once weekly by intramuscular (IM) injection. Randomization will be stratified according to whether or not the subject received therapy with IFN β-1a or glatiramer acetate in the 4 weeks prior to study entry and in accordance with the following 3 age groups:

10 to <13 years: at least 10 evaluable (for primary endpoint) subjects

13 to <15 years: at least 20 evaluable (for primary endpoint) subjects

15 to <18 years: at least 60 evaluable (for primary endpoint) subjects

The goal is to obtain a total of at least 100 evaluable subjects. At least 30 evaluable subjects must be male.

2.2. Overall Study Duration and Follow-Up

Part 1 will consist of Screening (up to 6 weeks), Treatment Period (96 weeks), and Safety Follow-Up for those subjects who are not continuing into Part 2. All subjects who complete the Week 96 Visit will be eligible to participate in Part 2. Part 1 will be reported separate from Part 2. A statistical analysis plan for Part 2 of this study will be produced.

End of Study for Subjects

The end of Part 1 of the study is the last subject, last visit for final collection of data at week 96 for subjects who participate in Part 2. If a subject is not participating in Part 2, the end of the study will be the Safety Follow-Up visit. This visit is up to 4 weeks after the last dose of study treatment.

3. STUDY ACTIVITIES

Table 1: Study Activities - Part 1

Tests and Assessments[1]	Screening Visit											
Week	**(Within 6 Weeks of Baseline)**	**Baseline Visit (Day 1)**	**Wk 2 ±5D Safety Phone Call[2]**	**Wk4 ± 5D**	**Wk 8 ± 5D**	**Wk 12 ±5D**	**Wk 24 ± 5D**	**Wk 36 ± 5D**	**Wk 48 ± 5D**	**Wk 60 ± 5D**	**Wk 72 ± 5D**	**Wk 84 ± 5D**
Informed Consent or Assent[3]	X											
Eligibility Criteria	X	X										
Medical History[4]	X											
Hepatitis C Antibody and HBsAg Screen	X											
Randomization		X										
Physical Examination	X	X					X		X		X	
Body Weight	X	X		X	X	X	X	X	X	X	X	X
Height	X						X		X			
Tanner Score[5]	X								X			
Vital Signs[6]	X	X		X	X	X	X	X	X	X	X	X
12-Lead ECG	X	X[7]		X					X			
Hematology[8]	X	X		X	X	X	X	X	X	X	X	X
Blood Chemistry	X	X		X	X	X	X	X	X	X	X	X
PTT, PT, INR		X					X		X			
Urine Pregnancy Test[9, 10]	X	X		X	X	X	X	X	X	X	X	X
Urinalysis[11]	X	X		X	X	X	X	X	X	X	X	X
Endocrine Tests[12]		X							X			

Tests and Assessments[1]	**Screening Visit**											
Week	**(Within 6 Weeks of Baseline)**	**Baseline Visit (Day 1)**	**Wk 2 ±5D Safety Phone Call[2]**	**Wk4 ± 5D**	**Wk 8 ± 5D**	**Wk 12 ±5D**	**Wk 24 ± 5D**	**Wk 36 ± 5D**	**Wk 48 ± 5D**	**Wk 60 ± 5D**	**Wk 72 ± 5D**	**Wk 84 ± 5D**
EDSS	X	X				X	X	X	X	X	X	X
Brain MRI Scan ± Gd[13, 14]		X					X		X		X	
Hand and Wrist X-ray[15]		X							X			
PedsQL, PedsQL Multidimensional Fatigue Scale		X					X		X		X	
BVMT-R		X							X			
SDMT		X							X			
Query Regarding Annual School/Grade Progression[16]		X							X			
Dispense Treatment		X[1]		X	X	X	X	X	X	X	X	X
Concomitant Therapy and Procedures			X									
SAEs Recording		Monitor and record throughout the study as described in Section 8.2 of the protocol										
AEs Recording			Monitor and record throughout the study as described in Section 8.2 of the protocol									

AE = adverse event; BVMT-R = Brief Visuospatial Memory Test - Revised; D = days; ECG = electrocardiogram; EDSS = Expanded Disability Status Scale; FSH = follicle-stimulating hormone; Gd = gadolinium; HBsAg = hepatitis B surface antigen; INR = international normalized ratio; LH = luteinizing hormone; LLN = lower limit of normal; MRI = magnetic resonance imaging; MS = multiple sclerosis; PedsQL = Pediatric Quality of Life Inventory; PT = prothrombin time; PTT = partial thromboplastin time; SAE = serious adverse event; SDMT = Symbol Digit Modalities Test; Wk = week.

Note: Study visits (weeks) are calculated relative to Baseline (Day 1).

1 All tests and evaluations are to be performed before dispensing initial study treatment.

2 At Week 2 ± 5D, subjects will receive a safety telephone call from the study site staff.

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 Medical history will include complete MS history of disease (including pubertal status at the onset of disease), MS diagnostic criteria, MS signs and symptoms, and MS treatment history.

5 Assessment of Tanner stages should be performed by a medical doctor experienced with this assessment. Information regarding Tanner staging will be collected at baseline for all male subjects and for female subjects who are premenarche and will be stopped once the subject's bone age reaches ≥16 years or once the subject is postmenarche.

[6] Subjects will have their body temperature, heart rate, respiratory rate, and diastolic and systolic blood pressure measured. Subjects must remain in the same body position for 5 minutes prior to having heart rate and blood pressure taken.
[7] Performed before dosing at this visit.
[8] Lymphocyte counts must be tested every 4 weeks in subjects with lymphocyte count <LLN. See Lymphocyte Follow-Up Visit in Table 2 in the protocol .
[9] For females of childbearing potential. Results must be known prior to dispensing study treatment.
[10] All urine pregnancy testing will be performed at the study site.
[11] Urine cytology must be performed if microscopic hematuria of unknown etiology is observed under either of the following conditions: a) hematuria is present on 2 consecutive tests, or b) hematuria is observed at the End of Study/Early Withdrawal/Safety Follow-Up Visit. If urine cytology is positive, the subject must permanently discontinue study treatment (see Table 8 in the protocol).
[12] Endocrine parameters to be tested will include insulin-like growth factor 1, insulin-like growth factor binding protein, FSH, LH, and estradiol (E-2) for females and testosterone, FSH, and LH for males. All endocrine tests will be collected at baseline for all male subjects and for female subjects who are premenarche and will stop being collected once the subject's bone age reaches ≥16 years or once the subject is postmenarche.
[13] MRI must not be performed within 30 days of receiving a course of steroids, with the exception of MRIs obtained for the purpose of relapse assessment.
[14] MRI must be performed and reviewed within 14 days prior to or on Day 1 (Baseline Visit), and at Weeks 24 ± 14 days, 48 ± 14 days, and 72 ± 14 days.
[15] An x-ray of the left hand and wrist to determine bone age will be performed at baseline for all male subjects and for female subjects who are premenarche, if permitted by the local regulatory authority. Assessment of this x-ray for determination of bone age should be performed by a radiologist experienced with this assessment. For subsequent visits, once the bone age is determined to be ≥16 years of age or once the subject is postmenarche, no further bone x-rays are required.
[16] If permitted by the local regulatory authority, subjects or caregivers will be posed the following question: "During the past year, did [you/the subject] progress from one [class/grade-level] to the next in school?"

Table 2: Study Activities (Unscheduled and Post-Treatment Visits) - Part 1

Tests and Assessments[1]	End of Part 1/ Baseline Part 2 Visit	Early Withdrawal Visit	Safety Follow-Up Visit[2]	Lymphocyte Follow-Up Visit[3]	Unscheduled Relapse Assessment Visit[4]
Week	**Wk 96 ± 5D**		**No Later Than Wk 100 ± 5D**		
Informed Consent or Assent	X[5]				
Physical Examination	X	X	X	X	X
Body Weight	X	X	X		X
Height	X	X	X		
Tanner Score[6]	X	X			
Vital Signs[7]	X	X	X	X	X
12-Lead ECG	X	X	X		
Hematology[8]	X	X	X	X	X
Blood Chemistry	X	X	X		X
PTT, PT, INR	X	X			
Urine Pregnancy Test[9, 10]	X	X	X		X
Urinalysis[11]	X	X	X		X
Endocrine Tests[12]	X	X			
EDSS	X	X			X
Brain MRI Scan ± Gd[13]	X	X			X
Hand and Wrist X-ray[14]	X	X			
PedsQL, PedsQL Multidimensional Fatigue Scale	X	X			X
BVMT-R	X	X			
SDMT	X	X			
Dispense Treatment	X				

Tests and Assessments[1]	**End of Part 1/ Baseline Part 2 Visit**	**Early Withdrawal Visit**	**Safety Follow-Up Visit[2]**	**Lymphocyte Follow-Up Visit[3]**	**Unscheduled Relapse Assessment Visit[4]**
Week	**Wk 96 ± 5D**		**No Later Than Wk 100 ± 5D**		
Relapse Assessment					X
Query Regarding Annual School/Grade Progression[15]	X				
Concomitant Therapy and Procedures	X			X	X
SAEs Recording	Monitor and record throughout the study as described in Section 8.2 of the protocol			X	X
AEs Recording	Monitor and record throughout the study as described in Section 8.2 of the protocol			X	X

AE = adverse event; BVMT-R = Brief Visuospatial Memory Test - Revised; D = days; ECG = electrocardiogram; EDSS = Expanded Disability Status Scale; FSH = follicle-stimulating hormone; Gd = gadolinium; HBsAg = hepatitis B surface antigen; INR = international normalized ratio; LH = luteinizing hormone; LLN = lower limit of normal; MRI = magnetic resonance imaging; MS = multiple sclerosis; PedsQL = Pediatric Quality of Life Inventory; PT = prothrombin time; PTT = partial thromboplastin time; SAE = serious adverse event; SDMT = Symbol Digit Modalities Test; Wk = week.

Note: Study visits (weeks) are calculated relative to Baseline (Day 1).

1 All tests and evaluations are to be performed before dispensing initial study treatment.

2 The Safety Follow-Up Visit will be conducted for subjects who will not continue in the Part 2 and for those who withdraw prematurely.

3 Subjects treated with BG00012 who complete, temporarily withhold, or permanently discontinue study treatment for any reason and have a lymphocyte count <LLN will be followed every 4 weeks for 24 weeks, then every 12 weeks (**or sooner, if clinically indicated or at the Investigator's discretion**) until the lymphocyte count is ≥LLN, for at least 48 weeks following BG00012 treatment discontinuation, or until initiation of another MS disease modifying therapy, whichever occurs first. Any subject treated with BG00012 in Part 1 with a lymphocyte count <LLN being followed at the Part 1 Week 96 Visit (including subjects who completed, are temporarily withholding, or permanently discontinued BG00012 treatment) will continue follow-up within Part 2 of the study.

4 Unscheduled Relapse Assessment Visit (assessment by the *treating* neurologist) to be carried out as soon as possible and within 72 hours of suspected relapse. See Section 6.3.3 and Section 6.9.2in the protocol for further details.

5 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 for Part 2.

6 Assessment of Tanner stages should be performed by a medical doctor experienced with this assessment. Information regarding Tanner staging will be collected at baseline for all male subjects and for female subjects who are premenarche and will be stopped once the subject's bone age reaches ≥16 years or once the subject is postmenarche.

7 Subjects will have their body temperature, heart rate, respiratory rate, and diastolic and systolic blood pressure measured. Subjects must remain in the same body position for 5 minutes prior to having heart rate and blood pressure taken.

8 Lymphocyte counts must be tested every 4 weeks in subjects with lymphocyte count <LLN. See Lymphocyte Follow-Up Visit.

9 For females of childbearing potential. Results must be known prior to dispensing study treatment.

10 All urine pregnancy testing will be performed at the study site.

11 Urine cytology must be performed if microscopic hematuria of unknown etiology is observed under either of the following conditions: a) hematuria is present on 2 consecutive tests, or b) hematuria is observed at the End of Study/Early Withdrawal/Safety Follow-Up Visit. If urine cytology is positive, the subject must permanently discontinue study treatment (see Table 8 in the protocol).

[12] Endocrine parameters to be tested will include insulin-like growth factor 1, insulin-like growth factor binding protein, FSH, LH, and estradiol (E-2) for females and testosterone, FSH, and LH for males. All endocrine tests will be collected at baseline for all male subjects and for female subjects who are premenarche and will stop beingcollected once the subject's bone age reaches ≥16 years or once the subject is postmenarche.

[13] MRI must not be performed within 30 days of receiving a course of steroids, with the exception of MRIs obtained for the purpose of relapse assessment.

[14] An x-ray of the left hand and wrist to determine bone age will be performed at baseline for all male subjects and for female subjects who are premenarche, if permitted by thelocal regulatory authority. Assessment of this x-ray for determination of bone age should be performed by a radiologist experienced with this assessment. For subsequentvisits, once the bone age is determined to be ≥16 years of age or once the subject is postmenarche, no further bone x-rays are required.

[15] If permitted by the local regulatory authority, subjects or caregivers will be posed the following question: "During the past year, did [you/the subject] progress fromone [class/grade-level] to the next in school?"

4. INTERIM ANALYSIS

Only the data from Part 2 of 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

The study is not powered for the primary endpoint of Part 1. The sample size is primarily based on feasibility, with the goal of having 50 evaluable subjects at the 96 week timepoint of Part 1 for each treatment group.

Based on an estimated dropout rate of approximately 30% over 2 years, a total of 142 subjects will need to be enrolled to have at least 100 evaluable subjects (50 subjects/treatment group) after 2 years of treatment.

With respect to the primary endpoint of Part 1, if the proportion of subjects free of new or newly enlarging T2 hyperintense lesions is approximately 25%, the width of the 95% CI for the proportion will be approximately 0.24. If the proportion is around 40%, the width of the 95% CI will be approximately 0.28.

This sample size will provide approximately 82% power for the key secondary endpoint of Part 1 of number of new or newly enlarging T2 hyperintense lesions at Week 24. The assumptions were based on historical data on treatment effect for IFN β 1a (Avonex) and BG00012 on the number of T2 hyperintense lesions compared with placebo.

It is assumed that the mean (SD) will be 3.5 (6.3) and 1.22 (2.92) for the number of new or newly enlarging T2 hyperintense lesions at Week 24 for the IFN β 1a (Avonex) group and the BG00012 group, respectively (a 65% reduction over the IFN β 1a group). At Week 24, a 10% dropout rate is expected, resulting in about 63 evaluable subjects per group. Based on these assumptions, the study will have approximately 82% power to detect the difference between BG00012 and IFN β 1a. This power calculation is based on a negative binomial simulation.

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

Summary statistics along with 95% confidence intervals (CIs) will be presented for both discrete and continuous efficacy outcomes. P-values may be supplied to describe significance. Safety data (laboratory assessments, vital signs, adverse events) will be summarized by treatment received. Efficacy data will be summarized as randomized.

6.1.1. Summary of Baseline Data

Baseline data are defined as data collected prior to the administration of BG00012 or Interferon β-1a on Day 1 of study 109MS306. If data on Day 1 is not available, screening assessments may be used provided they are within 6 weeks of the baseline visit. Demographics and baseline characteristics will be summarized using descriptive statistics for each treatment group and overall.

If there are clinically relevant imbalances in important baseline characteristics, appropriate statistical methods will be used to analyze the endpoint (e.g., logistic regression) to adjust for the baseline covariates. Summary statistics and 95% CIs will be presented from the model.

6.1.2. Accounting of Subjects

Number of subjects who enrolled into the 109MS306 study, number randomized, number who received at least one dose of BG00012 or Interferon β-1a, number completing treatment, number completing the study, number entering the long term extension (Part 2), number discontinuing prior to Week 96 and reason for early withdrawal, will be summarized by treatment and overall.

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 109MS306), age group (10 - <13, 13 - <15, 15 - <18) will be summarized for each treatment and overall. In addition, baseline height (cm) and weight (kg) and Tanner Score (if applicable) will also be summarized.

Medical history will be summarized by treatment and overall for subjects randomized in 109MS306 that had experienced certain maladies prior to entering the study. The number and percentage of subjects within each category will be summarized.

MS Pediatric Diagnostic Criteria (Krupp) will be summarized by treatment and overall for the subjects who are randomized in to the study.

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 by treatment and overall.

History of MS for the subjects randomized in 109MS306 will be summarized. This includes time since first MS symptoms and diagnosis, dominant hand, time since most recent relapse, and number of relapses prior to screening in study 109MS306 (prior 12 months, 2 years, and 3 years). In addition, the MS treatment history, including IFN β-1a or glatiramer acetate treatment use in the 4 weeks prior to study entry, will be summarized categorically for each therapy code by treatment and overall using counts and percents.

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 109MS306). The World Health Organization (WHO) Drug Dictionary will be used for coding concomitant medications. The Medical Dictionary for Regulatory Activities (MedDRA, version 19.1) 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 by treatment and overall.

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 study treatment (BG00012 or Interferon β-1a) during study 109MS306, total amount of study treatment received and overall compliance will be summarized. Compliance for each subject is defined as the total amount of study drug received divided by the number of days on treatment.

6.1.7. Visit Windows

For summary purposes, visit windows are defined for each scheduled visit. If the visit falls between the midpoint of 2 scheduled visits, the assigned visit will be the closest scheduled visit to the assessment. If at least 2 visits fall within this interval, the value closes to the scheduled visit will be used in summaries. 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. If a subject withdraws after receiving at least one dose of study drug, 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.

6.2. Efficacy Analysis

6.2.1. Analysis Population

Intent-to-Treat (ITT) Population: subjects who were randomized and received at least 1 dose of study treatment.

Completers Population: subjects from the ITT Population who completed Week 96 of the study and who have MRI data for Week 96.

6.2.2. Analysis Methods

In general, continuous variables will be summarized using summary statistics (mean, standard deviation [SD], median, minimum, and maximum) by treatment group, and categorical variables will be presented using frequency distributions by treatment group. Where appropriate, 95% CIs for mean, median, or proportions may also be presented. In addition, statistical modeling may be used to analyze the data. Binary outcomes may be analyzed by the logistic regression model. In general, the number of new or newly enlarging T2 lesions and new T1 hypointense lesions (i.e., new nonenhancing T1 hypointense lesions) or number of relapses will be analyzed by the negative binomial regression model. The number of Gd-enhancing lesions will be analyzed using the ordinal logistic regression model or Wilcoxon rank-sum test. Continuous responses (such as Quality of Life measures) will be analyzed by analysis of variance or analysis of covariance (ANCOVA). Time to first relapse or time to 12-week confirmed EDSS progressionwill be presented based on the Kaplan-Meier method and analyzed using the Cox proportional hazards model.

Twelve week confirmed EDSS progression is defined as at least a 1.0 point increase in the EDSS from baseline EDSS $\geq$ 1.0 that is sustained for 12 weeks, or at least a 1.5 point increase on the EDSS from baseline EDSS = 0 that is sustained for 12 weeks. A tentative EDSS progression is confirmed when this minimum EDSS change is present on the next study visit occurring after 74 days or longer from the initial observation. The 74 day interval is based on the visit windows allowed in the protocol around the target visit day.

The date of the initial visit at which the minimum increase in the EDSS is met will be the date of onset of the progression (tentative progression).

Progression will not be confirmed at a visit where a relapse is also occurring. A subject is considered to be having a relapse for at least 29 days after the start date of onset of a protocol-defined relapse. If a subject meets the defined criteria of sustained progression and is also having a relapse, the subject will be required to meet the defined minimum criteria at the subsequent visit.

Relapses are defined as new or recurrent neurologic symptoms not associated with fever or infection, lasting at least 24 hours, and accompanied by new objective neurological findings upon examination by the examining neurologist. The subject must have objective signs on the examining neurologist's examination confirming the event. Suspected relapse information is recorded in the data base.

If a subject had a tentative progression prior to the start of alternative MS medication, the appropriate EDSS evaluation performed while taking alternative MS medication will be used to assess confirmation of the progression (if available). Otherwise, time to EDSS progression will

be censored at the date of starting alternative MS medication. Progression must start prior to or at the End of Treatment Period Visit. If a subject had a tentative progression at the End of Treatment Period Visit in Part 1 of 109MS306, then their time to EDSS progression will be censored at that time.

Death due to MS will be counted as progression. If the subject was in the midst of a tentative progression at the time of death (e.g. the EDSS evaluation prior to death is a tentative progression), the progression date will be the tentative progression start date. Otherwise, the progression date will be the date of death.

Subjects who do not progress prior to completing Week 96 or withdraw prior to Week 96 will have their time to progression date censored at their last visit date during Part 1.

In general, the stratification factor (i.e., IFN β-1a or glatiramer acetate treatment in 4 weeks prior to study entry, age group) will be included in statistical models. Other baseline covariates, such as MS Pediatric Diagnostic Criteria (Krupp), gender, baseline disease status (e.g. number of relapses in 1, 2, or 3 years prior to the study), baseline EDSS, previous IFN use, may be included in the model. An additional, separate efficacy analysis will be carried out based on pubertal status at disease initiation, obtained from the Tanner Staging at screening.

6.2.2.1. Primary Endpoint Analysis

The analysis of the primary endpoint, proportion of subjects free of new or newly enlarging T2 hyperintense lesions at Week 96 will include descriptive statistics (e.g., mean, SD, median) and CIs. The CIs for the proportion of subjects free of new or newly enlarging T2 hyperintense lesions at Week 96 for each treatment group will be presented. Data will be summarized using observed values. No data imputation will be used for missing observations. The primary analysis will be performed on the Completers Population.

A sensitivity analysis of the primary endpoint will be performed on the ITT Population. A logistic regression model may be used to analyze the proportion of subjects free of new or newly enlarging T2 lesions, adjusted for stratification randomization, (age group and IFN β-1a or glatiramer acetate use in the 4 weeks prior to study entry) and other baseline covariates, such as baseline T2 volume, MS Pediatric Diagnostic Criteria (Krupp), gender, baseline disease status (e.g. number of relapses in 1, 2, or 3 years prior to the study), baseline EDSS, previous IFN use.

6.2.2.2. Secondary Endpoint Analysis

6.2.2.2.1. Number of New or Newly Enlarging T2 Hyperintense Lesions at Weeks 24 and 96

Summary statistics for the number of new or newly enlarging T2 hyperintense lesions at both Weeks 24 and 96 will be presented by treatment group. A negative binomial regression model will be used to analyze the number of new or newly enlarging T2 hyperintense lesions at both Week 24 and at Week 96, with treatment group in the model and adjusted for randomization stratification (age group and IFN β-1a or glatiramer acetate use in the 4 weeks prior to study entry), and baseline number of T2 lesions. Formal statistical testing will be performed to compare the mean between the 2 treatment groups. For Week 24, the analysis will be based on subjects from the ITT Population who have observed data at Week 24. Similarly for Week 96. . Missing value imputation may be performed for this analysis.

As a sensitivity analysis, the number of new or newly-enlarging T2 hyperintense lesions over 96 weeks relative to baseline will be compared between the BG00012 and Interferon β-1a treatment groups using a negative binomial regression model on the observed number of new or newly enlarging T2 lesions at the subject's last visit prior to the earlier of Week 96 or the start of alternative MS therapy. The logarithmic transformation of the number of scans will be included in the model as the "offset" parameter**.** The model will be adjusted for the baseline volume of T2 hyperintense lesions, IFN β-1a or glatiramer acetate treatment in 4 weeks prior and baseline age group. Results of these models will be exponentiated to transform back to lesion counts.

6.2.2.2.2. Proportion of Subjects Free of New or Newly Enlarging T2 Hyperintense Lesions on Brain MRI Scans at Weeks 24 and 48

Summary statistics will be presented for each treatment group. Additionally, this endpoint may be analyzed using logistic regression, adjusted for baseline number and volume of T2 lesions and other stratification factors (e.g., age group, IFN β-1a or glatiramer acetate treatment use in the 4 weeks prior to study entry).

6.2.2.2.3. Proportion of Subjects Free of New MRI Activity (i.e., Free of Gd-enhancing and Free of New or Newly Enlarging T2 MRI Lesions on Brain MRI Scans) at Weeks 24, 48, and 96

Summary statistics will be presented for each treatment group. Additionally, this endpoint may be analyzed using logistic regression, adjusted for baseline number of Gd-enhancing lesions, and/or T2 lesions and other stratification factors (e.g. age group).

6.2.2.2.4. Time to First Relapse

Time to first relapse and estimated proportion of subjects relapsed will be presented based on the Kaplan-Meier method. If a subject does not experience a relapse during Part 1 of the study, they will be censored at their last visit in Part 1. Time to first relapse may also be analyzed using the

Cox proportional hazards model, adjusted for baseline relapse rate, baseline EDSS score, and other stratification factors (e.g. age group).

6.2.2.2.5. Proportion of Subjects Free of Relapse up to Week 96

The proportion of subjects relapse-free up to Week 96 will be summarized. In addition, for the ITT Population, the estimated proportion of subjects who are relapse-free up to Week 96 will be calculated based on the Kaplan-Meier method.

6.2.2.2.6. Annualized Relapse Rate at Weeks 48 and 96

ARR will be analyzed based on negative binomial regression, adjusted for baseline relapse rate, baseline EDSS score and stratification factors (IFN β-1a or glatiramer acetate treatment in 4 weeks prior to study entry, age group).

6.2.2.2.7. Fatigue as Measured by the PedsQL Multidimensional Fatigue Scale Scores and Quality of Life as Measured by the PedsQL

PedsQL Multidimensional Fatigue Scale is measured both by the subject's self-assessment and that of the parent. The fatigue scale contains 18 questions in 3 fatigue dimensions: General, Sleep/Rest and Cognitive. Scoring for each question is based on a 5-point Likert scale from 0 (Never) to 4 (Almost always). Each individual score is then reversed (subtracted from 4) and linearly transformed as follows:

0=100, 1=75, 2=50, 3=25, 4=0

For each dimension, total score will be the (sum of all the items)/(number of items answered). If more than 3 answers are missing within a dimension, the total score is not computed for that dimension and considered missing. A higher total score indicates lower problems.

PedsQL Quality of Life (QoL) is measured both by the subject's self-assessment and that of the parent. The QoL scale contains 23 questions in 4 dimensions: Physical, Emotional, Social and School. Scoring for each question is based on a 5-point Likert scale from 0 (Never) to 4 (Almost always). Each individual score is then reversed (subtracted from 4) and linearly transformed as follows:

0=100, 1=75, 2=50, 3=25, 4=0

For each dimension, total score will be the (sum of all the items)/(number of items answered). If more than half of the answers are missing within a dimension, the total score is not computed and considered missing. A higher total score indicates better quality of life.

At each scheduled visit, summary statistics will be presented for each dimension for both scales, by treatment group. Additionally, these endpoints will be analyzed using an ANCOVA, adjusted for baseline score, and stratification factors (IFN β-1a or glatiramer acetate treatment in 4 weeks

prior to study entry, age group). Results for each scale will be presented for the self-assessment and the parent assessment.

6.2.2.2.8. Change From Baseline to Week 96 in the EDSS Score

Summary statistics of change from baseline to Week 96 in EDSS score will be presented for each treatment group. Individual EDSS Functional Scale Scores and Ambulatory Scores, along with EDSS Scores will be listed for each subject.

6.2.2.3. Exploratory Endpoint Analysis

6.2.2.3.1. The analyses of the following Exploratory Endpoints will be similar to the analyses described in Section 6.2.2.2:

- Number of new or newly enlarging T2 hyperintense lesions on brain MRI scans at Weeks 48 and 72
- Proportion of subjects free of new or newly enlarging T2 hyperintense lesions on brain MRI scans at Week 72
- Proportion of subjects free of new MRI activity (i.e., free of Gd-enhancing and free of new or newly enlarging T2 MRI lesions on brain MRI scans) at Week 72
- Number of new T1 hypointense lesions on brain MRI scans at Weeks 24, 48, 72, and 96
- Number of Gd-enhancing lesions on brain MRI scans at Weeks 24, 48, 72, and 96

6.2.2.3.2. Time to progression of disability

Time to progression of disability at 96 weeks and estimated proportion of subjects progressed at week 96 will be presented based on the Kaplan-Meier method and analyzed using Cox regression. If a subject does not experience a disability progression during Part 1 of the study, they will be censored at their last visit in Part 1.

6.2.2.3.3. BVMT-R scores, SDMT scores and school progression

- BVMT-R scores, indicating the number correct, will be summarized for each trial (Trials 1, 2, and 3) at weeks 48 and 96 for each treatment using descriptive statistics. Change from baseline will also be summarized for this score.

- SDMT scores will be summarized at weeks 48 and 96 for each treatment using descriptive statistics. Change from baseline will also be summarized for this score.

- School progression query will be summarized at weeks 48 and 96 for each treatment using counts and proportions

6.2.3. Missing data

For all analyses using logistic regression and survival analyses, missing values may be imputed.

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 study medication (BG00012 or IFN β-1a).

6.3.2. Analysis Methods

Summaries of safety data will include descriptive statistics for continuous variables and frequency distributions for categorical variables. All AEs, laboratory abnormalities, ECG, and vital signs will be evaluated for safety. Incidence of treatment emergent AEs will be summarized for each treatment group and overall. An event is considered treatment emergent if the start date of the AE is on or after the first dose date or the existing AE worsened after the first dose date. Other safety data will also be summarized by treatment group.

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

Incidence of AEs will be summarized using frequency distribution tables; overall, by severity, and by relationship to study treatment. The summary tables will include incidences for system organ class (SOC) as well as for preferred terms (PT) within each system organ class. Similar incidence analyses will be summarized for SAEs and for the most common AEs. In addition to summaries of incidence by both SOC and PT, incidence of adverse events may also be summarized and presented by High-Level Group Term (HLGT) or High-Level Term (HLT), if considered appropriate for signal detection, in instances where the SOC level of summary is too broad but the PT level of summary is too granular.

AEs will be coded using the MedDRA dictionary (version 19.1). 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.

Summaries of the most frequent occurring AEs (PTs that occur in at least 5% of the subjects in any treatment group) will be presented by treatment group for each preferred term.

The incidence of AEs by SOC and PT may also be presented by time intervals (e.g., using a 12 week time interval). Other time intervals may be explored as well to elucidate trends over time. For such analyses, for a given time interval, the number of subjects who were followed for adverse events during that time interval will be presented along with the AE incidence during that time interval. Therefore, for a given SOC or PT, subjects will be counted only once for a given time interval but may be counted more than once across time intervals.

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 study treatment.

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 study treatment 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.

The incidence of AEs of special interest by PT will be presented by treatment group and overall. These will be summarized by SOC and PT and may include the following:

- Flushing and other related symptoms;
- Gastrointestinal tolerability (nausea, abdominal pain, diarrhea, etc.);
- Infections, including potential opportunistic infections;
- Ischaemic cardiovascular disorders;
- Hepatic disorders;

- Renal disorders;
- Malignancies;
- Lymphopenia and Leukopenia.

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: sodium, potassium, chloride, total bilirubin, alkaline phosphatase, ALT, AST, GGT, BUN, creatinine, bicarbonate, calcium, magnesium, phosphate, uric acid, and glucose
- Coagulation: partial thromboplastin time, prothrombin time, and international normalized ratio
- Urine pregnancy tests
- Endocrine tests (until the subject has reached bone age of ≥16 years or until the subject is postmenarche): insulin-like growth factor 1, insulin-like growth factor binding protein, follicle-stimulating hormone, luteinizing hormone, estradiol, and testosterone
- Urinalysis: color, specific gravity, pH, protein, glucose, blood, ketones, and microscopy (urine cytology, β_2-microglobulin, and microalbumin will be included in summaries if available)

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 normal baseline to any visit post baseline high/low status for all hematology and blood chemistry parameters, and shifts from normal baseline to high/positive status for urinalysis will be presented. In addition, shifts from baseline to the worst post-baseline value will be presented for relevant laboratory tests by treatment group by clinically relevant categories (e.g., <= ULN, >1 - <3 xULN, >=3 - 5 xULN, >5 – 10 xULN, >10 – 20 x ULN, >20 x ULN, etc.). For hematology parameters, shift table categories may be defined based on potentially clinically significant cutoffs (e.g., < 3.0 x 10^9/L and >= 16 x 10^9/L for WBC and <0.8 x 10^9/L, <0.5 x 10^9/L, and > 12 x 10^9/L for lymphocytes). For qualitative urinalysis parameters, categories may be defined based on the qualitative categories (e.g., normal/negative, trace, 1+, 2+, 3+, etc.).

Summary statistics at each visit will also be provided for all absolute laboratory values as well as change from baseline, by study treatment. 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 in certain laboratory assessments may be presented as well. These graphs will include eosinophils, lymphocytes, neutrophils, and liver function tests (bilirubin, AST, ALT, ALP, BILI, and GGT).

The number and percent of subjects who complete treatment in Part 1 (do not continue into Part 2), temporary withhold medication during Part 1, or completely discontinue treatment and have a lymphocyte count < LLN, will be summarized for both treatment groups and overall. The time until recovery (when the lymphocyte count >= LLN) will be summarized as well.

6.3.2.4. Radiological Safety Assessments

- Gd-enhanced brain MRIs for relapses – counts of Gd-enhanced lesions which can measure MRI activity
- X-ray of the left hand and wrist to determine bone age will be performed at baseline for all male subjects and for female subjects who are premenarche (if permitted by local regulatory authority) until the subject has reached bone age of ≥16 years or once the subject is postmenarche

These data will be summarized using either counts and percents or by descriptive statistics by study treatment along with the exploratory endpoints as follows:

6.3.2.5. 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	>38°C or an increase from baseline of at least 1°C
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
Respiratory Rate	<10 or >30 breaths per minute after taking dose

6.3.2.6. 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.

6.3.2.7. Height and Weight

The analysis of height and weight will be summarized at each timepoint by study treatment, presenting descriptive statistics for both, including both absolute values and change from baseline.

STATISTICAL ANALYSIS PLAN

Version No.: 1.0

Date: July 14, 2022

Authors: [redacted]

Study Title: Open-Label, Randomized, Multicenter, Multiple-Dose, Active-Controlled, Parallel-Group, Efficacy and Safety Study of BG00012 in Children From 10 to Less Than 18 Years of Age with Relapsing-Remitting Multiple Sclerosis, With Open-Label Extension

Name of Study Treatment: BG00012 (Tefidera (DMF) in pediatric population)

Protocol No.: 109MS306 Part 2 (LTE)

Study Phase: 3

APPROVAL

This document has been reviewed and approved by:		
[redacted], Ph.D.	DocuSigned by: [redacted]	14-Jul-2022 Date
[redacted], Ph.D.	DocuSigned by: [redacted]	15-Jul-2022 Date
[redacted], M.D.	DocuSigned by: [redacted]	15-Jul-2022 Date

VERSION HISTORY

SAP Version	Date	Primary Reasons for Amendment
0.1 (Stable interim SAP)	09-MAY-2022	N/A
1.0 (Final interim SAP)	14-JULY-2022	N/A

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
AESI	adverse event of special interest
ALC	absolute lymphocyte count
ALT	alanine transaminase
ARR	annualized relapse rate
AST	aspartate transaminase
BID	twice daily
BUN	blood urea nitrogen
BVMT-R	Brief Visuospatial Memory Test - Revised
CI	confidence interval
CM	concomitant medication
CSR	clinical study report
DMF	dimethyl fumarate
ECG	electrocardiogram
eCRF	electronic case report form
EDSS	Expanded Disability Status Scale
FSH	follicle-stimulating hormone
Gd	gadolinium
GGT	gamma-glutamyl-transferase
ICF	informed consent form
IFN	interferon
IFN β-1a	interferon β-1a
LH	luteinizing hormone
LLN	lower limit of normal
LTE	long term extension

MRI	magnetic resonance imaging
MS	multiple sclerosis
PedsQL	Pediatric Quality of Life Inventory
RRMS	relapsing-remitting multiple sclerosis
SAE	serious adverse event
SAP	Statistical Analysis Plan
SE	Standard error
SD	standard deviation
SDMT	Symbol Digit Modalities Test
ULN	upper limit of normal

1. Introduction

This statistical analysis plan (SAP) is intended to describe the planned analyses and considerations for the interim analysis of the long-term extension (LTE) phase of study 109MS306 (CONNECT). It is based on version 5 of the study protocol, dated 25 July 2017. The SAP is intended to outline the basic planned analyses to assess the long-term safety and efficacy profile of BG00012 (Tecfidera) and will include the analyses of selected safety and efficacy endpoints. Additional interim analyses may be performed as needed for regulatory reporting, safety updates, publications, or as otherwise required by the Sponsor.

2. Study Overview

2.1. Study Objectives and Endpoints

Study Primary Objective

The primary objective of Part 2 (LTE phase) is to evaluate the long-term safety of BG00012 in subjects who completed Week 96 in Part 1 of Study 109MS306.

Study Primary Endpoint

The primary endpoint of Part 2 is the incidence of adverse events (AEs), serious adverse events (SAEs), and discontinuations of BG00012 due to an AE.

Study Secondary Objectives

The secondary objective of Part 2 is to describe the long-term MS outcomes of BG00012 in subjects who completed Week 96 in Part 1 of Study 109MS306.

Study Secondary Safety Endpoints

Secondary endpoints include annualized relapse rate; EDSS; cognition as measured by BVMT-R, SDMT, and school progression query; vital signs; ECGs; clinical laboratory data; changes from baseline in height, weight, and bone age; and Tanner stage.

2.2. Study Design

Part 2 is an optional open-label extension phase for subjects who complete Week 96 in Part 1 and who meet the Part 2 entry criteria. Part 2 allows the collection of long-term (Approximately 5 years) safety and MS outcomes in subjects with RRMS treated with BG00012. Results from Part 2 will be reported separately from Part 1. In Part 2, subjects (excluding those who have stopped taking BG00012 and are continuing follow-up of lymphopenia) will receive open-label BG00012, 240 mg BID, orally, for 240 weeks.

Subjects who have discontinued BG00012 and are participating in Part 2 for follow-up lymphocyte monitoring will not be required to undergo study procedures other than the monitoring of lymphocytes and relevant safety assessments (i.e., AE collection, vital signs, and physical examination). All other routine study assessments are optional for this subset of subjects. They will be followed in Part 2 every 4 weeks for the 24 weeks following the discontinuation of BG00012, then every 12 weeks (*or sooner, if clinically indicated or at the*

Investigator's discretion) until the lymphocyte count is >LLN, for at least 48 weeks following BG00012 treatment discontinuation, or until initiation of another MS disease modifying therapy, whichever occurs first.

See Figure 1 for a schematic of the study design and the study activities in Table 1 and Table 2.

Figure 1: Study Design – Part 2 Extension

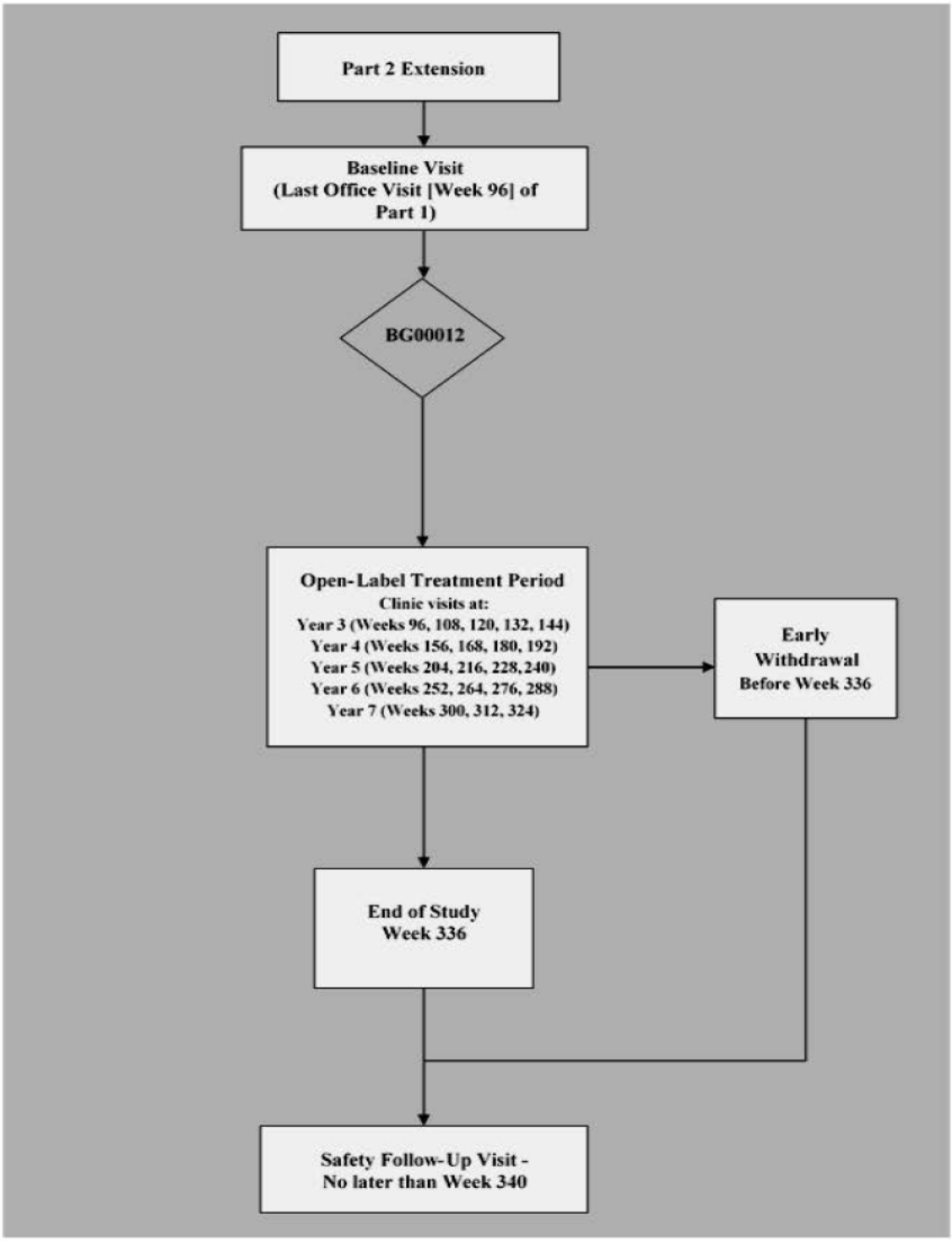

Table 1: CONNECT Part 2 (109MS306-LTE) Study Procedures

Year	**Year 3**						**Year 4**				**Year 5**				**Year 6**				**Year 7**		
Study Week (±7 days)	**96[1,2]**	98	**108**	**120**	**132**	**144**	**156**	**168**	**180**	**192**	**204**	**216**	**228**	**240**	**252**	**264**	**276**	**288**	**300**	**312**	**324**
Informed Consent and Assent[3]	X																				
Eligibility Criteria	X																				
Dispense Treatment[4]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination	X			X		X		X		X		X		X		X		X		X	
Body Weight	X			X		X		X		X		X		X		X		X		X	
Height	X			X		X		X		X		X		X		X		X		X	
Tanner Score[5]	X					X				X				X				X			
Vital Signs[6]	X			X		X		X		X		X		X		X		X		X	
12-Lead ECG	X					X				X				X				X			
Hematology[7]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood Chemistry	X			X		X		X		X		X		X		X		X		X	
Urinalysis[8]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine Pregnancy Test[9,10]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Endocrine Tests[11]	X					X				X				X				X			
Hand and Wrist X-ray[12]	X					X				X				X				X			
EDSS	X					X				X				X				X			
Brain MRI Scan ± Gd		MRIs may be obtained as per local guidelines and reviewed locally																			
PedsQL, PedsQL Multidimensional Fatigue Scale	X					X				X				X				X			
BVMT-R	X					X				X				X				X			
SDMT	X					X				X				X				X			

Year	Year 3						Year 4				Year 5				Year 6				Year 7		
Study Week (±7 days)	**96[1,2]**	98	**108**	**120**	**132**	**144**	**156**	**168**	**180**	**192**	**204**	**216**	**228**	**240**	**252**	**264**	**276**	**288**	**300**	**312**	**324**
Query Regarding Annual School/Grade Progression[13]	X					X				X				X				X			
Relapse Assessment		Monitor and record throughout the study																			
Concomitant Therapy		Monitor and record throughout the study																			
AEs Recording		Monitor and record throughout the study																			

AE = adverse event; BVMT-R = Brief Visuospatial Memory Test - Revised; ECG = electrocardiogram; EDSS = Expanded Disability Status Scale; FSH = follicle-stimulating hormone; Gd = gadolinium; LH = luteinizing hormone; MRI = magnetic resonance imaging; PedsQL = Pediatric Quality of Life Inventory; SDMT = Symbol Digit Modalities Test; WBC = white blood cell.

Note: Subjects who have discontinued BG00012 in Part 1 and are participating in Part 2 for follow up lymphocyte monitoring will not be required to undergo study procedures other than the monitoring of lymphocytes and relevant safety assessments (i.e., AE collection, vital signs, and physical examination). These subjects are required to have lymphocytes monitored in accordance with the schedule outlined in Table 9 of the Protocol, but are not required to undergo any additional routine study assessments. All other assessments are optional for this subset of subjects. These subjects will be followed in Part 2 every 4 weeks for the 24 weeks following the discontinuation of BG00012, then every 12 weeks (or sooner, if clinically indicated or at the Investigator's discretion) until the lymphocyte count is >LLN, for at least 48 weeks following BG00012 discontinuation, or until initiation of another MS disease modifying therapy, whichever occurs first.

1 Eligible subjects from Part 1 who consent to participate in Part 2 will be enrolled at the Part 1 Week 96 Visit; this will serve as the Baseline Visit for Part 2. Of note, Week 84 laboratory results may be used to confirm a subject's eligibility to participate in Part 2. Before entering Part 2, every examination and evaluation for Part 1 should be completed, with the following exception. Any subject treated with BG00012 in Part 1 with a lymphocyte count <LLN being followed at the Part 1 Week 96 Visit (including subjects who completed, are temporarily withholding, or permanently discontinued BG00012 treatment) will continue follow up within Part 2 of the study. If the Final Study Visit for Part 1 cannot be combined with the Baseline/Screening Visit for Part 2, the Baseline/Screening Visit for Part 2 must be done within 4 weeks of the Final Study Visit in Part 1; however, no tests need to be repeated.

2 Subjects who were randomized to receive IFN β-1a (Avonex) in Part 1 of the study will receive a starting dose of BG00012, 120 mg BID, orally, for 7 days followed by the maintenance dose of BG00012 240 mg BID, orally, for the remainder of the study. These subjects will also receive a safety telephone call from the study site staff 2 weeks ±5D after initiating BG00012.

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 All tests and evaluations are to be performed before dispensing initial study treatment.

5 Assessment of Tanner stages should be performed by a medical doctor experienced with this assessment. Information regarding Tanner staging will be collected at baseline for all male subjects and for female subjects who are premenarche and will be stopped once the subject's bone age reaches ≥16 years or once subject is postmenarche.

6 Subjects will have their body temperature, heart rate, respiratory rate, and diastolic and systolic blood pressure measured. Subjects must remain in the same body position for 5 minutes prior to having heart rate and blood pressure taken.

7 Lymphocyte counts must be tested every 4 weeks in subjects with lymphocyte count <LLN. See Lymphocyte Follow-Up Visit in Table 4.

8 Urine cytology must be performed if microscopic hematuria of unknown etiology is observed under either of the following conditions: a) hematuria is present on 2 consecutive tests, or b) hematuria is observed at the End of Study/Early Withdrawal/Safety Follow-Up Visit. If urine cytology is positive, the subject must permanently discontinue study treatment (see Table 8 of the Protocol).

9 For females of childbearing potential. Results must be known prior to dispensing study treatment.

10 All urine pregnancy testing will be performed at the study site.

[11] Endocrine parameters to be tested will include insulin-like growth factor 1; insulin-like growth factor binding protein; FSH, LH, and estradiol (E-2) for females and testosterone, FSH, and LH for males. All endocrine tests will be collected at baseline for all male subjects and for female subjects who are premenarche and will stop being collected once the subject's bone age reaches ≥16 years or once the subject is postmenarche.

[12] An x-ray of the left hand and wrist to determine bone age will be performed at baseline for all male subjects and for female subjects who are premenarche, if permitted by the local regulatory authority. Assessment of this x-ray for determination of bone age should be performed by a radiologist experienced with this assessment. For subsequent visits, once the bone age is determined to be ≥16 years of age or once the subject is postmenarche no further bone x-rays are required.

[13] If permitted by the local regulatory authority, subjects or caregivers will be posed the following question: "During the past year, did [you/the subject] progress from one [class/grade-level] to the next in school?"

Table 2: CONNECT Part 2 (109MS306-LTE) Study Activities (Unscheduled and Post-Treatment Visits)

Tests and Assessments[1]	End of Study Visit/Early Withdrawal (Week 336 ± 7 days)	Safety Follow-Up Visit (No Later Than Week 340)[2]	Lymphocyte Follow-Up[3]	Unscheduled Relapse Assessment Visit[4]
Physical Examination	X	X	X	X
Body Weight	X	X		X
Height	X	X		
Tanner Score[5]	X			
Vital Signs[6]	X	X	X	X
12-Lead ECG	X	X		
Hematology[7]	X	X	X	X
Blood Chemistry	X	X		X
Urinalysis[8]	X	X		X
Urine Pregnancy Test[9]	X	X		X
Endocrine Tests[10]	X			
EDSS	X			X
Hand and Wrist X-ray[11]	X			
Brain MRI Scan ± Gd[12]				X
PedsQL, PedsQL Multidimensional Fatigue Scale	X			X
BVMT-R	X			
SDMT	X			
Query Regarding Annual School/Grade Progression [13]	X			
Relapse Assessment				X
Concomitant Therapy and Procedures Recording	X			
AE/SAE Reporting	Monitor and record throughout the study as described in Section 8.2			

AE = adverse event; BVMT-R = Brief Visuospatial Memory Test - Revised; ECG = electrocardiogram; EDSS = Expanded Disability Status Scale; FSH = follicle-stimulating hormone; Gd = gadolinium; LH = luteinizing hormone; LLN = lower limit of normal; MRI = magnetic resonance imaging; PedsQL = Pediatric Quality of Life Inventory; SAE = serious adverse event; SDMT = Symbol Digit Modalities Test.

[1] All tests and evaluations are to be performed before dispensing initial study treatment.

[2] The Safety Follow-Up Visit will be conducted no later than 4 weeks after the last dose of study treatment for subjects who will complete Part 2 and for those who withdraw prematurely.

[3] Subjects treated with BG00012 who complete, temporarily withhold, or permanently discontinue study treatment for any reason and have a lymphocyte count <LLN will be followed every 4 weeks for 24 weeks, then every 12 weeks (**or sooner, if clinically indicated or at the Investigator's discretion**) until the lymphocyte count is ≥LLN, for at least 48 weeks following BG00012 treatment discontinuation, or until initiation of another MS disease modifying therapy, whichever occurs first. Any subject treated with BG00012 in Part 1 with a lymphocyte count <LLN being followed at the Part 1 Week 96 Visit (including subjects who completed, are temporarily withholding, or permanently discontinued BG00012 treatment) will continue follow-up within Part 2 of the study.

[4] Unscheduled Relapse Assessment Visit (assessment by the *treating* neurologist) to be carried out as soon as possible and within 72 hours of suspected relapse. Subjects in the Czech Republic must begin treatment for an acute relapse within 5 days of symptom onset, even if a scheduled MRI scan has not yet been performed.

[5] Assessment of Tanner stages should be performed by a medical doctor experienced with this assessment. Information regarding Tanner staging will be collected at baseline for all male subjects and for female subjects who are premenarche and will be stopped once the subject's bone age reaches ≥16 years or once the subject is postmenarche.

[6] Subjects will have their body temperature, heart rate, respiratory rate, and diastolic and systolic blood pressure measured. Subjects must remain in the same body position for 5 minutes prior to having heart rate and blood pressure taken.

[7] Lymphocyte counts must be tested every 4 weeks in subjects with lymphocyte count <LLN. See footnote 3.

[8] Urine cytology must be performed if microscopic hematuria of unknown etiology is observed under either of the following conditions: a) hematuria is present on 2 consecutive tests, or b) hematuria is observed at the End of Study/Early Withdrawal/Safety Follow-Up Visit. If urine cytology is positive, the subject must permanently discontinue study treatment (see Table 8 of the Protocol)

[9] All urine pregnancy testing will be performed at the study site.

[10] Endocrine parameters to be tested will include insulin-like growth factor 1, insulin-like growth factor binding protein, FSH, LH, and estradiol (E-2) for females and testosterone, FSH, and LH for males. All endocrine tests will be collected at baseline for all male subjects and for female subjects who are premenarche and will stop being collected once the subject's bone age reaches ≥16 years or once the subject is postmenarche.

[11] An x-ray of the left hand and wrist to determine bone age will be performed at baseline for all male subjects and for female subjects who are premenarche, if permitted by the local regulatory authority. Assessment of this x-ray for determination of bone age should be performed by a radiologist experienced with this assessment. For subsequent visits, once the bone age is determined to be ≥16 years of age or once the subject is postmenarche no further bone x-rays are required.

[12] Brain MRI scan will be reviewed locally.

[13] If permitted by the local regulatory authority, subjects or caregivers will be posed the following question: "During the past year, did [you/the subject] progress from one [class/grade-level] to the next in school?"

2.3. Sample Size Considerations

There is no formal sample size calculation for Part 2 of the 109MS306 study. The number of subjects in the Part 2 of the study and in this interim analysis is determined by the number of subjects who completed Part 1 of Study 109MS306 and who were eligible and chose to enroll in study 109MS306 LTE (Part 2).

3. Definitions

Expanded Disability Status Scale (EDSS): A method of quantifying disability due to MS and monitoring changes in disability level over time. The EDSS scale ranges from 0 to 10 in 0.5-unit increments (with one exception - there is no 0.5 level).

Pediatric Quality of Life Scale (PedsQL): A modular questionnaire that measures health-related quality of life in children and adolescents. The core scales are physical functioning, emotional functioning, social functioning, and school functioning.

Relapse: Relapses are defined as new or recurrent neurologic symptoms not associated with fever or infection, lasting at least 24 hours, and accompanied by new objective neurological findings upon examination by the examining neurologist. The subject must have objective signs on the examining neurologist's examination confirming the event. New or recurrent neurologic symptoms that evolve gradually over months should be considered disease progression, not an acute relapse, and should not be treated with steroids. New or recurrent neurologic symptoms that occur less than 30 days following the onset of a protocol-defined relapse were considered part of the same relapse.

3.1. Dates and Points of Reference

Baseline (or baseline of Part 2) is defined as the latest available value prior to or on the date of the first dose of BG00012 in Study 109MS306 LTE (Part 2 of Study 109MS306).

End of Study Date is the date of the last available measurement before/on the cutoff date for 109MS306 LTE, including the lymphocyte follow up measurements.

Lymphocyte recovery baseline is defined as the last observed value collected on or prior to the date of temporary dose interruption or study drug discontinuation. For subjects treated with BG00012 in Part 1 with a lymphocyte count <LLN being followed at the Part 1 Week 96 Visit and continued within Part 2 of the study, the lymphocyte recovery baseline will be derived using Part 1 lymphocyte data.

See Table 3 for the analysis visit windows and Table 4 for the lymphocyte follow up visit windows.

Table 3: Analysis visit windows. Visit values in parentheses are study weeks relative to 109MS306 Part 1, to correspond to Table 1 and Table 2 Analysis Visits.

Frequency	Assessments	Analysis Week Visit Relative to Part 2 Baseline (*relative to Part 1 Baseline*)	Analysis Visit Target Day (Analysis Window)
Q 12 W	Hematology, Urinalysis, Urine pregnancy test	Study Day 1 (*96*)	Day 1 (low-1)
		Week 12 (*108*)	Day 85 (2-127)
		Week 24 (*120*)	Day 169 (128- 211)
		Week 36 (*132*)	Day 253 (212- 295)
		Week 48 (*144*)	Day 337 (296- 379)
		Week 60 (*156*)	Day 421 (380- 463)
		Week 72 (*168*)	Day 505 (464- 547)
		Week 84 (*180*)	Day 589 (548- 631)
		Week 96 (*192*)	Day 673 (632- 715)
		Week 108 (*204*)	Day 757 (716- 799)
		Week 120 (*216*)	Day 841 (800- 883)
		Week 132 (*228*)	Day 925 (884- 967)
		Week 144 (*240*)	Day 1009 (968-1051)
		Week 156 (*252*)	Day 1093 (1052-1135)
		Week 168 (*264*)	Day 1177 (1136-1219)
		Week 180 (*276*)	Day 1261 (1220-1303)
		Week 192 (*288*)	Day 1345 (1304-1387)
		Week 204 (*300*)	Day 1429 (1388-1471)
		Week 216 (*312*)	Day 1513 (1472-1555)
		Week 228 (*324*)	Day 1597 (1556-1639)
		Week 240 *(336)*	Day 1681 (1640-1695)
		Week 244 *(340)*	Day 1709 (1696-high)
Q 24 W	Physical Examination (Body weight, Height), Vital Signs, Blood Chemistry	Study Day 1 (96)	Day 1 (low-1)
		Week 24 *(120)*	Day 169 (128-253)
		Week 48 *(144)*	Day 337 (254-421)
		Week 72 *(168)*	Day 505 (422-589)
		Week 96 *(192)*	Day 673 (590-757)
		Week 120 *(216)*	Day 841 (758-925)
		Week 144 *(240)*	Day 1009 (926-1093)
		Week 168 *(264)*	Day 1177 (1094-1261)
		Week 192 *(288)*	Day 1345 (1262-1429)
		Week 216 *(312)*	

Frequency	Assessments	Analysis Week Visit Relative to Part 2 Baseline (*relative to Part 1 Baseline*)	Analysis Visit Target Day (Analysis Window)
		Week 240 *(336)* Week 244 *(340)*	Day 1513 (1430-1597) Day 1681 (1598-1695) Day 1709 (1696-high)
Q 48 W	EDSS (note: the same window definitions will be followed for the following parameters in the final CSR analyses: Endocrine testing, Hand and wrist X-ray, BVMT-R, SDMT, Annual query regarding school progress, PedsQL, PedsQL Multidimensional Fatigue Scale)	Study Day 1 *(96)* Week 48 *(144)* Week 96 *(192)* Week 144 *(240)* Week 192 *(288)* Week 240 *(336)*	Day 1 (low-1) Day 337 (2-505) Day 673 (506-841) Day 1009 (842-1177) Day 1345 (1178-1513) Day 1681 (1514-high)

Table 4: Analysis visit windows for the lymphocyte follow up. Visits are mapped every 4 weeks for 24 weeks and then every 12 weeks, relative to the Lymphocyte recovery baseline.

Study Period	Assessments	Analysis Week Visit Relative to Day 1 of the Lymphocyte Follow up Period	Analysis Visit Target Day (Analysis Window) Relative to Day 1 of the Lymphocyte Follow up Period
Lymphocyte follow up[1]	Hematology, Physical Examination, Vital signs in the lymphocyte follow-up	Day 1 *(Recovery baseline)* Week 4 Week 8 Week 12 Week 16 Week 20 Week 24 Week 36 Week 48	Day 1 (low-1) Day 29 (2-43) Day 57 (44-71) Day 85 (72-99) Day 113 (100-127) Day 141 (128-155) Day 169 (156- 211) Day 253 (212- 295) Day 337 (296- high)

[1] The lymphocyte follow-up visits are prescribed every 4 weeks for the first 24 weeks following BG00012 discontinuation and every 12 weeks thereafter, until the lymphocyte count exceeds LLN. However, the change to 12 weeks between visits may occur earlier than 24 weeks if clinically indicated or at the PI's discretion.

Study Day 1: The date of the first dose of BG00012 in 109MS306 LTE.

For dates on or after Study Day 1,

Study Day = Date of Interest – Date of Study Day 1 + 1.

For dates prior to Study Day 1,

Study Day = Date of Interest – Date of Study Day 1.

(Note: There is no Study Day 0.)

For dates in the lymphocyte follow up analysis:

Study Day in the Lymphocyte Follow up Period = Date of Interest – Date of Day 1 of the Lymphocyte Follow up Period + 1 (for dates on/after Day 1)

Study Day in the Lymphocyte Follow up Period = Date of Interest – Date of Day 1 of the Lymphocyte Follow up Period (for dates before Day 1, e.g., day of the baseline measurement)

If there is more than one visit within a window, the visit closest to the target visit day will be used. If multiple evaluations are equally close to the date of the target visit day, then the earliest evaluation will be selected for inclusion in the analysis. If several samples are collected on the same day but at different times, the earliest time will be used. If there are no visits within the window, then a visit outside of the window for analysis will not be assigned.

3.2. Analysis Sets

Three analysis sets will be defined for the interim analysis:

Efficacy Analysis Set

The Efficacy Analysis Set is defined as all subjects who completed Part 1 of the Study and received at least one dose of BG00012 in Part 2 (LTE). This is the main population for analyses of efficacy.

Safety Analysis Set

The Safety Analysis Set is defined as all subjects who completed Part 1 of the Study and received at least one dose of BG00012 in Part 2 (LTE). This is the main population for analyses of safety (excluding the lymphocyte recovery analysis).

Subjects treated with BG00012 who complete, temporarily withhold, or permanently discontinue study treatment for any reason and have a lymphocyte count <LLN, will be followed up every 4 weeks for 24 weeks, then every 12 weeks (or sooner, if clinically indicated or at the Investigator's discretion) until the lymphocyte count is ≥LLN, for at least 48 weeks following BG00012 treatment discontinuation, or until initiation of another MS disease modifying therapy, whichever occurs first. Any subject treated with BG00012 in Part 1 with a lymphocyte count

<LLN being followed at the Part 1 Week 96 Visit (including subjects who completed, are temporarily withholding, or permanently discontinued BG00012 treatment) continued follow-up within Part 2 of the study. Subjects who have discontinued BG00012 and are participating in Part 2 for follow-up lymphocyte monitoring will not be required to undergo study procedures other than the monitoring of lymphocytes and relevant safety assessments (i.e., AE collection, vital signs, and physical examination). All other routine study assessments are optional for this subset of subjects.

Lymphocyte Recovery Analysis Set

The Lymphocyte Recovery Analysis Set includes subjects who have ALC < LLN at the last observed value collected on or prior to the date of temporary dose interruption or at the treatment discontinuation (in Part 1 or in Part 2) and have at least one ALC value during the lymphocyte follow-up period. This set includes three types of subjects:

a) All subjects who: received at least one dose of BG00012 in Part 1, completed Part 1 of the Study or initiated a lymphocyte follow up in part 1, and continued the follow-up of lymphopenia in Part 2;
b) All subjects who received at least one dose of BG00012 in Part 1, initiated a lymphocyte follow-up in Part 1, and had all the lymphocyte follow-up measurements in Part 1. Note: these subjects were already included in the lymphocyte analyses of part 1;
c) All subjects who received at least one dose of BG00012 in Part 2 (LTE) and had a lymphocyte follow up in Part 2.

This is the main population for the lymphocyte recovery analysis.

3.3. Study Treatment

BG00012/BG00012: subjects who took BG00012 in Part 1 and in Part 2 of the Study. In Part 2, subjects are taking BG00012 orally at a dose of 240 mg BID (excluding those who have stopped taking BG00012 in Part 1 and continued follow-up of lymphopenia).

Avonex/BG00012: subjects who took Avonex in Part 1 of the Study and BG00012 in Part 2. In Part 2, subjects are taking BG00012 orally at a starting dose of 120 mg BID for 7 days, followed by a maintenance dose of BG00012 240 mg BID for the remainder of the study.

BG00012: subjects who took BG00012 in Part 1 or in Part 2 of the Study. This treatment group is defined for the lymphocyte recovery analysis.

In general, analyses will be presented by previous treatment group of Part 1 (BG00012/BG00012 and Avonex/BG00012) and for the overall population. Lymphocyte recovery data will be presented for the BG00012 treatment group in the Lymphocyte Recovery Analysis Set.

3.4. Study Periods

Subjects (or their legally authorized representative [e.g., parent or legal guardian], where applicable) must provide informed consent before any Part 2 baseline tests are performed. When

a subject signs the ICF for Part 2 of the study, that subject is enrolled in Part 2. Subjects who have a nonclinically significant out-of-range laboratory result at Week 84 of Part 1 may be retested 1 time only, at the discretion of the Investigator. Participating study sites are required to document all subjects initially considered for inclusion in Part 2 of the study. If a subject is excluded from Part 2 of the study, the reasons for exclusion will be documented in the subject's eCRF. Any subject treated with BG00012 in Part 1 with a lymphocyte count <LLN being followed at the Part 1 Week 96 Visit (including subjects who completed, are temporarily withholding, or permanently discontinued BG00012 treatment) will continue follow-up within Part 2 of the study.

The following time periods will be defined for efficacy and safety analyses:

109MS306 Part 2 Study Period is defined for the Safety Analysis Sets. This is the time between the first dose date in 109MS306 Part 2 and the date of the last available measurement before/on the cutoff date for 109MS306 LTE (End of Study Date, defined above). This is the study period for analyses of safety (excluding the lymphocyte recovery analysis).

109MS306 Part 2 Treatment Period is defined for the Efficacy Analysis Set. This is the time between the first dose date in 109MS306 Part 2 and the date of the last available measurement before/on the cutoff date for 109MS306 LTE, excluding measurements performed after Day 1 of the Lymphocyte Follow up Period (defined below) for subjects who have the lymphocyte follow up in Part 2 of the Study (The measurements during the lymphocyte follow-up are excluded, since no efficacy monitoring is required and subjects do not undergo study procedures other than the monitoring of lymphocytes and relevant safety assessments, i.e., AE collection, vital signs, and physical examination during the lymphocyte follow up). This is the study period for analyses of efficacy.

The Lymphocyte Follow up Period is defined for subjects in the Lymphocyte Recovery Analysis Set as the time starting from the date of temporary dose interruption or study drug discontinuation. This is Part 1 data combined with Part 2 data for subjects who have stopped taking BG00012 in Part 1 and continued follow-up of lymphopenia in Part 2, Part 1 data for subjects who had all lymphocyte follow up measurements in Part 1, and Part 2 data for subjects who started taking BG00012 in Part 2 with a lymphocyte follow up starting in Part 2.

3.5. Key Derived Variables

Time-to-Lymphocyte-Recovery (TTLR), in days, is defined as:

TTLR = Date of sample when Lymphocyte count $\geq$ LLN for the first time in the Lymphocyte Follow up Period - Date of Day 1 of the Lymphocyte Follow up Period (Date of temporary dose interruption or study drug discontinuation) + 1.

3.6. Stratification Factors and Subgroup Variables

Stratification Factors

N/A

Subgroup Variables

N/A

4. List of Planned Study Analyses

For this interim analysis, the primary analysis of the primary endpoint of Part 2 will be summaries of the incidence of treatment-emergent AEs, SAEs, and discontinuations from study treatment due to AEs. Analysis of the secondary endpoints in Part 2 will include summaries of ARR; summaries of changes from baseline in EDSS; summaries of the incidence of clinically relevant vital signs, ECG, and laboratory abnormalities; summaries of changes from baseline in height, weight, and bone age; and summaries over time of Tanner stage.

4.1. Primary Analysis

AEs will be coded using the Medical Dictionary for Regulatory Activities Version 24.1.

All AEs, laboratory abnormalities, ECG, and vital signs will be evaluated for safety. Incidence of AEs will be summarized for all subjects in the Safety Analysis Set, by treatment group and overall during the 109MS306 Part 2 Study Period.

Clinical laboratory evaluations include hematology, blood chemistry, and urinalysis. Shifts in laboratory assessments will be summarized for each treatment group. Summary of quantitative laboratory values and change from baseline values may also be presented. .

The analysis of vital signs will focus on clinically relevant abnormalities.

The definitions of these clinically relevant abnormalities are shown in Table 5 below.

Table 5: Vital Sign abnormality criteria.

Vital Sign	Criteria for Abnormalities
Body Temperature	>38°C or an increase from baseline of ≥1°C
Heart Rate	>120 beats per minute (bpm) or an increase from baseline of >20 bpm, or <50 bpm or a decrease from baseline of >20 bpm
Systolic Blood Pressure	>180 mmHg or an increase from baseline of >40 mmHg, or <90 mmHg or a decrease from baseline of >30 mmHg
Diastolic Blood Pressure	>105 mmHg or an increase from baseline of >30 mmHg, or <50 mmHg or a decrease from baseline of >20 mmHg
Respiratory Rate	<10 or >30 breaths per minute after taking dose

5. Statistical Methods for Planned Analyses

5.1. General Principles

SAS® version 9.4 or later 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.

Date imputations

See Table 6 below for instructions on date imputation for AEs and CMs.

Table 6. Date imputation rules for AE and CM.

	Missing	Condition	Imputed Value
Start date (AE, concomitant medication)	Day	The event started in the same year and month as Study Day 1	Study Day 1
		Otherwise	01

	Missing	Condition	Imputed Value
	Day and month	The event started in the same year as Study Day 1	Study Day 1
		Otherwise	01JAN
	Year missing		No imputation will be performed
Stop date (AE, concomitant medication)	Day	The event stopped in the same year and month as the End of Study date	The End of Study date or the analysis data cut-off date, whichever is later
		Otherwise	The last day of the month
	Day and month	The event stopped in the same year as the End of Study date	The End of Study date or the analysis data cut-off date
		Otherwise	31DEC
	Year Missing		No imputation will be performed

5.2. Participant Accountability

Number of subjects who enrolled into the 109MS306 Part 2 study, number who received at least one dose of BG00012 number completing the study, number discontinuing prior to Week 324 and reason for early withdrawal, will be summarized by treatment and overall.

5.3. Demographic and Baseline Characteristics

Demographic and baseline characteristics, including age (in years, at the time of consent to study 109MS306 Part 2), age group (10 - 12, 13 - 14, 15 - 17), race, baseline height (cm) and weight (kg) and Tanner Score (if applicable) will be summarized using descriptive statistics, by treatment group and overall, for subjects in the Safety Analysis Set. Tanner score and bone age may be listed rather than summarized if the majority of subjects are mature at the Part 2 baseline.

5.4. Protocol Deviations

Major and minor protocol deviations will be listed in the final CSR only.

5.5. Study Treatment Exposure and Concomitant Medications

Concomitant medication is defined as any prescribed or over-the-counter medication used during the study (on or after Day 1 of 109MS306 LTE). The World Health Organization (WHO) Drug Dictionary (WHODRUG Global September 2021) will be used for coding concomitant medications. The Medical Dictionary for Regulatory Activities (MedDRA, version 24.1) 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 by treatment and overall.

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

5.6. Efficacy Endpoints

For the purpose of this interim analysis, efficacy endpoints will be limited to EDSS scores and relapse rates.

General Analysis Methods for Efficacy Endpoints

In general, continuous variables will be summarized using summary statistics (mean, standard deviation [SD], median, minimum, and maximum) by treatment group, and categorical variables will be presented using frequency distributions by treatment group. Where appropriate, 95% CIs for mean, median, or proportions may also be presented. In addition, statistical modeling may be used to analyze the data.

Annualized Relapse Rate (ARR)

The ARR will be analyzed with a negative binomial regression model for the Efficacy Analysis Set. The logarithmic transformation of the time-on-study (expressed in years of 365.25 days) will be used as an offset term in the model. If the data are under-dispersed (assessed using the Pearson Chi-Squared statistic) or if the negative binomial model does not converge, a Poisson regression model will be used instead. The Poisson model will be adjusted for over-dispersion using a Pearson scale parameter. The treatment group is the previous group of Part 1 of the Study (BG00012/BG00012 or Avonex/BG00012). The adjustment will be performed with the following characteristics: number of relapses in a year prior to the first dose in Part 2, age group at Baseline (baseline of Part 2) and EDSS at Baseline (baseline of Part 2).

EDSS Score

Summary statistics of the EDSS scores and their change from baseline (Part 2 baseline) will be presented for the Efficacy Analysis Set for each treatment group and for the overall population, by visit. Individual EDSS Functional Scale Scores and Ambulatory Scores, along with EDSS Scores will be listed for each subject.

5.7. Safety Endpoints

Safety General Analysis Methods for Safety Endpoints

All treatment-emergent AEs during the 109MS306 Part 2 Study Period, laboratory abnormalities, ECG, and vital signs will be included in the evaluation for safety An event is considered treatment emergent if the start date of the AE is on or after the first dose date in Part 2 or the existing AE worsened after the first dose date in Part 2. Baseline values and visit windows for safety summaries are defined in the same way as they are for efficacy analyses.

Any deaths that occurred during the study will be listed and relevant information including timing of the death relative to study treatment, concomitant medications, the investigator assessment of the cause of death will be provided.

STAN Tables

The STAN 2.1 package will be provided. The analysis population for safety summaries will be the Safety Analysis Set.

Analysis Methods
Summaries of safety data will include descriptive statistics for continuous variables and frequency distributions for categorical variables. In general, the incidence of treatment emergent AEs will be summarized for each treatment group and overall.

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.

Clinical Adverse Events
Incidence of AEs will be summarized using frequency distribution tables; overall, by severity, and by relationship to study treatment. The summary tables will include incidences for system organ class (SOC) as well as for preferred terms (PT) 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.

AEs will be coded using the MedDRA dictionary (version 24.1).

Summaries of the most frequent occurring AEs (PTs that occur in at least 5% of the subjects in any treatment group) will be presented by treatment group for each preferred term.

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 study treatment.

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 study treatment 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.

The incidence of AEs of special interest (AESI) by PT will be presented by treatment group and overall. These will be summarized by SOC and PT and may include the following:

- Flushing and other related symptoms;
- Gastrointestinal tolerability (nausea, abdominal pain, diarrhea, etc.);
- Infections, including potential opportunistic infections;
- Ischaemic cardiovascular disorders;
- Hepatic disorders;
- Renal disorders;
- Malignancies;
- Lymphopenia and Leukopenia.

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: sodium, potassium, chloride, total bilirubin, alkaline phosphatase, ALT, AST, GGT, BUN, creatinine, bicarbonate, calcium, magnesium, phosphate, uric acid, and glucose
- Urinalysis: color, specific gravity, pH, protein, glucose, blood, ketones, and microscopy (urine cytology, β_2-microglobulin, and microalbumin will be included in summaries if available)

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 normal baseline to any visit post baseline high/low status for all hematology and blood chemistry parameters and shifts from normal baseline to high/positive status for urinalysis

will be presented. For qualitative urinalysis parameters, categories may be defined based on the qualitative categories (e.g., normal/negative, trace, 1+, 2+, 3+, etc.). All positive readings will be classified as "Abnormal" for shift purposes. All values will be listed.

Summary statistics at each visit will also be provided for all absolute laboratory values (including ALC) as well as change from baseline, by study treatment. 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 in certain laboratory assessments may be presented as well. These graphs will include eosinophils, lymphocytes, neutrophils, and liver function tests (bilirubin, AST, ALT, ALP, BILI, and GGT). In addition, a graphical display of the mean (+/- SE) of the ALC values for the whole part 2 of the Study in the Safety Analysis Set will be Presented.

Lymphocyte Recovery Analyses

The by-visit summary of actual ALC values, their change and percent change from the Lymphocyte recovery baseline during the Lymphocyte Follow-up Period will be presented for the Lymphocyte Recovery Analysis Set. In addition, a graphical display of the mean (+/- SE) of the actual ALC for the Lymphocyte Recovery Period in the Lymphocyte Recovery Analysis Set will be presented. The time until recovery (when the lymphocyte count >= LLN) will be listed. Additional analyses exploring absolute lymphocyte counts and time to ALC recovery may be conducted.

Additional safety tables

Exposure and study duration

A table summarizing cumulative exposure to BG00012 and study duration by age group and overall will be provided.

5.8. Pharmacokinetic Endpoints

N/A

5.9. Pharmacodynamic Endpoints

N/A

5.10. Patient Reported Outcomes (PROs)

N/A

5.11. Other Analyses

5.12. Statistical Considerations for Interim Analysis

Interim analyses will be performed as needed during the 109MS306 LTE phase to support regulatory requirements.

6. Changes from Protocol-Specified Analyses

N/A.

7. Summary of Changes from the Previous Version of the SAP

N/A. First interim analysis SAP for the study LTE.

8. References

N/A.

APPENDICES

None.