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
NCT Number:	NCT02283853
Document Date:	25 July 2017

Biogen MA Inc.
225 Binney Street
Cambridge, MA 02142
United States

Biogen Idec Research Limited
Innovation House
70 Norden Road
Maidenhead Berkshire
SL6 4AY
United Kingdom

PROTOCOL NUMBER: 109MS306

PHASE OF DEVELOPMENT: 3

PROTOCOL 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

EUDRA CT NUMBER: 2013-002318-11

DATE: 25 July 2017
Version 5
FINAL
Supersedes previous Version 4 dated 08 February 2016

SPONSOR SIGNATURE PAGE

Protocol 109MS306, Version 5.0 was approved by:

[redacted]

25 July 2017

[redacted], MD

Date

[redacted]

Biogen

SPONSOR SIGNATURE PAGE

Protocol 109MS306, Version 5.0 was approved by:

[redacted] 28 July 2017

[redacted], MD Date

[redacted]

Biogen

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1. SPONSOR INFORMATION

Biogen MA Inc.
225 Binney Street
Cambridge, MA 02142
United States

Biogen Idec Research Limited
Innovation House
70 Norden Road
Maidenhead, Berkshire
SL6 4AY
United Kingdom

For urgent medical issues in which the study's Medical Director should be contacted, please refer to the Study Reference Guide's Official Study Contact List for complete contact information.

Biogen may transfer any or all of its study-related responsibilities to a contract research organization and other third parties; however, Biogen retains overall accountability for these activities.

2. 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

3. SYNOPSIS

This is a brief summary. For details refer to the body of the protocol.

Protocol Number:	109MS306
Protocol 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
Version Number:	5
Name of Study Treatment:	BG00012 (dimethyl fumarate; Tecfidera®)
Study Indication:	Multiple sclerosis (MS)
Phase of Development:	3
Rationale for the Study:	Study 109MS306 is designed to collect data to evaluate the safety, tolerability, and efficacy of BG00012 in pediatric subjects with relapsing-remitting multiple sclerosis (RRMS). In adult subjects with RRMS, BG00012 demonstrated efficacy and safety in 2 large Phase 3 studies, Study 109MS301 (DEFINE) and Study 109MS302 (CONFIRM), and BG00012 (Tecfidera) has been approved in the United States and other countries for adult use. In these Phase 3 studies, BG00012 had a significant effect on clinical endpoints of relapses and disability, as well as magnetic resonance imaging (MRI) endpoints, including the number and volume of new or newly enlarging T2 hyperintense lesions, gadolinium (Gd)-enhancing lesions, and new T1 hypointense lesions compared with placebo. These effects were seen as early as 6 months and were maintained over the 2 years of the studies. With no approved MS therapies in the pediatric population, there exists a significant need for approved treatment options. In the adult population, BG00012 is a therapeutic option with demonstrated efficacy and an acceptable tolerability and safety profile combined with the ease of oral

administration. This study is being conducted in 2 parts:

Part 1, the randomized, active control phase, will assess the safety, tolerability, efficacy, and health outcomes of BG00012 in pediatric subjects with RRMS compared with a disease-modifying treatment.

Part 2, the extension phase of the study, will assess the long-term safety and health outcomes in BG00012-treated subjects with RRMS.

Study Objectives and Endpoints:

Part 1 (Randomized Phase) Objectives

The main objectives of Part 1 are as follows:

- To evaluate the safety, tolerability, and efficacy of BG00012 in pediatric subjects with RRMS, as compared with a disease-modifying treatment
- To assess health outcomes and evolution of disability

Part 1 Endpoints

Primary: The primary endpoint of Part 1 is the proportion of subjects free of new or newly enlarging T2 hyperintense lesions on brain MRI scans at Week 96.

Secondary:

- 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 adverse events (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 monitoring of liver function, renal function, hematologic, and coagulation parameters
- Fatigue as measured by the Pediatric Quality of Life Inventory (PedsQL™) Multidimensional Fatigue Scale scores
- Quality of life as measured by the PedsQL
- Change from baseline to Week 96 in the Expanded Disability Status Scale (EDSS) score

Exploratory:

- 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

- Brief Visuospatial Memory Test - Revised (BVMT-R) scores (to assess learning/memory), Symbol Digit Modalities Test (SDMT) scores (to assess processing speed), and school progression query at Weeks 48 and 96

Part 2 (Extension Phase) Objectives

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

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.

Part 2 Endpoints

Primary: The primary endpoint of Part 2 is the incidence of AEs, SAEs, and discontinuations of BG00012 due to an AE.

Secondary: The secondary endpoints of Part 2 are 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.

Study Design:

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.

Subjects will be randomly assigned in a 1:1 ratio to treatment with BG00012 or interferon β-1a (IFN β-1a). 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 years 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.

Part 2 will be 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 will allow for the collection of long-term (approximately 5 years) safety and MS outcomes in subjects with RRMS treated with BG00012.

Rationale for Dose and Schedule Selection:

Safety, tolerability, and efficacy of BG00012 240 mg twice daily (BID) have been established and evaluated in adults with MS as young as 18 years of age and with weights as low as 34.0 kg in 2 Phase 3 pivotal studies in MS. In addition, there are no apparent differences in the kinetics and metabolism across the age range from 18 to 56 years, suggesting that disposition of BG00012 is not likely to change with age.

In adults, after oral administration, dimethyl fumarate (DMF) is well absorbed and extensively metabolized by esterases to its primary active metabolite, monomethyl fumarate (MMF). Downstream metabolism of DMF/MMF occurs through the tricarboxylic acid cycle, with exhalation of CO_2 serving as a major route of elimination.

Published data [Zhu 2009] indicate that there were no notable differences in the expression and activities of esterases in juveniles (12 to 18 years old) when compared with adults. Furthermore, the Phase 3 clinical studies 109MS301 and 109MS302 included adults with body weights as low as 34 kg without any observed efficacy or safety concerns. For these reasons, BG00012 240 mg BID, the approved dose in adults, has been chosen for this study.

Rationale for Comparator Product

An active comparator will be used in this open-label study because interferon β has been approved in some areas of the world for the treatment of pediatric MS and is commonly used in clinical practice to treat pediatric patients with MS. Avonex® (IFN β-1a) is marketed around the world as a therapeutic option for patients with relapsing forms of MS to slow the accumulation of physical disability and decrease the frequency of clinical exacerbations. Efficacy was demonstrated in adult patients with MS who had experienced a first clinical episode and had MRI features consistent with MS. The use of IFN β-1a in pediatric patients is well documented and appears to have an acceptable safety profile [Adams 1999; Ghezzi 2005; Mikaeloff 2001; Pohl 2005; Waubant and Chabas 2009].

Study Location: This study will be conducted globally at approximately 50 centers.

Number of Planned Subjects: Approximately 142 subjects will be enrolled.

Study Population: Male and female subjects, aged from 10 to less than 18 years old, with RRMS who have experienced at least 1 relapse within the last 12 months prior to Day 1, or at least 2 relapses within the last 24 months prior to Day 1, or evidence of Gd-enhancing lesions of the brain on MRI within 6 weeks prior to Day 1. Subjects must be neurologically stable, with no evidence of relapse within 50 days and no evidence of corticosteroid treatment within 30 days before Day 1

Detailed criteria are described in the protocol.

Treatment Groups: **Part 1**

BG00012 Treatment Group: Subjects 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.

Interferon Treatment Group (active control): IFN β-1a (Avonex) doses will be titrated during the first 4 weeks and will be started at a dose of 7.5 μg; the dose will be increased by 7.5 μg each week for 3 weeks until the recommended

	dose of 30 µg is achieved. Following titration, subjects will receive IFN β-1a (Avonex) 30 µg once weekly intramuscular. **Part 2** Subjects will receive BG00012, 240 mg BID, orally, for 240 weeks. 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.
Duration of Treatment and Follow-up:	In Part 1, subjects will have clinic visits at Screening (within 6 weeks of Baseline); Baseline (Day 1); and Weeks 4, 8, 12, 24, 36, 48, 60, 72, 84, and 96. At Week 2, subjects will receive a follow-up safety telephone call (see Table 1 and Table 2). Subjects who choose not to enroll in Part 2 will have a Safety Follow-Up Visit no later than 4 weeks (Week 100) after taking the final dose. Subjects who withdraw from the study prematurely will complete the Early Withdrawal Visit and the Safety Follow-Up Visit no later than 4 weeks after taking their final dose. Subjects who complete, temporarily withhold, or permanently discontinue BG00012 treatment for any reason and have a lymphocyte count less than the lower limit of normal (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. In Part 2, subjects will have clinic visits every 12 weeks up to Week 336 and a Safety Follow-Up Visit no later than 4 weeks after the last dose of BG00012. During Part 2, subjects 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.

Criteria for Evaluation:

Efficacy:

- Brain MRI parameters will include the following:
  - new or newly enlarging T2 hyperintense lesions
  - total Gd-enhancing lesions
  - new T1 hypointense lesions
- Clinical parameters will include the following:
  - assessment of protocol-defined relapses
  - EDSS scores
  - BVMT-R scores
  - SDMT scores
  - school progression query

Health Outcomes: The patient-reported outcomes evaluated in this study will be the PedsQL Multidimensional Fatigue Scale scores and the PedsQL scores.

Safety: Safety will be monitored through the following:

- AEs, SAEs, and concomitant therapy and procedure recording
- physical examinations, including body weight, height, and Tanner score
- vital sign measurements, including body temperature, heart rate, systolic and diastolic blood pressure, and respiratory rate

- 12-lead ECG readings

The following laboratory tests will be performed:

- hematology
- blood chemistry
- coagulation (in Part 1 only)
- urine pregnancy test
- endocrine tests (until the subject has reached bone age of ≥16 years or once the subject is postmenarche): insulin-like growth factor 1, insulin-like growth factor binding protein, follicle-stimulating hormone, luteinizing hormone, estradiol, and testosterone
- urinalysis

The following radiological tests will be performed:

- Gd-enhanced MRIs for relapses
- 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

Statistical Methods:

The primary analysis of the primary endpoint of Part 1 will include the following:

- Data will be presented as descriptive statistics and confidence intervals (CIs). The CIs for the proportion of subjects free of new or newly enlarging T2 lesions at Week 96 for each treatment group will be presented.
- Data will be summarized using observed values. No special method will be used to handle missing information.

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. 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. A negative binomial regression model will be used to analyze the key secondary endpoint of Part 1 of the study (i.e., number of new or newly enlarging T2 hyperintense lesions at Week 24), with treatment group in the model and adjusted for age group used in the randomization stratification and the baseline number of T2 lesions. Formal statistical testing will be performed to compare the mean between the 2 treatment groups. The analysis will be based on subjects from the Intent-to-Treat (ITT) Population who have observed data at Week 24. The number of new or newly enlarging T2 hyperintense lesions at other timepoints will be analyzed in a similar way. Analyses of other secondary efficacy endpoints in Part 1 will be based on subjects from the Completers Population, as well as subjects from the ITT Population. Missing value imputation may be performed. Analysis of the secondary endpoints in Part 2 will include summaries of ARR and summaries of changes from baseline in EDSS, SDMT, BVMT-R scores, and school progression query; 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. Data will be summarized for the overall population as well as separately for pre- and post-pubertal subjects.
Interim Analysis:	In Part 2, study data 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.
Sample Size Determination:	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 2-year 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 made 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 (standard deviation) 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.

Because Part 2 is an extension of Part 1, the sample size will be determined by the number of eligible subjects who completed Part 1 of the study.

4. STUDY SCHEMATIC AND SCHEDULE OF EVENTS FOR STUDY 109MS306

4.1. Study Schematics for Parts 1 and 2

The study design for Part 1 (Randomized Phase) of Study 109MS306 is shown in Figure 1, and the study activities are shown in Table 1 and Table 2.

The study design for Part 2 (Extension Phase) of Study 109MS306 is shown in Figure 2, and the study activities for Part 2 are shown in Table 3 and Table 4.

Figure 1: Study Design for the Randomized Phase - Part 1

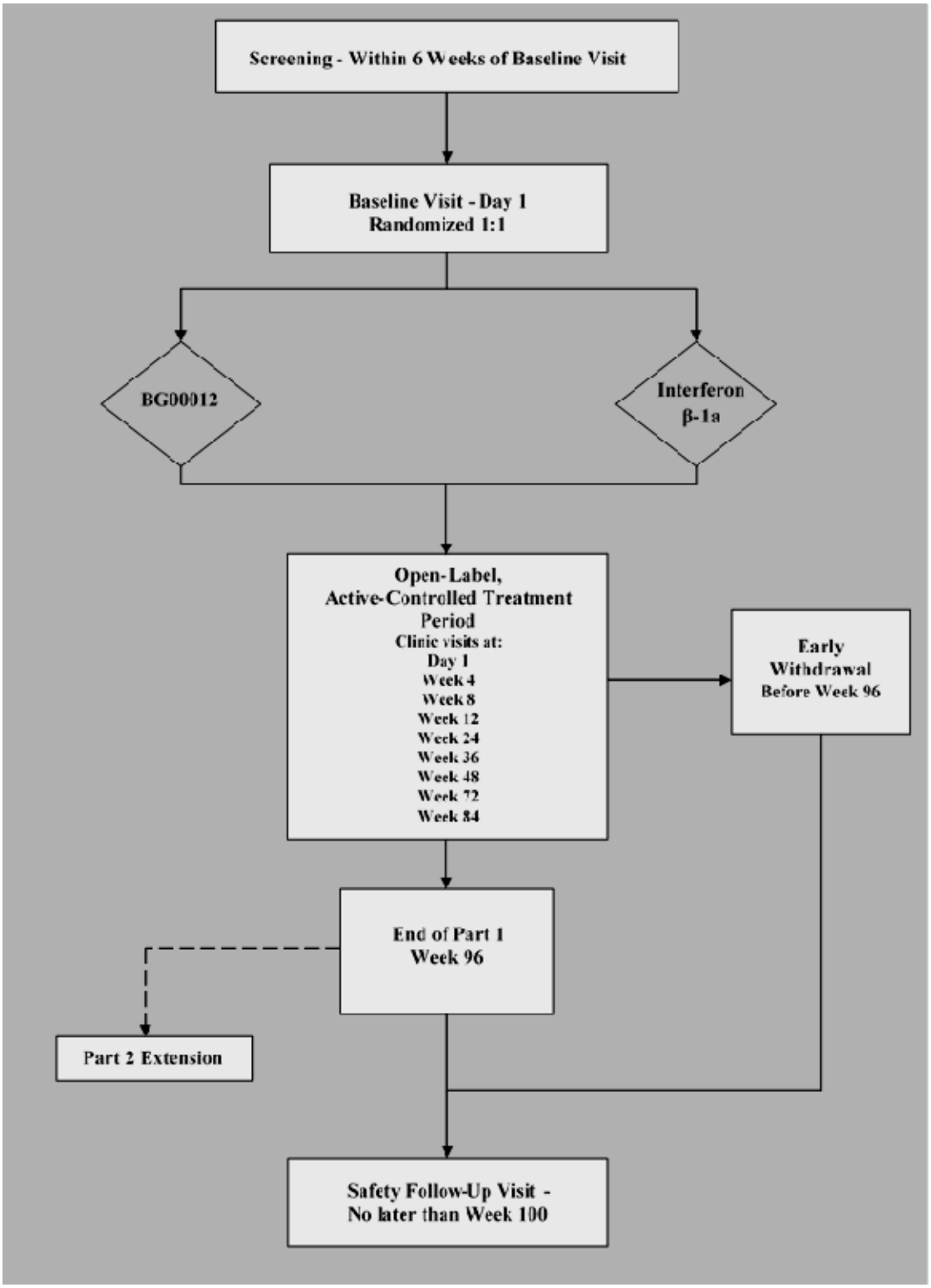
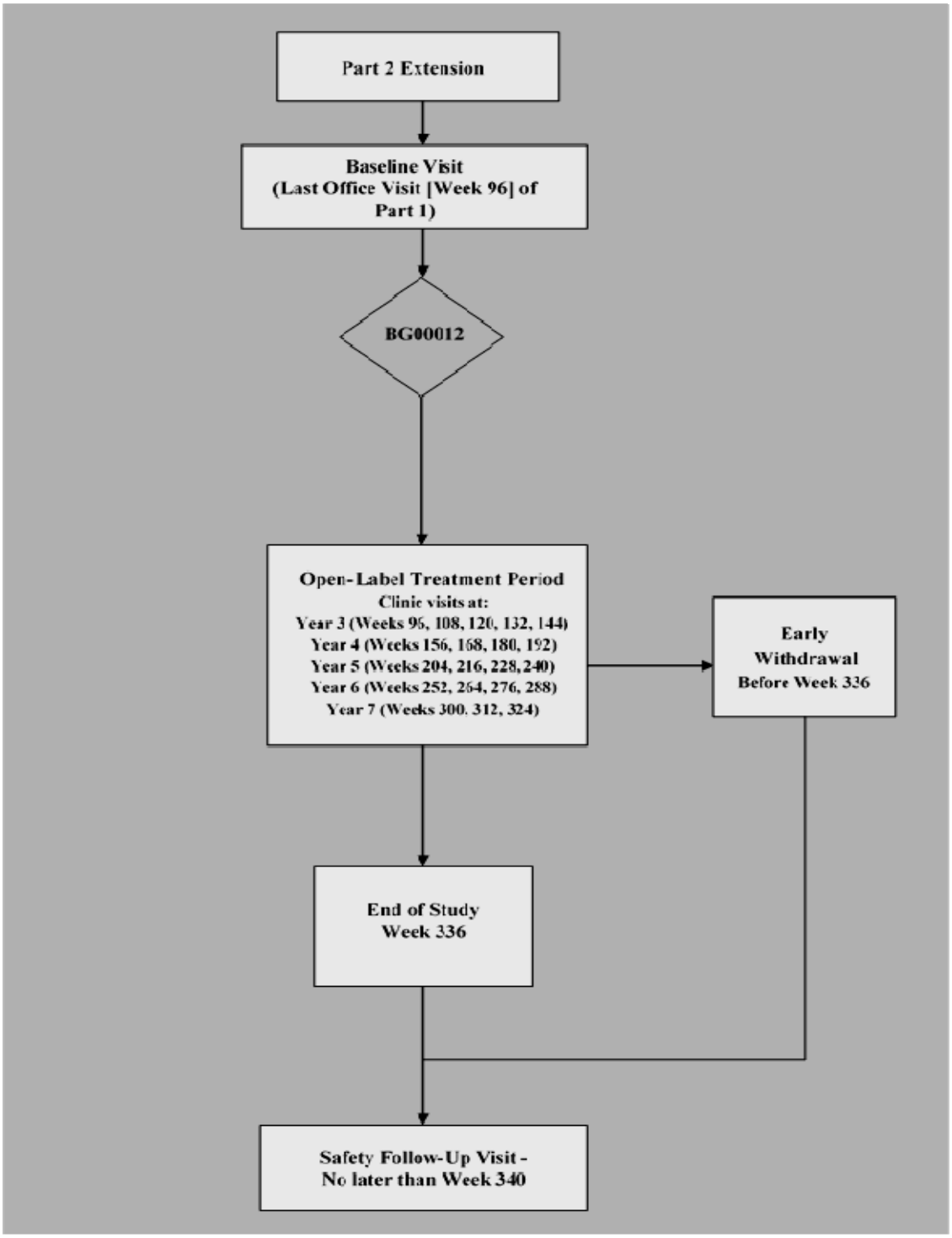


Figure 2: Study Design - Part 2 Extension



See Figure 3 in Section 6.6.4.2 for the follow-up of subjects with lymphocyte count < lower limit of normal (LLN) who have permanently or temporarily discontinued BG00012 in Part 1.

4.2. Schedule of Events

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										
AEs Recording			Monitor and record throughout the study as described in Section 8.2									

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 .
[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).
[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			X	X
AEs Recording	Monitor and record throughout the study as described in Section 8.2			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 6.9.2 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).

[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] 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.

[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 from one [class/grade-level] to the next in school?"

Table 3: Study Activities - Part 2

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, 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).

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

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. See Section 6.3.3 and Section 6.9.2 for further details.

[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 Lymphocyte Follow-Up Visit.

[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).

[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?"

4.3. Additional Information

Subjects in the BG00012 treatment group can either swallow the BG00012 capsules whole (preferred) or open the capsules and mix with food **immediately** prior to consumption.

4.3.1. Blood Volumes

Every effort was made to collect the minimum blood volume needed per protocol assessment. The blood volumes required for this study do not exceed the recommended pediatric blood volume limits for sampling, i.e., volumes do not exceed 3% of the total blood volumes during a period of 4 weeks and volumes do not exceed 1% at any single visit [European Commission 2008]. For example, in a 30-kg child (the lowest possible weight permitted in this study), it was estimated that 1% of the total volume would be approximately 21 mL. Children weighing more than 30 kg would have higher permitted amounts. The total blood volumes drawn at each visit are provided in Table 5, Table 6, and Table 7.

Table 5: Blood Volumes by Visit - Part 1

	Screening Visit												End of Study/ Early Withdrawal	Safety Follow-Up Visit	Lymphocyte Follow-Up Visit	Unscheduled Relapse Assessment Visit
Week	(Within 6 Weeks of Baseline)	Baseline Visit (Day 1)	Wk 2 ±5D Safety Phone Call	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	Wk 96 ± 5D	No later Than Wk 100 ± 5D		
Blood Draw Volume (mL)	4.8	12.9	0.0	2.5	2.5	2.5	4.0	2.5	9.0	2.5	2.5	2.5	12.9	2.3	1.2	2.3

Wk = week.

Table 6: Blood Volumes by Visit - Part 2 Treatment Period

	Year 3			Year 4				Year 5				Year 6				Year 7			
	Wk 108	Wk 120	Wk 132	Wk 144	Wk 156	Wk 168	Wk 180	Wk 192	Wk 204	Wk 216	Wk 228	Wk 240	Wk 252	Wk 264	Wk 276	Wk 288	Wk 300	Wk 312	Wk 324
Blood Draw Volume (mL)	1.2	2.3	1.2	11.5	1.2	2.3	1.2	11.5	1.2	2.3	1.2	11.5	1.2	2.3	1.2	11.5	1.2	2.3	1.2

Wk = week.

Table 7: Blood Volumes for Unscheduled and Post-Treatment Visits for Part 2

	End of Study Visit/Early Withdrawal (Week 336 ± 7 days)	Safety Follow-Up Visit (no later than Week 340)	Lymphocyte Follow-Up	Unscheduled Relapse Assessment Visit
Blood Draw Volume (mL)	11.5	2.3	1.2	2.3

4.3.2. Site Personnel

For each subject, the Principal Investigator of the site will designate the following investigational site personnel:

- A primary and backup *treating* neurologist
- A primary and backup *treating* nurse or study coordinator
- A primary and backup *examining* neurologist
- A magnetic resonance imaging (MRI) technician
- A radiologist
- A pharmacist (or authorized designee)

Where specified, evaluations described in this section must be performed only by the personnel indicated.

The primary *treating* neurologist will be responsible for the following activities:

- Management of the routine neurological care of the subject
- Assessment (including assignment of causality) and treatment of adverse events (AEs) and multiple sclerosis (MS) relapses
- Review of selected hematology and blood chemistry results from the central laboratory to assess whether the subject's study treatment should be temporarily withheld or permanently discontinued as per the criteria detailed in Section 6.6.3 and Section 6.6.4.

The *treating* neurologist may designate other medical personnel (i.e., the backup *treating* neurologist or the *treating* nurse) at the investigational site to perform some of the tests and evaluations listed under "*treating* neurologist." If there is more than 1 *treating* neurologist available at a given site such that each is assigned to particular subjects, then these *treating* neurologists may act as backup for each other. The same holds true for the *treating* nurses.

Hematology, blood chemistry, and urinalysis data will be sent to the investigational sites to aid in management of the subject. As with other laboratory and clinical information, these data should NOT be reviewed by the *examining* neurologist or the backup *examining* neurologist.

The primary *treating* nurse or study coordinator will be responsible for the following activities:

- Assisting the *treating* neurologist in subject management, including the treatment of AEs, the treatment and assessment of disease relapses, and the recording of AEs and concomitant medications.

- Obtaining Brief Visuospatial Memory Test - Revised (BVMT-R) score, Symbol Digit Modalities Test (SDMT) score, Pediatric Quality of Life Inventory (PedsQL™) score, a PedsQL Multidimensional Fatigue Scale score, and school progression query at the scheduled timepoints required in the protocol.

- Monitoring accountability of study treatment at subject level.

The *examining* neurologist or EDSS-certified rater will be responsible for the following activities:

- Obtaining an Expanded Disability Status Scale (EDSS) score based on a detailed neurological examination at the scheduled timepoints required in the protocol

- Obtaining an EDSS score each time a subject is referred by the *treating* neurologist, based on the *treating* neurologist's assessment of a possible relapse at the unscheduled Relapse Assessment Visit.

- The *examining* neurologist must not be involved with any other aspect of subject care and management. Further, the *examining* neurologist is not to serve as *treating* neurologist for any subjects at a given investigational site. To ensure consistency across sites, *examining* neurologists must undergo a standardized training session on EDSS scoring prior to enrollment of subjects at their site. The backup *examining* neurologist will conduct subject evaluations ONLY if the primary *examining* neurologist is unavailable due to illness, vacation, or travel. All sites should attempt to maintain the same *examining* neurologist throughout the study. If an *examining* neurologist has to be replaced, the new *examining* neurologist must undergo a training session. The communication of new findings on the neurologic examination from the *examining* neurologist to the *treating* neurologist is permitted (because findings on the neurologic examination may be important in the routine care of the subject, e.g., medical management of relapses). The roles of *treating* and *examining* neurologist (primary and backup) are NOT interchangeable even for different subjects. The *examining* neurologist must remain blinded to AEs, concomitant medications, laboratory data, MRI scan data, and any other data that have the potential of revealing the treatment assignment.

The MRI technician will be responsible for performing a brain MRI scan with and without gadolinium (Gd) at all protocol-required timepoints. Study-specific MRI scan procedures and protocols with and without Gd, which will be provided prior to study start, must be followed in

Part 1. Subjects should be offered the use of topical anesthetics for venipuncture, and an intravenous (IV)-line insertion must be performed for injection of Gd.

The radiologist will be responsible for and should be experienced with the assessment of hand and wrist x-rays for the determination of bone age.

The pharmacist (or authorized designee) will be responsible for storage, distribution, and site accountability of study treatment.

5. INTRODUCTION

MS is a chronic autoimmune and neurodegenerative disorder of the central nervous system (CNS) that is characterized by inflammation, demyelination, and oligodendrocyte and neuronal loss. It is the most common demyelinating disorder of the CNS, affecting approximately 2.5 million people worldwide, and it typically affects young to middle-aged adults. Although not usually reported in pediatric patients, 2.2% to 4.4% of all MS cases are in pediatric patients [Chitnis 2011]. Girls are affected more than boys, and most cases are relapsing-remitting multiple sclerosis (RRMS).

5.1. Profile of Previous Experience

5.1.1. Preclinical Experience With BG00012

Nonclinical safety studies were performed to support the development of BG00012 for the treatment of MS. CNS, respiratory, and cardiovascular safety studies demonstrated no drug-related adverse effects on those systems, which is consistent with human data. There were no findings of mutagenicity, fertility, and teratogenicity. Repeat-dose toxicology studies were performed in rodents (mouse and rat) and non-rodents (dog and monkey). The findings in the liver, forestomach, and testis were concluded to be of limited concern to human risk. In the male rat juvenile toxicology study that specifically evaluated the reproductive organs, there were no toxicology findings. Kidney findings seen in animals were not observed in humans. In life-time carcinogenicity studies, renal tumors were attributed to a rodent-specific event of the exacerbation of nephropathy.

An overview of preclinical data with BG00012 is provided in the Investigator's Brochure.

5.1.2. Relevant Clinical Experience With BG00012

BG00012 240 mg twice daily (BID) is currently approved for the treatment of adult patients with MS in the United States (US) and other countries.

The efficacy and safety of BG00012 are well established based on data from the clinical development program for BG00012 in MS that included 6 clinical studies that were conducted in subjects with RRMS. A total 2665 subjects with MS received at least 1 dose of BG00012. Of these, 2513 subjects with MS received BG00012 in the Phase 2 and 3 placebo-controlled efficacy and safety studies and/or their uncontrolled extension studies accounting for approximately 6100 subject-years of exposure. Of the 2513 subjects 1606 received BG00012 at a dose of 240 mg BID or higher for ≥2 years, 1075 for ≥3 years, 872 for ≥4 years, and 303 for ≥5 years. The maximum duration of exposure to BG00012 for any subject with MS was 6.5 years.

The efficacy of BG00012 on MS in adults was assessed in Study C-1900, a Phase 2, randomized, placebo-controlled study in subjects with RRMS, 2 Phase 3 studies (Study 109MS301 [DEFINE] and Study 109MS302 [CONFIRM]) in subjects with RRMS, and in an ongoing Phase 3 extension study (Study 109MS303).

Results of Phase 3 clinical studies demonstrate that BG00012 given as 240 mg BID or 3 times daily (TID) is an efficacious treatment for RRMS. Consistent and substantial evidence of clinical efficacy has been shown by significant reductions in measurements of relapse and disability progression versus placebo. Clinical efficacy was supported by positive and consistent effects on MRI measures of disease activity. A robust treatment effect was evident within the initial 6 months of treatment and was sustained for up to 2 years of treatment.

Overall, safety data from the clinical development program showed that BG00012 was well tolerated and has an acceptable safety profile. In the BG00012 BID group, the most common AEs (incidence ≥5%) that also occurred at an incidence of ≥2% higher than in the placebo group were flushing and hot flush, gastrointestinal (GI) events (diarrhea, nausea, abdominal pain upper, abdominal pain, vomiting, and dyspepsia), skin events (pruritus, rash, and erythema), nasopharyngitis, urinary tract infection, upper respiratory tract infection, albumin urine present, proteinuria, and microalbuminuria. The AE profile was similar for subjects who received 240 mg TID.

In placebo-controlled studies, decreases in mean white blood cell (WBC) and lymphocyte counts were observed over the first year of treatment (approximately 10% and 30%, respectively) with both doses of BG00012. Mean WBC and lymphocyte counts then plateaued and remained stable, even during longer periods of observation of approximately 3.5 years. An analysis of the data did not show a clear correlation between infections, serious infections, and lymphocyte counts. No increased risk of infection, serious infection, or opportunistic infection was observed in subjects treated with BG00012 in the placebo-controlled studies. In October 2014, in the 109MS303 extension study in adult subjects, in the setting of severe, prolonged lymphopenia for 3.5 years, a subject developed progressive multifocal leukoencephalopathy. With open-label and marketed use of BG00012, there has been no other evidence of increased risk of infections, serious infections, or opportunistic infections.

BG00012 was also associated with a small increase in the incidence of elevations of liver transaminases compared to placebo. In the controlled studies, this increase was primarily due to differences that occurred within the first 6 months of treatment. The majority of subjects with elevations had alanine transaminase (ALT) or aspartate transaminase (AST) levels <3 times the upper limit of normal (ULN). No patients had elevations of ALT or AST ≥3 × ULN associated with an elevation in total bilirubin of >2 × ULN. There were no cases of hepatic failure due to BG00012. During extended treatment with BG00012, ALT and AST levels remained stable through 3.5 years of observation. Based on these data, there appears to be a transient increase in liver transaminases with BG00012 relative to placebo that does not appear to be associated with any increase in clinically significant liver pathology.

Although the kidney was identified as a target organ of BG00012 toxicity in nonclinical studies, subjects treated with BG00012 in the clinical studies did not appear to have a higher risk of renal or urinary events. Small increases in proteinuria were observed, but the increases did not appear to be clinically significant. On laboratory evaluation, there were no clinically relevant changes in blood urea nitrogen (BUN), creatinine, electrolytes, calcium, phosphorus, parathyroid hormone, or 1,25-dihydroxyvitamin D. In the Phase 3 studies (Study 109MS301 and Study 109MS302), there were no differences between placebo and BG00012 BID in the incidence of proteinuria on 2 consecutive urinalyses (defined as trace or greater) or on findings of 3+ or 4+ protein, both of which are potential indicators of significant proteinuria and renal dysfunction. In addition, there was no evidence of changes in β2-microglobulin and microalbumin, 2 more sensitive and specific markers of renal tubular dysfunction, over time even during longer periods of observation of approximately 3.5 years.

In the controlled studies, there was no increased incidence of malignancies in subjects who received BG00012 compared with placebo. The types of malignancies observed and their incidence were within expected background rates.

The pharmacokinetics, efficacy, and safety of BG00012 on pediatric MS were evaluated in Study 109MS202, an open-label multicenter, multiple-dose study that enrolled 22 subjects 13 to 17 years of age. The dosing regimen was the same as the approved BG00012 dosing regimen in adults with RRMS. The pharmacokinetics, efficacy, and safety results in the pediatric subjects in Study 109MS202 were consistent with the overall BG00012 experience to date in adult healthy volunteers and adult subjects with RRMS. BG00012 was effective in reducing brain MRI lesions over a 24-week Treatment Period. Pharmacokinetic parameters in pediatric and adult subjects were comparable. The safety and tolerability profile of BG00012 was consistent with that observed in previously conducted studies in adult subjects with RRMS.

5.2. Study Rationale

Study 109MS306 is designed to collect data to evaluate the safety, tolerability, and efficacy of BG00012 in pediatric subjects with RRMS.

In adult subjects with RRMS, BG00012 demonstrated efficacy and safety in 2 large Phase 3 studies, Study 109MS301 (DEFINE) and Study 109MS302 (CONFIRM) and BG00012 (Tecfidera®) has been approved in the US and other countries for adult use. In these Phase 3 studies, BG00012 had a significant effect on clinical endpoints of relapses and disability, as well as MRI endpoints, including the number and volume of new or newly enlarging T2 hyperintense lesions, Gd-enhancing lesions, and new T1 hypointense lesions compared with placebo. These effects were seen as early as 6 months and were maintained over the 2 years of the studies.

With no approved MS therapies in the pediatric population, there is a need for approved treatment options. In the adult population, BG00012 is an oral therapy with demonstrated efficacy and an acceptable tolerability and safety profile. This study is being conducted to evaluate BG00012 in the pediatric population.

Part 1, the randomized, active control phase, will assess the safety, tolerability, efficacy, and health outcomes of BG00012 in pediatric subjects with RRMS compared with a disease modifying treatment.

Part 2, the extension phase of the study, will assess long-term safety and health outcomes in subjects with RRMS treated with BG00012.

5.3. Rationale for Dose and Schedule Selection

In 2 Phase 3 pivotal studies, safety, tolerability, and efficacy of BG00012 240 mg BID have been established and evaluated in adults with MS as young as 18 years of age and with weights as low as 34.0 kg. Moreover, the safety and efficacy profile was unchanged regardless of weight. In addition, there are no apparent differences in the kinetics and metabolism across the age range from 18 to 56 years, suggesting that disposition of BG00012 is not likely to change with age.

In adults, after oral administration, dimethyl fumarate (DMF) is well absorbed and extensively metabolized by esterases to its primary active metabolite, monomethyl fumarate (MMF). Downstream metabolism of DMF/MMF occurs through the tricarboxylic acid cycle, with exhalation of CO_2 serving as a major route of elimination.

Published data [Zhu 2009] indicate that there were no notable differences in the expression and activities of esterases in juveniles (12 to 18 years old) when compared with adults. For these reasons, BG00012 240 mg BID, the approved dose in adults, has been chosen for this study. Also, consistent with the recommended dosing in adults, the starting dose for BG00012 in this study will be 120 mg BID, orally, and should be increased to 240 mg BID after 7 days.

Rationale for Comparator Product

An active comparator will be used in this open-label study because interferon β (IFN β) has been approved in some areas of the world for the treatment of pediatric MS and is commonly used in clinical practice to treat pediatric patients with MS. Avonex® (IFN β-1a) is marketed around the world as a therapeutic option for patients with relapsing forms of MS to slow the accumulation of physical disability and decrease the frequency of clinical exacerbations. Efficacy was demonstrated in adult patients with MS who had experienced a first clinical episode and had MRI features consistent with MS. The use of IFN β-1a in pediatric patients is well documented and appears to have an acceptable safety profile [Adams 1999; Ghezzi 2005; Mikaeloff 2001; Pohl 2005; Waubant and Chabas 2009].

6. PART 1

6.1. Part 1 Main Objectives

The main objectives of Part 1 are as follows:

- To evaluate the safety, tolerability, and efficacy of BG00012 in pediatric subjects with RRMS, as compared with a disease-modifying treatment.
- To assess health outcomes and evolution of disability.

6.2. Part 1 Endpoints

6.2.1. Primary Endpoint

The primary endpoint of Part 1 is the proportion of subjects free of new or newly enlarging T2 hyperintense lesions on brain MRI scans at Week 96.

6.2.2. Secondary Endpoints

The secondary endpoints of Part 1 are as follows:

- 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

6.2.3. 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 $\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
- BVMT-R scores (to assess learning/memory) and SDMT scores (to assess processing speed), and school progression query at Weeks 48 and 96

6.3. Part 1 Study Design

6.3.1. 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 β-1a, 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.

Subjects will have clinic visits at Screening (within 6 weeks of Baseline); Baseline (Day 1); and Weeks 4, 8, 12, 24, 36, 48, 60, 72, 84, and 96. At Week 2, subjects will receive a follow-up safety telephone call.

Subjects with abnormal laboratory values after Week 12 (after which clinic visits occur once every 3 months) will be returned to the initial every-4-week schedule for the laboratory assessments until laboratory values are normalized (see Section 6.6.3). Subjects treated with BG00012 who complete, temporarily withhold, or permanently discontinue BG00012 treatment for any reason and have a lymphocyte count less than the lower limit of normal (<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 (see Section 6.6.4). 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.

Treatment of an acute event may proceed at the discretion of the *treating* neurologist only after the *examining* neurologist has completed his/her examination. Treatment of an acute event of relapse with intravenous methylprednisolone (IVMP) may proceed at the discretion of the *treating* neurologist and will not affect the subject's eligibility to continue in the study. The subject will continue on their assigned study treatment while being treated with IVMP.

Dose reduction will be allowed for subjects who are unable to tolerate treatment due to flushing and/or GI disturbance (Section 6.6.3.1). Dosing interruptions (or permanent discontinuation) will be required in the event of significantly elevated liver or renal function tests or decreased WBC or lymphocyte counts (Sections 6.6.3.1 and 6.6.4.1). Subjects who prematurely discontinue study treatment should remain in the study and continue protocol scheduled evaluations (Section 6.7.1).

See Figure 1 for the Part 1 study design. Tests and assessments for Part 1 are outlined in Table 1 and Table 2. A full clinical study report (CSR) will be written at the end of Part 1.

6.3.2. Overall Part 1 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.

Subjects with abnormal laboratory values after Week 12 (after which clinic visits occur once every 3 months) who are allowed to resume BG00012 dosing will be returned to the initial every 4-week schedule for safety assessments (clinical and laboratory safety assessments). 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 (see Section 6.6.4). 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.

Subjects who are allowed to resume BG00012 dosing following a 2- to 4-week interruption will restart dosing at a reduced dose for 1 week. Subjects must also return to the initial every-4-week visit schedule for safety assessments (see Section 6.10 for clinical and laboratory safety assessments) for 2 consecutive normal laboratory assessments before reverting to the every-3-month schedule.

Subjects who choose not to enroll in Part 2 will have a Safety Follow-Up Visit no later than 4 weeks after taking the final dose. Subjects who prematurely withdraw from the study will complete the Early Withdrawal Visit and the Safety Follow-Up Visit no later than 4 weeks after taking their final dose. The Unscheduled Relapse Assessment Visit and Lymphocyte Follow-Up Visit will be performed as necessary.

Subject eligibility for the study will be determined within a maximum of 6 weeks prior to Baseline (Day 1).

6.3.2.1. Treatment

Eligible subjects will have clinic visits at Baseline (Day 1) and Weeks 4, 8, 12, 24, 36, 48, 60, 72, and 84 during the Treatment Period.

6.3.2.2. Post-Treatment

Subjects who prematurely **withdraw from the study** should complete all study assessments for the Early Withdrawal Visit at the time of withdrawal.

Subjects who will not participate in Part 2 will return to the site for the End of Part 1 Visit (Week 96).

6.3.2.3. Follow-Up

Subjects who prematurely **withdraw from the study** will complete the study assessments for the Safety Follow-Up Visit no later than 4 weeks after the last dose of study treatment.

Subjects who opt not to continue in Part 2 must complete the Safety Follow-Up Visit no later than Week 100.

Subjects treated with BG00012 who complete, temporarily withhold, or permanently discontinue BG00012 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 (see Section 6.6.4). 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.

6.3.3. Relapses

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 should be considered part of the same relapse and would not be treated with IVMP within the protocol.

If a subject experiences new neurologic symptoms, the subject or caregiver must contact the *treating* neurologist or *treating* nurse as soon as possible and within 48 hours of the onset of symptoms to complete a Telephone Questionnaire to determine the necessity of an unscheduled Relapse Assessment Visit. If required, the subject will then be evaluated in person by the *treating* neurologist at the unscheduled Relapse Assessment Visit, which is to be conducted as soon as possible and within 72 hours of the onset of the potential relapse. If, in the opinion of the *treating* neurologist, an MS relapse may have occurred, the subject must also be evaluated by the *examining* neurologist as soon as possible and within 5 days of the onset of the symptoms. The *examining* neurologist is to perform a detailed neurologic examination and obtain an EDSS score. New objective findings on neurological examination performed by the *examining* neurologist are required to confirm that a protocol-defined relapse has occurred. Subjects may not begin corticosteroid treatment of the relapse per protocol until after the *examining* neurologist has examined them. The *examining* neurologist is permitted to report the examination findings to the *treating* neurologist so that he/she can evaluate treatment options.

Relapse Assessment Visits are to be conducted as soon as possible and within 72 hours of the onset of any new or worsening neurologic symptoms or suspected protocol-defined relapse (Figure 4). Unscheduled Relapse Assessment Visits should not modify or replace the subjects' visit schedule.

6.3.3.1. Treatment of Relapses on Scheduled or Unscheduled Visits

Treatment of an acute relapse may proceed at the discretion of the *treating* neurologist only after the *examining* neurologist has completed his/her examination and only after a Gd-enhancing MRI of the brain has been performed as per Figure 4. The treatment for relapse in this study is either 3 days or 5 days with IVMP, up to 1000 mg/day. Methylprednisolone can be given once a day or in divided doses. Any changes to this treatment should first be discussed with the Biogen Medical Director or designee.

Steroid retreatment of the same relapse is not allowed unless approved by the Biogen Medical Director or designee, who may consult with the lead Principal Investigator of that country.

6.4. Part 1 Selection of Subjects

6.4.1. Inclusion Criteria

To be eligible to participate in this study, candidates must meet the following eligibility criteria at the time of randomization (Day 1) or at the timepoint specified in the individual eligibility criterion listed:

1. Ability of parents, legal guardians, and/or subjects to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information (PHI) in accordance with national and local subject privacy regulations. Subjects will provide assent in addition to the parental or guardian consent, as appropriate, as per local regulations.

2. Males and females aged from 10 to less than 18 years old at the time of informed consent or assent.

3. Must have a body weight of ≥30 kg.

4. Must have a diagnosis of RRMS according to the International Pediatric Multiple Sclerosis Study Group criteria for pediatric MS (2013) [Krupp 2013] (consensus definition for pediatric RRMS).

5. Must be ambulatory with a baseline EDSS score between 0 and 5.5, inclusive.

6. Must have experienced at least 1 of the following 3 conditions:

    a) at least 1 relapse within the last 12 months prior to Day 1, with a prior brain MRI demonstrating lesions consistent with MS, or

b) at least 2 relapses within the last 24 months prior to Day 1, with a prior brain MRI demonstrating lesions consistent with MS, or

c) evidence of Gd-enhancing lesions of the brain on an MRI performed within the 6 weeks prior to Day 1.

7. Must be neurologically stable, with no evidence of relapse within 50 days prior to Day 1 and no evidence of corticosteroid treatment within 30 days prior to Day 1.

8. Subjects of childbearing potential who are sexually active must be willing to practice effective contraception during the study and be willing and able to continue contraception for at least 30 days after their final dose of study treatment.

6.4.2. Exclusion Criteria

Candidates will be excluded from study entry if any of the following exclusion criteria exist at the time of randomization (Day 1) or at the timepoint specified in the individual criterion listed:

Medical History

1. Primary progressive, secondary progressive, or progressive relapsing MS (as defined by [Lublin and Reingold 1996]). These conditions require the presence of continuous clinical disease worsening over a period of at least 3 months. Subjects with these conditions may also have superimposed relapses but are distinguished from relapsing-remitting subjects by the lack of clinically stable periods or clinical improvement.

2. Disorders mimicking MS, such as other demyelinating disorders (e.g., acute disseminated encephalomyelitis), systemic autoimmune disorders (e.g., Sjögren disease, lupus erythematosus), metabolic disorders (e.g., dystrophies), and infectious disorders.

3. History of premalignant or malignant disease. Subjects with basal cell carcinoma that has been completely excised prior to screening will remain eligible.

4. History of severe allergic or anaphylactic reactions, or known drug hypersensitivity to DMF, fumaric acid esters, or interferon β-1a (IFN β-1a).

5. History of abnormal laboratory results indicative of any significant endocrinologic, hematologic, hepatic, immunologic, metabolic, urologic, renal, and/or any other major disease that would preclude participation in a clinical study.

6. History of clinically significant cardiovascular, pulmonary, GI, dermatologic, growth, developmental, psychiatric (including depression), neurologic (other than MS), and/or other major disease that would preclude participation in a clinical study.

7. History of human immunodeficiency virus.

8. History of drug or alcohol abuse (as defined by the Investigator) within the 2 years prior to Day 1.

9. An MS relapse that has occurred within 50 days prior to Day 1 AND/OR the subject has not stabilized from a previous relapse prior to Day 1.

10. History or positive test result at Screening for hepatitis C virus antibody or hepatitis B virus (defined as positive for hepatitis B surface antigen [HBsAg] or hepatitis B core antibody [HBcAb]). Subjects with immunity to hepatitis B from either active vaccination (defined as negative HBsAg, positive hepatitis B surface antibody [HBsAb] and negative HBcAb) or from previous natural infection (defined as negative HBsAg, positive HBsAb IgG, and positive HBcAb) are eligible to participate in the study (definitions are based on the Centers for Disease Control and Prevention [CDC]'s interpretation of the hepatitis B serology panel [CDC 2007]; Appendix 4, Section 25]).

11. Any of the following abnormal blood test results at Screening:

    - ALT, AST, or gamma-glutamyl-transferase (GGT) $\geq 2 \times$ ULN
    - leukocytes $<3500/mm^3$
    - eosinophils $>0.7 \times 10^3/\mu L$ or >0.7 GI/L
    - absolute lymphocyte count <LLN

12. Proteinuria (1+ or greater) at Screening confirmed by a spot protein/creatinine ratio (with morning void) >0.2 mg/mg approximately 2 weeks later. Note: Documented benign proteinuria is not exclusionary.

    OR

    Any of the following additional abnormal urine tests at Screening confirmed by a second urinalysis approximately 2 weeks later:

    - hematuria, without known etiology
    - glycosuria, without known etiology

    Note: If a subject has a positive test at Screening and the etiology is known (e.g., due to menses or urinary tract infection in the case of hematuria or due to recent steroid use or elevated serum glucose in the case of glycosuria), a repeat test is not required.

Treatment History

13. Any previous treatment with Fumaderm® or BG00012.

14. Prior treatment with any of the following:
    - total lymphoid irradiation
    - cladribine
    - T-cell or T-cell receptor vaccination
    - any therapeutic monoclonal antibody, with the exception of rituximab (see Exclusion Criterion 15) or natalizumab (see Exclusion Criterion 16)
15. Prior treatment with any of the following medications within the 12 months prior to Day 1:
    - mitoxantrone
    - cyclophosphamide
    - rituximab
16. Prior treatment with any of the following medications or procedures within 6 months prior to Day 1:
    - fingolimod
    - teriflunomide
    - natalizumab
    - cyclosporine
    - azathioprine
    - methotrexate
    - mycophenolate mofetil
    - laquinimod
    - IV immunoglobulin
    - plasmapheresis or cytapheresis
17. Treatment with any of the following medications within 30 days prior to Day 1:

- steroids (IV or oral corticosteroid treatment, including agents that may act through the corticosteroid pathway [e.g., low dose naltrexone])

- 4-aminopyridine or related products (except subjects on a stable dose of controlled-release fampridine for 3 months)

18. Current enrollment in any other investigational drug study or participation in any other investigational study within the 6 months prior to Day 1.

Miscellaneous

19. Female subjects considering becoming pregnant or breastfeeding while in the study or who are pregnant or breastfeeding.

20. Inability to comply with study requirements.

21. Other unspecified reasons that, in the opinion of the Investigator or Biogen, make the subject unsuitable for enrollment.

22. Subjects for whom MRI was contraindicated, e.g., who had pacemakers or other contraindicated implanted metal devices, were allergic to Gd, had renal impairment, or had claustrophobia that could not be medically managed.

6.5. Part 1 Enrollment and Randomization Procedures

6.5.1. Enrollment and Screening

Subjects must be consented before any screening tests or assessments are performed. At the time of consent, the subject will be enrolled into the study. Participating study sites are required to document all screened candidates initially considered for inclusion in this study. If a subject is excluded from the study, the reasons for exclusion will be documented in the subject's source documents and on the screening log.

6.5.2. Randomization of Subjects

Subjects will be randomized at the Baseline Visit (Day 1), after all baseline assessments have been completed and after the Investigator has verified that they are eligible per criteria in Sections 6.4.1 and 6.4.2. No subject may begin treatment prior to randomization and assignment of a unique subject identification number. Any subject identification numbers that are assigned will not be reused even if the subject does not receive treatment.

Subjects will be randomized to receive BG00012 or IFN β-1a in a 1:1 ratio and 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 according to 3 age groups (10 to <13 years, 13 to <15 years, and 15 to <18 years). Subjects who withdraw from the study may not be replaced.

See the Study Reference Manual for details on randomization and registration.

6.5.3. Blinding Procedures

This is an open-label study.

6.6. Part 1 Treatment of Subjects

Biogen will provide investigational product to sites in Canada. Biogen Idec Research Limited will provide investigational products to all other countries.

See Section 6.8 (Part 1 Study Treatment Management) for specifics on the preparation, storage, handling, disposal, and accountability of study treatment.

6.6.1. Treatment Schedule and Administration

6.6.1.1. BG00012

BG00012 will be taken orally. Subjects will take 1 capsule orally at a dose of 120 mg BID for the first 7 days and 2 capsules orally at a dose of 240 mg BID thereafter.

Subjects will be instructed to swallow each BG00012 capsule whole and not chewed. The capsule and its contents are not to be crushed, divided, dissolved, sucked, or chewed since the enteric-coating of the microtablets in the capsule helps to prevent irritant effects on the stomach. If unable to swallow the capsule, the capsule may be opened and the contents mixed with food ***immediately*** prior to consumption.

Study site staff should refer to the Directions for Handling and Administration (DHA) located in the Study Reference Manual for specific instructions on the handling, preparation, administration, and disposal of the study treatment.

See Figure 1 for schematic on the study design.

6.6.1.2. Interferon β-1a (Avonex)

IFN β-1a (Avonex) at 30 μg administered IM once weekly is marketed around the world as a therapy for patients with relapsing forms of MS to slow the accumulation of physical disability and decrease the frequency of clinical exacerbations. Efficacy has also been demonstrated in patients with MS who have experienced a first clinical episode and have MRI features consistent with MS.

The most frequently reported AEs are flu-like symptoms, fever, and fatigue.

Avonex will be self-administered (or given via a proxy) once weekly beginning with Day 1/Baseline. Avonex doses will be titrated during the first 4 weeks of the Study Treatment Period using the Avostartgrip™ titration kit. Avonex will be started at a dose of 7.5 μg and the

dose will be increased by 7.5 µg each week for 3 weeks until the recommended dose of 30 µg is achieved to reduce the incidence and severity of flu-like symptoms that may occur when initiating Avonex therapy at a dose of 30 µg. Note: At the discretion of the treating neurologist, dose titration may not be necessary. Following titration, Avonex will be administered once weekly by IM injection according to local prescribing information.

All training procedures for the Avonex Prefilled Syringe and Avonex Pens will be outlined in the Study Reference Guide.

Avonex doses should be taken within 2 days of the scheduled dose of Avonex. If the subject is unable to have the dose within 2 days, this dose should be skipped, and the next dose should be taken as scheduled. Doses should not be doubled to make up for missed doses.

For additional information on Avonex, see the Avonex label.

6.6.2. Treatment Precautions

Medications for the treatment of severe hypersensitivity reactions (e.g., epinephrine for subcutaneous injections, diphenhydramine for injection) should be available for immediate use.

See the DHA for detailed instructions.

6.6.2.1. Management of Subjects Receiving Avonex

For additional information on the management of subjects receiving Avonex, refer to the local prescribing information for Avonex.

6.6.3. Modification of Dose and/or Treatment Schedule for BG00012

6.6.3.1. BG00012 Dose Reduction

Dose reduction will be allowed only for subjects who are unable to tolerate BG00012 *due to flushing and/or GI disturbances* (dose reductions will not be allowed for abnormal laboratory values; for management of abnormal laboratory values, see Section 6.6.3.2, Section 6.6.3.3, and Section 6.6.3.4). Subjects who do not tolerate BG00012 will reduce their dose by taking one 120-mg capsule BID for up to 4 weeks. Within 4 weeks at the reduced dose, subjects will resume taking 2 capsules BID. If the subject is still unable to tolerate BG00012, the subject must discontinue BG00012 as described in Section 6.7.1. Any subject who prematurely discontinues dosing with BG00012 may remain in the study and continue protocol scheduled tests and assessments.

6.6.3.2. BG00012 Dosing Interruption for Abnormal Laboratory Values

BG00012 must be temporarily withheld when any of the following laboratory values meet the threshold limits defined in Table 8 (laboratory abnormalities that require immediate and permanent discontinuation of study treatment are also specified in Table 8).

Table 8: Laboratory Criteria Requiring Withholding or Permanent Discontinuation of BG00012 Treatment

Laboratory Parameter	Laboratory Result	Required Action
AST or ALT	>3 × ULN	The Investigator should repeat the test as soon as possible. If the retest value confirms AST or ALT >3 × ULN, the study treatment must be withheld. If the value remains >3 × ULN for ≥4 weeks after discontinuation of BG00012, then the subject **must *permanently* discontinue study treatment with BG00012, and the event must be recorded as an AE.**
Creatinine	>1.2 × ULN	The Investigator should repeat the test as soon as possible. If the retest value confirms that creatinine is >1.2 × ULN, the study treatment must be withheld. If the value remains >1.2 × ULN for ≥4 weeks after discontinuation of study treatment, then the subject **must *permanently* discontinue study treatment with BG00012**, **and the event must be recorded as an AE.**
WBC	<2000/mm^3	The Investigator should repeat the test as soon as possible. If the retest value confirms that WBC count is <2000/mm^3, the study treatment must be withheld. If the value remains <2000/mm^3 for ≥4 weeks after discontinuation of study treatment, then the subject **must *permanently* discontinue study treatment with BG00012, and the event must be recorded as an AE.**
Urinalysis	Positive Hematuria on Microscopy	The Investigator should repeat the test as soon as possible. If the retest confirms microscopic hematuria without known etiology, the study treatment must be withheld. Urine cytology must be performed under the following conditions: a) hematuria is present on 2 consecutive tests, or b) hematuria is observed at the End of Study Visit, Early Withdrawal Visit, or Safety Follow-Up Visit. If hematuria persists for ≥4 weeks after discontinuation of study treatment or if cytology is positive, then the subject **must *permanently* discontinue study treatment with BG00012, and the event must be recorded as an AE. Subjects should be referred to a nephrologist for further investigation.**

AE = adverse event; ALT = alanine transaminase; AST = aspartate transaminase; ULN = upper limit of normal; WBC = white blood cell.

While dosing is withheld, subjects will continue tests and assessments according to the schedule defined in the protocol (and may also undergo additional assessments to evaluate the laboratory abnormality as per the Investigator's standard practice). In addition, subjects (whether dosing temporarily withheld or permanently discontinued) must have the abnormal laboratory result rechecked at least every 2 weeks (rechecks will be run at the central laboratory) until resolution

or stabilization of the laboratory value. Depending on the severity and clinical significance of the abnormality, the Investigator may need to perform the retests more frequently.

Subjects who have abnormal laboratory values as described in Table 8 sustained on 3 consecutive occasions (i.e., for more than 4 consecutive weeks) must permanently discontinue dosing with BG00012 study treatment.

6.6.3.3. Resumption of Dosing With BG00012

Resumption of BG00012 is to be considered on a case-by-case basis and must be discussed with the Medical Monitor. However, subjects who have abnormal laboratory values as described in Table 8 sustained on 3 consecutive occasions (i.e., for more than 4 consecutive weeks) must permanently discontinue dosing with BG00012.

Subjects with abnormal laboratory values after Week 12 (after which clinic visits occur once every 3 months) who are allowed to resume BG00012 dosing following a 2- to 4-week interruption will restart dosing at a reduced dose for 1 week. Subjects must also return to the initial every-4-week visit schedule for safety assessments (see Section 6.10 for clinical and laboratory safety assessments) for 2 consecutive normal laboratory assessments before reverting to the every 3-month schedule. Subjects will take 1 capsule BID for 1 week. After 1 week at the reduced dose, subjects will take 2 capsules BID.

6.6.3.4. Subsequent Development of Additional Laboratory Abnormalities

Subjects who subsequently develop the same abnormal laboratory value at any other time during the study must permanently discontinue dosing with BG00012 (i.e., only 1 dosing interruption is allowed for each subject for the same laboratory abnormality). However, subjects who subsequently experience a different laboratory abnormality can have study treatment with BG00012 withheld again. For example, if a subject had dosing temporarily withheld for an abnormal ALT, then had dosing resume after ALT returned to acceptable limits, and subsequently developed abnormal WBCs, the subject may have BG00012 withheld again. However, only 2 dosing interruptions are allowed for each subject.

Any subject who experiences abnormal laboratory results (which meet the criteria defined in Table 8) on a third occasion must discontinue dosing with BG00012 for the remainder of the study.

6.6.3.5. Abnormal Urinalyses That Require Additional Evaluation

Subjects who develop any of the following abnormal urine laboratory values must have the test repeated 2 weeks later:

- urinary casts (other than hyaline casts)
- glycosuria (trace or greater) in the setting of normal serum glucose

If the abnormality persists on retesting, the subject should be fully investigated for possible causes and referred for evaluation by a nephrologist if appropriate in the opinion of the Investigator.

Subjects who demonstrate 1+ or greater proteinuria on a urine dipstick (and do not have a documented history of prior benign proteinuria) should have a spot protein/creatinine ratio (on morning void). If spot protein/creatinine ratio is >0.2 mg/mg, the subject should be fully investigated for possible causes and referred for evaluation by a nephrologist if appropriate in the opinion of the Investigator.

6.6.4. Schedule for Subjects Treated With BG00012 With Abnormal Lymphocyte Count

6.6.4.1. Schedule in Part 1 for Subjects Treated With BG00012 With Lymphocyte Count <LLN

For subjects treated with BG00012, the required action described in Table 9 must be taken when the lymphocyte count is <LLN.

Table 9: Lymphocyte Count Criteria Requiring Additional Testing and/or Permanent Discontinuation of BG00012 Treatment

Laboratory Parameter and Treatment Status	Laboratory Result	Required Action
Lymphocyte count Active treatment with BG00012	<LLN	The Investigator should repeat the test within 2 weeks. If retest confirms that lymphocyte count is <LLN, lymphocyte count should be closely monitored (at least every 4 weeks).
Lymphocyte count Active treatment with BG00012	<500/mm^3	The Investigator should repeat the test as soon as possible. If retest confirms that lymphocyte count is <500/mm^3, lymphocyte count should be closely monitored (at least every 4 weeks). If lymphocyte count is <500/mm^3 for more than 6 months, study treatment must be permanently discontinued.
Lymphocyte count Subjects who complete, temporarily withhold, or permanently discontinue BG00012 treatment for any reason	<LLN	Subjects 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. Subjects treated with BG00012 who complete, temporarily withhold, or permanently discontinue study treatment with a lymphocyte count <LLN at the end of Part 1 (including at the End of Part 1/Week 96 Visit) will continue follow-up within Part 2 of the study.

LLN = lower limit of normal

If BG00012 is permanently discontinued due to lymphocyte count <500/mm^3, subjects may continue protocol-required tests and assessments and also undergo lymphocyte follow-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 (see Table 2). If the lymphocyte count does not recover, the treating neurologist should contact the Medical Monitor.

6.6.4.2. Schedule for Subjects Who Complete, Temporarily Withhold, or Permanently Discontinue BG00012 for Any Reason and Have a Lymphocyte Count <LLN

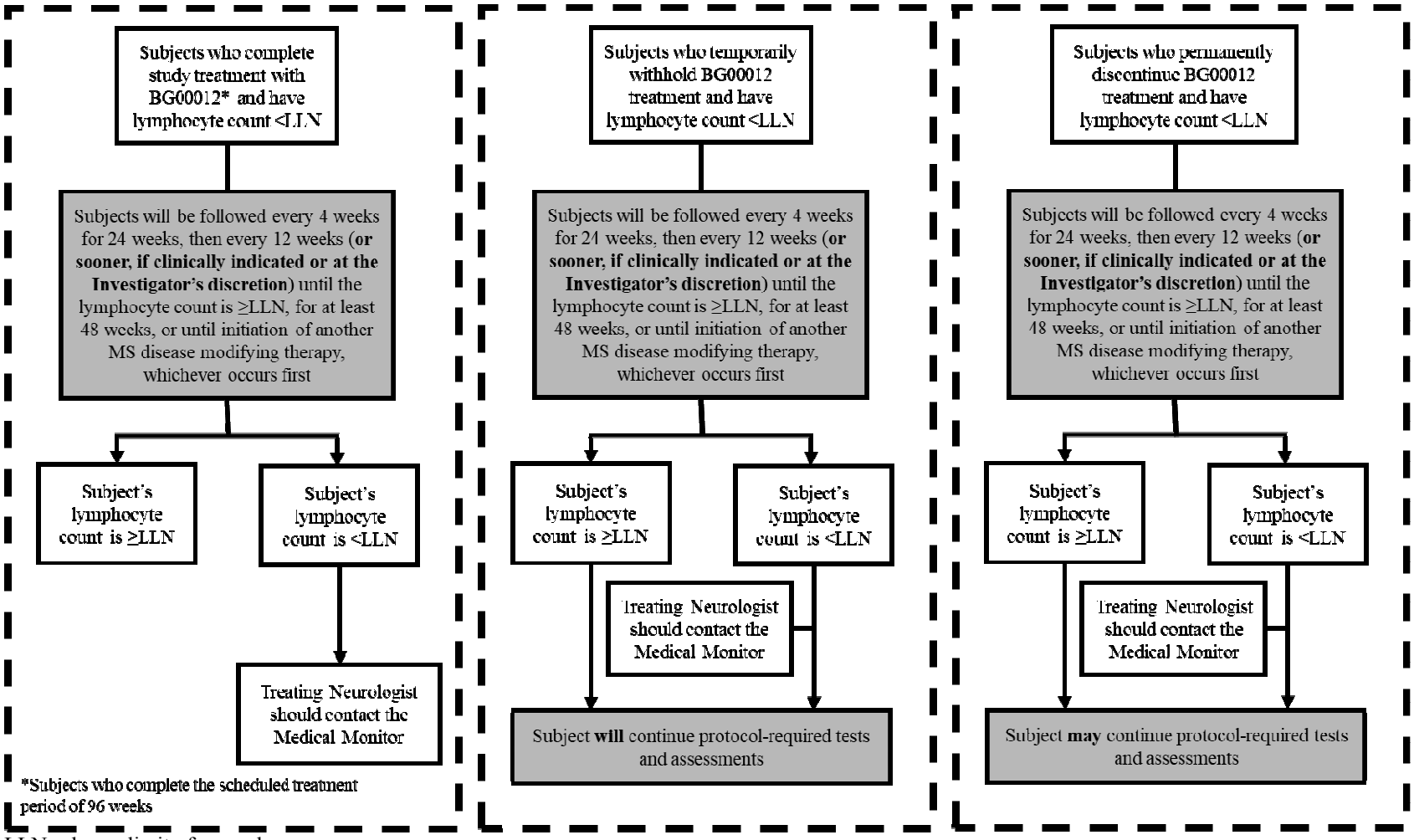
Subjects treated with BG00012 who complete the 96-week Treatment Period and who have a lymphocyte count <LLN will be followed every 4 weeks for 24 weeks, then every 12 weeks (**or sooner, if clinically indicated or at the Investigator's discretion**) until the lymphocyte count is ≥LLN, for at least 48 weeks following BG00012 treatment discontinuation, or until initiation of

another MS disease modifying therapy, whichever occurs first. If the lymphocyte count does not recover after 48 weeks, the treating neurologist should contact the Medical Monitor. Subjects who complete, temporarily withhold, or permanently discontinue study treatment with a lymphocyte count <LLN at the end of Part 1 (including at the End of Part 1/Week 96 Visit) will continue follow-up within Part 2 of the study.

Subjects who temporarily withhold or permanently discontinue BG00012 treatment for any reason (see Section 6.6.3) and who have a lymphocyte count <LLN will continue protocol-required tests and assessments and also undergo lymphocyte follow-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 (see Table 2). If the lymphocyte count does not recover after 48 weeks, the treating neurologist should contact the Medical Monitor.

See Figure 3 for a schedule for subjects who complete, temporarily withhold, or permanently discontinue BG00012 treatment for any reason and who have a lymphocyte count <LLN.

Figure 3: Schedule for Subjects Who Complete, Temporarily Withhold, or Permanently Discontinue BG00012 for Any Reason and Have a Lymphocyte Count <LLN



LLN = lower limit of normal

Note: 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.

6.6.5. Treatment Compliance

Compliance with study treatment (BG00012 or IFN β-1a) dosing is to be monitored and recorded by study site staff. Compliance for BG00012 will be monitored by capsule count and captured in the electronic case report form (eCRF). Compliance for Avonex administration will be reported and captured in the eCRF.

6.6.6. Concomitant Therapy and Procedures

6.6.6.1. Concomitant Therapy

A concomitant therapy is any drug or substance administered between signing the informed consent form (ICF) and the Safety Follow-Up Visit.

A concomitant procedure is any therapeutic intervention (e.g., surgery/biopsy, physical therapy) or diagnostic assessment (e.g., blood gas measurement, bacterial cultures) performed from the time the subject is enrolled in the study until the subject's Safety Follow-Up Visit, unless the subject is being followed for study-related toxicity.

Allowed Concomitant Therapy

Symptomatic therapy, such as treatment for spasticity, depression, or fatigue, is not restricted, but should be optimized as early as possible during screening in an attempt to maintain consistent treatment for the duration of the study.

Subjects should be instructed not to start taking any new medications, including non-prescribed drugs, unless they have received permission from the Investigator.

Disallowed Concomitant Therapy

Concomitant treatment with any of the following is not allowed while receiving study treatment, unless approved by the Biogen Medical Director, or as otherwise described in this protocol:

- Any alternative drug treatments directed toward the treatment of MS such as chronic immunosuppressant therapy or other immunomodulatory treatments (including, but not limited to interferon-beta, interferon-alpha, glatiramer acetate, natalizumab, cyclophosphamide, methotrexate, azathioprine, 4-aminopyridine or related products, etc.), with the exception of acute management of protocol-defined relapse (as described below).

- Any investigational product, including investigational symptomatic therapies for MS and investigational therapies for non-MS indications.

- Any systemic steroid therapy including, but not limited to, oral corticosteroids (e.g., prednisone) or periodic (e.g., monthly) treatment with IVMP, except for

protocol-defined treatment of relapses as described in Section 6.6.6.3. Steroids that are administered by non-systemic routes (e.g., topical, inhaled) are allowed.

- Total lymphoid irradiation, cladribine, T-cell or T-cell receptor vaccination, any therapeutic monoclonal antibody, mitoxantrone, cyclosporine, IV immunoglobulin, plasmapheresis, or cytapheresis.

Subjects who receive any of these restricted medications without approval from the Biogen Medical Director(s) will be required to permanently discontinue study treatment and will be withdrawn from the study as outlined in Section 6.7.

The use of concomitant therapies or procedures defined above must be recorded on the subject's eCRF, according to instructions for eCRF completion. AEs related to the administration of these therapies or procedures must be documented on the appropriate eCRF.

6.6.6.2. Concomitant Procedures

A concomitant procedure is any therapeutic intervention (e.g., surgery/biopsy, physical therapy) or diagnostic assessment (e.g., blood gas measurement, bacterial cultures) performed between the time the subject is enrolled in the study and the Safety Follow-Up Visit, which is to occur no later than 4 weeks after taking their final dose.

The use of concomitant therapies or procedures defined above must be recorded on the subject's eCRF, according to instructions for eCRF completion. AEs related to administration of these therapies or procedures must be documented on the appropriate eCRF.

6.6.6.3. Treatment of Relapses on Scheduled or Unscheduled Visits

The only protocol-approved treatment for relapse in this study is either 3 days or 5 days with IVMP, up to 1000 mg/day. Methylprednisolone can be given once a day or in divided doses. Subjects may also refuse relapse treatment. Any deviations from this recommended treatment must first be discussed with the Biogen Medical Director or designee.

Study treatment dosing is to continue uninterrupted during IVMP treatment.

6.6.7. Continuation of Treatment

All subjects who continue treatment in the study until Week 96 will be offered the option to enter Part 2. All subjects who enter Part 2 will receive BG00012. Subjects who do not enter Part 2 will be encouraged to complete all post-treatment assessments at the Safety Follow-Up Visit no later than 4 weeks after taking their final dose.

6.7. Part 1 Withdrawal of Subjects From Study Treatment and/or the Study

6.7.1. Discontinuation of Study Treatment

Unless otherwise indicated, a subject must permanently discontinue study treatment for any of the following reasons:

- The subject becomes pregnant. Study treatment must be immediately discontinued. Report the pregnancy according to the instructions in Section 8.5.4.
- The subject desires to discontinue treatment under this protocol.
- The subject experiences a medical emergency that necessitates permanent discontinuation of study treatment.
- The subject develops >3 × ULN elevations in ALT or AST that are *sustained* for 4 consecutive weeks after BG00012 treatment is withheld (see Table 8).
- The subject develops a >1.2 × ULN elevation in creatinine that is *sustained* for 4 consecutive weeks after BG00012 treatment is withheld (see Table 8).
- The subject develops decreased WBC count <2000/mm^3 that is *sustained* for 4 consecutive weeks after BG00012 treatment is withheld (see Table 8).
- The subject experiences more than 1 deviation of the same laboratory parameter while receiving BG00012 treatment that meets the threshold limits defined in Table 8 at any time during the study.
- The subject develops lymphocyte count <500/mm^3 for more than 6 months while receiving BG00012 treatment (see Table 9).
- The subject experiences more than 2 different deviations of laboratory parameters while receiving BG00012 treatment that meet the threshold limits defined in Table 8 and Table 9 at any time during the study. On a third occasion, the subject is required to discontinue dosing for the remainder of the study.
- The subject experiences positive urine cytology while receiving BG00012 treatment (following microscopic hematuria of unknown etiology on 2 consecutive visits) [see Table 8].
- The subject develops renal dysfunction based on a nephrologist's evaluation.
- The subject cannot tolerate study treatment.

- The subject receives any of the disallowed concomitant medications described in the protocol unless approval was given by the Biogen Medical Director. Note: IVMP for treatment of a protocol-defined relapse is allowed as detailed in Section 6.6.6.3.

- At the discretion of the Investigator for medical reasons or for noncompliance.

The reason for discontinuation of study treatment must be recorded in the subject's eCRF.

Subjects who experience MS relapse or disability progression during the study may continue participation in the study.

Subjects who discontinue treatment may remain in the study and continue protocol-required tests and assessments.

6.7.2. Withdrawal of Subjects From Study

Subjects must be withdrawn from the study for any one of the following reasons:

- The subject withdraws consent.

- The subject is unwilling or unable to comply with the protocol.

The reason for the subject's withdrawal from the study must be recorded in the subject's eCRF.

Subjects who withdraw from the study prematurely should complete the Early Withdrawal Visit and the Safety Follow-Up Visit no later than 4 weeks after taking their final dose of BG00012 or IFN β-1a.

6.8. Part 1 Study Treatment Management

Study treatment must be stored in a secure location. Accountability for study treatment is the responsibility of the Investigator. More details concerning this responsibility are included in Section 6.8.1.4.

Study treatment must only be dispensed by a pharmacist or medically qualified staff. Study treatment is to be dispensed only to subjects enrolled in this study.

Study site staff should refer to the DHA located in the Study Reference Manual for specific instructions on the handling, preparation, administration, and disposal of the study treatment. **The DHA supersedes all other references (e.g., Investigator's Brochure).**

6.8.1. BG00012

BG00012 is a drug product formulated as enteric-coated microtablets in gelatin capsules (blue and white) for oral administration. Each capsule contains 120 mg BG00012.

Excipients for the manufacturing of the enteric-coated microtablets include microcrystalline cellulose, croscarmellose sodium, talc, colloidal anhydrous silica (colloidal silicon dioxide), magnesium stearate, triethyl citrate, methacrylic acid-methyl methacrylate copolymer, methacrylic acid-ethyl acrylate copolymer, simethicone, sodium lauryl sulfate, and polysorbate 80. Excipients for the manufacturing of the capsule shell include gelatin, titanium dioxide, and indigotin.

The contents of the study treatment label will be in accordance with all applicable regulatory requirements. BG00012 should not be used after the expiration date.

6.8.1.1. BG00012 Preparation

The individual preparing BG00012 should first carefully review the instructions provided in the DHA.

BG00012 will be provided as capsules. Drug wallets will be prepared for the BG00012 treatment group to ensure that the appropriate treatment is provided to each subject. Drug wallets will be supplied from Interactive Voice/Web Response System (IXRS) at specific timepoints during the study so that the appropriate wallets are correctly dispensed to a subject at the required timepoints throughout the study.

If the packaging is damaged, or if there is anything unusual about the appearance or attributes of the drug wallet or drug, it should not be used. The drug wallet in question should be quarantined at the study site and the problem immediately reported to Biogen.

6.8.1.2. BG00012 Storage

BG00012 is to be stored at room temperature (15°C to 25°C or 59°F to 77°F), in a secured, locked cabinet with limited access.

6.8.1.3. BG00012 Handling and Disposal

The Investigator must destroy or return all unused BG00012 as instructed by Biogen.

If any BG00012 supplies are to be destroyed at the study site, the institution/Principal Investigators must obtain prior approval by Biogen. After such destruction, the institution/Principal Investigators must notify Biogen, in writing, of the method of destruction, the date of destruction, and the location of destruction.

6.8.1.4. BG00012 Accountability

The study site must maintain accurate records demonstrating dates and amount of study treatment received, to whom dispensed (subject by subject accounting), amount returned by the subject, and accounts of any study treatment returned to Biogen or accidentally or deliberately destroyed.

Unless otherwise notified, all drug wallets, both used and unused, must be saved for study treatment accountability. At the end of the study, reconciliation must be made between the amount of BG00012 supplied, dispensed, and subsequently destroyed or returned to Biogen. A written explanation must be provided for any discrepancies.

6.8.2. Comparator Product

6.8.2.1. Interferon β-1a (Avonex) Preparation

IFN β-1a (Avonex) will be provided by Biogen according to local regulations. It will be supplied as a liquid prefilled (Luer lock) syringe (i.e., Avonex Prefilled Syringe) and autoinjector pen (i.e., Avonex Pen®) for self-administration by IM (or via a proxy) once weekly in countries in which the Avonex Pen is approved. In countries in which the Avonex Pen is not approved, the Avonex Prefilled Syringe will be provided. These syringes are intended for SINGLE USE INJECTION only. In addition, the Avostartgrip titration kit and Avonex Prefilled Syringes will be provided for the first 4 weeks of the Study Treatment Period.

Once a dose of Avonex is prepared for a subject, it can only be administered to that subject. Any Avonex remaining in the device should not be used for another subject.

The Avonex supplied, which will be dispensed to subjects at each scheduled visit, will contain a sufficient supply of Avonex Prefilled Syringes and IM needles and Avonex Pen needles for each dosing interval.

The Avonex Prefilled Syringe is formulated as a sterile clear liquid for IM injection. Each 0.5 mL of IFN β-1a in a prefilled glass syringe contains 30 μg of IFN β-1a. Other ingredients include sodium acetate trihydrate, glacial acetic acid, arginine hydrochloride, and polysorbate 20 in Water for Injection at a pH of approximately 4.8. Using the World Health Organization's natural IFN β standards, 30 μg of IFN β-1a contains approximately 6 million International Units of antiviral activity. The activity against other standards is not known.

6.8.2.2. Interferon β-1a (Avonex) Storage

The Avonex Prefilled Syringes and Avonex Pens (autoinjectors) must be stored in a secured location at 2°C to 8°C (36°F to 46°F) and must not be frozen. The Avonex Prefilled Syringes and Avonex Pens should not be exposed to temperatures such as those found in a hot car or glove compartment. One Avonex Prefilled Syringe or Avonex Pen (autoinjector) should be taken out of the refrigerator approximately 30 minutes prior to use to warm up to room temperature.

The contents of the study treatment label will be in accordance with all applicable regulatory requirements. Avonex should not be used after the expiration, expiry, or use by date.

To ensure that the most up-to-date procedures are followed when storing Avonex for clinical use, follow the instructions provided in the current prescribing information that is included in the Pharmacy Manual for reference.

6.8.2.3. Interferon β-1a (Avonex) Handling and Disposal

The study site must maintain accurate records demonstrating dates and amount of Avonex received, to whom dispensed (subject by subject accounting), and accounts of any Avonex accidentally or deliberately destroyed.

All Avonex Prefilled Syringes and Avonex Pens, both used and unused, must be saved for study treatment accountability. At the end of the study, reconciliation must be made between the amount of Avonex supplied, dispensed, destroyed, or subsequently returned to Biogen. A written explanation must be provided for any discrepancies.

6.9. Part 1 Efficacy Assessments

6.9.1. MRI Efficacy Assessments

The following MRI tests/assessments will be performed to assess the efficacy of BG00012:

- Brain MRI parameters will include the following:
  - new or newly enlarging T2 hyperintense lesions
  - total Gd-enhancing lesions
  - new T1 hypointense lesions

The MRIs will be forwarded to an independent, blinded, central MRI center for assessment. Each site must perform a test scan prior to enrollment of study subjects at that site.

See Section 4 for the timing of assessments.

6.9.2. Clinical Efficacy Assessments

The following clinical tests/assessments will be performed to assess the efficacy of BG00012:

- Relapse assessment: The assessment of protocol-defined relapses, which 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 *treating* neurologist, that are confirmed upon evaluation by the *examining* neurologist. New or recurrent neurologic symptoms that evolve gradually over months should be considered disability 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 should be considered part of the same relapse and should not be treated with IVMP within the protocol.
- EDSS scores

- BVMT-R scores
- SDMT scores
- School progression query

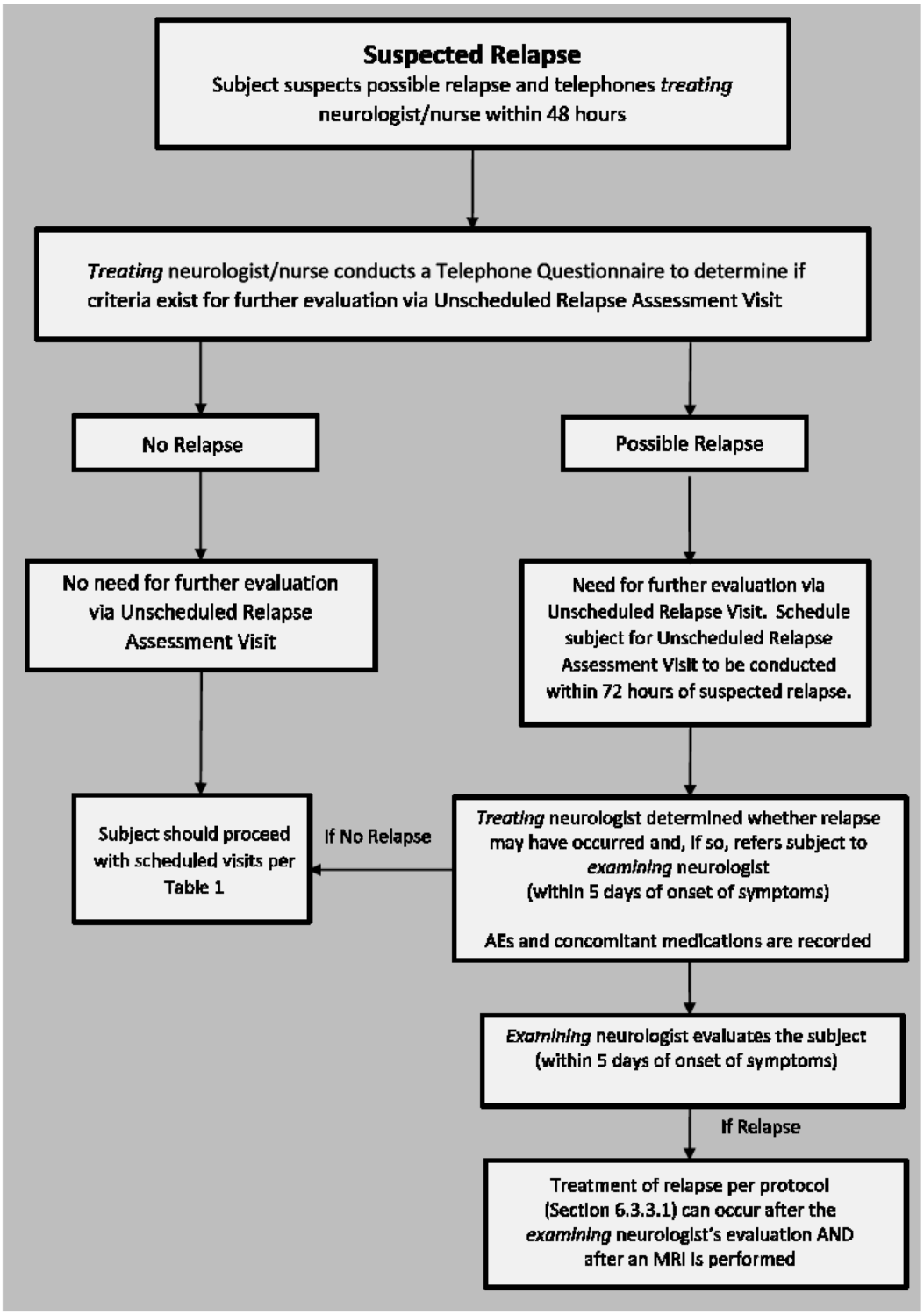
See Section 4 for the timing of assessments.

Subjects who suspect they are experiencing a relapse (new symptoms or worsening symptoms) need to telephone or have their caregiver telephone the *treating* neurologist or *treating* nurse as soon as possible and within 48 hours of the onset of the symptoms. The following tests and evaluations are to be performed by the required study personnel:

- *treating* neurologist/*treating* nurse (as soon as possible and within 72 hours of the onset of symptoms)
  - determination of whether or not a relapse may have occurred, and refer to the *examining* neurologist, if warranted
  - monitoring/recording of concomitant medications
  - monitoring/recording of AEs
- *examining* neurologist (as soon as possible and within 5 days of the onset of symptoms)
  - EDSS

Determination of EDSS scores is to be performed as soon as possible and within 5 days of the onset of symptoms by the required study personnel, as described in the Flow Diagram for Relapse Evaluation (Figure 4).

Figure 4: Flow Diagram for Relapse Evaluation



Note: All steps should be performed as soon as possible and within the specified duration from the onset of symptoms.

6.9.3. Additional Assessments

- PedsQL Multidimensional Fatigue Scale scores
- PedsQL scores
- Telephone questionnaire to determine the necessity of an Unscheduled Relapse Assessment Visit

6.10. Part 1 Safety Assessments

6.10.1. Clinical Safety Assessments

The following clinical assessments will be performed to assess the safety profile of BG00012:

- AEs and SAEs monitoring (Section 8)
- concomitant therapy and procedure monitoring
- physical examinations, including body weight, height, and Tanner Score (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.)
- vital sign measurements: body temperature, heart rate, systolic and diastolic blood pressure, and respiratory rate
- 12-lead ECG readings

See Section 4 for the timing of assessments.

6.10.2. Laboratory and Radiological Safety Assessments

Safety will be monitored through the following:

- Gd-enhanced brain MRIs for relapses
- 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
- 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 test

- 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

See Section 4 for the timing of assessments.

7. PART 2

7.1. Part 2 Objectives

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

7.2. Part 2 Endpoints

7.2.1.1. Primary Endpoint

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

7.2.1.2. Secondary 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.

7.3. Part 2 Study Design

7.3.1. Overview

Part 2 will be 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 will allow for 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 2 for a schematic of the study design. A final CSR will be written at the end of Part 2.

7.3.2. Overall Part 2 Duration and Follow-Up

Part 2 will have a duration of approximately 5 years, consisting of a 240-week Treatment Period and a Safety Follow-Up Visit no later than 4 weeks after the last dose of study treatment. An Unscheduled Relapse Assessment Visit and Lymphocyte Follow-Up Visit will be performed as necessary.

7.3.2.1. Day 1 of Part 2 (Part 1 Week 96)

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 (see Section 10.3). When a subject signs the ICF for Part 2 of the study, that subject is considered to be enrolled in Part 2. Subjects who have a nonclinically significant out-of-range laboratory result at Week 84 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.

7.3.2.2. Treatment

Beginning at Week 96, all subjects (excluding those who have stopped taking BG00012 and are continuing follow-up of lymphopenia) will receive BG00012, 240 mg BID, orally, for 240 weeks. 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.

7.3.2.3. Post-Treatment

Subjects will return to the study site for the End of Study Visit (Week 336).

Subjects who prematurely withdraw from the study should complete all study assessments for the End of Study Visit at the time of withdrawal.

7.3.2.4. Follow-Up

Subjects who complete or prematurely withdraw from the study should be encouraged to complete the study assessments for the Safety Follow-Up Visit no later than Week 340 or 4 weeks after the last dose of study treatment, whichever occurs sooner.

Subjects 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 (see Section 7.6.4).

7.3.3. Relapses

Refer to Section 6.3.3.

7.3.3.1. Treatment of Relapses on Scheduled or Unscheduled Visits

Treatment of relapses in Part 2 will be the same as in Part 1 (see Section 6.3.3.1).

7.3.4. Study Stopping Rules

Biogen may terminate this study (Parts 1 and/or 2) at any time, after informing Investigators. Investigators will be notified by Biogen or designee if the study is placed on hold, completed, or closed.

7.3.5. End of Study

The end of study is last subject, last visit for final collection of data for the primary outcome in Part 2.

7.4. Part 2 Selection of Subjects

7.4.1. Inclusion Criteria

To be eligible to participate in this study, candidates must meet the following eligibility criteria at their Week 96 Visit or at the timepoint specified in the individual eligibility criterion listed:

1. Ability of parents, legal guardians, and/or subjects to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use confidential health information in accordance with national and local subject privacy regulations. Subjects will provide assent in addition to the parental or guardian consent, as appropriate, per local regulations.

2. Subjects who completed Part 1 (Week 96 Visit), as per protocol.

   Note: 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.

3. Subjects of childbearing potential who are sexually active must be willing to practice effective contraception during the study and be willing and able to continue contraception for at least 30 days after their final dose of study treatment. For further details of contraceptive requirements for this study, please refer to Section 8.5.3.

7.4.2. Exclusion Criteria

Candidates will be excluded from study entry if any of the following exclusion criteria exist at their Part 1 Week 96 Visit or at the timepoint specified in the individual criterion listed:

1. Unwillingness or inability to comply with study requirements, including the presence of any condition (physical, mental, or social) that is likely to affect the subject's ability to comply with the protocol.

2. Any significant changes in medical history occurring after enrollment in Part 1, including laboratory test abnormalities or current clinically significant conditions that, in the opinion of the Investigator, would have excluded the subject's participation in Part 1. The Investigator must re-assess the subject's medical fitness for participation and consider any factors that would preclude treatment.

3. Subjects who could not tolerate BG00012 in Part 1.

4. History of malignancy.

5. History of severe allergic or anaphylactic reactions or known drug hypersensitivity to DMF or fumaric acid esters.

6. Subjects who received Avonex in Part 1 and have any of the following abnormal blood test results at Week 84:

    - ALT ≥2 times the ULN
    - AST ≥2 times the ULN
    - Gamma-glutamyl-transferase ≥2 times the ULN
    - Leukocytes <3500/mm^3
    - Eosinophils >0.7 × $10^3/\mu L$ or >0.7 GI/L
    - Absolute lymphocyte count <LLN

7. Subjects who were required to permanently discontinue BG00012 in Part1 of the study, with the exception of subjects with lymphocyte count remaining <LLN at the End of Part 1 (Week 96 Visit) who will continue follow-up in Part 2 of the study.

8. Female subjects considering becoming pregnant or breastfeeding while in the study or who are pregnant or breastfeeding.

9. Other unspecified reasons that, in the opinion of the Investigator or Biogen, make the subject unsuitable for enrollment.

7.5. Part 2 Enrollment Procedures

7.5.1. Enrollment and Baseline Assessments

Subjects must provide consent before any Part 2 baseline tests or assessments are performed. At the time of consent, the subject will be enrolled into Part 2 of the study. Participating study sites are required to document all subjects initially considered for inclusion into Part 2 of the study. If a subject is excluded from the study, the reasons for exclusion will be documented in the subject's eCRF.

7.6. Part 2 Treatment of Subjects

Refer to Section 6.6 for details.

7.6.1. Study Treatment Schedule and Administration

BG00012 will be taken orally. Subjects will take 2 capsules orally at a dose of 240 mg BID. 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.

Refer to Section 6.6.1.1 for details of BG00012 administration.

7.6.2. Treatment Precautions

Treatment precautions observed in Part 1 of the study should also be observed in Part 2 (see Section 6.6.2).

7.6.3. Modification of Dose and/or Treatment Schedule for BG00012

Rules for the modification of treatment dose/schedule in Part 2 are the same as in Part 1 (see Section 6.6.3).

Subjects at the end of Part 1 for whom BG00012 is being temporarily withheld on the basis of abnormal laboratory values (in accordance with Table 8) should continue to have BG00012 withheld and the laboratory tests repeated, as specified for Part 1. If the abnormal laboratory findings fail to reach the target values specified in Table 8 within 4 weeks, then BG00012 should be permanently discontinued.

7.6.4. Treatment Schedule for Subjects With Abnormal Lymphocyte Count

7.6.4.1. Schedule in Part 2 for Subjects With Lymphocyte Count <LLN

Subjects who received BG00012 in Part 1 and enter Part 2 with a lymphocyte count <LLN must be managed in accordance with Table 9 (see Section 6.6.4.1).

7.6.4.2. Schedule for Subjects Who Complete, Temporarily Withhold, or Permanently Discontinue BG00012 for Any Reason and Have a Lymphocyte Count <LLN

Subjects who complete, temporarily withhold, or permanently discontinue study treatment (or are being followed) with a lymphocyte count <LLN at the Part 1 Week 96 Visit will continue follow-up within Part 2 of the study.

In Part 2, the schedule for subjects who complete, temporarily withhold, or permanently discontinue study treatment for any reason and have a lymphocyte count <LLN in Part 1 is detailed in Figure 3 (Section 6.6.4.2) and Table 4 (Section 4.2).

7.6.5. Treatment Compliance

Compliance in Part 2 will be monitored and recorded as in Part 1 (see Section 6.6.5).

7.6.6. Concomitant Therapy and Procedures

Guidelines for concomitant therapy and procedures in Part 2 are the same as those in Part 1 (see Section 6.6.6).

7.7. Part 2 Withdrawal of Subjects From Study Treatment and/or the Study

Guidelines for discontinuation of BG00012 treatment or withdrawal of subjects from the study in Part 2 are the same as those in Part 1 (see Section 6.7), with the following exceptions:

- Subjects who permanently discontinue BG00012 and have a lymphocyte count greater than or equal to the lower limit of normal (LLN) will be withdrawn from the study after the Safety Follow-Up Visit (see Section 7.3.2.4)

- Subjects who permanently discontinue BG00012 and have a lymphocyte count less than 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. If the lymphocyte count does not recover after 48 weeks, the treating neurologist should contact the Medical Monitor.

All subjects that permanently discontinue BG00012 will have the Safety Follow-Up Visit 4 weeks (±5 days) after last dose of BG00012.

7.8. Part 2 Study Treatment Management

Management of BG00012 in Part 2 of the study is the same as in Part 1 (see Section 6.8).

7.9. Part 2 Efficacy Assessments

Clinical efficacy assessments, with the exception of MRIs, will be the same as in Part 1 (see Section 6.9.2); additional assessments will be the same as in Part 1 (see Section 6.9.3).

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.

7.10. Part 2 Safety Assessments

Safety assessments will be the same as in Part 1 (see Section 6.10) except for coagulation assessments, which will not be performed in Part 2.

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) [Table 4]. All other routine study assessments are optional for this subset of subjects.

8. SAFETY DEFINITIONS, MONITORING, AND REPORTING

Throughout the course of the study, every effort must be made to remain alert to possible AEs. If an AE occurs, the first concern should be for the safety of the subject. If necessary, appropriate medical intervention should be provided.

At the signing of the ICF, each subject must be given the names and telephone numbers of study site staff for reporting AEs and medical emergencies.

8.1. Definitions

8.1.1. Serious Pretreatment Event

A serious pretreatment event is any event that meets the criteria for SAE reporting (as defined in Section 8.1.3) and occurs after the subject signs the ICF, but before administration of study treatment.

8.1.2. Adverse Event

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. Additionally, AEs are defined to include laboratory abnormalities leading to treatment discontinuation.

8.1.3. Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose:

- results in death
- in the view of the Investigator, places the subject at immediate risk of death (a life-threatening event); however, this does not include an event that, had it occurred in a more severe form, might have caused death
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity, or
- results in a congenital anomaly/birth defect.

An SAE may also be any other medically important event that, in the opinion of the Investigator, may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. (Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or convulsions occurring at home that do not require an inpatient hospitalization.)

If a subject is hospitalized due to local requirements for administration of the study treatment, the hospitalization should not be considered an SAE unless one of the requirements mentioned above is met.

8.2. Monitoring and Recording Events

8.2.1. Serious Pretreatment Events

A serious pretreatment event experienced by the subject after signing and dating the ICF, but before administration of study treatment, is to be recorded on the SAE Form and faxed to Biogen Safety and Benefit-Risk Management (SABR) or designee within 24 hours of the study site staff becoming aware of the event (see Section 8.2.5).

8.2.2. Adverse Events

Any AE experienced by the subject between the time of first dose of study treatment and the Safety Follow-Up Visit is to be recorded on the eCRF, regardless of the severity of the event or its relationship to study treatment.

8.2.3. Serious Adverse Events

Any SAE experienced by the subject between the time of signing informed consent and the Safety Follow-Up Visit is to be recorded on an SAE Form, regardless of the severity of the event or its relationship to study treatment. SAEs must be reported to the Sponsor (or designee).

Any SAE ongoing when the subject completes the study or discontinues from the study will be followed by the Investigator until the event has resolved, stabilized, or returned to baseline status.

8.2.4. All Events

All events must be assessed to determine the following:

- If the event meets the criteria for an SAE as defined in Section 8.1.3.
- The relationship of the event to study treatment as defined in Section 8.3.1.
- The severity of the event as defined in Section 8.3.2.

8.2.5. Immediate Reporting of Serious Adverse Events

In order to adhere to all applicable laws and regulations for reporting an SAE, the study site must formally notify Biogen SABR or designee within 24 hours of the study site staff becoming aware of the SAE. It is the Investigator's responsibility to ensure that the SAE reporting information and procedures are used and followed appropriately.

Reporting Information for SAEs

Any Serious Event that occurs between the time that the subject has signed informed consent and the Safety Follow-Up Visit must be reported to Biogen SABR or designee within 24 hours of the study site staff becoming aware of the event.

A report ***must be submitted*** to Biogen SABR or designee regardless of the following:

- whether or not the subject has undergone study-related procedures
- whether or not subject has received study treatment
- the severity of the event
- the relationship of the event to study treatment

To report initial or follow-up information on a Serious Event, fax or email a completed SAE Form to the following: QuintilesIMS Lifecycle Safety.

Fax: See the Study Reference Manual

Email: QSHNSAE@quintiles.com

8.2.5.1. Deaths

Death is an outcome of an event. The event that resulted in death should be recorded and reported on the appropriate eCRF. All causes of death must be reported as SAEs. The Investigator should make every effort to obtain and send death certificates and autopsy reports to Biogen SABR or designee.

8.3. Safety Classifications

8.3.1. Relationship of Events to Study Treatment

The following definitions should be considered when evaluating the relationship of AEs and SAEs to the study treatment:

Relationship of Event to Study Treatment	
Not related	An AE will be considered "not related" to the use of the investigational drug if there is not a possibility that the event has been caused by the product under investigation. Factors pointing toward this assessment include, but are not limited to: the lack of reasonable temporal relationship between administration of the drug and the event, the presence of a biologically implausible relationship between the product and the AE (e.g., the event occurred before administration of drug), or the presence of a more likely alternative explanation for the AE.
Related	An AE will be considered "related" to the use of the investigational drug if there is a possibility that the event may have been caused by the product under investigation. Factors that point toward this assessment include, but are not limited to: a positive rechallenge, a reasonable temporal sequence between administration of the drug and the event, a known response pattern of the suspected drug, improvement following discontinuation or dose reduction, a biologically plausible relationship between the drug and the AE, or a lack of an alternative explanation for the AE.

8.3.2. Severity of Events

The following definitions should be considered when evaluating the severity of AEs and SAEs:

Severity of Event	
Mild	Symptoms barely noticeable to subject or does not make subject uncomfortable; does not influence performance or functioning; prescription drug not ordinarily needed for relief of symptom(s) but may be given because of personality of subject.
Moderate	Symptoms of a sufficient severity to make subject uncomfortable; performance of daily activity is influenced; subject is able to continue in study; treatment for symptom(s) may be needed.
Severe	Symptoms cause severe discomfort; symptoms cause incapacitation or significant impact on subject's daily life; severity may cause cessation of treatment with study treatment; treatment for symptom(s) may be given and/or subject hospitalized.

8.3.3. Expectedness of Events

Expectedness of all AEs will be determined according to the Investigator's Brochure.

8.4. Prescheduled or Elective Procedures or Routinely Scheduled Treatments

A prescheduled or elective procedure or a routinely scheduled treatment will not be considered an SAE, even if the subject is hospitalized; the study site must document all of the following:

- The prescheduled or elective procedure or routinely scheduled treatment was scheduled (or was on a waiting list to be scheduled) prior to obtaining the subject's consent to participate in the study.

- The condition requiring the prescheduled or elective procedure or routinely scheduled treatment was present before and did not worsen or progress in the opinion of the Investigator between the subject's consent to participate in the study and the time of the procedure or treatment.

- The prescheduled or elective procedure or routinely scheduled treatment is the sole reason for the intervention or hospital admission.

8.5. Procedures for Handling Special Situations

8.5.1. Overdose

An overdose is any dose of study treatment given to a subject or taken by a subject that exceeds the dose described in the protocol. Overdoses are not considered AEs; however, all overdoses should be recorded on an Overdose Form and faxed to Biogen SABR or designee within 24 hours. An overdose should be reported even if it does not result in an AE. Overdoses do not need to be recorded in the eCRF; dosing information is recorded on the eCRF.

8.5.2. Medical Emergency

In a medical emergency requiring immediate attention, study site staff will apply appropriate medical intervention, according to current standards of care. The Investigator or designee should contact the Medical Monitor at QuintilesIMS (+1-973-659-6677 or, alternatively, +1-570-819-8565).

8.5.3. Contraception Requirements

All subjects of childbearing potential who are sexually active must practice effective contraception during the study and be willing and able to continue contraception for 30 days after their last dose of study treatment.

For the purposes of this study, women of childbearing potential are defined as all women physiologically capable of becoming pregnant.

For the purposes of the study, effective contraception is defined as follows:

For females:

- Using 1 or more of the following acceptable methods of contraception: surgical sterilization (e.g., bilateral tubal ligation), intrauterine contraception or device, hormonal contraception, or any 2 barrier methods (a combination of male or female condom with spermicide; diaphragm, sponge, cervical cap).

- Abstinence can be considered an acceptable method of contraception at the discretion of the Investigator. Periodic abstinence (e.g., calendar, ovulation, symptothermal,

post-ovulation methods) and withdrawal are not considered acceptable methods of contraception.

For males:

- Effective male contraception includes a vasectomy with negative postvasectomy semen analysis, or the use of condoms with spermicide.
- Abstinence can be considered an acceptable method of contraception at the discretion of the Investigator.

8.5.4. Pregnancy

Subjects should not become pregnant during the study. If a female subject becomes pregnant, study treatment must be discontinued immediately. The Investigator must report the pregnancy by faxing the appropriate form within 24 hours of the study site staff becoming aware of the pregnancy to QuintilesIMS Lifecycle Safety (fax: see the Study Reference Manual; email QSHNSAE@quintiles.com).

The Investigator or study site staff must report the outcome of the pregnancy to QuintilesIMS Lifecycle Safety.

Note that congenital abnormalities/birth defects in the offspring of male or female subjects should be reported if conception occurred during the study treatment period.

8.5.5. Regulatory Reporting

Suspected unexpected serious adverse reactions (SUSARs) are SAEs that are unexpected and judged by the Investigator or the Sponsor to be related to the study treatment administered.

Biogen SABR (or designee) will report SUSARs to the appropriate regulatory authorities and Investigators as required, according to local law.

8.6. Investigator Responsibilities

The Investigator's responsibilities include the following:

- Monitor and record all AEs, including SAEs, regardless of the severity or relationship to study treatment.
- Determine the seriousness, relationship, and severity of each event.
- Determine the onset and resolution dates of each event.
- Monitor and report all pregnancies and follow up on and report the outcome of the pregnancy.

- Complete an SAE Form for each serious event and fax it to Biogen SABR or designee within 24 hours of the study site staff becoming aware of the event.

- Pursue SAE follow-up information actively and persistently. Follow-up information must be reported to Biogen SABR or designee within 24 hours of the study site staff becoming aware of new information.

- Ensure all AE and SAE reports are supported by documentation in the subjects' medical records.

- Report SAEs to local ethics committees (ECs), as required by local law.

8.7. Biogen Responsibilities

Biogen's responsibilities include the following:

- Before study site activation and subject enrollment, the Clinical Monitor or designee is responsible for reviewing with study site staff the definitions of AE and SAE, as well as the instructions for monitoring, recording, and reporting AEs and SAEs.

- Biogen is to notify all appropriate regulatory authorities, central ECs, and Investigators of SAEs, as required by local law, within required time frames.

9. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

9.1. Part 1

9.1.1. Description of Objectives

See Section 6.1 for the objectives of Part 1.

9.1.2. Description of Endpoints

See Section 6.2 for the primary, secondary, and exploratory endpoints of Part 1.

9.1.3. Demography and Baseline Disease Characteristics

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% confidence intervals (CIs) will be presented from the model.

9.1.4. Efficacy

9.1.4.1. 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.

9.1.4.2. General Methods of Analysis

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 progression will be presented based on the Kaplan-Meier method and analyzed using the Cox proportional hazards model. 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 the statistical model. Other baseline covariates, if included in the model, will be specified in the Statistical Analysis Plan (SAP). An additional, separate efficacy analysis will be carried out based on pubertal status at disease initiation.

9.1.4.3. Primary Endpoint Analysis

Primary endpoint: proportion of subjects free of new or newly enlarging T2 lesions at Week 96.

The primary analysis of the primary endpoint will include the following:

- Data will be presented as descriptive statistics (e.g., mean, SD, median) and CIs. The CIs for the proportion of subjects free of new or newly enlarging T2 lesions at Week 96 for each treatment group will be presented.

- Data will be summarized using observed values. No special method will be used to handle missing information.

The primary analysis of the primary endpoint will be performed on the Completers Population.

A sensitivity analysis of the primary endpoint will be performed on the ITT Population. For this analysis, missing values may be imputed. A logistic regression model may be used to analyze the proportion of subjects free of new or newly enlarging T2 lesions, adjusted for age group and other baseline covariates. Details will be described in the SAP.

9.1.4.4. Secondary Endpoints Analysis

Key secondary endpoint: number of new or newly enlarging T2 hyperintense lesions at Week 24.

Summary statistics for the number of lesions 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 Week 24, with treatment group in the model and adjusted for randomization stratification factors (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. Details will be described in the SAP. The analysis will be based on subjects from the ITT Population who have observed data at Week 24. An additional sensitivity analysis based on all subjects from the ITT Population may also be performed. Missing value imputation may be performed for this analysis. The number of new or newly enlarging T2 hyperintense lesions at other timepoints will be analyzed in a similar way.

Additional Secondary Endpoints:

Analyses of other secondary efficacy endpoints will be based on subjects from the Completers Population. An additional analysis based on the ITT Population may also be conducted.

Number of New or Newly Enlarging T2 Hyperintense Lesions at Week 96

Summary statistics will be presented for each treatment group. A negative binomial regression model similar to that described for the number of lesions at Week 24 will be implemented.

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 of T2 lesions and age group.

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 age group.

Time to First Relapse

Time to first relapse and estimated proportion of subjects relapsed will be presented based on the Kaplan-Meier method. Time to first relapse may also be analyzed using the Cox proportional hazards model, adjusted for baseline relapse rate, baseline EDSS score, and age group.

Proportion of Subjects Free of Relapse up to Week 96

The proportion of subjects relapsed 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 may be calculated based on the Kaplan-Meier method.

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 age group.

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

Summary statistics will be presented for each treatment group. Additionally, these 2 endpoints will be analyzed using an ANCOVA, adjusted for baseline score and age group.

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.

Analysis methods for other secondary endpoints (safety endpoints) are described in Section 9.1.5.

The general analysis method for each type of endpoint has been described in Section 9.1.4.2.

9.1.4.5. Exploratory Endpoints Analysis

Analysis methods for exploratory efficacy endpoints will be similar to those described for the secondary endpoint. See Section 9.1.4.2 or Section 9.1.5 for the analysis method for each endpoint. BVMT-R, SDMT, and school progression query will be summarized for each treatment group using descriptive statistics by visit.

9.1.5. Safety

9.1.5.1. Analysis Population

The Safety Population is defined as subjects who received at least 1 dose of study treatment.

9.1.5.2. Methods of Analysis

9.1.5.2.1. Adverse Events

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

All AEs, laboratory abnormalities, ECG, and vital signs will be evaluated for safety. Incidence of AEs will be summarized for each treatment group. Other safety data will also be summarized by treatment group.

9.1.5.2.2. Clinical Laboratory Abnormalities

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. Additionally, lymphocyte count over time (including recovery from lymphocyte counts <LLN) will be summarized using descriptive statistics.

9.1.5.2.3. Vital Signs

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

The definitions of these clinically relevant abnormalities are shown in Table 10.

Table 10: Criteria to Determine Clinically Relevant Abnormalities in Vital Signs

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 <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

9.1.6. Sample Size Considerations

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.

9.2. Part 2

9.2.1. Description of Objectives

See Section 7.1 for the objectives of Part 2.

9.2.2. Description of Endpoints

See Section 7.2 for the primary and secondary endpoints of Part 2.

9.2.2.1. General Methods of Analysis

In general, continuous variables will be summarized using summary statistics (mean, standard deviation [SD], median, minimum, and maximum), and categorical variables will be presented using frequency distributions. Where appropriate, 95% CIs for mean, median, or proportions may also be presented.

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, SDMT, and BVMT-R scores, and school progression query; 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. Data will be summarized for the overall population as well as separately for pre- and post-pubertal subjects.

9.2.3. Demography and Baseline Disease Characteristics

Demographics and baseline characteristics will be summarized using descriptive statistics.

9.2.4. Efficacy

9.2.4.1. Analysis Population

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

9.2.5. Safety

Safety analyses will be as in Part 1 of the study (see Section 9.1.5).

9.2.6. Interim Analyses

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.

9.2.7. Sample Size Considerations

Because Part 2 is an extension of Part 1, the sample size will be determined by the number of eligible subjects who completed Part 1 of the study.

10. ETHICAL REQUIREMENTS

Biogen and the Investigator must comply with all instructions, regulations, and agreements in this protocol and applicable International Conference on Harmonisation (ICH) and Good Clinical Practice (GCP) guidelines and conduct the study according to local regulations.

10.1. Declaration of Helsinki

This study will be performed in alignment with the ethical principles outlined in the Declaration of Helsinki.

10.2. Ethics Committee

The Investigator must obtain EC approval of the protocol, ICF, and other required study documents prior to starting the study. The Sponsor or designee will submit documents on behalf of the investigational sites in countries other than the US.

If the Investigator makes any changes to the ICF, Biogen must approve the changes before the ICF is submitted to the EC. A copy of the approved ICF must be provided to Biogen. After approval, the ICF must not be altered without the agreement of the relevant EC and Biogen.

It is the responsibility of the Principal Investigators to ensure that all aspects of institutional review are conducted in accordance with current governmental regulations.

Biogen must receive a letter documenting EC approval, which specifically identifies the protocol, protocol number, and ICF, prior to the initiation of the study. Protocol amendments will be subject to the same requirements as the original protocol.

A progress report must be submitted to the EC at required intervals and not less than annually.

At the completion or termination of the study, the investigational site must submit a close-out letter to the EC and Biogen.

10.3. Subject Information and Consent

Prior to performing any study-related activities under this protocol, including screening tests and assessments, written informed consent with the approved ICF must be obtained from the subject's parent or legal guardians, as applicable, in accordance with local practice and regulations. Written subject assent may also be obtained prior to performing any study-related activities from subjects who are able to read and understand the assent form and a brief summary of the study process, benefits, and risks.

The background of the proposed study, the procedures, the benefits and risks of the study, and that study participation is voluntary for the subject must be explained to the subject. The subject

and the subject's parents or legal guardians must be given sufficient time to consider whether to participate in the study.

A copy of the signed ICF and authorizations will be given to the parents or legal guardians. A copy of the signed assent form, if obtained, will be given to the subject. Confirmation of a subject's informed consent and assent, if appropriate, must also be documented in the subject's medical record prior to any testing under this protocol, including screening tests and assessments.

Each consent form should contain an authorization allowing the Principal Investigators and Biogen to use and disclose PHI (i.e., subject-identifiable health information) in compliance with local law.

The signed consent and assent forms will be retained with the study records.

10.4. Subject Data Protection

Prior to any testing under this protocol, including screening tests and assessments, candidates must also provide all authorizations required by local law (e.g., PHI authorization in North America).

The subject will not be identified by name in the eCRF or in any study reports, and these reports will be used for research purposes only. Biogen, its partners and designees, ECs, and various government health agencies may inspect the records of this study. Every effort will be made to keep the subject's personal medical data confidential.

10.5. Compensation for Injury

Biogen maintains appropriate insurance coverage for clinical studies and will follow applicable local compensation laws.

10.6. Conflict of Interest

The Investigators should address any potential conflicts of interest (e.g., financial interest in the Sponsor) with the subject before the subject makes a decision to participate in the study.

10.7. Registration of Study and Disclosure of Study Results

Biogen will register the study and poststudy results regardless of outcome on a publicly accessible website in accordance with the applicable laws and regulations.

11. ADMINISTRATIVE PROCEDURES

11.1. Study Site Initiation

The Investigator must not screen any subjects prior to completion of a study initiation visit, conducted by Biogen or designee. This initiation visit will include a detailed review of the protocol and study procedures.

11.2. Quality Assurance

During and/or after completion of the study, quality assurance officers named by Biogen or the regulatory authorities may wish to perform on-site audits. The Investigator will be expected to cooperate with any audit and to provide assistance and documentation (including source data) as requested.

11.3. Monitoring of the Study

The Principal Investigators must permit study-related monitoring by providing direct access to source data and to the subjects' medical histories.

The Clinical Monitors will visit the Investigator(s) at regular intervals during the course of the study and after the study has completed, as appropriate.

During these visits, eCRFs and supporting documentation related to the study will be reviewed and any discrepancies or omissions will be resolved.

The monitoring visits must be conducted according to the applicable ICH and GCP guidelines to ensure protocol adherence, quality of data, study treatment accountability, compliance with regulatory requirements, and continued adequacy of the investigational site and its facilities.

11.4. Study Funding

Biogen is the Sponsor of the study and is funding the study. All financial details are provided in the separate contracts between the institution, Investigator, and Biogen.

11.5. Publications

Details are included in the clinical trial agreement for this study.

12. FURTHER REQUIREMENTS AND GENERAL INFORMATION

12.1. External Contract Organizations

12.1.1. Contract Research Organization

A contract research organization (CRO), QuintilesIMS, will be responsible for administrative aspects of the study including, but not limited to, study initiation, monitoring, and management of SAE reports. Before subjects are screened at each study site, the CRO will review study responsibilities with the Investigators and other study site staff, as appropriate.

12.1.2. Interactive Voice/Web Response System

IXRS will be used in this study. Before subjects are screened or enrolled, the IXRS vendor will provide each study site with appropriate training and a user manual.

12.1.3. Remote Data Capture

Subject information will be captured and managed by study sites on eCRFs by a remote data capture (RDC) system developed and supported by RDC vendor and configured by Biogen.

12.1.4. Central Laboratories for Laboratory Assessments

A central laboratory has been selected by Biogen to analyze the safety laboratory samples collected for this study.

12.1.5. Central Facility for Other Assessments

A central facility has been selected by Biogen to read and interpret all MRIs conducted in Part 1 for this study.

12.2. Study Committees

An independent Data Safety Monitoring Board (DSMB) will monitor the progress of the study, review interim safety data, and oversee the safety of subjects participating in this study. The specifics regarding the DSMB organization and procedures will be outlined in the DSMB Charter.

12.3. Changes to Final Study Protocol

All protocol amendments must be submitted to the EC and Regulatory Authorities if required by local law. Protocol modifications that affect subject safety, the scope of the investigation, or the scientific quality of the study must be approved by the EC before implementation of such

modifications to the conduct of the study. If required by local law, such modifications must also be approved by the appropriate regulatory agency prior to implementation.

However, Biogen may, at any time, amend this protocol to eliminate an apparent immediate hazard to a subject. In this case, the appropriate regulatory authorities will be notified subsequent to the modification.

In the event of a protocol modification, the subject consent form may require similar modifications (see Section 10.2 and Section 10.3).

12.4. Ethics Committee Notification of Study Completion or Termination

Where required, the Health Authorities and ECs must be notified of completion or termination of this study, and sent a copy of the study synopsis in accordance with necessary timelines.

12.5. Retention of Study Data

The minimum retention time for study records will meet the strictest standard applicable to that site, as dictated by any institutional requirements or local laws or regulations. Prior to proceeding with destruction of records, the Investigator must notify Biogen in writing and receive written authorization from Biogen to destroy study records. In addition, the Investigator must notify Biogen of any changes in the archival arrangements including, but not limited to, archival at an off-site facility or transfer of ownership if the Investigator leaves the site.

12.6. Study Report Signatory

Biogen will designate one of the participating Study Investigators as a signatory for the study report. This determination will be made by several factors, including, but not limited to, the Investigator's experience and reputation in the studied indication, the Investigator's contribution to the study in terms of design, management, and/or subject enrollment, or by other factors determined to be relevant by Biogen.

13. REFERENCES

Adams AB, Tyor WR, Holden KR. Interferon beta-1b and childhood multiple sclerosis. Pediatr Neurol. 1999;21(1):481-3.

CDC. Interpretation of the hepatitis B serology panel. [CDC, 2007; Appendix A]. http://www.cdc.gov/hepatitis/HBV/PDFs/SerologicChartv8.pdf.

Chitnis T, Krupp L, Yeh A, et al. Pediatric multiple sclerosis. Neurol Clin. 2011;29(2):481-505.

European Commission. Ethical considerations for clinical trials on medicinal products conducted with the paediatric population. 2008. p. 34.

Ghezzi A. Childhood-juvenile multiple sclerosis: clinical characteristics and treatment. Expert Rev Neurother. 2005;5(3):403-11.

Krupp LB, Tardieu M, Amato MP, et al. International Pediatric Multiple Sclerosis Study Group criteria for pediatric multiple sclerosis and immune-mediated central nervous system demyelinating disorders: revisions to the 2007 definitions. Mult Scler. 2013;19(10):1261-7.

Lublin FD, Reingold SC. Defining the clinical course of multiple sclerosis: results of an international survey. National Multiple Sclerosis Society (USA) Advisory Committee on Clinical Trials of New Agents in Multiple Sclerosis. Neurology. 1996;46(4):907-911.

Mikaeloff Y, Moreau T, Debouverie M, et al. Interferon-beta treatment in patients with childhood-onset multiple sclerosis. J Pediatr. 2001;139(3):443-6.

Pohl D, Rostasy K, Gärtner J, et al. Treatment of early onset multiple sclerosis with subcutaneous interferon beta-1a. Neurology. 2005;64(5):888-890.

Waubant E, Chabas D. Pediatric multiple sclerosis. Curr Treat Options Neurol. 2009;11(3):203-10.

Zhu HJ, Appel DI, Jiang Y, et al. Age- and sex-related expression and activity of carboxylesterase 1 and 2 in mouse and human liver. Drug Metab Dispos. 2009;37(9):1819-25.

14. SIGNED AGREEMENT OF THE STUDY PROTOCOL

I have read the foregoing protocol, "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" and agree to conduct the study according to the protocol and the applicable ICH guidelines and GCP regulations, and to inform all who assist me in the conduct of this study of their responsibilities and obligations.

_____

Investigator's Signature Date

_____

Investigator's Name (Print)

_____

Study Site (Print)

Biogen MA Inc.
225 Binney Street
Cambridge, MA 02142
United States

Biogen Idec Research Limited
Innovation House
70 Norden Road
Maidenhead Berkshire
SL6 4AY
United Kingdom

AMENDMENT SUMMARY

Biogen Protocol 109MS306

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

Version 5

Date: Final 25 July 2017

EUDRA CT Number: 2013-002318-11

Version 5 of the protocol has been prepared for this amendment, which supersedes Version 4.

PRIMARY REASON FOR AMENDMENT

The primary reason for this amendment to Protocol 109MS306 is to incorporate changes approved by the Pediatric Committee (PDCO) of the European Medicines Agency (EMA) for a modification to the Pediatric Investigation Plan (PIP) for the study. These changes include:

- a) Removal of the pharmacokinetics (PK)/pharmacodynamics (PD) substudy
- b) Decreasing the required number of 10 to 12-year-old subjects from 20 evaluable subjects to 10 evaluable subjects
- c) Removal of the requirement for a minimum number of prepubertal subjects
- d) Removal of the washout requirement for interferon β1a (IFN β-1a) and glatiramer acetate (GA)
- e) Addition of stratification of randomization by whether or not the subject had received therapy with IFN β-1a or glatiramer acetate in the 4 weeks prior to study entry

New text is shown in **bold** type; deleted text is shown with a ~~strikethrough~~.

a) Section 6.1, Part 1 Main Objectives, and Section 6.2.2, Secondary Endpoints

Now reads:

6.1. Part 1 Main Objectives

The main objectives of Part 1 are as follows:

- To evaluate the safety, tolerability, and ~~effect on the disease course~~**efficacy** of BG00012 in pediatric subjects with RRMS, as compared with a disease-modifying treatment.
- ~~To assess PK and PD parameters in a representative subset of pediatric subjects~~
- To assess health outcomes and evolution of disability

6.2.2 Secondary Endpoints

The secondary endpoints of Part 1 are as follows:

- 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
- ~~BG00012 PK parameters derived from PK subset data analysis: area under the concentration-time curve from time 0 to 10 hours (AUC_{0-10}), maximum observed plasma concentration (C_{max}), time to reach maximum observed plasma concentration (T_{max}), lag time, elimination half-life ($t_{½}$), apparent clearance (Cl/F), and apparent volume of distribution (V/F)~~
- ~~PD parameters, derived from PD subset data analysis: changes in the nuclear factor (erythroid-derived 2)-like 2-activation pathway markers nicotinamide adenine dinucleotide phosphate [NAD(P)H] dehydrogenase, quinone 1 (NQO-1) and heme oxygenase 1 (HO-1)~~

Rationale: The prior version of the PIP called for a 12 subject PK/PD substudy. However, participation in this voluntary substudy has been low. Biogen recently completed Study 109MS202, which evaluated the PK/PD of BG00012 in 22 pediatric subjects with relapsing-remitting multiple sclerosis (RRMS). On the basis of the availability of data from Study 109MS202, PDCO agreed that the requirement for a PK/PD substudy could be removed from the PIP.

This change also affects Section 3, Synopsis; Section 4.1, Study Schematics for Parts 1 and 2; Section 4.2, Schedule of Events (Table 1, Table 2, and Table 3 [removed]); Section 4.3, Additional Information (including removal of prior Section 4.3.1, Pharmacokinetic Assessments; Section 4.3.2, Pharmacodynamic Assessments; and updating of Table 5 Blood Volumes by Visit – Part 1); Section 5.2, Study Rationale; Section 5.3, Rationale for Dose and Schedule Selection; Section 6.3.1, Overview; Section 6.3.2.1, Treatment; Section 6.4.2, Exclusion Criteria, Exclusion Criterion 23; Section 6.9, Part 1 Efficacy, BG00012 Concentration, and Pharmacodynamic Assessments (header changes to the Part 1 Efficacy Assessments); the former Section 6.9.3, Pharmacokinetic (BG00012 Concentration) Assessments (section removed); the former Section 6.9.4, Pharmacodynamic Assessments (section removed); Section 7.10, Part 2 Safety Assessments; Section 9.1.4.4, Secondary Endpoint Analysis; prior Section 9.1.5, Pharmacokinetics (section and subsections removed); prior Section 9.1.6, Pharmacodynamics (section and subsections removed); and Section 12.1.4, Central Laboratories for Laboratory Assessments.

b and **c)** Section 6.3.1, Overview

Now reads:

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 β-1a, administered at a dose of 30 μg once weekly by intramuscular (IM) injection. Randomization will be stratified according **to whether or not the subject receive therapy with IFN β-1a or glatiramer acetate in the 4 weeks prior to study entry and in accordance with** ~~to~~ the following 3 age groups:

- 10 to <13 years: at least ~~20~~ **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. ~~At least 20% of the evaluable subjects must be prepubertal at Screening (Tanner score less than II).~~

Rationale:

b) F**or the number of evaluable subjects age 10 to <13 years:** The previous requirement was for at least 20 evaluable subjects in this age range (out of 100 total evaluable in the study aged 10 to <18 years). However, epidemiological data indicate that the proportion of 10 to 12 year-olds among 10 to 17 year-old patients is perhaps 5-10% (and among subjects enrolled to date, the proportion has been 6%). Based on the information provided regarding the proportion of subjects in the age range of interest, PDCO agreed with a reduction in the required number of 10 to 12 year-olds from 20 evaluable to 10 evaluable. The total number of evaluable subjects remains the same.

This change also affects Section 3, Synopsis.

c) F**or the requirement for a minimum number of prepubertal subjects:** The previous requirement was for at least 20 subjects to be prepubertal. Epidemiological data on the proportion of pediatric multiple sclerosis (MS) patients who are prepubertal are scarce. However, Biogen's experience in Study 109MS306 indicates that prepubertal pediatric MS subjects are even rarer than those in the 10 to 12 year-old age range (this rarity may be related to the influence of hormonal factors on disease course). Of the over 75 subjects enrolled to date, 0 subjects have been prepubertal at screening. On the basis of this information regarding the proportion of prepubertal subjects, PDCO agreed with removal of the requirement to enroll a minimum number of prepubertal subjects.

This change also affects Section 3, Synopsis.

A separate efficacy analysis will be performed based on pubertal status at disease onset. In order to collect data for this analysis, medical history will now also include pubertal status at disease onset, see Section 4.2, Schedule of Events (Table 1). In addition, a brief statement regarding the additional, separate efficacy analysis by pubertal status at disease initiation has been added to Section 9.1.4.2, General Methods of Analysis.

d) Section 6.4.2, Exclusion Criteria (former Exclusion Criteria #17)

Now reads:

17. ~~Prior treatment with any of the following within 4 weeks prior to Day 1:~~

- ~~glatiramer acetate~~
- ~~IFN β (subjects who are positive for neutralizing antibodies to IFN β may receive IFN β treatment up to 2 weeks prior to Day 1)~~

Rationale: The previous requirement was for a 4-week washout for interferon (IFN) and GA prior to enrollment (and longer washouts for more potent disease modifying therapies [DMTs] such as natalizumab). Other studies in pediatric MS (e.g., the fingolimod study PARADIGMS) have not required a washout for IFN or glatiramer acetate and historical PK/PD data indicated that a 4-week washout is unnecessary for IFN and glatiramer acetate. Since the primary endpoint is determined at 2 years of treatment, the impact of any carryover effects during the first few weeks of a subject's participation in the trial would be minor to negligible. To mitigate the influence of even these minor carry-over effects, a stratification of randomization by whether or not subjects received therapy in the 4 weeks prior to study entry was proposed. Moreover, eliminating the washout period would have the advantage of reducing the probability of disease progression that might otherwise occur during this period. For these reasons, PDCO agreed with removal of the washout period for IFN and glatiramer acetate.

e) Section 6.5.2, Randomization of Subjects

Now reads:

Subjects will be randomized to receive BG00012 or IFN β-1a in a 1:1 ratio and 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 according** to 3 age groups (10 to <13 years, 13 to <15 years, and 15 to <18 years). Subjects who withdraw from the study may not be replaced.

Rationale: In justifying elimination of the 4-week washout for IFN β-1a and glatiramer acetate, PDCO agreed that the carryover effects from these therapies could be mitigated by stratifying randomization of subjects by whether or not they had received therapy with IFN β-1a and GA in the 4 weeks prior to study entry.

This change also affects Section 3, Synopsis; Section 6.3.1, Overview; Section 9.1.4, Efficacy; Section 9.1.4.2, General Methods of Analysis; and Section 9.1.4.4, Secondary Endpoint Analysis.

SUMMARY OF MAJOR CHANGES TO THE PROTOCOL

Changes to the protocol are presented chronologically. New text is shown in **bold** type; deleted text is shown with a ~~strikethrough~~.

Section 3, Synopsis

The Synopsis was revised to reflect changes made throughout the protocol.

Section 4.1, Study Schematics for Parts 1 and 2

Change: The footnote for Figure 2 was clarified to include subjects continuing into Part 2 for follow-up of lymphopenia.

Now reads:

See Figure 2 in Section 6.6.4.2 for the follow-up of subjects with lymphocyte count < lower limit of normal (LLN) **who have permanently or temporarily discontinued BG00012 in Part 1**.

Rationale: This change was made for alignment and clarity throughout the protocol regarding the continuation of subjects into Part2 for continued lymphocyte follow-up.

Section 4.2, Schedule of Events

Change: The footnote for the Medical history row was clarified to indicate the pubertal status at onset of disease will be collected.

Now reads as follows for Table 1:

[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.

Rationale: This change was made to clarify the collection of medical history information regarding the pubertal status at the onset of disease as required by PDCO.

Section 4.2, Schedule of Events

Change: The footnote for the Tanner score row was clarified to specify that it will be collected at baseline for female subjects who are premenarche.

Now reads as follows for Table 1, Table 2 (footnote 6), Table 3 and Table 4:

[5] Assessment of Tanner stages should be performed by a medical doctor experienced with this assessment. ~~Collection of i~~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.

Rationale: This change was made to clarify the collection of Tanner staging at baseline, as prior wording was not that Tanner staging of female subjects at baseline need not be obtained for postmenarchal subjects.

This change also affects Section 6.10.1, Clinical Safety Assessments.

Section 4.2, Schedule of Events

Change: The footnote for the hematology row was modified to specify testing every 4 weeks for the broader group of subjects with lymphocyte count less than the lower limit of normal (LLN).

Now reads as follows for Table 1:

[8] ~~Hematology testing~~**Lymphocyte counts** must be ~~performed~~**tested** every 4 weeks in subjects with lymphocyte count <~~500/mm^3~~**LLN**. **See Lymphocyte Follow-Up Visit in Table 2.**

Now reads as follows for Table 3:

[7] ~~Hematology testing~~**Lymphocyte counts** must be ~~performed~~**tested** every 4 weeks in subjects with lymphocyte count <~~500/mm^3~~**LLN**. **See Lymphocyte Follow-Up Visit in Table 4.**

Now reads as follows for Table 2 and Table 4:

[7] ~~Hematology testing~~**Lymphocyte counts** must be ~~performed~~**tested** every 4 weeks in subjects with lymphocyte count <~~500/mm^3~~**LLN**. **See Lymphocyte Follow-Up Visit.**

Rationale: This change was made for consistency with the lymphocyte monitoring requirements in Section 6.6.4.1, Table 9 (Lymphocyte Count Criteria Requiring Additional Testing and/or Permanent Discontinuation of BG00012 Treatment), which specify monitoring every 4 weeks for lymphocyte count <LLN as well as <500/mm^3.

This change also affects Section 6.6.4.1, Schedule in Part 1 for Subjects with Lymphocyte Count <LLN.

Section 4.2, Schedule of Events

Change: The footnotes on the urinalysis row of these tables were modified to specify 2 subconditions for urine cytology testing.

Now reads as follows for Table 1, Table 2, Table 3 (footnote 8), and Table 4 (footnote 8):

[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**~~Table 9~~).

Rationale: This change was made for clarity, specifically to clarify that urine cytology must be performed at the End of Study/Early Withdrawal/Safety Follow-Up Visit only if hematuria is observed at that visit.

This change also affects Section 6.6.3.2, Dosing Interruption for Abnormal Laboratory Values, Table 8; and Section 6.7.1, Discontinuation of Study Treatment.

Section 4.2, Schedule of Events

Change: The footnote on the endocrine tests row was modified to specify that it will be collected at baseline for subjects who are premenarche.

Now reads as follows for Table 1, Table 2, Table 3 (footnote 11), Table 4 (footnote 10):

[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.

Rationale: This change was made to clarify the endocrine testing at baseline, as prior wording was not clear that endocrine testing at baseline need not be obtained for postmenarchal subjects.

This changes also affects Section 4.2, Schedule of Events, Table 3; and Section 6.10.2, Laboratory and Radiological Safety Assessments.

Section 4.2, Schedule of Events

Change: The footnote on the hand and wrist x-ray row of these tables were modified to specify requirements for the x-ray relative to the menarche status of the subject.

Now reads as follows for Table 1, Table 2 (footnote 14), Table 3 (footnote 12), and Table 4 (footnote 11):

~~18~~**15** An x-ray of the left hand and wrist to determine bone age will be performed at ~~B~~**b**aseline **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. ~~If~~**For subsequent visits, once** the bone age is determined to be ≥16 years of age **or once the subject is postmenarche**, ~~this indicates that the patient has reached full pubertal status and~~ no further bone x-rays are required.

Rationale: This change was made to more explicitly state that hand and wrist x-rays (including the Baseline x-ray) do not need to be obtained once subjects have reached menarche.

This change also affects Section 3, Synopsis and Section 6.10.2, Laboratory and Radiological Safety Assessments.

Section 4.2, Schedule of Events

Change: The footnote for the Lymphocyte Follow-Up Visit was clarified to indicate that this applies to subjects treated with BG00012 and to include additional details about follow-up timing and inclusion in Part 2 of the study.

Now reads as follows for Table 2:

[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 (~~unless~~ **or sooner, if** clinically indicated ~~more often~~ or at the Investigator's discretion) until the lymphocyte count is ≥LLN, ~~or~~ for **at least** 48 weeks following treatment discontinuation**, or until initiation of another MS disease modifying therapy**, whichever occurs sooner**. 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.**

Rationale: This change was made to more explicitly state the schedule for follow-up of subjects who have a lymphocyte count <LLN while being treated with BG00012.

This change also affects Section 6.3.1, Overview; Section 6.3.2, Overall Part 1 Duration and Follow-Up; Section 6.3.2.3, Follow-Up; Section 6.6.4.2, Schedule for Subjects Who Complete, Temporarily Withhold, or Permanently Discontinue BG00012 for Any Reason and Have a

Lymphocyte Count <LLN (including Figure 3); and Section 7.3.2.1, Day 1 of Part 2 (Part 1 Week 96).

Section 4.2, Schedule of Events

Change: A note was added at the bottom of the prior Table 4 (now Table 3) to clarify monitoring and follow-up instructions for subjects who have discontinued BG00012 and are participating in Part 1 for follow-up lymphocyte monitoring.

Now reads as follows for Table 3:

NOTE: 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). These subjects are required to have lymphocytes monitored in accordance with the schedule outlined in Table 9, 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 sooner.

Rationale: This change allows for continued monitoring of the lymphocyte count for subjects who have lymphocyte counts <LLN in accordance with Part 1.

This change also affects Section 4.2 Schedule of Events, Table 4 (Footnote 3); Section 7.3.1, Overview; Section 7.9, Part 2 Efficacy Assessments; and Section 7.10, Part 2, Safety Assessments.

Section 4.2, Schedule of Events

Change: The footnote for Table 3 for the Part 1 week 96 Visit and start of Part 2 was clarified to distinguish between subjects entering Part 2 for treatment with BG00012 and those entering for continued lymphocyte follow-up.

Now reads as follows for Table 3:

[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 ~~starting study treatment for~~**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.

Rationale: This change was made to more explicitly state the schedule for follow-up of subjects who have a lymphocyte count <LLN.

Section 4.2, Schedule of Events

Change: The time period for the heading for Lymphocyte Follow-Up in Table 4 for Part 2 was removed, as the duration of follow-up may be up to 48 weeks after the last dose instead of 24 weeks and the description is included in Footnote 3 for the table.

Now reads as follows for Table 4:

Column Heading: Lymphocyte Follow-Up ~~(Up to 24 Weeks After Last Dose)~~[3]

[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 sooner. 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.**

Rationale: This change was to minimize confusion over the timing and duration of Lymphocyte Follow-Up visits during Part 2.

Section 4.2, Schedule of Events

Change: A footnote was added to Table 4 to indicate that before dispensing study treatment all tests and evaluations required for the visit should be completed.

Now reads as follows for Table 4:

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

Rationale: This change was included to minimize the risk of dispensing treatment before determining that a subject is eligible to proceed with BG00012 treatment in Part 2.

Section5.1.2, Relevant Clinical Experience with BG00012

Change: A paragraph was added to include information from Study 109MS202 with BG00012 in pediatric subjects.

Now reads as:

The pharmacokinetics, efficacy, and safety of BG00012 in pediatric multiple sclerosis (MS) were evaluated in Study 109MS202, an open-label multicenter, multiple-dose study that enrolled 22 subjects 13 to 17 years of age. The dosing regimen was the same as the approved BG00012 dosing regimen in adults with RRMS. The pharmacokinetics, efficacy and safety results in the pediatric subjects in Study 109MS202 were consistent with the overall BG00012 experience to date in adult healthy volunteers and adult subjects with RRMS. BG00012 was effective in reducing brain MRI lesions over a 24-week Treatment Period. Pharmacokinetic parameters in pediatric and adult subjects were comparable, and the safety and tolerability profile of BG00012 was consistent with that observed in previously conducted studies in adult subjects with RRMS

Rationale: This change was included to provide relevant clinical information that is currently available.

Section 6.3.2.3, Follow-up

Change: The wording that made completion of the study assessments for the Safety Follow-up Visit optional no later than 4 weeks after the last dose of study treatment was made mandatory.

Now reads:

Subjects who prematurely withdraw from the study will complete the study assessments for the Safety Follow-up Visit no later than 4 weeks after the last dose of study treatment.

Subjects who opt not to continue in Part 2 must complete the Safety Follow-Up Visit no later than Week 100.

~~Subjects who prematurely **withdraw from the study** should be encouraged to complete the study assessments for the Safety Follow-up Visit no later than 4 weeks after the last dose of study treatment.~~

Rationale: The Safety Follow-up Visit was not intended to be optional and the wording was clarified to reflect the importance of completing the Safety Follow-up Visit.

This change also affects Section 6.6.6.2, Concomitant Procedures.

Section 6.3.3, Relapses

Change: Modifications were made to the description of the relapse assessments to clarify the timing of and personnel responsible for the unscheduled Relapse Assessment Visit and related evaluations.

Now reads:

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 ~~*treating*~~***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 should be considered part of the same relapse and would not be treated with IVMP within the protocol.

If a subject experiences new neurologic symptoms, the subject or caregiver must contact the *treating* neurologist or *treating* nurse **as soon as possible and** within 48 hours of the onset of symptoms to complete a Telephone Questionnaire to determine the necessity of an unscheduled Relapse Assessment Visit. If required, the subject will then be evaluated in person by the *treating* neurologist **at the unscheduled Relapse Assessment Visit, which is to be conducted as soon as possible and** within 72 hours of the onset of the potential relapse. If, in the opinion of the *treating* neurologist, an MS relapse may have occurred, the subject must also be evaluated

by the *examining* neurologist **as soon as possible and** within 5 days of the onset of the symptoms. The *examining* neurologist is to perform a detailed neurologic examination and obtain an EDSS score. New objective findings on neurological examination performed by the *examining* neurologist are required to confirm that a protocol-defined relapse has occurred. Subjects may not begin corticosteroid treatment of the relapse per protocol until after the *examining* neurologist has examined them. The *examining* neurologist is permitted to report the examination findings to the *treating* neurologist so that he/she can evaluate treatment options.

Relapse Assessment Visits are to be conducted **as soon as possible and** within 72 hours of the onset of any new or worsening neurologic symptoms or suspected protocol-defined relapse (~~Figure 1~~**Figure 4**). Unscheduled Relapse Assessment Visits should not modify or replace the subjects' visit schedule.

Rationale: These changes clarify that the unscheduled Relapse Assessment Visit refers to the evaluation by the *treating* neurologist that occurs prior to any evaluation by the *examining* neurologist, and more clearly describe its timing. In addition, they indicate that each step or evaluation should be performed as soon as possible and that the durations given are maximum durations relative to the onset of symptoms. The reference to the figure was changed to correct a previous error.

This change also affects Section 4.2, Schedule of Events (Table 2 [footnote 4] and Table 4 [footnote 4]); Section 4.3.2, Site Personnel; and Section 6.9.2, Clinical Efficacy Assessments, including Figure 4.

Section 6.4.1, Inclusion Criteria

Change: The text of Inclusion Criterion 6 was broken into bullets to describe the options for the relevant conditions.

Now reads:

6. Must have experienced **at least 1 of the following 3 conditions:**

   a) at least 1 relapse within the last 12 months prior to Day 1 ~~or at least 2 relapses within the last 24 months prior to Day 1~~, with a prior brain MRI demonstrating lesions consistent with MS, or

   b) at least 2 relapses within the last 24 months prior to Day 1, with a prior brain MRI demonstrating lesions consistent with MS, or

   c) evidence of Gd-enhancing lesions of the brain on an MRI performed within the 6 weeks prior to Day 1.

Rationale: This change clarifies that subjects who do not meet the relapse criteria (a or b) may still be eligible for the study if they show evidence of Gd-enhancing lesions of the brain (c).

Section 6.4.2, Exclusion Criteria

Change: Exclusion Criterion 4 for allergic reactions or hypersensitivity to DMF or related compounds has been expanded to include interferon β-1a.

Now reads:

4. History of severe allergic or anaphylactic reactions, or known drug hypersensitivity to DMF**,** ~~or~~ fumaric acid esters**, or interferon β-1a (IFN β-1a)**.

Rationale: This change was made for subject safety to exclude subjects with a history of allergic reaction or anaphylactic reactions or known drug hypersensitivity to interferon β-1a, the comparator product for this study.

Section 6.6.4.1, Schedule in Part 1 for Subjects **Treated With BG00012** With Lymphocyte Count <~~500/mm^3~~LLN, Table 10

Change: Subjects treated with BG00012 who complete, temporarily withhold, or permanently discontinue study treatment with a lymphocyte count <LLN at the end of Part 1 (including at the end of Part 1/Week 96 Visit) will continue follow-up within Part 2 of the study.

Now reads:

~~BG00012 must be permanently discontinued when the lymphocyte count meets the threshold limits defined in Table 10~~**For subjects treated with BG00012, the required action described in Table 9 must be taken when the lymphocyte count is <LLN.**

Table 9~~10~~: Lymphocyte Count Criteria Requiring **Additional Testing and/or** Permanent Discontinuation of BG00012 Treatment

Laboratory Parameter **and Treatment Status**	Laboratory Result	Required Action
Lymphocyte count ~~on study treatment~~ **Active treatment with BG00012**	<LLN	The Investigator should repeat the test within 2 weeks. If retest confirms that lymphocyte count is <LLN, lymphocyte count should be closely monitored (at least every 4 weeks).
Lymphocyte count **Active treatment with BG00012**	<500/mm^3	The Investigator should repeat the test as soon as possible. If re-test confirms that lymphocyte count is <500/mm^3, lymphocyte count should be closely monitored (at least every 4 weeks). If lymphocyte count is <500/mm^3 for more than 6 months, study treatment must be permanently discontinued.
Lymphocyte count ~~in s~~Subjects who complete, temporarily withhold, or permanently discontinue ~~study~~ **BG00012** treatment for any reason	<LLN	Subjects will be followed every 4 weeks for 24 weeks, then every 12 weeks (~~unless~~ **or sooner, if** clinically indicated ~~more often~~ or at the Investigator's discretion) until the lymphocyte count is ≥LLN, or for **at least** 48 weeks following ~~treatment~~BG00012 discontinuation **or until initiation of another MS disease modifying therapy** whichever occurs sooner. **Subjects treated with BG00012 who complete, temporarily withhold, or permanently discontinue study treatment with a lymphocyte count <LLN at the end of Part 1 (including at the End of Part 1/Week 96 Visit) will continue follow-up within Part 2 of the study.**

LLN = lower limit of normal

Rationale: For subjects who complete, temporarily withhold, or permanently discontinue study treatment, this change specifies that follow-up evaluation for low lymphocyte count that starts or is ongoing at the end of Part 1 of the study will occur during Part 2 of the study. Follow-up within Part 2 of the study will allow earlier completion of Part 1 data collection for these subjects and a more rapid completion of the Part 1 clinical study report.

This change also affects Section 3, Synopsis; Section 4.2, Schedule of Events (Table 2, Table 3, and Table 4); Section 6.3.1, Overview; Section 6.3.2, Overall Part 1 Duration and Follow-Up; Section 6.3.2.3, Follow-Up; Section 6.6.4.2, Schedule for Subjects Who Complete, Temporarily Withhold, or Permanently Discontinue BG00012 for Any Reason and Have a Lymphocyte Count

<LLN, including Figure 3; Section 7.3.2.1, Day 1 of Part 2 (Part 1 Week 96); Section 7.3.2.4, Follow-Up; Section 7.4.1, Inclusion Criteria; Section 7.4.2, Exclusion Criteria, Exclusion Criterion 5 (removed last bullet, for lymphocyte count <500/mm^3); Section 7.6.4.2, Schedule for Subjects Who Complete, Temporarily Withhold, or Permanently Discontinue BG00012 for Any Reason and Have a Lymphocyte Count <LLN; and Section 7.7, Part 2 Withdrawal of Subjects From Study Treatment and/or the Study.

Section 7.3.1, Overview

Change: A clarification was added to reflect that Subjects in Part 2 will receive study treatment, excluding those continuing follow-up for lymphopenia.

Now reads:

Results from Part 2 will be reported separately from Part 1. In Part 2, ~~all~~ 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.

Rationale: This change was added to increase clarity that subjects who had discontinued BG00012, but were continuing lymphocyte monitoring from Part 1 during Part 2 of the study would not be receiving BG00012.

This change also affects Section 7.3.2.2, Treatment.

Section 7.4.2, Exclusion Criteria (for Part 2)

Change: Exclusion Criteria numbering was fixed, Exclusion Criterion 6 (previously Exclusion Criterion 5) for abnormal blood tests has been narrowed to only subjects who received Avonex in Part 1 and have certain specified abnormal blood test results, which have been updated and a new Exclusion Criterion has been added.

Now reads:

6. ~~Any of the following abnormal blood tests at Week 84~~**Subjects who received Avonex in Part 1 and have any of the following abnormal blood test results at Week 84:**
    - ALT **≥2**~~>3~~ times the ULN
    - AST **≥2**~~>3~~ times the ULN
    - Gamma-glutamyl-transferase **≥2**~~>3~~ times the ULN
    - **Leukocytes <3500/mm^3**
    - ~~Creatinine >1.2 times the ULN~~
    - ~~WBC count <2000/mm^3~~
    - **Eosinophils >0.7 × 10^3/µL or >0.7 GI/L**
    - **Absolute** ~~L~~**l**ymphocyte count ~~<500/mm^3~~**<LLN**

7. **Subjects who were required to permanently discontinue BG00012 in Part1 of the study, with the exception of subjects with lymphocyte count remaining <LLN at the End of Part 1 (Week 96 Visit) who will continue follow-up in Part 2 of the study.**

Rationale: If subjects treated with BG00012 in Part 1 did not have laboratory abnormalities during Part 1 that met the criteria for withholding or discontinuing treatment with BG00012 at the end of Part 1, then they are eligible for continued treatment in Part 2. For subjects who received Avonex in Part 1, eligibility for transition to treatment with BG00012 in Part 2 has been clarified to align with the requirements to enroll in Part 1 of the study.

Section 7.6.3, Modification of Dose and/or Treatment Schedule for BG00012

Change: Subjects at the end of Part 1 for whom BG00012 is being temporarily withheld on the basis of abnormal laboratory values should have BG00012 continue to be withheld and the laboratory tests repeated until the values return to target values within 4 weeks; if target values are not met by that time, BG00012 should be permanently discontinued.

Now reads:

Rules for the modification of treatment dose/schedule in Part 2 are the same as in Part 1 (see Section 6.6.3).

Subjects at the end of Part 1 for whom BG00012 is being temporarily withheld on the basis of abnormal laboratory values (in accordance with Table 8) should have BG00012 continue to be withheld and the laboratory tests repeated, as specified for Part 1. If the abnormal laboratory findings fail to reach the target values specified in Table 8 within 4 weeks, then BG00012 should be permanently discontinued.

Rationale: This change allows for the continued follow-up and potential restart of treatment with BG00012 for subjects at the end of Part 1 for whom BG00012 is being temporarily withheld on the basis of abnormal laboratory values.

Section 7.6.4.1, Schedule in Part 2 for Subjects With Lymphocyte Count <LLN

Change: Clarified requirements for subjects who enter Part 2 with <LLN.

Now reads:

Subjects who received BG00012 in Part 1 and enter Part 2 with a lymphocyte count <LLN must be managed in accordance with Table 9 ~~The schedule in Part 2 is as in Part 1~~ (see Section 6.6.4.1).

Rationale: This change clarifies how to manage the subjects that are entering Part 2 with a lymphocyte count <LLN and includes a reference to Table 9 for specific details.

Section 7.7, Part 2 Withdrawal of Subjects From Study Treatment and/or the Study

Change: The timing of and requirement to complete the Safety Follow-up Visit for subjects who permanently discontinue in Part 2 were clarified.

Now reads:

All subjects that permanently discontinue BG00012 will have the Safety Follow-Up Visit 4 weeks (±5 days) after last dose of BG00012.

Rationale: The Safety Follow-up Visit was not intended to be optional and the wording was clarified to reflect the timing and importance of completing the Safety Follow-up Visit.

Section 9.1.5.2.2, Clinical Laboratory Abnormalities

Change: The section was clarified to indicate the recovery of lymphocyte counts would be included in the summarization of the lymphocyte count over time.

Now reads:

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. Additionally, lymphocyte count over time **(including recovery from lymphocyte counts <LLN)** will be summarized using descriptive statistics.

Rationale: This change was made to align with the clarifications throughout the protocol for the follow-up of lymphopenia.

SUMMARY OF MINOR CHANGES TO THE PROTOCOL

The following minor changes were made to the protocol, as appropriate:

- The version number and date were updated throughout the protocol.
- A Sponsor Signature Page was added to satisfy updated requirements from the Sponsor's protocol template.
- Footnotes on the column headers for Tests and Assessments, Lymphocyte Follow-Up, and Unscheduled Relapse Assessment Visit that were previously missed were added to Section 4.2 Schedule of Events, Table 4 Study Activities (Unscheduled and Post-Treatment Visits) – Part 2. Footnote 2 in Table 3 was moved from Week 98 to Week 96.
- Numbering of exclusion criteria for Part 1 has been corrected in Section 6.4.1 to accommodate the removal of Inclusion Criterion #17.
- Numbering of the inclusion and exclusion criteria for Part 2 of the study has been corrected in Section 7.4, Part 2 Selection of Subjects (this does not appear as a tracked change).
- "BG00012 treatment" replaced "study treatment" or was added in appropriate locations for greater clarity. In addition, clarifications were added to text that is specifically referring to subjects receiving BG00012 in Part 1. This change was made throughout the protocol.
- The word "efficacy" replaced the phrase "effect on the disease course" throughout the protocol to increase clarity.
- It was specified throughout the protocol that the completion of Part 1 is completion of Week 96 of the study.
- In Part 2, the term "secondary" replaced "additional" for the associated objectives and endpoints.
- As subjects may not be in the pediatric age range when they start Part 2 of the study, the word "pediatric" was removed from the description for Part 2, as appropriate.
- "IMS" was added to Quintiles Lifecycle Safety so that it now reads Quintiles**IMS** Lifecycle Safety.
- Minor formatting and editing changes were made throughout.

Biogen MA Inc.
250 Binney Street
Cambridge, MA 02142
United States

Biogen Idec Research Limited
Innovation House
70 Norden Road
Maidenhead Berkshire
SL6 4AY
United Kingdom

AMENDMENT SUMMARY

Biogen Protocol 109MS306

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

Version 4

Date: 08 February 2016

EUDRA CT Number: 2013-002318-11

Version 4 of the protocol has been prepared for this amendment, which supersedes Version 3.

PRIMARY REASONS FOR AMENDMENT

The primary reasons for this amendment to Protocol 109MS306 are as follows:

- To add in a long-term extension study required by the pediatric committee of the European Medicines agency
- Extend the follow-up period from 24 weeks to 48 weeks for subjects who complete, temporarily withhold, or permanently discontinue study treatment for any reason and have a lymphocyte count less than the lower limit of normal (<LLN), as described in the most recent version of the Investigator's Brochure.

New text is shown in **bold** type; deleted text is shown with a ~~strikethrough~~.

Section 7, Part 2

Now reads:

7.1 Part 2 Objectives

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

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

7.2. Part 2 Endpoints

7.2.1.1. Primary Endpoint

The primary endpoint is the incidence of AEs, SAEs, and discontinuations of study treatment due to an AE.

7.2.1.2. Additional Endpoints

Additional 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.

Rationale: There is a pediatric investigation plan (PIP) long-term extension requirement for safety, efficacy, and growth and development measures for 5 years.

This change also affects the following:

- Title
- Section 3, Synopsis
- Section 4.1, Study Schematics for Part 1 and Part 2
- Section 4.2, Schedule of Events (Table 4 and Table 5)
- Section 4.3.3, Blood Volumes (Table 6, Table 7, and Table 8)
- Section 4.3.4, Site Personnel
- Section 5.2, Study Rationale
- Section 6, Part 1
- Section 7.3, Part 2 Study Design
- Section 7.4, Part 2 Selection of Subjects
- Section 7.5, Part 2 Enrollment Procedures
- Section 7.6, Part 2 Treatment of Subjects
- Section 7.7, Part 2 Withdrawal of Subjects From Study Treatment and/or the Study
- Section 7.8, Part 2 Study Treatment Management
- Section 7.9, Part 2 Efficacy Assessments
- Section 7.10, Part 2 Safety Assessments
- Section 9.1, Part 1
- Section 9.2, Part 2

Section 6.3.1, Part 1 Overview

Now reads:

[...]

Subjects who complete, temporarily withhold, or permanently discontinue study treatment for any reason and have a lymphocyte count <LLN will be followed every 4 weeks ~~until the lymphocyte count is ≥LLN or for 24 weeks after the last dose (whichever is sooner)~~ **for 24 weeks, then every 12 weeks (unless clinically indicated more often or at the Investigator's discretion) until the lymphocyte count is ≥LLN, or for 48 weeks following drug discontinuation, whichever occurs sooner** (see Section 6.6.4).

[...]

Rationale: As a safety measure, management of lymphocyte count is revised to ensure subjects with lymphopenia are followed up for longer than 6 months after study drug discontinuation, as there is no evidence that full recovery can be expected within 6 months following treatment cessation.

This change also affects the following:

- Section 3, Synopsis
- Section 4.2, Schedule of Events (all Tables were updated or created new to incorporate both parts of the study)
- Section 4.3.4, Site Personnel
- Section 6, Part 1 (all subsequent sections were updated to move out 1 level)
- Section 6.3.2, Overall Part 1 Duration and Follow-Up
- Section 6.3.2.4, Follow-Up
- Section 6.6.4.1, Schedule in Part 1 for Subjects With Lymphocyte Count <500/mm^3
- Section 6.6.4.2, Schedule in Part 1 for Subjects Who Complete, Temporarily Withhold, or Permanently Discontinue Study Treatment for Any Reason and Have a Lymphocyte Count <LLN
- Section 12.1.5, Central Facility for Other Assessments

SUMMARY OF MAJOR CHANGES TO THE PROTOCOL

Changes to the protocol are presented chronologically. New text is shown in **bold** type; deleted text is shown with a ~~strikethrough~~.

Section 3, Synopsis

The Synopsis was revised to reflect changes made throughout the protocol.

Section 4.2, Schedule of Events (Table 1)

Change: Added rows for annual endocrine tests, hand and wrist x-rays, Brief Visuospatial Memory Test - Revised (BVMT-R), Symbol Digit Modalities Test (SDMT), and annual school query. Additionally, it was specified that tests for luteinizing hormone and follicle-stimulating hormone would be performed in both male and female subjects. Vitamin D and parathyroid hormone (PTH) levels were removed. The columns/rows corresponding to End of Study/Early Withdrawal, Safety Follow-up, Lymphocyte Follow-up, and Unscheduled Relapse Assessment Visits were moved to their own table (Table 2). Footnotes were added/revised to address Tanner stage, bone age, and pre-dose PD sample.

Now reads:

~~Table 1: Study Activities for Study 109MS306~~

~~Tests and Assessments[1]~~	~~Screening Visit~~												~~End of Study/ Early Withdrawal~~	~~Safety Follow-Up Visit[2]~~	~~Lymphocyte Follow-Up Visit[3]~~	~~Unscheduled Relapse Assessment Visit[4]~~
~~Week~~	~~(Within 6 Weeks of Baseline)~~	~~Baseline Visit (Day 1)~~	~~Wk 2 ±5D Safety Phone Call[5]~~	~~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~~	~~Wk 96 ± 5D~~	~~Wk 100 ± 5D~~		
~~Informed Consent or Assent[6]~~	~~X~~															
~~Eligibility Criteria~~	~~X~~	~~X~~														
~~Medical History[7]~~	~~X~~															
~~Hepatitis C Antibody and HBsAg Screen~~	~~X~~															
~~Randomization~~		~~X~~														
~~Physical Examination~~	~~X~~	~~X~~					~~X~~		~~X~~		~~X~~		~~X~~	~~X~~	~~X~~	~~X~~
~~Body Weight~~	~~X~~	~~X~~		~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~		~~X~~
~~Height~~	~~X~~						~~X~~		~~X~~				~~X~~	~~X~~		
~~Tanner Score[8]~~	~~X~~								~~X~~				~~X~~			
~~Vital Signs[9]~~	~~X~~	~~X~~		~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~
~~12-Lead ECG~~	~~X~~	~~X[10]~~		~~X~~					~~X~~				~~X~~	~~X~~		
~~Hematology[11]~~	~~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~~	~~X~~	~~X~~	~~X~~		~~X~~
~~PTT, PT, INR~~		~~X~~					~~X~~		~~X~~				~~X~~			

Tests and Assessments[1]	Screening Visit												End of Study/ Early Withdrawal	Safety Follow-Up Visit[2]	Lymphocyte Follow-Up Visit[3]	Unscheduled Relapse Assessment Visit[4]
Week	(Within 6 Weeks of Baseline)	Baseline Visit (Day 1)	Wk 2 ±5D Safety Phone Call[5]	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	Wk 96 ± 5D	Wk 100 ± 5D		
Urine Pregnancy Test[12,13]	X	X		X	X	X	X	X	X	X	X	X	X	X		X
Urinalysis[14]	X	X		X	X	X	X	X	X	X	X	X	X	X		X
Vitamin D and PTH Levels	X	X							X				X	X		
EDSS	X	X				X	X	X	X	X	X	X	X			X
Whole Blood for PD Biomarkers NQO-1, HO-1[16]		X[17,18]		X[18]		X[18]	X[18]		X[18]		X[18]		X[18]			
PK Assessments				See Table 3												
Brain MRI Scan ± Gd[19,20]		X					X		X		X		X			X
PedsQL, PedsQL Multidimensional Fatigue Scale		X					X		X		X		X			X
Dispense Treatment		X[1]		X	X	X	X	X	X	X	X	X	X			
Relapse Assessment																X
Concomitant Therapy and Procedures			X												X	X
SAEs Recording		Note: Study visits (weeks) are calculated relative to Baseline (Day 1). Monitor and record throughout the study as described in Section 8.2													X	X

~~Tests and Assessments[1]~~	~~Screening Visit~~												~~End of Study/ Early Withdrawal~~	~~Safety Follow-Up Visit[2]~~	~~Lymphocyte Follow-Up Visit[3]~~	~~Unscheduled Relapse Assessment Visit[4]~~
~~Week~~	~~(Within 6 Weeks of Baseline)~~	~~Baseline Visit (Day 1)~~	~~Wk 2 ±5D Safety Phone Call[5]~~	~~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~~	~~Wk 96 ± 5D~~	~~Wk 100 ± 5D~~		
~~AEs Recording~~			~~Monitor and record throughout the study as described in Section 8.2~~												~~X~~	~~X~~

Table 1: Study Activities ~~for Study 109MS306~~ **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	~~End of Study/ Early Withdrawal~~	~~Safety Follow Up Visit[3]~~	~~Lymphocyte Follow Up Visit[3]~~	~~Unscheduled Relapse Assessment Visit[4]~~
Informed Consent or Assent[3]	X												~~Wk 96 ± 5D~~	~~Wk 100 ± 5D~~		
Eligibility Criteria	X	X														
Medical History[4]	X															
Hepatitis C Antibody and HBsAg Screen	X															
Randomization		X														
Physical Examination	X	X					X		X		X		~~X~~	~~X~~	~~X~~	~~X~~
Body Weight	X	X		X	X	X	X	X	X	X	X	X	~~X~~	~~X~~		~~X~~
Height	X						X		X				~~X~~	~~X~~		
Tanner Score[5]	X								X				~~X~~			
Vital Signs[6]	X	X		X	X	X	X	X	X	X	X	X	~~X~~	~~X~~	~~X~~	~~X~~
12-Lead ECG	X	X[7]		X					X				~~X~~	~~X~~		
Hematology[8]	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	X	~~X~~	~~X~~		~~X~~
PTT, PT, INR		X					X		X				~~X~~			
Urine Pregnancy Test[9, 10]	X	X		X	X	X	X	X	X	X	X	X	~~X~~	~~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	~~End of Study/ Early Withdrawal~~	~~Safety Follow Up Visit[3]~~	~~Lymphocyte Follow Up Visit[3]~~	~~Unscheduled Relapse Assessment Visit[4]~~
Urinalysis[11]	X	X		X	X	X	X	X	X	X	X	X	~~X~~	~~X~~		~~X~~
~~Vitamin D and PTH Levels~~	~~X~~	~~X~~							~~X~~				~~X~~	~~X~~		
Endocrine Tests[12]		**X**							**X**							
EDSS	X	X				X	X	X	X	X	X	X	~~X~~			~~X~~
Whole Blood for PD Biomarkers NQO-1, HO-1[13]		X[14, 15]		X[15]		X[15]	X[15]		X[15]		X[15]		~~X~~			
PK Assessments				See Table 3												
Brain MRI Scan ± Gd[16, 17]		X					X		X		X		~~X~~			~~X~~
Hand and Wrist X-ray[18]		X							X							
PedsQL, PedsQL Multidimensional Fatigue Scale		X					X		X		X		~~X~~			~~X~~
BVMT-R		**X**							**X**							
SDMT		**X**							**X**							
Query Regarding Annual School/Grade Progression[19]		**X**							**X**							
Dispense Treatment		X[1]		X	X	X	X	X	X	X	X	X				
~~Relapse Assessment~~																~~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	~~End of Study/ Early Withdrawal~~	~~Safety Follow Up Visit[3]~~	~~Lymphocyte Follow Up Visit[3]~~	~~Unscheduled Relapse Assessment Visit[4]~~
Concomitant Therapy and Procedures			X												~~X~~	~~X~~
SAEs Recording	~~Note: Study visits (weeks) are calculated relative to Baseline (Day 1).~~ Monitor and record throughout the study as described in Section ~~15.2~~ 8.2														~~X~~	~~X~~
AEs Recording		Monitor and record throughout the study as described in Section ~~15.2~~ 8.2													~~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; HO-1 = heme oxygenase 1; INR = international normalized ratio; **LH = luteinizing hormone; LLN = lower limit of normal;** MRI = magnetic resonance imaging; MS = multiple sclerosis; NQO-1 = NAD(P)H dehydrogenase, quinone 1; PD = pharmacodynamics; PedsQL = Pediatric Quality of Life Inventory; PK = pharmacokinetics; 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, 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. Collection of information regarding Tanner staging 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 Hematology testing must be performed every 4 weeks in subjects with lymphocyte count <500/mm^3.

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 present on 2 consecutive tests or 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 9).

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 stop being collected once the subject's bone age reaches ≥16 years or once the subject is postmenarche.**

13 PD assessments will be collected in the subset of subjects who consent to participate in the PD/PK subset.

14 Predose PD sample will be taken at Baseline prior to the first dose of BG00012.

15 Samples for PD assessments will be collected between 4 and 10 hours after dosing with BG00012.

[16] 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.

[17] 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.

[18] **An x-ray of the left hand and wrist to determine bone age will be performed at Baseline 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. If the bone age is determined to be ≥16 years of age, this indicates that the patient has reached full pubertal status and no further bone x-rays are required.**

[19] **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) - for 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
Whole Blood for PD Biomarkers NQO-1, HO-1[13]	X[14]	X[14]			
PK Assessments					
Brain MRI Scan ± Gd[15]	X	X			X
Hand and Wrist X-ray[16]	X	X			
PedsQL, PedsQL Multidimensional Fatigue Scale	X	X			X
BVMT-R	X	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		
SDMT	X	X			
Dispense Treatment	X				
Relapse Assessment					X
Query Regarding Annual School/Grade Progression[17]	X				
Concomitant Therapy and Procedures	X			X	X
SAEs Recording	Monitor and record throughout the study as described in Section 8.2			X	X
AEs Recording	Monitor and record throughout the study as described in Section 8.2			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; HO-1 = heme oxygenase 1; INR = international normalized ratio; LH = luteinizing hormone; LLN = lower limit of normal; MRI = magnetic resonance imaging; MS = multiple sclerosis; NQO-1 = NAD(P)H dehydrogenase, quinone 1; PD = pharmacodynamics; PedsQL = Pediatric Quality of Life Inventory; PK = pharmacokinetics; 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 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 (unless clinically indicated more often or at the Investigator's discretion) until the lymphocyte count is ≥LLN, or for 48 weeks following treatment discontinuation, whichever occurs sooner.

4 Unscheduled Relapse Assessment Visit to be carried out within 72 hours of suspected relapse.

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. Collection of information regarding Tanner staging 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 Hematology testing must be performed every 4 weeks in subjects with lymphocyte count <500/mm^3.

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 present on 2 consecutive tests or 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 9).

[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 stop being collected once the subject's bone age reaches ≥16 years or once the subject is postmenarche.**

[13] **PD assessments will be collected in the subset of subjects who consent to participate in the PD/PK subset.**

[14] **Samples for PD assessments will be collected between 4 and 10 hours after dosing with BG00012.**

[15] **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.**

[16] **An x-ray of the left hand and wrist to determine bone age will be performed at Baseline 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. If the bone age is determined to be ≥16 years of age, this indicates that the patient has reached full pubertal status and no further bone x-rays are required.**

[17] **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?"**

Rationale: Endocrine tests were added to clarify these tests are separate from the PD assessments. Hand and wrist x-rays were included as an assessment of bone age. BVMT-R was added to measure the learning and memory abilities and SDMT was added to test for cognitive processing speed. The annual query regarding school progression was added to serve as an additional metric of a subject's cognitive function. All of the above parameters will help assess multiple sclerosis (MS) outcomes in pediatric subjects and were included in Part 1 to help establish a baseline result.

Monitoring of vitamin D and PTH levels were initially included to help assess for potential renal toxicity. No subsequent evidence of renal toxicity was found, and therefore monitoring of vitamin D and PTH are no longer considered necessary.

These changes also affect the following:

- Section 2, List of Abbreviations (BVMT-R, FSH, LH, and SDMT)
- Section 4.2, Schedule of Events (Table 4 and Table 5)
- Section 4.3.4, Site Personnel (BVMT-R and SDMT)
- Section 6.2.3, Exploratory Endpoints (BVMT-R and SDMT)
- Section 6.9.2, Clinical Efficacy Assessments (BVMT-R and SDMT)
- Section 6.10.2, Laboratory and Radiological Safety Assessments (hand and wrist x-rays, endocrine tests, and vitamin D and PTH)

Section 6.2.3, Exploratory Endpoints

Change: Added BVMT-R and SDMT as exploratory endpoints in Part 1.

Now reads:

The exploratory endpoints of ~~this study~~**Part 1** are as follows:

- [...]
- Time to progression of disability at ~~2 years~~ **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**

Rationale: The addition of BVMT-R and SDMT was done to align with the PIP requirements as well as to provide baseline measurements for these assessments in Part 2.

Section 6.4.1, Inclusion Criteria

Change: Modified the definition of relapsing-remitting multiple sclerosis (RRMS).**Now reads:**4. Must have a diagnosis of RRMS **according to the International Pediatric Multiple Sclerosis Study Group criteria for pediatric MS (2013) [Krupp 2013]** (consensus definition for pediatric RRMS) ~~[Krupp 2007]~~.

Rationale: The definition of RRMS was updated to align with the most recent definition and as agreed to with the pediatric committee of the European Medicines Agency.

This change also affects Section 13, References.

Section 6.4.2, Exclusion Criteria

Change: Modified proteinuria as an exclusion criterion.**Now reads:**12. **Proteinuria (1+ or greater) at Screening confirmed by a spot protein/creatinine ratio (with morning void) >0.2 mg/mg approximately 2 weeks later. Note: Documented benign proteinuria is not exclusionary.**

OR

Any of the following **additional** abnormal urine tests at Screening confirmed by a second urinalysis approximately 2 weeks later:

- ~~proteinuria (1+ or greater) and/or spot protein/creatinine ratio (with AM void) >0.2 mg. Note: Documented benign proteinuria is not exclusionary.~~
- hematuria, without known etiology
- glycosuria, without known etiology

Rationale: The exclusion criterion was updated to clarify the use of spot protein/creatinine ratio to assess proteinuria and the timeframe in which it needs to be performed.

This change also affects Section 6.6.3.2, Dosing Interruption for Abnormal Laboratory Values.

Change: Shortened the period between prior immunomodulatory treatment and Day 1 of the study. Additionally, interferon-alpha was removed from the list of prohibited prior medications.**Now reads:**17. Prior treatment with any of the following within ~~3 months~~ **4 weeks** prior to Day 1:

- glatiramer acetate
- ~~interferon-alpha~~
- IFN β (subjects who are positive for neutralizing antibodies to IFN β may receive IFN β treatment up to 2 weeks prior to Day 1)

Rationale: Interferon-alpha was removed from the list as it was originally included in error. The prior treatment time frame was decreased from 3 months to 4 weeks because from a pharmacokinetic and pharmacodynamic perspective, neither interferon-beta (IFN β-1a) nor glatiramer acetate (GA) require a washout period of 3 months. Serum activity levels of IFN β-1a typically peak within 24 hours (following intramuscular or subcutaneous administration) and thereafter fall below detectable limits within 48 hours (72 hours post dose). Biological response marker levels have been noted to increase within 12 hours of dosing; peak serum levels have been observed approximately at 48 hours after injection and remain elevated for more than 4 days.

The pharmacokinetics of GA has not been fully investigated, although limited data are available from healthy controls and animals. A study was performed to quantify GA in human sera after subcutaneous injection of a single, supratherapeutic dose of 60 mg, to healthy volunteers. In all 9 subjects, the time to reach the maximum concentration (T_{max}) was between 15 and 30 minutes, except for 1 subject who had an additional peak at 240 minutes. In all subjects, GA levels returned to baseline after 30 to 60 minutes after injection. Twenty-four hours after injection of the 60-mg dose, the levels of the immunorecognizable GA fragments in the serum of 15 of the 17 subjects were below the quantification limit of 25 to 50 ng/mL.

Thus, based on these observations, a 4-week washout period is considered adequate to ensure that both IFN β-1a and GA have been eliminated, and no additional pharmacodynamics effects would be expected.

Section 6.6.4.1, Schedule in Part 1 for Subjects With Lymphocyte Count <500/mm^3

Change: Added new rows for handling of subjects with lymphocyte counts <LLN in Table 10.

Now reads:

Table 10: Lymphocyte Count Criteria Requiring Permanent Discontinuation of BG00012 Treatment

Laboratory Parameter	Laboratory Result	Required Action
Lymphocyte count on study treatment	**<LLN**	**The Investigator should repeat the test within 2 weeks. If retest confirms that lymphocyte count is <LLN, lymphocyte count should be closely monitored (at least every 4 weeks).**
Lymphocyte count	<500/mm^3	The Investigator should repeat the test as soon as possible. If re-test confirms that lymphocyte count is <500/mm^3, lymphocyte count should be closely monitored (at least every 4 weeks). If lymphocyte count is <500/mm^3 for more than 6 months, study treatment must be permanently discontinued.
Lymphocyte count in subjects who complete, temporarily withhold, or permanently discontinue BG00012 for any reason	**<LLN**	**Subjects will be followed at least every 4 weeks for 24 weeks and then every 12 weeks (unless clinically indicated more often or at the Investigator's discretion) until the lymphocyte count is ≥LLN or for 48 weeks after the last dose (whichever is sooner).**

Rationale: The table was updated to clarify monitoring of lymphocyte counts and to be consistent with other Tecfidera® protocols.

Section 6.10.2, Laboratory and Radiological Safety Assessments

Change: Added several assessments for safety.

Now reads:

6.10.2 Laboratory **and Radiological** Safety Assessments

~~The following laboratory tests will be performed to assess the safety profile of BG00012~~ **Safety will be monitored through the following:**

- **Gd-enhanced brain MRIs for relapses**
- **X-ray of the left hand and wrist to determine bone age (if permitted by local regulatory authority)**
- 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 test**
- **endocrine tests: insulin-like growth factor 1, insulin-like growth factor binding protein, follicle-stimulating hormone, luteinizing hormone, estradiol, and testosterone**
- ~~vitamin D and PTH~~
- urinalysis: color, specific gravity, pH, protein, glucose, blood, ketones, and microscopy

Rationale: Hand and wrist x-rays and endocrine testing were added to align with requirements for the PIP.

Section 8.1.3, Serious Adverse Event

Change: Added a condition for considering hospitalizations for study treatment administration as a serious adverse event.

Now reads:

If a subject is hospitalized due to local requirements for administration of the study treatment, the hospitalization should not be considered an SAE unless one of the requirements mentioned above is met.

Rationale: The additional text was added for clarification and to align with the other pediatric study protocols.

SUMMARY OF MINOR CHANGES TO THE PROTOCOL

The following minor changes were made to the protocol, as appropriate:

- The version number, date, Biogen logo, company name and address, and contact information were updated as appropriate throughout the protocol.
- The Sponsor Signature Page was deleted in keeping with the current Biogen approval process; the Signature page will be added electronically.Typographical errors and formatting were corrected.
- Nomenclature for months and weeks was updated to weeks as applicable throughout the document for consistency. Additionally, dosing information, to include regimen and drug name were updated throughout for consistency and clarity.
- Part 1 and/or Part 2 were added throughout the protocol for clarity and consistency.
- Text regarding the visit window for the Safety Follow-up visit was revised to note this visit would occur no later than 4 weeks after the last dose.
- Section 2, List of Abbreviations, was updated.
- In Section 4.3.2, Pharmacodynamic Assessments, the schedule of sample collection for PD assessments was clarified. Samples will be collected pre-dose and between 4 and 10 hours after dosing with BG00012.
- In Section 4.3.3, Blood Volumes, Table 6, Blood Volumes by Visit - 1, the blood volumes for subjects in the PD/PK subset were corrected to 10.0 and 16.5 mL at the Screening and Baseline visits, respectively. The volumes were inadvertently miscalculated. Tables 7 and 8 were added to include blood volumes for Part 2.
- In Section 4.3.4, Site Personnel, an EDSS-certified rater was included as personnel who are responsible for obtaining EDSS scores.
- In Section 6.3.1, Overview, it was specified that Figure 1 was replaced to show the **Part 1** study design.
- In Section 6.3.2, Overall Part 1 Duration and Follow-Up, was updated. The phrase “for those subjects not continuing into Part 2” was added to specify that this subset of subjects will only get 96 weeks of treatment.
- Description about Study Stopping Rules was moved from Section 6.3.4 to Section 7.3.4 and End of Study from Section 6.3.5 to Section 7.3.5.
- In Section 6.6.3.**5**, Abnormal Urinalyses That Require Additional Evaluation, it was clarified that the spot protein/creatinine ratio should be presented as mg/**mg.**

- The paragraphs on the General Methods of Analysis were moved from Section 9.2.4.2 to Section 9.2.2.1.

Biogen Idec MA Inc.
14 Cambridge Center
Cambridge, MA 02142, USA

Biogen Idec Research Limited
Innovation House
70 Norden Road
Maidenhead Berkshire
SL6 4AY
United Kingdom

AMENDMENT SUMMARY

Biogen Idec Protocol 109MS306

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

Version 3

Date: 16 January 2015

EUDRA CT Number: 2013-002318-11

Version 3 of the protocol has been prepared for this amendment, which supersedes Version 2.

PRIMARY REASON FOR AMENDMENT

Progressive multifocal leukoencephalopathy (PML) has occurred in the setting of severe, prolonged lymphopenia following BG00012 administration. Severe, prolonged lymphopenia is a known risk factor for PML. In the controlled and uncontrolled BG00012 clinical studies in adult subjects, 2% of subjects experienced lymphocyte counts $<0.5 \times 10^9$/L for at least 6 months. In these subjects, the majority of lymphocyte counts remained $<0.5 \times 10^9$/L with continued therapy. The study protocol is being amended to enable the early identification of subjects who are at risk for developing severe, prolonged lymphopenia, and to provide additional guidance on the management of such subjects.

New text is shown in **bold** type; deleted text is shown with a ~~strikethrough~~.

Section 10.4, Treatment Schedule for Subjects With Abnormal Lymphocyte Count

Now reads:

10.4.1 Schedule for Subjects with Lymphocyte Count <500/mm^3

BG00012 must be permanently discontinued when the lymphocyte count meets the threshold limits defined in Table 5.

Table 5: Lymphocyte Count Requiring Permanent Discontinuation of BG00012 Treatment

Laboratory Parameter	Laboratory Result	Required Action
Lymphocyte count	**<500/mm^3**	**The Investigator should repeat the test as soon as possible. If re-test confirms that lymphocyte count is <500/mm^3, lymphocyte count should be closely monitored (at least every 4 weeks). If lymphocyte count is <500/mm^3 for more than 6 months, study treatment must be permanently discontinued.**

If study treatment is permanently discontinued due to lymphocyte count <500/mm^3, subjects may continue protocol-required tests and assessments and also undergo lymphocyte follow-up every 4 weeks until the lymphocyte count is ≥LLN or for 24 weeks after the last dose (whichever is sooner) [see Table 1]. If the lymphocyte count does not recover, the treating neurologist should contact the Medical Monitor.

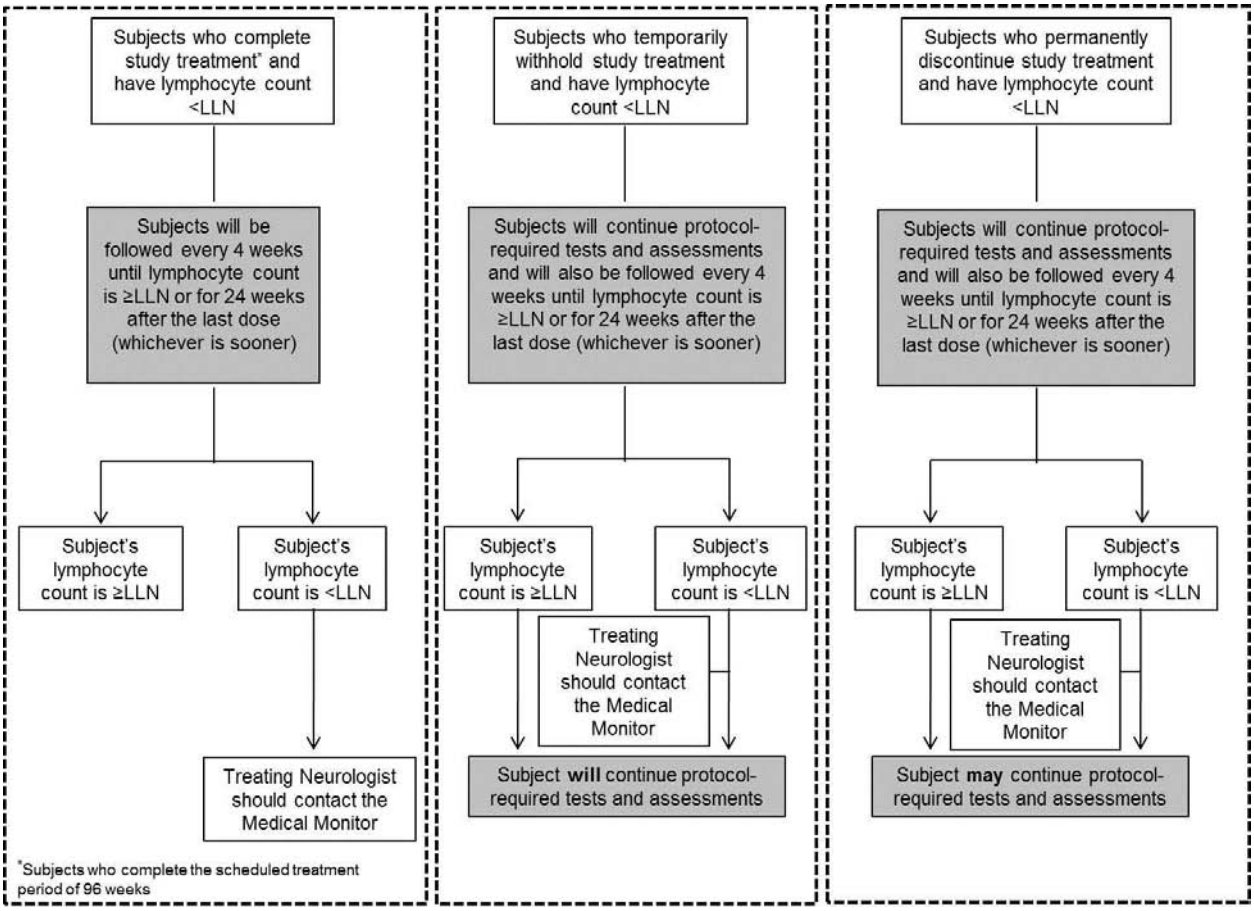
10.4.2 Schedule for Subjects Who Complete, Temporarily Withhold or Permanently Discontinue Study Treatment for Any Reason and Have a Lymphocyte Count <LLN

Subjects who complete the 96-week treatment period and who have a lymphocyte count <LLN will be followed every 4 weeks until the lymphocyte count is ≥LLN or for 24 weeks after the last dose (whichever is sooner). If the lymphocyte count does not recover after 24 weeks, the treating Neurologist should contact the Medical Monitor.

Subjects who temporarily withhold or permanently discontinue study treatment for any reason (see Section Error! Reference source not found.**) and who have a lymphocyte count <LLN will continue protocol-required tests and assessments and also undergo lymphocyte follow-up every 4 weeks until the lymphocyte count is ≥LLN or for 24 weeks after the last dose (whichever is sooner) [see** Error! Reference source not found.**]. If the lymphocyte count does not recover after 24 weeks, the treating neurologist should contact the Medical Monitor.**

See Figure 1 for a schedule for subjects who complete, temporarily withhold, or permanently discontinue study treatment for any reason and who have a lymphocyte count <LLN.

Figure 1: Schedule for Subjects Who Complete, Temporarily Withhold, or Permanently Discontinue Study Treatment for Any Reason and Have a Lymphocyte Count <LLN



Rationale: Severe, prolonged lymphopenia is a known risk factor for PML. The rationale for this change is to enable the early identification of subjects who are at risk for developing severe, prolonged lymphopenia, and to provide additional guidance on when study treatment should be permanently discontinued in these subjects.

This change also affects Section 4.1 Study Schematic; Table 1, Study Activities for Study 109MS306; Table 3, Blood Volumes by Visit; Section 4.3.4 Study Personnel; Section 7.1, Study Overview; Section 7.2, Overall Study Duration and Follow-Up; Section 7.2.4, Follow-Up; Section 8.2, Exclusion Criteria; Section 11.1, Discontinuation of Study Treatment; and Section 16.7.2.2, Clinical Laboratory Abnormalities.

SUMMARY OF MAJOR CHANGES TO THE PROTOCOL

Changes to the protocol are presented chronologically. New text is shown in **bold** type; deleted text is shown with a ~~strikethrough~~.

Section 3, Synopsis

The Synopsis was revised to reflect changes made throughout the protocol

Section 4.3.1, Pharmacokinetic Assessments

Change: Text has been revised.**Now reads:**

Blood samples for PK assessments will be collected in the subset of subjects who consent to participate in the PD/PK subset. These subjects will be required to fast for approximately 10 hours prior to the PK sampling day. After a fast of approximately 10 hours, subjects must eat a standard ~~high fat~~ meal ~~(approximately 150 calories from protein, 250 calories from carbohydrate, and 500 calories from fat)~~ 30 minutes prior to BG00012 administration. Subjects should consume this meal in 30 minutes or less. BG00012 must be administered 30 minutes after the start of the meal. Subjects must swallow the BG00012 capsules whole with 240 mL (8 fluid ounces) of water or other fluids (e.g., milk or juice). No food should be allowed for at least 4 hours after dosing. Water is allowed during this period, except for 1 hour before administration through 1 hour after BG00012 administration. Blood samples (9 × 1-mL samples) will be collected after dosing via an indwelling cannula or by venipuncture. Subjects must be administered their second dose of study treatment after completion of the PK sample collection.

Rationale: Consumption of a high fat meal is not deemed necessary for PK assessments in this study population. Therefore, subjects will consume a standard meal.

This change also affects Table 2, Schedule for PK Assessments (Subset of Subjects) and Section 7.2.2, Treatment.

Section 8.1, Inclusion Criteria

Change: Text has been revised.

Now reads:

6. Must have experienced at least 1 relapse within the last 12 months prior to Day 1 or at least 2 relapses within the last 24 months prior to Day 1, with a prior brain MRI demonstrating lesions consistent with MS, or evidence of Gd-enhancing lesions of the brain on an MRI performed within the 6 weeks prior to Day 1.

Rationale:

Inclusion criterion #6 has been revised for alignment with other pediatric MS studies.

Section 8.2, Exclusion Criteria

Change: Text has been revised.

Now reads:

4. History of severe allergic or anaphylactic reactions or known drug hypersensitivity to DMF or fumaric acid esters.

…

12. Any of the following abnormal urine tests at Screening confirmed by a second urinalysis approximately 2 weeks later:

    - proteinuria (1+ or greater) **and/or spot protein/creatinine ratio (with AM void) >0.2 mg. Note: Documented benign proteinuria is not exclusionary.**
    - hematuria, without known etiology
    - glycosuria, without known etiology

Note: If a subject has a positive test at Screening and the etiology is known (e.g., due to menses or urinary tract infection in the case of hematuria or due to recent steroid use or elevated serum glucose in the case of glycosuria), a repeat test is not required.

Rationale:

Exclusion criterion #4 has been revised for alignment with other MS studies. Exclusion criterion #12 has been revised for alignment with other pediatric MS studies to clarify that subjects with benign proteinuria will not be excluded.

This change also affects Section 10.3.4, Abnormal Urinalyses That Require Additional Evaluation.

SUMMARY OF MINOR CHANGES TO THE PROTOCOL

The following minor changes were made to the protocol:

- The version number and date were updated throughout the protocol.
- Typographical errors and formatting were corrected throughout the protocol.
- Signatory information was revised for alignment with current practice.
- Section 1, Sponsor Information, was updated.
- Section 2, List of Abbreviations, was updated.
- Revisions have been made to the following sections for accuracy, consistency and/or clarification:
  - Section 5.1.2, Relevant Clinical Experience With BG00012
  - Section 5.2, Study Rationale
  - Section 7.2.5, Relapses
  - Section 10.1.2, Interferon β-1a (Avonex)
  - Section 13.1, Laboratory Efficacy Assessments
  - Section 13.1.2, Clinical Efficacy Assessments
  - Section 16.6.2, Method of Analysis
  - Section 17.1, Declaration of Helsinki
  - Section 19.1.1, Contract Research Organization
  - Section 19.1.5, Central Facility for Other Assessments

Biogen Idec MA Inc.
14 Cambridge Center
Cambridge, MA 02142, USA

Biogen Idec Research Limited
Innovation House
70 Norden Road
Maidenhead Berkshire
SL6 4AY
United Kingdom

AMENDMENT SUMMARY

Biogen Idec Protocol 109MS306

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

Version 2

Date: 10 February 2014

EUDRA CT Number: 2013-002318-11

Version 2 of the protocol has been prepared for this amendment, which supersedes Version 1.

PRIMARY REASON FOR AMENDMENT

The primary reason for this amendment to Protocol 109MS306 is to add blood sample volumes to address the 2008 European Union (EU) Guidance for pediatric studies in which sample blood volume collection is recommended to be included in the protocol.

New text is shown in **bold** type; deleted text is shown with a ~~strikethrough~~.

Section 4.3.3, Blood Volumes

Now reads:

Every effort was made to collect the minimum blood volume needed per protocol assessment. The blood volumes required for this study do not exceed the recommended pediatric blood volume limits for sampling, i.e., volumes do not exceed 3% of the total blood volumes during a period of 4 weeks and volumes do not exceed 1% at any single visit [European Commission 2008]. For example, in a 30-kg child (the lowest possible weight permitted in this study), it was estimated that 1% of the total volume would be approximately 21 mL. Children weighing more than 30 kg would have higher permitted amounts. The total blood volumes drawn at each visit are provided in Table 3. The approximate amount of blood drawn over the entire study period will range from 68.5 mL from subjects not in the PD/PK subset and 115 mL from subjects who participate in the PD/PK subset.

Rationale: The EU requirements for pediatric studies [European Commission 2008] requested that blood sampling volumes be described and justified in the protocol. The blood sample volumes were included in the informed consent but not in Version 1 of the protocol; therefore, Section 4.3.3, Blood Volumes was added to Version 2 of the protocol.

Table 3: Blood Volumes by Visit

		Open-Label, Active-Controlled Treatment Period											End of Study/ Early Withdrawal	Safety Follow-Up Visit[2]	Unscheduled Relapse Assessment Visit[3]
Week	**Screening Visit (Within 6 Weeks of Baseline)**	**Baseline Visit (Day 1)**	**Wk 2 ±5D Safety Phone Call[4]**	**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**	**Wk 96 ± 5D**	**Wk 100 ± 5D**	
Subjects **not** in the PD/PK subset: Blood Draw Volume (mL)	10.0	9.0	0.0	2.5	2.5	2.5	4.0	2.5	9.0	2.5	2.5	2.5	9.0	7.5	2.5
Subjects **in** the PD/PK subset: Blood Draw Volume (mL)	12.5	14.0	0.0	16.5	2.5	7.5	9.0	2.5	14.0	2.5	7.5	2.5	14.0	7.5	2.5

Wk = week.

SUMMARY OF MAJOR CHANGES TO THE PROTOCOL

Changes to the protocol are presented chronologically. New text is shown in **bold** type; deleted text is shown with a ~~strikethrough~~.

Section 4.3.1, Pharmacokinetic Assessments

Change: The text was updated to reflect the blood samples to be collected.

Now reads:

Blood samples (~~maximum total of 16 mL~~**9 × 1-mL samples**) will be collected after dosing via an indwelling cannula or by venipuncture.

Rationale: The text was revised to provide updated blood volume to be collected.

Section 4.3.2, Pharmacodynamic Assessments

Change: The text was updated to reflect the blood samples to be collected.

Now reads:

Samples for the PD assessments will be collected between 4 and 10 hours after dosing **(7 × 5-mL samples) and at Screening (1 × 2.5-mL sample)**.

Rationale: The text was revised to provide updated blood volume to be collected.

SUMMARY OF MINOR CHANGES TO THE PROTOCOL

The following minor changes were made to the protocol, as appropriate:

- The version number and date were updated throughout the protocol.
- The Synopsis was revised to reflect changes made throughout the protocol.
- Text from the current version of the Investigator's Brochure was used to update Section 5.1.2, Relevant Clinical Experience With BG00012, for this protocol.
- Text from the Investigational Medicinal Product Dossier was used when referring to a reference in Section 5.3, Rationale for Dose and Schedule Selection, in this protocol.
- The European Commission has approved Tecfidera as a treatment for people with MS in the EU. This approval was added to the text of the protocol.
- A new table (Table 3) was added, requiring correction of table numbers throughout the protocol.
- Typographical errors were fixed and edits were made for clarity.