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SPONSOR SIGNATURE PAGE

Protocol 109MS311 was approved by:

[redacted], MD

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Date

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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
ARR	annualized relapse rate
AST	aspartate transaminase
BID	twice daily
BUN	blood urea nitrogen
CNS	central nervous system
CRO	contract research organization
DHA	Directions for Handling and Administration
DMF	dimethyl fumarate
eCRF	electronic case report form
EDSS	Expanded Disability Status Scale
GCP	Good Clinical Practice
GI	gastrointestinal
ICF	informed consent form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IV	intravenous
IVMP	intravenous methylprednisolone
LLN	lower limit of normal
MMF	monomethyl fumarate
MRI	magnetic resonance imaging
MS	multiple sclerosis
PK	pharmacokinetics
PTH	parathyroid hormone
RRMS	relapsing-remitting multiple sclerosis
SABR	Safety and Benefit-Risk Management
SAE	serious adverse event
SUSAR	suspected unexpected serious adverse reaction
TID	3 times daily
ULN	upper limit of normal
US	United States
WBC	white blood cell

3. SYNOPSIS

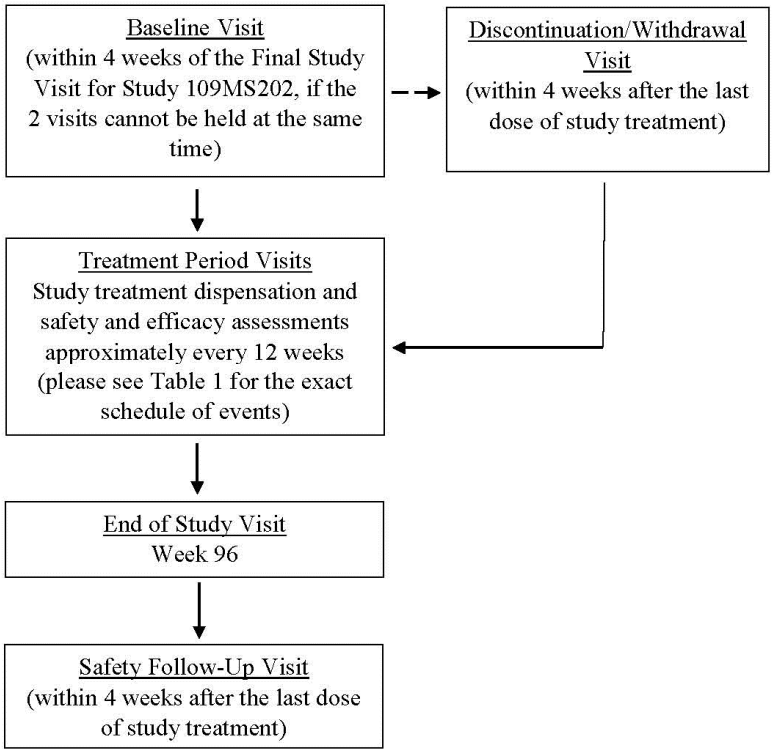
Protocol Number:	109MS311
Protocol Title:	A Multicenter Extension Study to Determine the Long-Term Safety and Efficacy of BG00012 in Pediatric Subjects With Relapsing-Remitting Multiple Sclerosis
Version Number	3.0
Name of Study Treatment:	BG00012 (Dimethyl Fumarate; Tecfidera®)
Study Indication:	Relapsing-remitting multiple sclerosis (RRMS)
Study Rationale	With no approved multiple sclerosis (MS) therapies in the pediatric population, there exists a significant unmet need for approved treatment options. In the adult population, BG00012 is a therapeutic option with demonstrated efficacy and acceptable tolerability and safety profiles combined with the ease of oral administration. BG00012 was first approved (as Tecfidera) in the United States in 2013 for the treatment of adult patients with relapsing forms of MS and has since been approved in Europe and other regions. This study will extend therapy from the ongoing BG00012 pediatric Study 109MS202, in which the pharmacokinetics and efficacy of BG00012 in pediatric subjects with RRMS are being evaluated, in order to further evaluate the long-term safety and efficacy of BG00012 in these subjects.
Phase of Development:	3
Study Objectives and Endpoints:	The primary objective of the study is to evaluate the long-term safety of BG00012 in subjects who completed Study 109MS202. The primary endpoint that relates to this objective is the incidence of adverse events (AEs), serious AEs, and discontinuations of study treatment due to an AE Secondary objectives and endpoints are as follows: To evaluate the long-term efficacy of BG00012. • The total number of new or newly enlarging T2 hyperintense lesions on brain magnetic

	resonance imaging scans • The annualized relapse rate • The proportion of subjects who experience 1 or more relapses during the study period To describe the long-term MS outcomes in subjects who completed Study 109MS202. • The degree of disability as measured by the Expanded Disability Status Scale (EDSS) and disability progression (as measured by at least a 1.0-point increase on the EDSS from baseline EDSS ≥1.0 that is sustained for 24 weeks or at least a 1.5-point increase on the EDSS from baseline EDSS = 0 that is sustained for 24 weeks)
Study Design:	This is a multicenter, open-label extension of Study 109MS202 that is designed to evaluate the long-term safety and efficacy of BG00012 in pediatric subjects.
Study Location:	Approximately 20 sites globally are planned.
Number of Planned Subjects:	The number of subjects who are eligible for this study will be determined by the number of subjects who have completed Study 109MS202 as per protocol.
Study Population:	This study will be conducted in subjects who completed Study 109MS202 as per protocol. Detailed criteria are described in Section 8.
Treatment Groups:	All subjects will receive BG00012 240 mg twice daily (2 capsules of 120 mg).
Duration of Treatment and Follow-up:	The treatment period is 96 weeks (2 years) and the Follow-Up Safety Visit will take place 4 weeks after the last dose of study treatment.

4. STUDY SCHEMATIC AND SCHEDULE OF ACTIVITIES FOR STUDY 109MS311

4.1. Study Schematic

Figure 1: Study Design



4.2. Schedule of Activities

Table 1: Study Activities for Study 109MS311

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

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

[1] Tests and assessments must be completed prior to study treatment dispensation.

[2] The Final Study Visit for Study 109MS202 will serve as the Baseline Visit for this extension study. The Final Study Visit from Study 109MS202 can be within 4 weeks of the Baseline Visit for Study 109MS311 if the 2 visits cannot be combined.

[3] Written informed consent from the subject's parents or legal guardians and assent from the subject, if appropriate, must be obtained prior to performing any study-related procedures.

[4] MS-related medical history will include complete MS history of disease, MS diagnostic criteria, MS signs and symptoms, and MS treatment history.

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

[6] For females of childbearing potential. Results must be known prior to study treatment dispensation.

[7] Urine cytology must be performed at all visits indicated if a subject experiences hematuria (of unknown etiology) at 2 consecutive visits. If urine cytology is positive for malignant cells, the subject must permanently discontinue study treatment.

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

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

[10] The time between the Week 24 MRI and the Week 16 MRI must be the same as the time between the Day 0 MRI and Week -8 MRI in Study 109MS202 within a window of ±3 days. For example, if the Day 0 and Week -8 MRIs for a particular subject occurred 8 weeks apart in Study 109MS202, then the Week 24 MRI in Study 109MS311 should be 8 weeks ± 3 days after the Week 16 MRI. If necessary, the Week 24 MRI may be conducted separately from the Week 24 clinic visit. Similarly, the time between the Week 72 MRI and the Week 64 MRI must be the same as the time between the Day 0 MRI and Week -8 MRI in Study 109MS202 within a window of ±3 days. If necessary, the Week 72 MRI may be conducted separately from the Week 72 clinic visit.

[11] Initial dispensation of study treatment may require an additional visit on or around Day 7. Laboratory results must be evaluated and eligibility confirmed prior to dispensation of study treatment.

Table 2: Additional Study Activities for Study 109MS311

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

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

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

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

[3] Subjects who complete, temporarily withhold, or permanently discontinue study treatment for any reason and have a lymphocyte count <LLN will continue protocol-required visits and assessments and be followed every 4 weeks for 24 weeks and then every 3 months (**unless clinically indicated more often or at the Investigator's discretion**) until the lymphocyte count is ≥LLN or for 52 weeks after the last dose, or until one of the following occurs: 1) the subject continues on commercial BG00012 following study withdrawal/completion, or 2) the subject is initiated on another MS disease-modifying therapy. Note: lymphocyte counts ≥LLN at 2 consecutive visits are required.

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

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

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

[7] For females of childbearing potential.

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

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

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

4.3. Additional Information

4.3.1. Blood Volumes

Every effort must be made to collect the minimum blood volume needed per protocol. 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 or 1% at any single visit [European Commission 2008]. For example, in a 30-kg child (the lowest weight permitted in this study), it is 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 will be 5 mL or less. The approximate amount of blood to be drawn over the entire study period will be 50 mL.

5. INTRODUCTION

5.1. Overview of Multiple Sclerosis

Multiple sclerosis (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. MS primarily affects adults, with clinical onset occurring most commonly between the ages of 20 and 40 years [O'Connor and Canadian Multiple Sclerosis Working Group 2002]. Approximately 2.2% to 4.4% of all MS cases have onset during adolescence or childhood [Chitnis 2011], with girls affected more than boys, and most cases being relapsing-remitting multiple sclerosis (RRMS).

5.2. Current Therapies for Multiple Sclerosis

Despite the availability of several therapies approved for the treatment of adult patients with MS, there remains an unmet need for safe and effective treatments for pediatric patients with MS. Currently, there are no treatments that are approved to treat pediatric MS, and no randomized controlled clinical studies have been completed that demonstrate that the agents available for treatment of MS in adults are safe and effective in pediatric patients. Moreover, there are no data on the pharmacological characterization of any of the disease-modifying MS therapies in pediatric patients. Thus, current treatment options for pediatric patients with MS are adapted from therapeutic paradigms for adult patients, with dosing recommendations based solely on adult subject data and expert opinion.

The most commonly used therapies in the pediatric population are interferons and glatiramer acetate [Waldman 2011]. Relative to placebo, these agents have been shown to reduce relapse rate by approximately 30% and may decrease disease progression [Jacobs 2000; Johnson 1995; Paty and Li 1993; PRISMS Study Group 2001; The IFNB Multiple Sclerosis Study Group 1993].

Other therapies currently approved for use in adults with MS include the following:

- Natalizumab: a humanized monoclonal antibody directed against α4 integrins [Polman 2006]
- Fingolimod: a selective oral immunosuppressant that is metabolized to a functional antagonist of sphingosine 1-phosphate receptors on lymphocytes [Kappos 2010]
- Mitoxantrone: a synthetic antineoplastic anthracenedione that intercalates into DNA, interfering with its synthesis and repair [Chitnis 2012]
- Teriflunomide: an immunosuppressive drug inhibiting pyrimidine synthesis by blocking dihydroorotate dehydrogenase [O'Connor 2011]
- Alemtuzumab: a monoclonal antibody directed against cluster of differentiation 52 [Cohen 2012]

- Tecfidera®: a dimethyl fumarate (DMF)-containing drug that activates the Nrf2 antioxidant response pathway to mitigate inflammatory stress [Ghoreschi 2011; Nguyen 2003]

5.3. Profile of Previous Experience With BG00012

5.3.1. Nonclinical Safety Experience

Nonclinical safety studies were performed to support the development of BG00012 (Tecfidera®) 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, impaired fertility, or teratogenicity. Repeat-dose toxicology studies were performed in rodents (mouse and rat) and non-rodents (dog and monkey). Findings in these studies in the liver, forestomach, and testis concluded that there is limited concern related 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 lifetime carcinogenicity studies, renal tumors were attributed to a rodent-specific exacerbation of nephropathy.

See the Investigator's Brochure for more detailed information on nonclinical studies as well as information on nonclinical pharmacology and pharmacokinetic (PK) studies.

5.3.2. Clinical Experience

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

The efficacy and safety of BG00012 are well established and based on data from Phase 2 and 3 placebo-controlled safety and efficacy studies (Studies C-1900 Part 1, 109MS301 [DEFINE], and 109MS302 [CONFIRM]) and their uncontrolled extensions (Studies C-1900 Part 2 and 109MS303 [ENDORSE]). In these studies, over 2500 subjects received treatment with BG00012. The overall exposure to BG00012 in these subjects was approximately 6100 subject-years as of September 2013.

Results of the Phase 3 clinical studies demonstrate that BG00012 240 mg BID or 3 times daily (TID) is an efficacious treatment for RRMS. In these Phase 3 studies, BG00012 resulted in a significant reduction in the risk of relapse and annualized relapse rate (ARR), and the treatment had a positive effect on 12-week Expanded Disability Status Scale (EDSS) disability progression, with statistical significance achieved in Study 109MS301. A robust, statistically significant effect was also observed on magnetic resonance imaging (MRI) endpoints, including the number and volume of new or newly enlarging T2 hyperintense lesions, gadolinium-enhancing lesions, and new or newly enlarging T1 hypointense lesions compared with placebo. Efficacy was seen as early as 6 months and maintained over the 2-year span of Studies 109MS301 and 109MS302. In the ongoing Phase 3, uncontrolled extension Study 109MS303 (ENDORSE), which includes subjects who completed Studies 109MS301 or 109MS302, sustained efficacy was observed through 5 years of treatment, and the safety profile of continued BG00012 treatment was consistent with that observed in the 2-year Phase 3 studies.

Overall, safety data from the clinical development program showed that BG00012 was well tolerated and has an acceptable safety profile. In the BG00012 240 mg BID group, the most common adverse events (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 dose regimens of BG00012. Mean WBC and lymphocyte counts then plateaued and remained stable, even during longer periods of observation of approximately 5.25 years. 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. With open-label and marketed use of BG00012, progressive multifocal leukoencephalopathy has been observed in the setting of severe and prolonged lymphopenia. There has been no other evidence of increased risk of infections, serious infections, or other opportunistic infections (in open-label and marketed use of BG00012).

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 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 (PTH), or 1,25-dihydroxyvitamin D. In the Phase 3 studies (Studies 109MS301 and 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 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 over time in β2-microglobulinuria and microalbuminuria, which are more sensitive and specific markers of renal tubular dysfunction, 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.

5.4. Study Rationale

In adult subjects with RRMS, BG00012 demonstrated efficacy and had an acceptable safety profile in 2 Phase 3 studies, Studies 109MS301 and 109MS302. With no approved therapies, there exists a significant unmet need for MS treatment options in the pediatric population. In the adult population, BG00012 is a therapeutic option with demonstrated efficacy and acceptable tolerability and safety profiles combined with the ease of oral administration. This study will extend therapy from the ongoing BG00012 pediatric Study 109MS202, in which the PK and efficacy of BG00012 in pediatric subjects with RRMS are being evaluated, in order to further evaluate the long-term safety and efficacy of BG00012 in these subjects.

5.5. Rationale for Dosing Regimen

The BG00012 dosage selected for this study (240 mg BID) is the approved BG00012 dosing regimen in adult patients with MS.

In adults, after oral administration, DMF is well absorbed and extensively metabolized by esterases to its primary active metabolite, monomethyl fumarate (MMF). As a result, DMF is not quantifiable in plasma, and all PK analyses have been performed based on MMF concentrations. Downstream metabolism of DMF/MMF occurs through the tricarboxylic acid cycle, with exhalation of carbon dioxide serving as a major route of elimination. The PK of BG00012 has been thoroughly evaluated in adults. Body weight is a significant covariant for BG00012 exposure in that the area under the curve and the maximum concentration are decreased by 2% and 1.4%, respectively, for every 1-kg increase in body weight within the weight range of 45 to 112 kg. This translates to a 2-fold increase in exposure levels as body weight decreases from 112 to 45 kg.

Despite the effect of body weight changes on the exposure levels of BG00012, data from the pivotal Phase 3 studies suggested that the variability in exposure did not affect safety and efficacy measures in adult patients. Notably, the efficacy and tolerability profiles of BG00012 at 240 mg BID were indistinguishable from those at 240 mg TID, with a wide range of overlapping exposures between the 2 dosages.

A Phase 1 PK study (Study 109MS101) revealed no apparent differences in the kinetics of BG00012 across the age range of 21 to 51 years once the weight relationship was accounted for.

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. These findings suggest that the disposition of BG00012 is unlikely to change with age for the target population (10 to 18 year olds).

Taken together, these data indicate that 240 mg BID, the approved dose in adults, should be tolerable in pediatric subjects meeting the inclusion criteria for the parent study (109MS202) and the current extension study. As such, this dose was chosen for the parent and current studies.

6. STUDY OBJECTIVES AND ENDPOINTS

6.1. Primary Objective and Endpoint

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

The primary endpoint that relates to this objective is the incidence of AEs, serious AEs (SAEs), and discontinuations of study treatment due to an AE.

6.2. Secondary Objectives and Endpoints

A secondary objective is to evaluate the long-term efficacy of BG00012.

The endpoints that relate to this objective are the total number of new or newly enlarging T2 hyperintense lesions on brain MRI scans, the ARR, and the proportion of subjects who experience 1 or more relapses during the study period.

Another secondary objective is to describe the long-term MS outcomes in subjects who completed Study 109MS202.

The endpoint that relates to this objective is the degree of disability as measured by the EDSS and disability progression (as measured by at least a 1.0-point increase on the EDSS from baseline EDSS ≥1.0 that is sustained for 24 weeks, or at least a 1.5-point increase on the EDSS from baseline EDSS = 0 that is sustained for 24 weeks).

7. STUDY DESIGN

7.1. Study Overview

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

See Figure 1 for a schematic of the study design.

7.2. Overall Study Duration and Follow-Up

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

7.2.1. Enrollment

Subject eligibility for the study will be determined at the Final Study Visit for Study 109MS202 or within 4 weeks prior to study entry. The Final Study Visit for Study 109MS202 will serve as the Baseline Visit for this study.

7.2.2. Treatment

Eligible subjects will report to the study site to receive study treatment approximately every 12 weeks for up to 96 weeks (2 years).

7.2.3. Follow-Up

Subjects are to return to the study site for a follow-up visit 4 weeks after their last treatment visit (Visit 10 at Week 96 [±5 days]).

Subjects who withdraw prematurely from the study will complete the Early Withdrawal Visit, which should be conducted as soon as possible and no later than 4 weeks after the subject's last dose of study treatment. Subjects who withdraw prematurely should be encouraged to complete the Safety Follow-Up Visit 4 weeks after the last dose of study treatment.

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) will be followed every 4 weeks for 24 weeks and then every 3 months (**unless clinically indicated more often or at the Investigator's discretion**) until the lymphocyte count is ≥LLN or for 52 weeks after the last dose, or until one of the following occurs: 1) the subject continues on commercial BG00012 following study withdrawal/completion, or 2) the subject is initiated on another MS disease-modifying therapy.

7.3. Relapses

Suspected relapses during this study will be evaluated and confirmed according to the protocol by the Investigator. 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 Investigator. 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 would not be treated with intravenous methylprednisolone (IVMP) within the protocol.

If a subject experiences new neurologic symptoms, then the subject or caregiver must contact the Investigator 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 Investigator within 5 days of the onset of the potential relapse. The Investigator is to perform a relapse assessment and obtain an EDSS score. To ensure consistency across sites, Investigators must undergo a standardized training session on EDSS scoring prior to enrollment of subjects at their site. New objective findings on neurological examination performed by the Investigator are required to determine if a protocol-defined relapse has occurred. Subjects may not begin corticosteroid treatment of the relapse per protocol until the Investigator has examined them.

Treatment of an acute event of relapse with IVMP may proceed at the discretion of the Investigator and will not affect the subject's eligibility to continue in the study. If an Unscheduled Relapse Assessment Visit occurs within 7 days of a scheduled clinic visit, then the 2 visits may take place on the same day; however, MRIs must be conducted according to the schedule outlined in Section 4.2.

7.4. Study Stopping Rules

Biogen may terminate this study at any time, after informing the Investigators. Biogen will notify Investigators when the study is to be placed on hold, completed, or terminated.

7.5. End of Study

The end of study is last subject, last visit for final collection of data.

8. SELECTION OF SUBJECTS

8.1. Inclusion Criteria

To be eligible to participate in this study, candidates must meet the following eligibility criteria at 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 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, as per protocol, the previous BG00012 clinical study 109MS202 and remain on BG00012 treatment at 240 mg BID.
3. All female subjects of childbearing potential and all male subjects must practice effective contraception during the study and for at least 30 days after their last dose of study treatment. For further details of contraceptive requirements for this study, please refer to Section 15.5.

8.2. Exclusion Criteria

Candidates will be excluded from study entry if any of the following exclusion criteria exist at Day 1 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 the parent Study 109MS202, including laboratory test abnormalities or current clinically significant conditions that in the opinion of the Investigator would have excluded the subject's participation from the parent study. The Investigator must re-review the subject's medical fitness for participation and consider any factors that would preclude treatment.
3. Subjects from Study 109MS202 who could not tolerate study treatment.
4. History of malignancy.
5. History of severe allergic or anaphylactic reactions or known drug hypersensitivity to DMF or fumaric acid esters.
6. Any of the following abnormal blood tests:
   - ALT >3 times the ULN
   - AST >3 times the ULN
   - Gamma-glutamyl-transferase >3 times the ULN

- Creatinine >1.2 times the ULN
- WBC count <2000/mm^3
- Lymphocyte count <500/mm^3

7. Female subjects considering becoming pregnant or breastfeeding while in the study or who are pregnant or breastfeeding.
8. Other unspecified reasons that, in the opinion of the Investigator or Biogen, make the subject unsuitable for enrollment.

9. ENROLLMENT AND REGISTRATION

9.1. Screening and Enrollment

Subjects (or their legally authorized representative [e.g., parent or legal guardian], where applicable) must provide informed consent before any screening tests are performed (see Section 17.3). When a subject signs the informed consent form (ICF), that subject is considered to be enrolled in the study. Subjects who have a nonclinically significant out-of-range laboratory result may be rescreened 1 time only at the discretion of the Investigator. 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.

9.2. Registration of Subjects

Subjects will be registered at Day 1, after all baseline assessments have been completed and after the Investigator has verified that the subjects are eligible per criteria in Sections 8.1 and 8.2. No subject may begin treatment prior to assignment of a unique identification number (registration). Any subject identification numbers that are assigned will not be reused even if the subject does not receive treatment.

Refer to the Study Reference Guide for details on registration.

9.3. Blinding Procedures

Not applicable.

10. DISCONTINUATION OF STUDY TREATMENT AND/OR WITHDRAWAL OF SUBJECTS FROM THE STUDY

10.1. Discontinuation of Study Treatment

A subject *must* permanently discontinue BG00012 for any of the following reasons:

- The subject becomes pregnant. Study treatment must be discontinued immediately. Report the pregnancy according to the instructions in Section 15.4.1.
- The subject experiences a medical emergency that necessitates permanent discontinuation of study treatment.
- The subject has lymphocyte count <500/mm^3 for 6 months as outlined in Table 4 and Table 5 .
- The subject experiences a protocol-specified change in laboratory values that necessitates permanent discontinuation of treatment as outlined in Table 3 and Table 4.
- The subject cannot tolerate study treatment.
- The subject receives any of the disallowed concomitant medications for this study.
- The subject or subject's parent/legal guardian desires to discontinue treatment.
- 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 discontinue treatment may remain in the study and continue protocol-required tests and assessments.

10.2. Withdrawal of Subjects From Study

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

- The subject or the subject's parent/guardian withdraws consent.
- The subject enrolls into another interventional clinical study.
- 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.

11. STUDY TREATMENT USE

11.1. Regimen

BG00012 will be taken orally at a dose of 240 mg BID.

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.

Refer to and follow the Directions for Handling and Administration (DHA).

11.2. Modification of Dose and/or Treatment Schedule

11.2.1. Dosing Interruption for Abnormal Laboratory Values

BG00012 must be temporarily withheld and/or permanently discontinued when any of the following laboratory values meet the threshold limits defined in Table 3 (laboratory abnormalities that require immediate and permanent discontinuation of study treatment are also specified in Table 3).

Table 3: Laboratory Criteria Requiring Withholding or Permanent Discontinuation of Treatment

Laboratory Parameter	Laboratory Result	Required Action
AST (SGOT) or ALT (SGPT)	>3 × ULN	The Investigator should repeat the test as soon as possible. If the retest value confirms AST or ALT >3 × ULN, then the study treatment must be withheld. If the value remains >3 × ULN for ≥4 weeks after discontinuation of study treatment, then the subject **must *permanently* discontinue study treatment, 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, then 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, and the event must be recorded as an AE.**

Laboratory Parameter	Laboratory Result	Required Action
WBC	$<2000/mm^3$	The Investigator should repeat the test as soon as possible. If the retest value confirms that WBC count is $<2000/mm^3$, then 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, 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 retest confirms microscopic hematuria without known etiology, then the study treatment must be withheld, and urine cytology performed. If hematuria persists for ≥4 weeks after discontinuation or if cytology is positive for malignant cells, then the subject **must *permanently* discontinue study treatment, 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; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; ULN = upper limit of normal; WBC = white blood cell.

Table 4 describes the management of lymphocytes <LLN for subjects during and after study treatment.

Table 4: Management of Lymphocyte Count <LLN

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 on study treatment	<500/mm^3	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 3 months (**unless clinically indicated more often or at the Investigator's discretion**) until the lymphocyte count is ≥LLN[1] or for 52 weeks after the last dose, or until one of the following occurs: 1) the subject continues on commercial BG00012 following study withdrawal/completion, or 2) the subject is initiated on another MS disease-modifying therapy.

LLN = lower limit of normal; MS = multiple sclerosis.
[1] Lymphocyte counts ≥LLN at 2 consecutive visits are required.

While dosing is withheld, subjects will continue tests and assessments according to Table 1 (and may also undergo additional assessments to evaluate the laboratory abnormality as per the Investigator's standard practice). In addition, subjects (whether on study treatment, having dosing temporarily withheld, or permanently discontinued) must have the abnormal laboratory result rechecked at the central laboratory as follows:

- For all analytes, with the exception of lymphocytes, results will be rechecked at least every 2 weeks 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.
- For lymphocytes, results will be rechecked at least every 4 weeks for 24 weeks and then every 3 months (**unless clinically indicated more often or at the Investigator's discretion**) until the lymphocyte count is ≥LLN or for 52 weeks after the last dose, or until one of the following occurs: 1) the subject continues on commercial BG00012 following study withdrawal/completion, or 2) the subject is initiated on another MS disease-modifying therapy. Depending on the severity and clinical significance of the abnormality, the Investigator may need to perform the retests more frequently.

11.2.2. Resumption of Study Treatment Dosing

Resumption of BG00012 treatment is to be considered on a case-by-case basis and must be discussed with the Medical Monitor.

Resumption of study treatment after an interruption

Subjects who are allowed to resume BG00012 dosing after an interruption of ≥2 weeks will restart dosing at a reduced dosage for 1 week. Subjects will take one 120-mg capsule BID for 1 week. After 1 week at the reduced dose, subjects will resume taking two 120-mg capsules BID.

11.2.3. 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 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, then 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 3) on a third occasion must discontinue dosing for the remainder of the study.

11.2.4. 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, then 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 AM void). If the spot protein/creatinine ratio is >0.2 mg/mg, then the subject should be fully investigated for possible causes and referred for evaluation by a nephrologist if appropriate in the opinion of the Investigator.

11.2.5. Treatment Schedule for Subjects With Abnormal Lymphocyte Count

11.2.5.1. 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 Criteria 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 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.

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 for 24 weeks and then every 3 months (**unless clinically indicated more often or at the Investigator's discretion**) until the lymphocyte count is ≥LLN or for 52 weeks after the last dose, or until one of the following occurs: 1) the subject continues on commercial BG00012 following study withdrawal/completion, or 2) the subject is initiated on another MS disease-modifying therapy [see Table 2]. During the lymphocyte follow-up, if the lymphocyte count does not recover to above LLN after 24 weeks, the treating neurologist should contact the Medical Monitor.

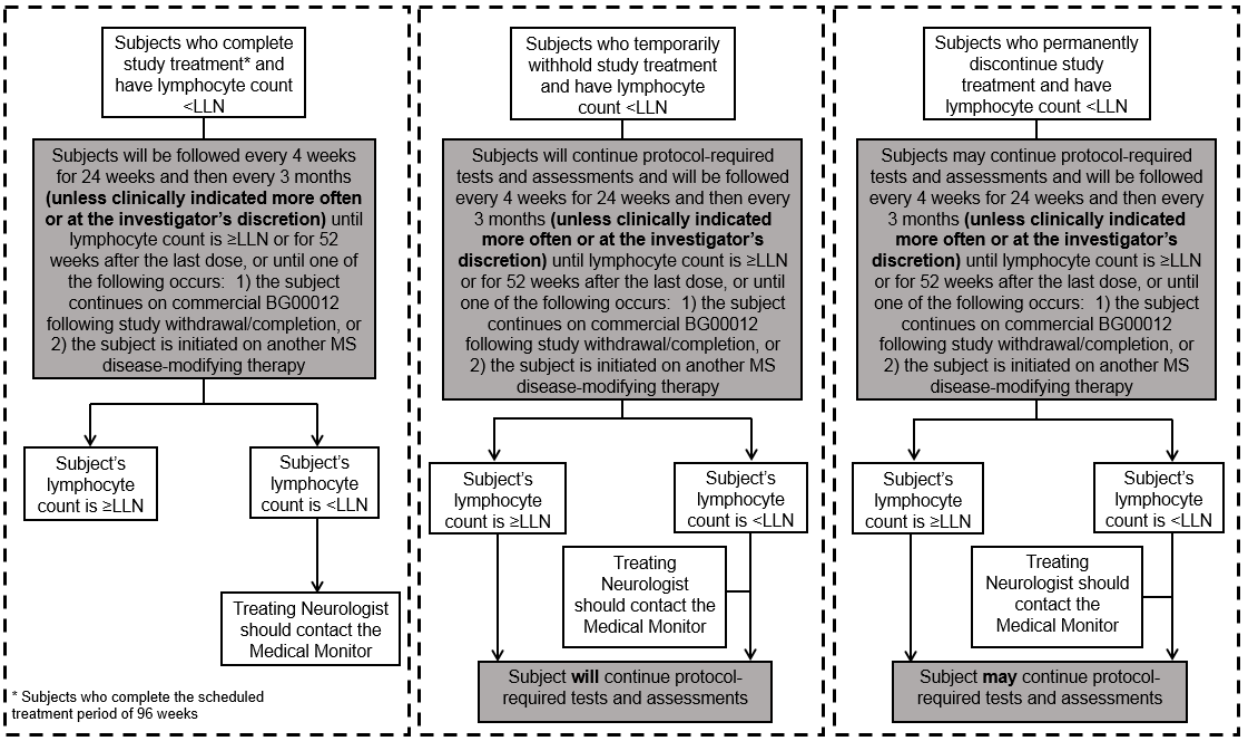
11.2.5.2. Schedule for Subjects Who Complete, Temporarily Withhold, or Permanently Discontinue Study Treatment for Any Reason and Have a Lymphocyte Count <LLN

Subjects who complete the 96-week treatment period and who have a lymphocyte count <LLN will be followed every 4 weeks for 24 weeks and then every 3 months (**unless clinically indicated more often or at the Investigator's discretion**) until the lymphocyte count is ≥LLN or for 52 weeks after the last dose, or until one of the following occurs: 1) the subject continues on commercial BG00012 following study withdrawal/completion, or 2) the subject is initiated on another MS disease-modifying therapy. During the lymphocyte follow-up, if the lymphocyte count does not recover to above LLN 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 10.1) 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 and then every 3 months (**unless clinically indicated more often or at the Investigator's discretion**) until the lymphocyte count is ≥LLN or for 52 weeks after the last dose, or until one of the following occurs: 1) the subject continues on commercial BG00012 following study withdrawal/completion, or 2) the subject is initiated on another MS disease-modifying therapy [see Table 4]. During the lymphocyte follow-up, if the lymphocyte count does not recover to above LLN after 24 weeks, the treating neurologist should contact the Medical Monitor.

See Figure 2 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 2: Schedule for Subjects who Complete, Temporarily Withhold, or Permanently Discontinue Study Treatment for Any Reason and Have a Lymphocyte Count <LLN



LLN = lower limit of normal.

11.2.6. Dosage Reductions

Dosage reduction will be allowed only for subjects **who are unable to tolerate BG00012 treatment due to flushing and/or GI disturbances** (dosage reductions will not be allowed for abnormal laboratory values; for management of abnormal laboratory values, see Sections 11.2.1, 11.2.2, and 11.2.3). Subjects who do not tolerate BG00012 treatment will reduce their dosage by taking one 120-mg capsule BID for up to 4 weeks. Within 4 weeks at the reduced dosage, subjects will resume taking the full dose of 240 mg (two 120-mg capsules) BID. If the subject is still unable to tolerate BG00012 treatment at the 240-mg BID dose, the subject may continue in the study taking the 120-mg BID dose.

11.3. 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.

11.4. Compliance

Compliance with treatment dosing is to be monitored and recorded by site staff. Compliance for BG00012 will be monitored by capsule count and captured in the eCRF.

11.5. Concomitant Therapy and Procedures

11.5.1. Concomitant Therapy

A concomitant therapy is any drug or substance administered between the Baseline Visit and the Safety Follow-Up Visit.

11.5.1.1. Allowed Concomitant Therapy

Symptomatic therapy, such as treatment for spasticity, depression, or fatigue, is not restricted but should be consistent for the duration of the study.

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

11.5.1.2. Disallowed Concomitant Therapy

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

- Any alternative drug treatments directed toward the treatment of MS, such as immunomodulatory treatments (including but not limited to, interferon-beta, glatiramer acetate, natalizumab, fingolimod, teriflunomide, alemtuzumab, mitoxantrone, mycophenolate mofetil, laquinimod, cyclophosphamide, methotrexate, azathioprine, cyclosporine, etc.) and 4-aminopyridine or related products with the exception of acute management of protocol-defined relapse (as described in Section 11.5.2).
- 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 11.5.2. Steroids that are administered by nonsystemic routes (e.g., topical, inhaled) are allowed.
- Total lymphoid irradiation, cladribine, T-cell or T-cell receptor vaccination, any therapeutic monoclonal antibody, intravenous (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 10.2.

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

11.5.2. 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 Final Study Visit.

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

11.5.3. Treatment of Relapses on Scheduled or Unscheduled Visits

The only protocol-approved treatment for relapse in this study is either 3 or 5 days with IVMP, up to 1000 mg/day. IVMP 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.

11.6. Continuation of Treatment

There is no provision for additional courses of BG00012 provided by Biogen beyond the treatment period defined in this protocol.

If and when BG00012 is commercially available at the time the study treatment period is completed, subjects will be allowed to take commercial BG00012 during the Safety Follow-Up Period if deemed appropriate by product labeling and at the discretion of their treating physician.

12. STUDY TREATMENT MANAGEMENT

Study site staff should follow the DHA for specific instructions on the handling, preparation, administration, and disposal of the study treatment. The DHA supersedes all other references (e.g., protocol).

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

12.1. 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.

12.1.1. BG00012 Preparation

BG00012 will be provided as capsules. Drug wallets will be prepared to ensure that the appropriate treatment is provided to each subject. Drug wallets will be supplied from Interactive Voice/Web Response System 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 study treatment, do not use the study treatment. The drug wallet in question should be quarantined at the study site and the problem immediately reported to Biogen.

12.1.2. BG00012 Storage

Study treatment must be stored in a secure location.

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. For the most up-to-date storage requirements, follow the instructions provided in the DHA.

12.1.3. BG00012 Handling and Disposal

The Investigator must return all used and unused drug wallets of BG00012 as instructed by Biogen unless approved for onsite destruction.

If any BG00012 supplies are to be destroyed at the study site, the institution or appropriate site personnel must obtain prior approval from Biogen by providing, in writing, the destruction policy or details of the method of destruction. After such destruction, Biogen must be notified, in writing, of the details of the study treatment destroyed (e.g., lot or kit numbers, quantities), the date of destruction, and proof of destruction.

12.1.4. BG00012 Accountability

Accountability for study treatment is the responsibility of the Investigator. 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 accidentally or deliberately destroyed or lost.

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, lost, or returned to Biogen. A written explanation must be provided for any discrepancies.

13. EFFICACY ASSESSMENTS

See Section 4 for the timing of all assessments.

13.1. Clinical Efficacy Assessments

The following clinical assessments will be performed to evaluate the efficacy of BG00012:

- Relapse assessment
- EDSS

13.2. MRI Efficacy Assessments

The following MRI efficacy assessments will be performed to evaluate the efficacy of BG00012:

- The total number of new or newly enlarging T2 hyperintense lesions from baseline as well as from the scan of the previous visit on brain MRI scans

14. SAFETY ASSESSMENTS

Refer to Section 4 for the timing of all safety assessments.

14.1. Clinical Safety Assessments

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

- Physical examinations, including body weight and height
- Vital sign measurements, including body temperature, pulse rate, and systolic and diastolic blood pressure
- 12-Lead electrocardiograms
- Concomitant therapy and procedure recording
- AE and SAE recording

14.2. Laboratory Safety Assessments

The following laboratory assessments will be performed to evaluate the safety profile of BG00012:

- Hematology: complete blood count with differential and platelet count
- Blood chemistry: sodium, potassium, chloride, bicarbonate, calcium, magnesium, phosphate, BUN, creatinine, uric acid, glucose, albumin, ALT, AST, gamma-glutamyl transferase, total bilirubin, and alkaline phosphatase
- Urinalysis: dipstick for blood, protein, and glucose (microscopic examination, if abnormal)
- Vitamin D and PTH levels

15. SAFETY DEFINITIONS, RECORDING, REPORTING, AND RESPONSIBILITIES

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 or his/her legally authorized representative and/or main caregiver must be given the names and telephone numbers of study site staff for reporting AEs and medical emergencies.

15.1. Definitions

15.1.1. 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.

Determination of whether an abnormal laboratory value meets the definition of an AE will be made by the Investigator. Although abnormal laboratory values are typically not considered AEs, the following considerations may result in an abnormal laboratory value being considered an AE:

- A laboratory test result that meets the criteria for an SAE
- A laboratory test result that requires the subject to receive specific corrective therapy
- A laboratory abnormality that the Investigator considers to be clinically significant

15.1.2. 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
- 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.)

15.1.3. 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.

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 in Section 15.1.2 is met.

15.2. Safety Classifications

15.2.1. Investigator Assessment of Events

All events must be assessed to determine the following:

- If the event meets the criteria for an SAE as defined in Section 15.1.2 .
- The relationship of the event to study treatment as defined in Section 15.2.2.
- The severity of the event as defined in Section 15.2.3.

15.2.2. 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 reasonable 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, 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 reasonable 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.

15.2.3. 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 symptoms 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 symptoms 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 symptoms may be given and/or subject hospitalized.

15.2.4. Expectedness of Events

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

15.3. Monitoring and Recording Events

15.3.1. Adverse Events

Any AE experienced by the subject between the time of first dose of study treatment in the extension study 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.

15.3.2. Serious Adverse Events

Any SAE experienced by the subject between the time of the signing of the ICF 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 Biogen Safety and Benefit-Risk

Management (SABR) or designee within 24 hours as described in Section 15.3.3. Follow-up information regarding an SAE also must be reported with 24 hours.

Subjects will be followed for all SAEs until the Safety Follow-Up Visit. Thereafter, the event should be reported to Biogen SABR or designee only if the Investigator considers the SAE to be related to study treatment.

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

15.3.3. 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 SAE that occurs between the time that the subject has signed the ICF 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. Thereafter, the event should be reported only if the Investigator considers it related to study treatment. 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 the 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 an SAE, please fax (please refer to the Study Reference Guide) or email [redacted].

15.3.3.1. Deaths

Death is an outcome of an event. The event that resulted in death should be recorded on the appropriate eCRF. All causes of death must be reported as SAEs within 24 hours of the site becoming aware of the event. The Investigator should make every effort to obtain and send death certificates and autopsy reports to Biogen SABR or designee. The term death should be reported as an SAE only if the cause of death is not known and cannot be determined.

15.3.4. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are SAEs that are unexpected and judged by the Investigator or Biogen 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.

15.4. Procedures for Handling Special Situations

15.4.1. Pregnancy

Subjects should not become pregnant during the study and for 30 days after their last dose of study treatment. If a female subject becomes pregnant, study treatment must be discontinued *immediately*.

The Investigator must report a pregnancy by faxing or emailing the appropriate form within 24 hours of the study site staff becoming aware of the pregnancy to Biogen SABR or designee (fax: please refer to the Study Reference Guide; email [redacted]. The Investigator or study site staff must report the outcome of the pregnancy to Biogen SABR or designee.

Congenital abnormalities and birth defects in the offspring of male or female subjects should be reported as an SAE if conception occurred during the study treatment period.

15.4.2. Overdose

An overdose is any dose of study treatment administered to a subject or taken by a subject that exceeds the dose assigned to the subject according to the protocol. Overdoses are not considered AEs and should not be recorded as an AE on the eCRF; however, all overdoses must be recorded on an Overdose form and faxed to Biogen SABR or designee within 24 hours of the site becoming aware of the overdose. An overdose must be reported to Biogen or designee even if the overdose does not result in an AE. If an overdose results in an AE, the AE must be recorded. If an overdose results in an SAE, both the SAE and Overdose forms must be completed and faxed to Biogen SABR or designee. All study treatment-related dosing information must be recorded on the dosing eCRF.

15.4.3. Medical Emergency

In a medical emergency requiring immediate attention, study site staff will perform appropriate medical interventions, according to current standards of care. The Investigator (or designee) should contact the study's Medical Director. Refer to the Study Reference Guide's Official Study Contact List for complete contact information.

15.4.3.1. Unblinding for Medical Emergency

Not Applicable

15.5. Contraception Requirements

Sexually active subjects of reproductive potential must practice effective contraception during the study and for at least 30 days after their last dose of study treatment. Investigators should advise subjects of the potential risks associated with pregnancy while taking BG00012 and on the appropriate use of contraceptives (as defined below).

For the purposes of the study, highly effective contraception is defined as use of 1 or more of the following:

For females:

- Established use of oral, injected, or implanted hormonal methods of contraception.
- Placement of an intrauterine device or intrauterine system.
- Barrier methods of contraception with use of a spermicide: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream suppository. The use of barrier contraceptives should always be supplemented with the use of a spermicide (where approved/applicable).
- Female surgical sterilization (e.g., bilateral tubal ligation).

For males:

- Effective male contraception includes the use of condoms with spermicide.

True abstinence, when this is consistent with the preferred and usual lifestyle of the subject, can be considered an acceptable method of contraception based on the evaluation of the Investigator who should also take into consideration the duration of the clinical trial. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not considered acceptable methods of contraception.

Pregnancy reporting is described in Section 15.4.1.

15.6. Safety Responsibilities

15.6.1. The Investigator

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 to study treatment, and severity of each event.
- Determine the onset and resolution dates of each event.
- Monitor and record all pregnancies and follow up on the outcomes.
- Complete an SAE form for each SAE 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.
- Report SAEs to local ethics committees, as required by local law.
- Ensure all AE and SAE reports are supported by documentation in the subjects' medical records.

- Pursue AE follow-up information, if possible, until the event has resolved or become stable.

15.6.2. Biogen

Biogen's responsibilities include the following:

- Before study site activation and subject enrollment, the Clinical Monitor 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 ethics committees, and Investigators of SAEs, as required by local law, within required time frames.

16. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

The objectives of the study and the endpoints to be analyzed are listed in Section 6.

16.1. Efficacy

16.1.1. Analysis Population

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

16.1.2. Methods of Analysis

16.1.2.1. Analysis of the Primary Endpoint

The primary analysis will be summaries of the incidence of treatment-emergent AEs, SAEs, and discontinuations from study treatment due to AEs.

16.1.2.2. Analysis of the Secondary Endpoints

The number of new or newly enlarging T2 hyperintense lesions on brain MRI scans will be summarized over time using descriptive statistics.

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

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

16.2. Pharmacokinetics

Not applicable.

16.3. Pharmacodynamics

Not applicable.

16.4. Biomarker Analyses/Pharmacogenomics

Not applicable.

16.5. Safety

16.5.1. Analysis Population

The safety population is defined as all subjects who received at least 1 dose of BG00012 in this study.

16.5.1.1. Adverse Events

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

The primary analysis will be summaries of the incidence of treatment-emergent AEs, SAEs, and discontinuations from study treatment due to AEs.

16.5.1.2. Clinical Laboratory Results

Clinical laboratory evaluations including hematology, blood chemistry, and urinalysis will be summarized using the incidence of shifts outside the normal range. In addition, summary statistics for quantitative laboratory values and changes from baseline will be presented. Lymphocyte count data will be summarized by timepoints on study treatment. Additionally, lymphocyte count over time post-treatment and the time to recovery will be descriptively summarized for subjects who develop decreases in lymphocyte count (<LLN).

16.5.1.3. Vital Signs

The analysis of vital signs will focus on clinically relevant abnormalities. The incidence of subjects experiencing these abnormalities will be summarized.

16.6. Antigenicity/Immunogenicity Data

Not applicable.

16.7. Interim Analyses

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

16.8. Sample Size Considerations

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

17. ETHICAL REQUIREMENTS

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

The Investigator may delegate responsibilities for study-related tasks where appropriate to individuals sufficiently qualified by education, training, and experience, in accordance with applicable ICH and GCP guidelines. The Investigator should maintain a list of the appropriately qualified persons to whom significant study-related duties have been delegated.

17.1. Declaration of Helsinki

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

17.2. Ethics Committee

The Investigator must obtain ethics committee approval of the protocol, ICF, and other required study documents prior to starting the study. Biogen 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 ethics committee. 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 ethics committee and Biogen.

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

Biogen must receive a letter documenting ethics committee 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 ethics committee 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 ethics committee and Biogen.

17.3. 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 or subject's legally authorized representative (e.g., parent or legal guardian), as applicable, in accordance with local practice and regulations.

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 (or the

subject's legally authorized representative). The subject must be given sufficient time to consider whether to participate in the study.

In addition, subjects who have the capacity should provide their assent to participate in the study. The level of information provided to subjects should match their level of understanding as determined by the Investigator and in accordance with applicable regulations and guidelines.

A copy of the signed and dated ICF and assent if applicable must be given to the subject or the subject's legally authorized representative. The signed and dated ICF will be retained with the study records. Local regulations must be complied with in respect to the final disposition of the original (wet signature) and copies of the signed and dated ICFs.

Confirmation of informed consent and assent if applicable must also be documented in the subject's medical record.

17.4. 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., Protected Health Information 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, ethics committees, 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.

17.5. Compensation for Injury

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

17.6. Conflict of Interest

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

17.7. Registration of Study and Disclosure of Study Results

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

18. ADMINISTRATIVE PROCEDURES

18.1. Study Site Initiation

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

18.2. Quality Assurance

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

18.3. Monitoring of the Study

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

The Clinical Monitor will visit the Investigator at regular intervals during 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.

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.

18.4. 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.

18.5. Publications

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

19. FURTHER REQUIREMENTS AND GENERAL INFORMATION

19.1. External Contract Organizations

Biogen will be responsible for all administrative aspects of this study including but not limited to study initiation, monitoring, management of AEs, and data management.

19.1.1. Contract Research Organization

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

19.1.2. Electronic Data Capture

Subject information will be captured and managed by study sites on eCRFs by a Web-based electronic data capture tool OR remote data capture tool developed and supported by iMedidata RAVE and configured by [redacted].

19.1.3. Central Laboratories for Laboratory Assessments

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

19.2. Study Committees

19.2.1. Advisory Committee

An advisory committee will be formed to provide scientific and medical direction for the study and to oversee the administrative progress of the study. The advisory committee will conduct regular reviews to monitor subject accrual and to monitor compliance with the protocol at individual study sites. The advisory committee will determine whether the study should be stopped or amended for reasons other than safety.

Members of the advisory committee will include the Medical Director, Clinical Operations Lead, and Project Statistician from Biogen, and participating Investigators. Biogen will designate one of the participating Investigators to be the chairperson of the advisory committee.

19.2.2. Independent Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) 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 IDMC organization and procedures will be outlined in the IDMC Charter.

19.3. Changes to Final Study Protocol

Protocol modifications that affect subject safety, the scope of the investigation, or the scientific quality of the study must be approved by the ethics committee 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 ICF may require corresponding modifications (see Section 17).

19.4. Ethics Committee Notification of Study Completion or Termination

Where required, the regulatory authorities and ethics committees must be notified of completion or termination of this study, and sent a copy of the study synopsis in accordance with necessary timelines.

19.5. 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 offsite facility or transfer of ownership if the Investigator leaves the site.

19.6. Study Report Signatory

Biogen will designate 1 or more 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.

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21. SIGNED AGREEMENT OF THE STUDY PROTOCOL

I have read the foregoing protocol, "A Multicenter Extension Study to Determine the Long-Term Safety and Efficacy of BG00012 in Pediatric Subjects With Relapsing-Remitting Multiple Sclerosis," 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)

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PROTOCOL NUMBER: 109MS311

PHASE OF DEVELOPMENT: 3

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

EUDRA CT NO: 2015-003282-29

DATE: 08 January 2016
Version 2.0
FINAL

SPONSOR SIGNATURE

Protocol 109MS311 was approved by:

[redacted], MD, MSc, MRCP

[redacted]

Biogen MA Inc.

8 Jan 2016
Date

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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
ARR	annualized relapse rate
AST	aspartate transaminase
BID	twice daily
BUN	blood urea nitrogen
CNS	central nervous system
CRO	contract research organization
DHA	Directions for Handling and Administration
DMF	dimethyl fumarate
eCRF	electronic case report form
EDSS	Expanded Disability Status Scale
GCP	Good Clinical Practice
GI	gastrointestinal
ICF	informed consent form
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IV	intravenous
IVMP	intravenous methylprednisolone
LLN	lower limit of normal
MMF	monomethyl fumarate
MRI	magnetic resonance imaging
MS	multiple sclerosis
PK	pharmacokinetics
PTH	parathyroid hormone
RRMS	relapsing-remitting multiple sclerosis
SABR	Safety and Benefit-Risk Management
SAE	serious adverse event
SUSAR	suspected unexpected serious adverse reaction
TID	3 times daily
ULN	upper limit of normal
US	United States
WBC	white blood cell

3. SYNOPSIS

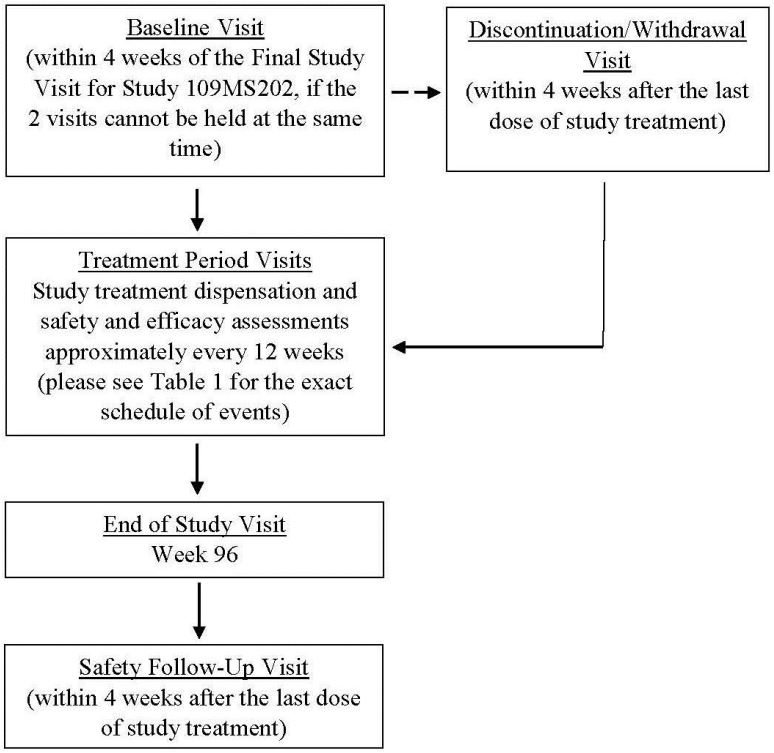
Protocol Number:	109MS311
Protocol Title:	A Multicenter Extension Study to Determine the Long-Term Safety and Efficacy of BG00012 in Pediatric Subjects With Relapsing-Remitting Multiple Sclerosis
Version Number	2.0
Name of Study Treatment:	BG00012 (Dimethyl Fumarate; Tecfidera®)
Study Indication:	Relapsing-remitting multiple sclerosis (RRMS)
Study Rationale	With no approved multiple sclerosis (MS) therapies in the pediatric population, there exists a significant unmet need for approved treatment options. In the adult population, BG00012 is a therapeutic option with demonstrated efficacy and acceptable tolerability and safety profiles combined with the ease of oral administration. BG00012 was first approved (as Tecfidera) in the United States in 2013 for the treatment of adult patients with relapsing forms of MS and has since been approved in Europe and other regions. This study will extend therapy from the ongoing BG00012 pediatric Study 109MS202, in which the pharmacokinetics and efficacy of BG00012 in pediatric subjects with RRMS are being evaluated, in order to further evaluate the long-term safety and efficacy of BG00012 in these subjects.
Phase of Development:	3
Study Objectives and Endpoints:	The primary objective of the study is to evaluate the long-term safety of BG00012 in subjects who completed Study 109MS202. The primary endpoint that relates to this objective is the incidence of adverse events (AEs), serious AEs, and discontinuations of study treatment due to an AE Secondary objectives and endpoints are as follows: To evaluate the long-term efficacy of BG00012. • The total number of new or newly enlarging T2 hyperintense lesions on brain magnetic

	resonance imaging scans • The annualized relapse rate • The proportion of subjects who experience 1 or more relapses during the study period To describe the long-term MS outcomes in subjects who completed Study 109MS202. • The degree of disability as measured by the Expanded Disability Status Scale (EDSS) and disability progression (as measured by at least a 1.0-point increase on the EDSS from baseline EDSS ≥1.0 that is sustained for 24 weeks or at least a 1.5-point increase on the EDSS from baseline EDSS = 0 that is sustained for 24 weeks)
Study Design:	This is a multicenter, open-label extension of Study 109MS202 that is designed to evaluate the long-term safety and efficacy of BG00012 in pediatric subjects.
Study Location:	Approximately 20 sites globally are planned.
Number of Planned Subjects:	The number of subjects who are eligible for this study will be determined by the number of subjects who have completed Study 109MS202 as per protocol.
Study Population:	This study will be conducted in subjects who completed Study 109MS202 as per protocol. Detailed criteria are described in Section 8.
Treatment Groups:	All subjects will receive BG00012 240 mg twice daily (2 capsules of 120 mg).
Duration of Treatment and Follow-up:	The treatment period is 96 weeks (2 years) and the Follow-Up Safety Visit will take place 4 weeks after the last dose of study treatment.

4. STUDY SCHEMATIC AND SCHEDULE OF ACTIVITIES FOR STUDY 109MS311

4.1. Study Schematic

Figure 1: Study Design



4.2. Schedule of Activities

Table 1: Study Activities for Study 109MS311

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

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

[1] Tests and assessments must be completed prior to study treatment dispensation.

[2] The Final Study Visit for Study 109MS202 will serve as the Baseline Visit for this extension study. The Final Study Visit from Study 109MS202 can be within 4 weeks of the Baseline Visit for Study 109MS311 if the 2 visits cannot be combined.

[3] Written informed consent from the subject's parents or legal guardians and assent from the subject, if appropriate, must be obtained prior to performing any study-related procedures.

[4] MS-related medical history will include complete MS history of disease, MS diagnostic criteria, MS signs and symptoms, and MS treatment history.

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

[6] For females of childbearing potential. Results must be known prior to study treatment dispensation.

[7] Urine cytology must be performed at all visits indicated if a subject experiences hematuria (of unknown etiology) at 2 consecutive visits. If urine cytology is positive for malignant cells, the subject must permanently discontinue study treatment.

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

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

[10] The time between the Week 24 MRI and the Week 16 MRI must be the same as the time between the Day 0 MRI and Week -8 MRI in Study 109MS202 within a window of ±3 days. For example, if the Day 0 and Week -8 MRIs for a particular subject occurred 8 weeks apart in Study 109MS202, then the Week 24 MRI in Study 109MS311 should be 8 weeks ± 3 days after the Week 16 MRI. If necessary, the Week 24 MRI may be conducted separately from the Week 24 clinic visit. Similarly, the time between the Week 72 MRI and the Week 64 MRI must be the same as the time between the Day 0 MRI and Week -8 MRI in Study 109MS202 within a window of ±3 days. If necessary, the Week 72 MRI may be conducted separately from the Week 72 clinic visit.

[11] Initial dispensation of study treatment may require an additional visit on or around Day 7. Laboratory results must be evaluated and eligibility confirmed prior to dispensation of study treatment.

Table 2: Additional Study Activities for Study 109MS311

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

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

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

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

[3] Subjects who complete, temporarily withhold, or permanently discontinue study treatment for any reason and have a lymphocyte count <LLN will continue protocol-required visits and assessments and be followed every 4 weeks for 24 weeks and then every 3 months (**unless clinically indicated more often or at the Investigator's discretion**) until the lymphocyte count is ≥LLN or for 52 weeks after the last dose (whichever is sooner).
[4] Vital signs include body temperature, pulse rate, and systolic/diastolic blood pressure measurements.
[5] Hematology testing must be performed every 4 weeks in subjects with lymphocyte count <LLN.
[6] Study treatment must be temporarily withheld or permanently discontinued if any of the laboratory values meet the criteria defined in the protocol.
[7] For females of childbearing potential.
[8] Urine cytology must be performed if a subject experiences hematuria (of unknown etiology) at 2 consecutive visits or at the Unscheduled Relapse Assessment Visit or the Discontinuation/Withdrawal Visit.
[9] An MRI must not be performed within 30 days of receiving a course of steroids.
[10] A brain MRI scan will be performed unless assessed in the last 30 days.

4.3. Additional Information

4.3.1. Blood Volumes

Every effort must be made to collect the minimum blood volume needed per protocol. 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 or 1% at any single visit [European Commission 2008]. For example, in a 30-kg child (the lowest weight permitted in this study), it is 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 will be 5 mL or less. The approximate amount of blood to be drawn over the entire study period will be 50 mL.

5. INTRODUCTION

5.1. Overview of Multiple Sclerosis

Multiple sclerosis (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. MS primarily affects adults, with clinical onset occurring most commonly between the ages of 20 and 40 years [O'Connor and Canadian Multiple Sclerosis Working Group 2002]. Approximately 2.2% to 4.4% of all MS cases have onset during adolescence or childhood [Chitnis 2011], with girls affected more than boys, and most cases being relapsing-remitting multiple sclerosis (RRMS).

5.2. Current Therapies for Multiple Sclerosis

Despite the availability of several therapies approved for the treatment of adult patients with MS, there remains an unmet need for safe and effective treatments for pediatric patients with MS. Currently, there are no treatments that are approved to treat pediatric MS, and no randomized controlled clinical studies have been completed that demonstrate that the agents available for treatment of MS in adults are safe and effective in pediatric patients. Moreover, there are no data on the pharmacological characterization of any of the disease-modifying MS therapies in pediatric patients. Thus, current treatment options for pediatric patients with MS are adapted from therapeutic paradigms for adult patients, with dosing recommendations based solely on adult subject data and expert opinion.

The most commonly used therapies in the pediatric population are interferons and glatiramer acetate [Waldman 2011]. Relative to placebo, these agents have been shown to reduce relapse rate by approximately 30% and may decrease disease progression [Jacobs 2000; Johnson 1995; Paty and Li 1993; PRISMS Study Group 2001; The IFNB Multiple Sclerosis Study Group 1993].

Other therapies currently approved for use in adults with MS include the following:

- Natalizumab: a humanized monoclonal antibody directed against α4 integrins [Polman 2006]
- Fingolimod: a selective oral immunosuppressant that is metabolized to a functional antagonist of sphingosine 1-phosphate receptors on lymphocytes [Kappos 2010]
- Mitoxantrone: a synthetic antineoplastic anthracenedione that intercalates into DNA, interfering with its synthesis and repair [Chitnis 2012]
- Teriflunomide: an immunosuppressive drug inhibiting pyrimidine synthesis by blocking dihydroorotate dehydrogenase [O'Connor 2011]
- Alemtuzumab: a monoclonal antibody directed against cluster of differentiation 52 [Cohen 2012]

- Tecfidera®: a dimethyl fumarate (DMF)-containing drug that activates the Nrf2 antioxidant response pathway to mitigate inflammatory stress [Ghoreschi 2011; Nguyen 2003]

5.3. Profile of Previous Experience With BG00012

5.3.1. Nonclinical Safety Experience

Nonclinical safety studies were performed to support the development of BG00012 (Tecfidera®) 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, impaired fertility, or teratogenicity. Repeat-dose toxicology studies were performed in rodents (mouse and rat) and non-rodents (dog and monkey). Findings in these studies in the liver, forestomach, and testis concluded that there is limited concern related 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 lifetime carcinogenicity studies, renal tumors were attributed to a rodent-specific exacerbation of nephropathy.

See the Investigator's Brochure for more detailed information on nonclinical studies as well as information on nonclinical pharmacology and pharmacokinetic (PK) studies.

5.3.2. Clinical Experience

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

The efficacy and safety of BG00012 are well established and based on data from Phase 2 and 3 placebo-controlled safety and efficacy studies (Studies C-1900 Part 1, 109MS301 [DEFINE], and 109MS302 [CONFIRM]) and their uncontrolled extensions (Studies C-1900 Part 2 and 109MS303 [ENDORSE]). In these studies, over 2500 subjects received treatment with BG00012. The overall exposure to BG00012 in these subjects was approximately 6100 subject-years as of September 2013.

Results of the Phase 3 clinical studies demonstrate that BG00012 240 mg BID or 3 times daily (TID) is an efficacious treatment for RRMS. In these Phase 3 studies, BG00012 resulted in a significant reduction in the risk of relapse and annualized relapse rate (ARR), and the treatment had a positive effect on 12-week Expanded Disability Status Scale (EDSS) disability progression, with statistical significance achieved in Study 109MS301. A robust, statistically significant effect was also observed on magnetic resonance imaging (MRI) endpoints, including the number and volume of new or newly enlarging T2 hyperintense lesions, gadolinium-enhancing lesions, and new or newly enlarging T1 hypointense lesions compared with placebo. Efficacy was seen as early as 6 months and maintained over the 2-year span of Studies 109MS301 and 109MS302. In the ongoing Phase 3, uncontrolled extension Study 109MS303 (ENDORSE), which includes subjects who completed Studies 109MS301 or 109MS302, sustained efficacy was observed through 5 years of treatment, and the safety profile of continued BG00012 treatment was consistent with that observed in the 2-year Phase 3 studies.

Overall, safety data from the clinical development program showed that BG00012 was well tolerated and has an acceptable safety profile. In the BG00012 240 mg BID group, the most common adverse events (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 dose regimens of BG00012. Mean WBC and lymphocyte counts then plateaued and remained stable, even during longer periods of observation of approximately 5.25 years. 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. With open-label and marketed use of BG00012, progressive multifocal leukoencephalopathy has been observed in the setting of severe and prolonged lymphopenia. There has been no other evidence of increased risk of infections, serious infections, or other opportunistic infections (in open-label and marketed use of BG00012).

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 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 (PTH), or 1,25-dihydroxyvitamin D. In the Phase 3 studies (Studies 109MS301 and 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 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 over time in β2-microglobulinuria and microalbuminuria, which are more sensitive and specific markers of renal tubular dysfunction, 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.

5.4. Study Rationale

In adult subjects with RRMS, BG00012 demonstrated efficacy and had an acceptable safety profile in 2 Phase 3 studies, Studies 109MS301 and 109MS302. With no approved therapies, there exists a significant unmet need for MS treatment options in the pediatric population. In the adult population, BG00012 is a therapeutic option with demonstrated efficacy and acceptable tolerability and safety profiles combined with the ease of oral administration. This study will extend therapy from the ongoing BG00012 pediatric Study 109MS202, in which the PK and efficacy of BG00012 in pediatric subjects with RRMS are being evaluated, in order to further evaluate the long-term safety and efficacy of BG00012 in these subjects.

5.5. Rationale for Dosing Regimen

The BG00012 dosage selected for this study (240 mg BID) is the approved BG00012 dosing regimen in adult patients with MS.

In adults, after oral administration, DMF is well absorbed and extensively metabolized by esterases to its primary active metabolite, monomethyl fumarate (MMF). As a result, DMF is not quantifiable in plasma, and all PK analyses have been performed based on MMF concentrations. Downstream metabolism of DMF/MMF occurs through the tricarboxylic acid cycle, with exhalation of carbon dioxide serving as a major route of elimination. The PK of BG00012 has been thoroughly evaluated in adults. Body weight is a significant covariant for BG00012 exposure in that the area under the curve and the maximum concentration are decreased by 2% and 1.4%, respectively, for every 1-kg increase in body weight within the weight range of 45 to 112 kg. This translates to a 2-fold increase in exposure levels as body weight decreases from 112 to 45 kg.

Despite the effect of body weight changes on the exposure levels of BG00012, data from the pivotal Phase 3 studies suggested that the variability in exposure did not affect safety and efficacy measures in adult patients. Notably, the efficacy and tolerability profiles of BG00012 at 240 mg BID were indistinguishable from those at 240 mg TID, with a wide range of overlapping exposures between the 2 dosages.

A Phase 1 PK study (Study 109MS101) revealed no apparent differences in the kinetics of BG00012 across the age range of 21 to 51 years once the weight relationship was accounted for.

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. These findings suggest that the disposition of BG00012 is unlikely to change with age for the target population (10 to 18 year olds).

Taken together, these data indicate that 240 mg BID, the approved dose in adults, should be tolerable in pediatric subjects meeting the inclusion criteria for the parent study (109MS202) and the current extension study. As such, this dose was chosen for the parent and current studies.

6. STUDY OBJECTIVES AND ENDPOINTS

6.1. Primary Objective and Endpoint

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

The primary endpoint that relates to this objective is the incidence of AEs, serious AEs (SAEs), and discontinuations of study treatment due to an AE.

6.2. Secondary Objectives and Endpoints

A secondary objective is to evaluate the long-term efficacy of BG00012.

The endpoints that relate to this objective are the total number of new or newly enlarging T2 hyperintense lesions on brain MRI scans, the ARR, and the proportion of subjects who experience 1 or more relapses during the study period.

Another secondary objective is to describe the long-term MS outcomes in subjects who completed Study 109MS202.

The endpoint that relates to this objective is the degree of disability as measured by the EDSS and disability progression (as measured by at least a 1.0-point increase on the EDSS from baseline EDSS ≥1.0 that is sustained for 24 weeks, or at least a 1.5-point increase on the EDSS from baseline EDSS = 0 that is sustained for 24 weeks).

7. STUDY DESIGN

7.1. Study Overview

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

See Figure 1 for a schematic of the study design.

7.2. Overall Study Duration and Follow-Up

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

7.2.1. Enrollment

Subject eligibility for the study will be determined at the Final Study Visit for Study 109MS202 or within 4 weeks prior to study entry. The Final Study Visit for Study 109MS202 will serve as the Baseline Visit for this study.

7.2.2. Treatment

Eligible subjects will report to the study site to receive study treatment approximately every 12 weeks for up to 96 weeks (2 years).

7.2.3. Follow-Up

Subjects are to return to the study site for a follow-up visit 4 weeks after their last treatment visit (Visit 10 at Week 96 [±5 days]).

Subjects who withdraw prematurely from the study will complete the Early Withdrawal Visit, which should be conducted as soon as possible and no later than 4 weeks after the subject's last dose of study treatment. Subjects who withdraw prematurely should be encouraged to complete the Safety Follow-Up Visit 4 weeks after the last dose of study treatment.

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) will be followed every 4 weeks for 24 weeks and then every 3 months (**unless clinically indicated more often or at the Investigator's discretion**) until the lymphocyte count is ≥LLN or for 52 weeks after the last dose (whichever is sooner).

7.3. Relapses

Suspected relapses during this study will be evaluated and confirmed according to the protocol by the Investigator. 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 Investigator. 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 would not be treated with intravenous methylprednisolone (IVMP) within the protocol.

If a subject experiences new neurologic symptoms, then the subject or caregiver must contact the Investigator 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 Investigator within 5 days of the onset of the potential relapse. The Investigator is to perform a relapse assessment and obtain an EDSS score. To ensure consistency across sites, Investigators must undergo a standardized training session on EDSS scoring prior to enrollment of subjects at their site. New objective findings on neurological examination performed by the Investigator are required to determine if a protocol-defined relapse has occurred. Subjects may not begin corticosteroid treatment of the relapse per protocol until the Investigator has examined them.

Treatment of an acute event of relapse with IVMP may proceed at the discretion of the Investigator and will not affect the subject's eligibility to continue in the study. If an Unscheduled Relapse Assessment Visit occurs within 7 days of a scheduled clinic visit, then the 2 visits may take place on the same day; however, MRIs must be conducted according to the schedule outlined in Section 4.2.

7.4. Study Stopping Rules

Biogen may terminate this study at any time, after informing the Investigators. Biogen will notify Investigators when the study is to be placed on hold, completed, or terminated.

7.5. End of Study

The end of study is last subject, last visit for final collection of data.

8. SELECTION OF SUBJECTS

8.1. Inclusion Criteria

To be eligible to participate in this study, candidates must meet the following eligibility criteria at 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 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, as per protocol, the previous BG00012 clinical study 109MS202 and remain on BG00012 treatment at 240 mg BID.
3. All female subjects of childbearing potential and all male subjects must practice effective contraception during the study and for at least 30 days after their last dose of study treatment. For further details of contraceptive requirements for this study, please refer to Section 15.5.

8.2. Exclusion Criteria

Candidates will be excluded from study entry if any of the following exclusion criteria exist at Day 1 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.
4. Any significant changes in medical history occurring after enrollment in the parent Study 109MS202, including laboratory test abnormalities or current clinically significant conditions that in the opinion of the Investigator would have excluded the subject's participation from the parent study. The Investigator must re-review the subject's medical fitness for participation and consider any factors that would preclude treatment.
5. Subjects from Study 109MS202 who could not tolerate study treatment.
6. History of malignancy.
7. History of severe allergic or anaphylactic reactions or known drug hypersensitivity to DMF or fumaric acid esters.
8. Any of the following abnormal blood tests:
   - ALT >3 times the ULN
   - AST >3 times the ULN
   - Gamma-glutamyl-transferase >3 times the ULN
   - Creatinine >1.2 times the ULN

- WBC count <2000/mm^3
- Lymphocyte count <500/mm^3

9. Female subjects considering becoming pregnant or breastfeeding while in the study or who are pregnant or breastfeeding.
10. Other unspecified reasons that, in the opinion of the Investigator or Biogen, make the subject unsuitable for enrollment.

9. ENROLLMENT AND REGISTRATION

9.1. Screening and Enrollment

Subjects (or their legally authorized representative [e.g., parent or legal guardian], where applicable) must provide informed consent before any screening tests are performed (see Section 17.3). When a subject signs the informed consent form (ICF), that subject is considered to be enrolled in the study. Subjects who have a nonclinically significant out-of-range laboratory result may be rescreened 1 time only at the discretion of the Investigator. 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.

9.2. Registration of Subjects

Subjects will be registered at Day 1, after all baseline assessments have been completed and after the Investigator has verified that the subjects are eligible per criteria in Sections 8.1 and 8.2. No subject may begin treatment prior to assignment of a unique identification number (registration). Any subject identification numbers that are assigned will not be reused even if the subject does not receive treatment.

Refer to the Study Reference Guide for details on registration.

9.3. Blinding Procedures

Not applicable.

10. DISCONTINUATION OF STUDY TREATMENT AND/OR WITHDRAWAL OF SUBJECTS FROM THE STUDY

10.1. Discontinuation of Study Treatment

A subject *must* permanently discontinue BG00012 for any of the following reasons:

- The subject becomes pregnant. Study treatment must be discontinued immediately. Report the pregnancy according to the instructions in Section 15.4.1.
- The subject experiences a medical emergency that necessitates permanent discontinuation of study treatment.
- The subject has lymphocyte count <500/mm^3 for 6 months as outlined in Table 4 and Table 5 .
- The subject experiences a protocol-specified change in laboratory values that necessitates permanent discontinuation of treatment as outlined in Table 3 and Table 4.
- The subject cannot tolerate study treatment.
- The subject receives any of the disallowed concomitant medications for this study.
- The subject or subject's parent/legal guardian desires to discontinue treatment.
- 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 discontinue treatment may remain in the study and continue protocol-required tests and assessments.

10.2. Withdrawal of Subjects From Study

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

- The subject or the subject's parent/guardian withdraws consent.
- The subject enrolls into another interventional clinical study.
- 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.

11. STUDY TREATMENT USE

11.1. Regimen

BG00012 will be taken orally at a dose of 240 mg BID.

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.

Refer to and follow the Directions for Handling and Administration (DHA).

11.2. Modification of Dose and/or Treatment Schedule

11.2.1. Dosing Interruption for Abnormal Laboratory Values

BG00012 must be temporarily withheld and/or permanently discontinued when any of the following laboratory values meet the threshold limits defined in Table 3 (laboratory abnormalities that require immediate and permanent discontinuation of study treatment are also specified in Table 3).

Table 3: Laboratory Criteria Requiring Withholding or Permanent Discontinuation of Treatment

Laboratory Parameter	Laboratory Result	Required Action
AST (SGOT) or ALT (SGPT)	>3 × ULN	The Investigator should repeat the test as soon as possible. If the retest value confirms AST or ALT >3 × ULN, then the study treatment must be withheld. If the value remains >3 × ULN for ≥4 weeks after discontinuation of study treatment, then the subject **must *permanently* discontinue study treatment, 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, then 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, and the event must be recorded as an AE.**

Laboratory Parameter	Laboratory Result	Required Action
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, then 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, 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 retest confirms microscopic hematuria without known etiology, then the study treatment must be withheld, and urine cytology performed. If hematuria persists for ≥4 weeks after discontinuation or if cytology is positive for malignant cells, then the subject **must *permanently* discontinue study treatment, 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; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; ULN = upper limit of normal; WBC = white blood cell.

Table 4 describes the management of lymphocytes <LLN for subjects during and after study treatment.

Table 4: Management of Lymphocyte Count <LLN

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 on study treatment	<500/mm^3	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 for 24 weeks and then every 3 months (**unless clinically indicated more often or at the Investigator's discretion**) until the lymphocyte count is ≥LLN or for 52 weeks after the last dose (whichever is sooner).

LLN = lower limit of normal.

While dosing is withheld, subjects will continue tests and assessments according to Table 1 (and may also undergo additional assessments to evaluate the laboratory abnormality as per the Investigator's standard practice). In addition, subjects (whether on study treatment, having

dosing temporarily withheld, or permanently discontinued) must have the abnormal laboratory result rechecked at the central laboratory as follows:

- For all analytes, with the exception of lymphocytes, results will be rechecked at least every 2 weeks 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.
- For lymphocytes, results will be rechecked at least every 4 weeks for 24 weeks and then every 3 months (**unless clinically indicated more often or at the Investigator's discretion**) until the lymphocyte count is ≥LLN or for 52 weeks after the last dose (whichever is sooner). Depending on the severity and clinical significance of the abnormality, the Investigator may need to perform the retests more frequently.

11.2.2. Resumption of Study Treatment Dosing

Resumption of BG00012 treatment is to be considered on a case-by-case basis and must be discussed with the Medical Monitor.

Resumption of study treatment after an interruption

Subjects who are allowed to resume BG00012 dosing after an interruption of ≥2 weeks will restart dosing at a reduced dosage for 1 week. Subjects will take one 120-mg capsule BID for 1 week. After 1 week at the reduced dose, subjects will resume taking two 120-mg capsules BID.

11.2.3. 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 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, then 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 3) on a third occasion must discontinue dosing for the remainder of the study.

11.2.4. 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, then 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 AM void). If the spot protein/creatinine ratio is >0.2 mg/mg, then the subject should be fully investigated for possible causes and referred for evaluation by a nephrologist if appropriate in the opinion of the Investigator.

11.2.5. Treatment Schedule for Subjects With Abnormal Lymphocyte Count

11.2.5.1. 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 Criteria 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 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.

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 for 24 weeks and then every 3 months (**unless clinically indicated more often or at the Investigator's discretion**) until weeks after the last dose until the lymphocyte count is ≥LLN or for 52 weeks after the last dose (whichever is sooner) [see Table 2]. If the lymphocyte count does not recover after 24 weeks, the treating neurologist should contact the Medical Monitor.

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

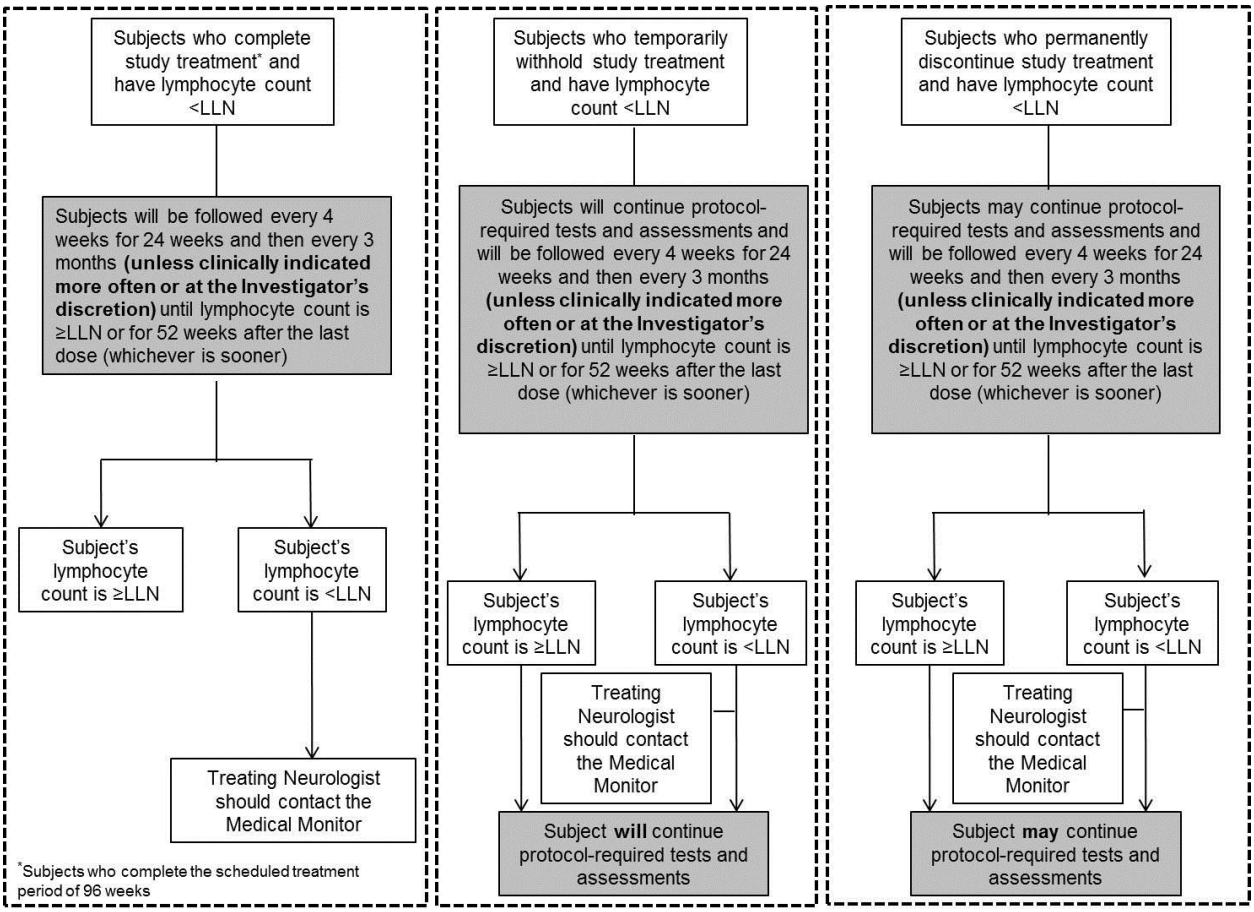
Subjects who complete the 96-week treatment period and who have a lymphocyte count <LLN will be followed every 4 weeks for 24 weeks and then every 3 months (**unless clinically indicated more often or at the Investigator's discretion**) until the lymphocyte count is ≥LLN or for 52 weeks after the last dose (whichever is sooner). 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 10.1) 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 and then every 3 months (**unless clinically indicated more often or at the Investigator's discretion**) until the lymphocyte count is ≥LLN or for 52 weeks after the last dose (whichever is sooner) [see

Table 4]. If the lymphocyte count does not recover after 24 weeks, the treating neurologist should contact the Medical Monitor.

See Figure 2 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 2: Schedule for Subjects who Complete, Temporarily Withhold, or Permanently Discontinue Study Treatment for Any Reason and Have a Lymphocyte Count <LLN



LLN = lower limit of normal.

11.2.6. Dosage Reductions

Dosage reduction will be allowed only for subjects **who are unable to tolerate BG00012 treatment due to flushing and/or GI disturbances** (dosage reductions will not be allowed for abnormal laboratory values; for management of abnormal laboratory values, see Sections 11.2.1, 11.2.2, and 11.2.3). Subjects who do not tolerate BG00012 treatment will reduce their dosage by taking one 120-mg capsule BID for up to 4 weeks. Within 4 weeks at the reduced dosage, subjects will resume taking the full dose of 240 mg (two 120-mg capsules) BID. If the subject is still unable to tolerate BG00012 treatment at the 240-mg BID dose, the subject may continue in the study taking the 120-mg BID dose.

11.3. 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.

11.4. Compliance

Compliance with treatment dosing is to be monitored and recorded by site staff. Compliance for BG00012 will be monitored by capsule count and captured in the eCRF.

11.5. Concomitant Therapy and Procedures

11.5.1. Concomitant Therapy

A concomitant therapy is any drug or substance administered between the Baseline Visit and the Safety Follow-Up Visit.

11.5.1.1. Allowed Concomitant Therapy

Symptomatic therapy, such as treatment for spasticity, depression, or fatigue, is not restricted but should be consistent for the duration of the study.

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

11.5.1.2. Disallowed Concomitant Therapy

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

- Any alternative drug treatments directed toward the treatment of MS, such as immunomodulatory treatments (including but not limited to, interferon-beta, glatiramer acetate, natalizumab, fingolimod, teriflunomide, alemtuzumab, mitoxantrone, mycophenolate mofetil, laquinimod, cyclophosphamide, methotrexate, azathioprine, cyclosporine, etc.) and 4-aminopyridine or related products with the exception of acute management of protocol-defined relapse (as described in Section 11.5.2).
- 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 11.5.2. Steroids that are administered by nonsystemic routes (e.g., topical, inhaled) are allowed.
- Total lymphoid irradiation, cladribine, T-cell or T-cell receptor vaccination, any therapeutic monoclonal antibody, intravenous (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 10.2.

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

11.5.2. 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 Final Study Visit.

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

11.5.3. Treatment of Relapses on Scheduled or Unscheduled Visits

The only protocol-approved treatment for relapse in this study is either 3 or 5 days with IVMP, up to 1000 mg/day. IVMP 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.

11.6. Continuation of Treatment

There is no provision for additional courses of BG00012 provided by Biogen beyond the treatment period defined in this protocol.

If and when BG00012 is commercially available at the time the study treatment period is completed, subjects will be allowed to take commercial BG00012 during the Safety Follow-Up Period if deemed appropriate by product labeling and at the discretion of their treating physician.

12. STUDY TREATMENT MANAGEMENT

Study site staff should follow the DHA for specific instructions on the handling, preparation, administration, and disposal of the study treatment. The DHA supersedes all other references (e.g., protocol).

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

12.1. 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.

12.1.1. BG00012 Preparation

BG00012 will be provided as capsules. Drug wallets will be prepared to ensure that the appropriate treatment is provided to each subject. Drug wallets will be supplied from Interactive Voice/Web Response System 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 study treatment, do not use the study treatment. The drug wallet in question should be quarantined at the study site and the problem immediately reported to Biogen.

12.1.2. BG00012 Storage

Study treatment must be stored in a secure location.

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. For the most up-to-date storage requirements, follow the instructions provided in the DHA.

12.1.3. BG00012 Handling and Disposal

The Investigator must return all used and unused drug wallets of BG00012 as instructed by Biogen unless approved for onsite destruction.

If any BG00012 supplies are to be destroyed at the study site, the institution or appropriate site personnel must obtain prior approval from Biogen by providing, in writing, the destruction

policy or details of the method of destruction. After such destruction, Biogen must be notified, in writing, of the details of the study treatment destroyed (e.g., lot or kit numbers, quantities), the date of destruction, and proof of destruction.

12.1.4. BG00012 Accountability

Accountability for study treatment is the responsibility of the Investigator. 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 accidentally or deliberately destroyed or lost.

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, lost, or returned to Biogen. A written explanation must be provided for any discrepancies.

13. EFFICACY ASSESSMENTS

See Section 4 for the timing of all assessments.

13.1. Clinical Efficacy Assessments

The following clinical assessments will be performed to evaluate the efficacy of BG00012:

- Relapse assessment
- EDSS

13.2. MRI Efficacy Assessments

The following MRI efficacy assessments will be performed to evaluate the efficacy of BG00012:

- The total number of new or newly enlarging T2 hyperintense lesions from baseline as well as from the scan of the previous visit on brain MRI scans

14. SAFETY ASSESSMENTS

Refer to Section 4 for the timing of all safety assessments.

14.1. Clinical Safety Assessments

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

- Physical examinations, including body weight and height
- Vital sign measurements, including body temperature, pulse rate, and systolic and diastolic blood pressure
- 12-Lead electrocardiograms
- Concomitant therapy and procedure recording
- AE and SAE recording

14.2. Laboratory Safety Assessments

The following laboratory assessments will be performed to evaluate the safety profile of BG00012:

- Hematology: complete blood count with differential and platelet count
- Blood chemistry: sodium, potassium, chloride, bicarbonate, calcium, magnesium, phosphate, BUN, creatinine, uric acid, glucose, albumin, ALT, AST, gamma-glutamyl transferase, total bilirubin, and alkaline phosphatase
- Urinalysis: dipstick for blood, protein, and glucose (microscopic examination, if abnormal)
- Vitamin D and PTH levels

15. SAFETY DEFINITIONS, RECORDING, REPORTING, AND RESPONSIBILITIES

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 or his/her legally authorized representative and/or main caregiver must be given the names and telephone numbers of study site staff for reporting AEs and medical emergencies.

15.1. Definitions

15.1.1. 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.

Determination of whether an abnormal laboratory value meets the definition of an AE will be made by the Investigator. Although abnormal laboratory values are typically not considered AEs, the following considerations may result in an abnormal laboratory value being considered an AE:

- A laboratory test result that meets the criteria for an SAE
- A laboratory test result that requires the subject to receive specific corrective therapy
- A laboratory abnormality that the Investigator considers to be clinically significant

15.1.2. 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
- 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.)

15.1.3. 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.

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 in Section 15.1.2 is met.

15.2. Safety Classifications

15.2.1. Investigator Assessment of Events

All events must be assessed to determine the following:

- If the event meets the criteria for an SAE as defined in Section 15.1.2 .
- The relationship of the event to study treatment as defined in Section 15.2.2.
- The severity of the event as defined in Section 15.2.3.

15.2.2. 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 reasonable 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, 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 reasonable 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.

15.2.3. 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 symptoms 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 symptoms 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 symptoms may be given and/or subject hospitalized.

15.2.4. Expectedness of Events

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

15.3. Monitoring and Recording Events

15.3.1. Adverse Events

Any AE experienced by the subject between the time of first dose of study treatment in the extension study 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.

15.3.2. Serious Adverse Events

Any SAE experienced by the subject between the time of the signing of the ICF 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 Biogen Safety and Benefit-Risk

Management (SABR) or designee within 24 hours as described in Section 15.3.3. Follow-up information regarding an SAE also must be reported with 24 hours.

Subjects will be followed for all SAEs until the Safety Follow-Up Visit. Thereafter, the event should be reported to Biogen SABR or designee only if the Investigator considers the SAE to be related to study treatment.

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

15.3.3. 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 SAE that occurs between the time that the subject has signed the ICF 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. Thereafter, the event should be reported only if the Investigator considers it related to study treatment. 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 the 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 an SAE, please fax (please refer to the Study Reference Guide) or email ([redacted].

15.3.3.1. Deaths

Death is an outcome of an event. The event that resulted in death should be recorded on the appropriate eCRF. All causes of death must be reported as SAEs within 24 hours of the site becoming aware of the event. The Investigator should make every effort to obtain and send death certificates and autopsy reports to Biogen SABR or designee. The term death should be reported as an SAE only if the cause of death is not known and cannot be determined.

15.3.4. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are SAEs that are unexpected and judged by the Investigator or Biogen 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.

15.4. Procedures for Handling Special Situations

15.4.1. Pregnancy

Subjects should not become pregnant during the study and for 30 days after their last dose of study treatment. If a female subject becomes pregnant, study treatment must be discontinued *immediately*.

The Investigator must report a pregnancy by faxing or emailing the appropriate form within 24 hours of the study site staff becoming aware of the pregnancy to Biogen SABR or designee (fax: please refer to the Study Reference Guide; email: [redacted]). The Investigator or study site staff must report the outcome of the pregnancy to Biogen SABR or designee.

Congenital abnormalities and birth defects in the offspring of male or female subjects should be reported as an SAE if conception occurred during the study treatment period.

15.4.2. Overdose

An overdose is any dose of study treatment administered to a subject or taken by a subject that exceeds the dose assigned to the subject according to the protocol. Overdoses are not considered AEs and should not be recorded as an AE on the eCRF; however, all overdoses must be recorded on an Overdose form and faxed to Biogen SABR or designee within 24 hours of the site becoming aware of the overdose. An overdose must be reported to Biogen or designee even if the overdose does not result in an AE. If an overdose results in an AE, the AE must be recorded. If an overdose results in an SAE, both the SAE and Overdose forms must be completed and faxed to Biogen SABR or designee. All study treatment-related dosing information must be recorded on the dosing eCRF.

15.4.3. Medical Emergency

In a medical emergency requiring immediate attention, study site staff will perform appropriate medical interventions, according to current standards of care. The Investigator (or designee) should contact the study's Medical Director. Refer to the Study Reference Guide's Official Study Contact List for complete contact information.

15.4.3.1. Unblinding for Medical Emergency

Not Applicable

15.5. Contraception Requirements

Sexually active subjects of reproductive potential must practice effective contraception during the study and for at least 30 days after their last dose of study treatment. Investigators should advise subjects of the potential risks associated with pregnancy while taking BG00012 and on the appropriate use of contraceptives (as defined below).

For the purposes of the study, highly effective contraception is defined as use of 1 or more of the following:

For females:

- Established use of oral, injected, or implanted hormonal methods of contraception.
- Placement of an intrauterine device or intrauterine system.
- Barrier methods of contraception with use of a spermicide: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream suppository. The use of barrier contraceptives should always be supplemented with the use of a spermicide (where approved/applicable).
- Female surgical sterilization (e.g., bilateral tubal ligation).

For males:

- Effective male contraception includes the use of condoms with spermicide.

True abstinence, when this is consistent with the preferred and usual lifestyle of the subject, can be considered an acceptable method of contraception based on the evaluation of the Investigator who should also take into consideration the duration of the clinical trial. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not considered acceptable methods of contraception.

Pregnancy reporting is described in Section 15.4.1.

15.6. Safety Responsibilities

15.6.1. The Investigator

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 to study treatment, and severity of each event.
- Determine the onset and resolution dates of each event.
- Monitor and record all pregnancies and follow up on the outcomes.
- Complete an SAE form for each SAE 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.
- Report SAEs to local ethics committees, as required by local law.
- Ensure all AE and SAE reports are supported by documentation in the subjects' medical records.

- Pursue AE follow-up information, if possible, until the event has resolved or become stable.

15.6.2. Biogen

Biogen's responsibilities include the following:

- Before study site activation and subject enrollment, the Clinical Monitor 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 ethics committees, and Investigators of SAEs, as required by local law, within required time frames.

16. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

The objectives of the study and the endpoints to be analyzed are listed in Section 6.

16.1. Efficacy

16.1.1. Analysis Population

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

16.1.2. Methods of Analysis

16.1.2.1. Analysis of the Primary Endpoint

The primary analysis will be summaries of the incidence of treatment-emergent AEs, SAEs, and discontinuations from study treatment due to AEs.

16.1.2.2. Analysis of the Secondary Endpoints

The number of new or newly enlarging T2 hyperintense lesions on brain MRI scans will be summarized over time using descriptive statistics.

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

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

16.2. Pharmacokinetics

Not applicable.

16.3. Pharmacodynamics

Not applicable.

16.4. Biomarker Analyses/Pharmacogenomics

Not applicable.

16.5. Safety

16.5.1. Analysis Population

The safety population is defined as all subjects who received at least 1 dose of BG00012 in this study.

16.5.1.1. Adverse Events

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

The primary analysis will be summaries of the incidence of treatment-emergent AEs, SAEs, and discontinuations from study treatment due to AEs.

16.5.1.2. Clinical Laboratory Results

Clinical laboratory evaluations including hematology, blood chemistry, and urinalysis will be summarized using the incidence of shifts outside the normal range. In addition, summary statistics for quantitative laboratory values and changes from baseline will be presented. Lymphocyte count data will be summarized by timepoints on study treatment. Additionally, lymphocyte count over time post-treatment and the time to recovery will be descriptively summarized for subjects who develop decreases in lymphocyte count (<LLN).

16.5.1.3. Vital Signs

The analysis of vital signs will focus on clinically relevant abnormalities. The incidence of subjects experiencing these abnormalities will be summarized.

16.6. Antigenicity/Immunogenicity Data

Not applicable.

16.7. Interim Analyses

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

16.8. Sample Size Considerations

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

17. ETHICAL REQUIREMENTS

Biogen, [redacted], 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.

The Investigator may delegate responsibilities for study-related tasks where appropriate to individuals sufficiently qualified by education, training, and experience, in accordance with applicable ICH and GCP guidelines. The Investigator should maintain a list of the appropriately qualified persons to whom significant study-related duties have been delegated.

17.1. Declaration of Helsinki

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

17.2. Ethics Committee

The Investigator must obtain ethics committee approval of the protocol, ICF, and other required study documents prior to starting the study. Biogen 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 ethics committee. 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 ethics committee and Biogen.

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

Biogen must receive a letter documenting ethics committee 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 ethics committee 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 ethics committee and Biogen.

17.3. 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 or subject's legally authorized representative (e.g., parent or legal guardian), as applicable, in accordance with local practice and regulations.

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 (or the

subject's legally authorized representative). The subject must be given sufficient time to consider whether to participate in the study.

In addition, subjects who have the capacity should provide their assent to participate in the study. The level of information provided to subjects should match their level of understanding as determined by the Investigator and in accordance with applicable regulations and guidelines.

A copy of the signed and dated ICF and assent if applicable must be given to the subject or the subject's legally authorized representative. The signed and dated ICF will be retained with the study records. Local regulations must be complied with in respect to the final disposition of the original (wet signature) and copies of the signed and dated ICFs.

Confirmation of informed consent and assent if applicable must also be documented in the subject's medical record.

17.4. 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., Protected Health Information 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, ethics committees, 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.

17.5. Compensation for Injury

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

17.6. Conflict of Interest

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

17.7. Registration of Study and Disclosure of Study Results

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

18. ADMINISTRATIVE PROCEDURES

18.1. Study Site Initiation

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

18.2. Quality Assurance

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

18.3. Monitoring of the Study

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

The Clinical Monitor will visit the Investigator at regular intervals during 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.

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.

18.4. 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.

18.5. Publications

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

19. FURTHER REQUIREMENTS AND GENERAL INFORMATION

19.1. External Contract Organizations

Biogen will be responsible for all administrative aspects of this study including but not limited to study initiation, monitoring, management of AEs, and data management.

19.1.1. Contract Research Organization

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

19.1.2. Electronic Data Capture

Subject information will be captured and managed by study sites on eCRFs by a Web-based electronic data capture tool OR remote data capture tool developed and supported by iMedidata RAVE and configured by [redacted].

19.1.3. Central Laboratories for Laboratory Assessments

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

19.2. Study Committees

19.2.1. Advisory Committee

An advisory committee will be formed to provide scientific and medical direction for the study and to oversee the administrative progress of the study. The advisory committee will conduct regular reviews to monitor subject accrual and to monitor compliance with the protocol at individual study sites. The advisory committee will determine whether the study should be stopped or amended for reasons other than safety.

Members of the advisory committee will include the Medical Director, Clinical Operations Lead, and Project Statistician from Biogen, and participating Investigators. Biogen will designate one of the participating Investigators to be the chairperson of the advisory committee.

19.2.2. Independent Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) 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 IDMC organization and procedures will be outlined in the IDMC Charter.

19.3. Changes to Final Study Protocol

Protocol modifications that affect subject safety, the scope of the investigation, or the scientific quality of the study must be approved by the ethics committee 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 ICF may require corresponding modifications (see Section 17).

19.4. Ethics Committee Notification of Study Completion or Termination

Where required, the regulatory authorities and ethics committees must be notified of completion or termination of this study, and sent a copy of the study synopsis in accordance with necessary timelines.

19.5. 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 offsite facility or transfer of ownership if the Investigator leaves the site.

19.6. Study Report Signatory

Biogen will designate 1 or more 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.

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21. SIGNED AGREEMENT OF THE STUDY PROTOCOL

I have read the foregoing protocol, "A Multicenter Extension Study to Determine the Long-Term Safety and Efficacy of BG00012 in Pediatric Subjects With Relapsing-Remitting Multiple Sclerosis," 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)

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PROTOCOL NUMBER: 109MS311

PHASE OF DEVELOPMENT: 3

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

EUDRA CT NO: 2015-003282-29

DATE: 18 August 2015
Version 1.0
FINAL

SPONSOR SIGNATURE

Protocol 109MS311 was approved by:

[redacted] 18 AUG 2015

[redacted], MD Date
[redacted]
[redacted]
Biogen MA Inc.

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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
ARR	annualized relapse rate
AST	aspartate transaminase
BID	twice daily
BUN	blood urea nitrogen
CNS	central nervous system
CRO	contract research organization
DHA	Directions for Handling and Administration
DMF	dimethyl fumarate
ECG	electrocardiogram
eCRF	electronic case report form
EDSS	Expanded Disability Status Scale
GCP	Good Clinical Practice
GI	gastrointestinal
ICF	informed consent form
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IV	intravenous
IVMP	intravenous methylprednisolone
LLN	lower limit of normal
MMF	monomethyl fumarate
MRI	magnetic resonance imaging
MS	multiple sclerosis
PK	pharmacokinetics
PTH	parathyroid hormone
RRMS	relapsing-remitting multiple sclerosis
SABR	Safety and Benefit-Risk Management
SAE	serious adverse event
SUSAR	suspected unexpected serious adverse reaction
TID	3 times daily
ULN	upper limit of normal
US	United States
WBC	white blood cell

3. SYNOPSIS

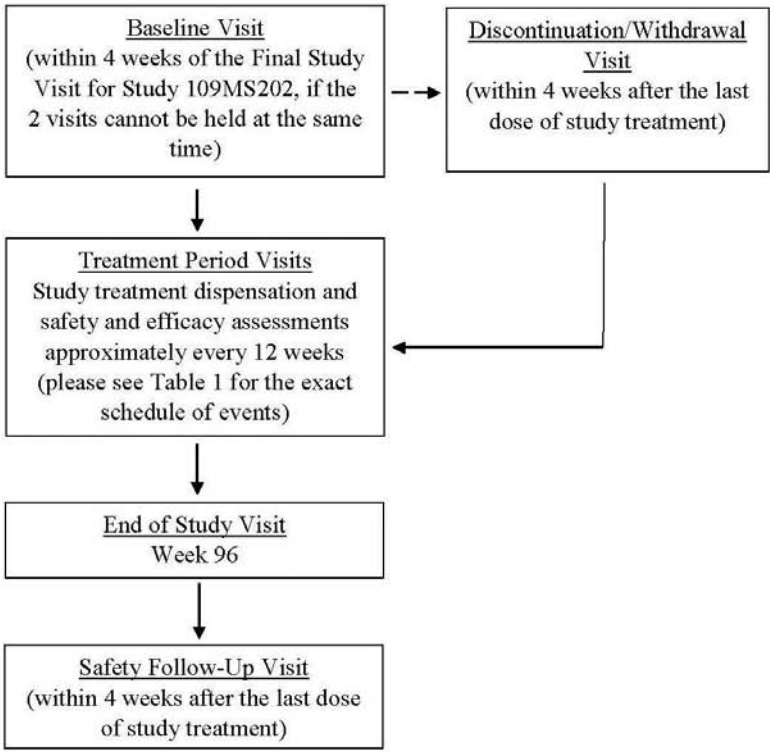
Protocol Number:	109MS311
Protocol Title:	A Multicenter Extension Study to Determine the Long-Term Safety and Efficacy of BG00012 in Pediatric Subjects With Relapsing-Remitting Multiple Sclerosis
Version Number	1.0
Name of Study Treatment:	BG00012 (Dimethyl Fumarate; Tecfidera®)
Study Indication:	Relapsing-remitting multiple sclerosis (RRMS)
Study Rationale	With no approved multiple sclerosis (MS) therapies in the pediatric population, there exists a significant unmet need for approved treatment options. In the adult population, BG00012 is a therapeutic option with demonstrated efficacy and acceptable tolerability and safety profiles combined with the ease of oral administration. BG00012 was first approved (as Tecfidera) in the United States in 2013 for the treatment of adult patients with relapsing forms of MS and has since been approved in Europe and other regions. This study will extend therapy from the ongoing BG00012 pediatric Study 109MS202, in which the pharmacokinetics and efficacy of BG00012 in pediatric subjects with RRMS are being evaluated, in order to further evaluate the long-term safety and efficacy of BG00012 in these subjects.
Phase of Development:	3
Study Objectives and Endpoints:	The primary objective of the study is to evaluate the long-term safety of BG00012 in subjects who completed Study 109MS202. The primary endpoint that relates to this objective is the incidence of adverse events (AEs), serious AEs, and discontinuations of study treatment due to an AE Secondary objectives and endpoints are as follows: To evaluate the long-term efficacy of BG00012. • The total number of new or newly enlarging T2 hyperintense lesions on brain magnetic

	resonance imaging (MRI) scans • The annualized relapse rate • The proportion of subjects who experience 1 or more relapses during the study period To describe the long-term MS outcomes in subjects who completed Study 109MS202. • The degree of disability as measured by the Expanded Disability Status Scale (EDSS) and disability progression (as measured by at least a 1.0-point increase on the EDSS from baseline EDSS ≥1.0 that is sustained for 24 weeks or at least a 1.5-point increase on the EDSS from baseline EDSS = 0 that is sustained for 24 weeks)
Study Design:	This is a multicenter, open-label extension of Study 109MS202 that is designed to evaluate the long-term safety and efficacy of BG00012 in pediatric subjects.
Study Location:	Approximately 20 sites globally are planned.
Number of Planned Subjects:	The number of subjects who are eligible for this study will be determined by the number of subjects who have completed Study 109MS202 as per protocol.
Study Population:	This study will be conducted in subjects who completed Study 109MS202 as per protocol. Detailed criteria are described in Section 8.
Treatment Groups:	All subjects will receive BG00012 240 mg twice daily (2 capsules of 120 mg).
Duration of Treatment and Follow-up:	The treatment period is 96 weeks (2 years) and the Follow-Up Safety Visit will take place 4 weeks after the last dose of study treatment.

4. STUDY SCHEMATIC AND SCHEDULE OF ACTIVITIES FOR STUDY 109MS311

4.1. Study Schematic

Figure 1: Study Design



4.2. Schedule of Activities

Table 1: Study Activities for Study 109MS311

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

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

[1] Tests and assessments must be completed prior to study treatment dispensation.

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

Table 2: Additional Study Activities for Study 109MS311

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

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

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

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

[3] Subjects who complete, temporarily withhold, or permanently discontinue study treatment for any reason and have a lymphocyte count <LLN will continue protocol-required visits and assessments and be followed every 4 weeks until the lymphocyte count is ≥LLN or for 24 weeks after the last dose (whichever is sooner).
[4] Vital signs include body temperature, pulse rate, and systolic/diastolic blood pressure measurements.
[5] Hematology testing must be performed every 4 weeks in subjects with lymphocyte count <500/mm^3.
[6] Study treatment must be temporarily withheld or permanently discontinued if any of the laboratory values meet the criteria defined in the protocol.
[7] For females of childbearing potential.
[8] Urine cytology must be performed if a subject experiences hematuria (of unknown etiology) at 2 consecutive visits or at the Unscheduled Relapse Assessment Visit or the Discontinuation/Withdrawal Visit.
[9] An MRI must not be performed within 30 days of receiving a course of steroids.
[10] A brain MRI scan will be performed unless assessed in the last 30 days.

4.3. Additional Information

4.3.1. Blood Volumes

Every effort must be made to collect the minimum blood volume needed per protocol. 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 or 1% at any single visit [European Commission 2008]. For example, in a 30-kg child (the lowest weight permitted in this study), it is 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 will be 5 mL or less. The approximate amount of blood to be drawn over the entire study period will be 50 mL.

5. INTRODUCTION

5.1. Overview of Multiple Sclerosis

Multiple sclerosis (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. MS primarily affects adults, with clinical onset occurring most commonly between the ages of 20 and 40 years [O'Connor and Canadian Multiple Sclerosis Working Group 2002]. Approximately 2.2% to 4.4% of all MS cases have onset during adolescence or childhood [Chitnis 2011], with girls affected more than boys, and most cases being relapsing-remitting multiple sclerosis (RRMS).

5.2. Current Therapies for Multiple Sclerosis

Despite the availability of several therapies approved for the treatment of adult patients with MS, there remains an unmet need for safe and effective treatments for pediatric patients with MS. Currently, there are no treatments that are approved to treat pediatric MS, and no randomized controlled clinical studies have been completed that demonstrate that the agents available for treatment of MS in adults are safe and effective in pediatric patients. Moreover, there are no data on the pharmacological characterization of any of the disease-modifying MS therapies in pediatric patients. Thus, current treatment options for pediatric patients with MS are adapted from therapeutic paradigms for adult patients, with dosing recommendations based solely on adult subject data and expert opinion.

The most commonly used therapies in the pediatric population are interferons and glatiramer acetate [Waldman 2011]. Relative to placebo, these agents have been shown to reduce relapse rate by approximately 30% and may decrease disease progression [Jacobs 2000; Johnson 1995; Paty and Li 1993; PRISMS Study Group 2001; The IFNB Multiple Sclerosis Study Group 1993].

Other therapies currently approved for use in adults with MS include the following:

- Natalizumab: a humanized monoclonal antibody directed against α4 integrins [Polman 2006]
- Fingolimod: a selective oral immunosuppressant that is metabolized to a functional antagonist of sphingosine 1-phosphate receptors on lymphocytes [Kappos 2010]
- Mitoxantrone: a synthetic antineoplastic anthracenedione that intercalates into DNA, interfering with its synthesis and repair [Chitnis 2012]
- Teriflunomide: an immunosuppressive drug inhibiting pyrimidine synthesis by blocking dihydroorotate dehydrogenase [O'Connor 2011]
- Alemtuzumab: a monoclonal antibody directed against cluster of differentiation 52 [Cohen 2012]

- Tecfidera®: a dimethyl fumarate (DMF)-containing drug that activates the Nrf2 antioxidant response pathway to mitigate inflammatory stress [Ghoreschi 2011; Nguyen 2003]

5.3. Profile of Previous Experience With BG00012

5.3.1. Nonclinical Safety Experience

Nonclinical safety studies were performed to support the development of BG00012 (Tecfidera®) 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, impaired fertility, or teratogenicity. Repeat-dose toxicology studies were performed in rodents (mouse and rat) and non-rodents (dog and monkey). Findings in these studies in the liver, forestomach, and testis concluded that there is limited concern related 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 lifetime carcinogenicity studies, renal tumors were attributed to a rodent-specific exacerbation of nephropathy.

See the Investigator's Brochure for more detailed information on nonclinical studies as well as information on nonclinical pharmacology and pharmacokinetic (PK) studies.

5.3.2. Clinical Experience

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

The efficacy and safety of BG00012 are well established and based on data from Phase 2 and 3 placebo-controlled safety and efficacy studies (Studies C-1900 Part 1, 109MS301 [DEFINE], and 109MS302 [CONFIRM]) and their uncontrolled extensions (Studies C-1900 Part 2 and 109MS303 [ENDORSE]). In these studies, over 2500 subjects received treatment with BG00012. The overall exposure to BG00012 in these subjects was approximately 6100 subject-years as of September 2013.

Results of the Phase 3 clinical studies demonstrate that BG00012 240 mg BID or 3 times daily (TID) is an efficacious treatment for RRMS. In these Phase 3 studies, BG00012 resulted in a significant reduction in the risk of relapse and annualized relapse rate (ARR), and the treatment had a positive effect on 12-week Expanded Disability Status Scale (EDSS) disability progression, with statistical significance achieved in Study 109MS301. A robust, statistically significant effect was also observed on magnetic resonance imaging (MRI) endpoints, including the number and volume of new or newly enlarging T2 hyperintense lesions, gadolinium-enhancing lesions, and new or newly enlarging T1 hypointense lesions compared with placebo. Efficacy was seen as early as 6 months and maintained over the 2-year span of Studies 109MS301 and 109MS302. In the ongoing Phase 3, uncontrolled extension Study 109MS303 (ENDORSE), which includes subjects who completed Studies 109MS301 or 109MS302, sustained efficacy was observed through 5 years of treatment, and the safety profile of continued BG00012 treatment was consistent with that observed in the 2-year Phase 3 studies.

Overall, safety data from the clinical development program showed that BG00012 was well tolerated and has an acceptable safety profile. In the BG00012 240 mg BID group, the most common adverse events (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 dose regimens of BG00012. Mean WBC and lymphocyte counts then plateaued and remained stable, even during longer periods of observation of approximately 5.25 years. 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. With open-label and marketed use of BG00012, progressive multifocal leukoencephalopathy has been observed in the setting of severe and prolonged lymphopenia. There has been no other evidence of increased risk of infections, serious infections, or other opportunistic infections (in open-label and marketed use of BG00012).

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 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 (PTH), or 1,25-dihydroxyvitamin D. In the Phase 3 studies (Studies 109MS301 and 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 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 over time in β2-microglobulinuria and microalbuminuria, which are more sensitive and specific markers of renal tubular dysfunction, 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.

5.4. Study Rationale

In adult subjects with RRMS, BG00012 demonstrated efficacy and had an acceptable safety profile in 2 Phase 3 studies, Studies 109MS301 and 109MS302. With no approved therapies, there exists a significant unmet need for MS treatment options in the pediatric population. In the adult population, BG00012 is a therapeutic option with demonstrated efficacy and acceptable tolerability and safety profiles combined with the ease of oral administration. This study will extend therapy from the ongoing BG00012 pediatric Study 109MS202, in which the PK and efficacy of BG00012 in pediatric subjects with RRMS are being evaluated, in order to further evaluate the long-term safety and efficacy of BG00012 in these subjects.

5.5. Rationale for Dosing Regimen

The BG00012 dosage selected for this study (240 mg BID) is the approved BG00012 dosing regimen in adult patients with MS.

In adults, after oral administration, DMF is well absorbed and extensively metabolized by esterases to its primary active metabolite, monomethyl fumarate (MMF). As a result, DMF is not quantifiable in plasma, and all PK analyses have been performed based on MMF concentrations. Downstream metabolism of DMF/MMF occurs through the tricarboxylic acid cycle, with exhalation of carbon dioxide serving as a major route of elimination. The PK of BG00012 has been thoroughly evaluated in adults. Body weight is a significant covariant for BG00012 exposure in that the area under the curve and the maximum concentration are decreased by 2% and 1.4%, respectively, for every 1-kg increase in body weight within the weight range of 45 to 112 kg. This translates to a 2-fold increase in exposure levels as body weight decreases from 112 to 45 kg.

Despite the effect of body weight changes on the exposure levels of BG00012, data from the pivotal Phase 3 studies suggested that the variability in exposure did not affect safety and efficacy measures in adult patients. Notably, the efficacy and tolerability profiles of BG00012 at 240 mg BID were indistinguishable from those at 240 mg TID, with a wide range of overlapping exposures between the 2 dosages.

A Phase 1 PK study (Study 109MS101) revealed no apparent differences in the kinetics of BG00012 across the age range of 21 to 51 years once the weight relationship was accounted for.

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. These findings suggest that the disposition of BG00012 is unlikely to change with age for the target population (10 to 18 year olds).

Taken together, these data indicate that 240 mg BID, the approved dose in adults, should be tolerable in pediatric subjects meeting the inclusion criteria for the parent study (109MS202) and the current extension study. As such, this dose was chosen for the parent and current studies.

6. STUDY OBJECTIVES AND ENDPOINTS

6.1. Primary Objective and Endpoint

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

The primary endpoint that relates to this objective is the incidence of AEs, serious AEs (SAEs), and discontinuations of study treatment due to an AE.

6.2. Secondary Objectives and Endpoints

A secondary objective is to evaluate the long-term efficacy of BG00012.

The endpoints that relate to this objective are the total number of new or newly enlarging T2 hyperintense lesions on brain MRI scans, the ARR, and the proportion of subjects who experience 1 or more relapses during the study period.

Another secondary objective is to describe the long-term MS outcomes in subjects who completed Study 109MS202.

The endpoint that relates to this objective is the degree of disability as measured by the EDSS and disability progression (as measured by at least a 1.0-point increase on the EDSS from baseline EDSS ≥1.0 that is sustained for 24 weeks, or at least a 1.5-point increase on the EDSS from baseline EDSS = 0 that is sustained for 24 weeks).

7. STUDY DESIGN

7.1. Study Overview

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

See Figure 1 for a schematic of the study design.

7.2. Overall Study Duration and Follow-Up

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

7.2.1. Enrollment

Subject eligibility for the study will be determined at the Final Study Visit for Study 109MS202 or within 4 weeks prior to study entry. The Final Study Visit for Study 109MS202 will serve as the Baseline Visit for this study.

7.2.2. Treatment

Eligible subjects will report to the study site to receive study treatment approximately every 12 weeks for up to 96 weeks (2 years).

7.2.3. Follow-Up

Subjects are to return to the study site for a follow-up visit 4 weeks after their last treatment visit (Visit 8 at Week 96 [±5 days]).

Subjects who withdraw prematurely from the study will complete the Early Withdrawal Visit, which should be conducted as soon as possible and no later than 4 weeks after the subject's last dose of study treatment. Subjects who withdraw prematurely should be encouraged to complete the Safety Follow-Up Visit 4 weeks after the last dose of study treatment.

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) will be followed every 4 weeks until the lymphocyte count is ≥LLN or for 24 weeks after the last dose (whichever is sooner).

7.3. Relapses

Suspected relapses during this study will be evaluated and confirmed according to the protocol by the Investigator. 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 Investigator. 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 would not be treated with intravenous methylprednisolone (IVMP) within the protocol.

If a subject experiences new neurologic symptoms, then the subject or caregiver must contact the Investigator 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 Investigator within 5 days of the onset of the potential relapse. The Investigator is to perform a relapse assessment and obtain an EDSS score. To ensure consistency across sites, Investigators must undergo a standardized training session on EDSS scoring prior to enrollment of subjects at their site. New objective findings on neurological examination performed by the Investigator are required to determine if a protocol-defined relapse has occurred. Subjects may not begin corticosteroid treatment of the relapse per protocol until the Investigator has examined them.

Treatment of an acute event of relapse with IVMP may proceed at the discretion of the Investigator and will not affect the subject's eligibility to continue in the study. If an Unscheduled Relapse Assessment Visit occurs within 7 days of a scheduled clinic visit, then the 2 visits may take place on the same day; however, MRIs must be conducted according to the schedule outlined in Section 4.2.

7.4. Study Stopping Rules

Biogen may terminate this study at any time, after informing the Investigators. Biogen will notify Investigators when the study is to be placed on hold, completed, or terminated.

7.5. End of Study

The end of study is last subject, last visit for final collection of data.

8. SELECTION OF SUBJECTS

8.1. Inclusion Criteria

To be eligible to participate in this study, candidates must meet the following eligibility criteria at 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 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, as per protocol, the previous BG00012 clinical study 109MS202 and remain on BG00012 treatment at 240 mg BID.
3. All female subjects of childbearing potential and all male subjects must practice effective contraception during the study and for at least 30 days after their last dose of study treatment. For further details of contraceptive requirements for this study, please refer to Section 15.5.

8.2. Exclusion Criteria

Candidates will be excluded from study entry if any of the following exclusion criteria exist at Day 1 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.
4. Any significant changes in medical history occurring after enrollment in the parent Study 109MS202, including laboratory test abnormalities or current clinically significant conditions that in the opinion of the Investigator would have excluded the subject's participation from the parent study. The Investigator must re-review the subject's medical fitness for participation and consider any factors that would preclude treatment.
5. Subjects from Study 109MS202 who could not tolerate study treatment.
6. History of malignancy.
7. History of severe allergic or anaphylactic reactions or known drug hypersensitivity to DMF or fumaric acid esters.
8. Any of the following abnormal blood tests:
   - ALT >3 times the ULN
   - AST >3 times the ULN
   - Gamma-glutamyl-transferase >3 times the ULN

- Creatinine >1.2 times the ULN
- WBC count <2000/mm^3
- Lymphocyte count <500/mm^3

9. Female subjects considering becoming pregnant or breastfeeding while in the study or who are pregnant or breastfeeding.
10. Other unspecified reasons that, in the opinion of the Investigator or Biogen, make the subject unsuitable for enrollment.

9. ENROLLMENT AND REGISTRATION

9.1. Screening and Enrollment

Subjects (or their legally authorized representative [e.g., parent or legal guardian], where applicable) must provide informed consent before any screening tests are performed (see Section 17.3). When a subject signs the informed consent form (ICF), that subject is considered to be enrolled in the study. Subjects who have a nonclinically significant out-of-range laboratory result may be rescreened 1 time only at the discretion of the Investigator. 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.

9.2. Registration of Subjects

Subjects will be registered at Day 1, after all baseline assessments have been completed and after the Investigator has verified that the subjects are eligible per criteria in Sections 8.1 and 8.2. No subject may begin treatment prior to assignment of a unique identification number (registration). Any subject identification numbers that are assigned will not be reused even if the subject does not receive treatment.

Refer to the Study Reference Guide for details on registration.

9.3. Blinding Procedures

Not applicable.

10. DISCONTINUATION OF STUDY TREATMENT AND/OR WITHDRAWAL OF SUBJECTS FROM THE STUDY

10.1. Discontinuation of Study Treatment

A subject *must* permanently discontinue BG00012 for any of the following reasons:

- The subject becomes pregnant. Study treatment must be discontinued immediately. Report the pregnancy according to the instructions in Section 15.4.1.
- The subject experiences a medical emergency that necessitates permanent discontinuation of study treatment.
- The subject has lymphocyte count <500/mm^3 for 6 months as outlined in Table 4 and Table 5 .
- The subject experiences a protocol-specified change in laboratory values that necessitates permanent discontinuation of treatment as outlined in Table 3 and Table 4.
- The subject cannot tolerate study treatment.
- The subject receives any of the disallowed concomitant medications for this study.
- The subject or subject's parent/legal guardian desires to discontinue treatment.
- 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 discontinue treatment may remain in the study and continue protocol-required tests and assessments.

10.2. Withdrawal of Subjects From Study

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

- The subject or the subject's parent/guardian withdraws consent.
- The subject enrolls into another interventional clinical study.
- 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.

11. STUDY TREATMENT USE

11.1. Regimen

BG00012 will be taken orally at a dose of 240 mg BID.

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.

Refer to and follow the Directions for Handling and Administration (DHA).

11.2. Modification of Dose and/or Treatment Schedule

11.2.1. Dosing Interruption for Abnormal Laboratory Values

BG00012 must be temporarily withheld and/or permanently discontinued when any of the following laboratory values meet the threshold limits defined in Table 3 (laboratory abnormalities that require immediate and permanent discontinuation of study treatment are also specified in Table 3).

Table 3: Laboratory Criteria Requiring Withholding or Permanent Discontinuation of Treatment

Laboratory Parameter	Laboratory Result	Required Action
AST (SGOT) or ALT (SGPT)	>3 × ULN	The Investigator should repeat the test as soon as possible. If the retest value confirms AST or ALT >3 × ULN, then the study treatment must be withheld. If the value remains >3 × ULN for ≥4 weeks after discontinuation of study treatment, then the subject **must *permanently* discontinue study treatment, 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, then 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, and the event must be recorded as an AE.**

Laboratory Parameter	Laboratory Result	Required Action
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, then 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, 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 retest confirms microscopic hematuria without known etiology, then the study treatment must be withheld, and urine cytology performed. If hematuria persists for ≥4 weeks after discontinuation or if cytology is positive for malignant cells, then the subject **must *permanently* discontinue study treatment, and the event must be recorded as an AE. Subjects should be referred to a nephrologist for further investigation.**
Urinalysis	Proteinuria ≥2+	The Investigator should repeat the test as soon as possible. If retest confirms proteinuria ≥2+ without known etiology, then the study treatment must be withheld. If proteinuria ≥2+ persists for ≥4 weeks after discontinuation, then the subject **must *permanently* discontinue study treatment, 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; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; ULN = upper limit of normal; WBC = white blood cell.

Table 4 describes the management of lymphocytes <LLN for subjects during and after study treatment.

Table 4: Management of Lymphocyte Count <LLN

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 on study treatment	<500/mm^3	If lymphocyte count is <500/mm^3 for more than 6 months, study treatment must be permanently discontinued.

Laboratory Parameter	Laboratory Result	Required Action
Lymphocyte count in subjects who complete or permanently discontinue BG00012 for any reason	<LLN	Subjects will be followed at least every 4 weeks until the lymphocyte count is ≥LLN or for 24 weeks after the last dose (whichever is sooner).

LLN = lower limit of normal.

While dosing is withheld, subjects will continue tests and assessments according to Table 1 (and may also undergo additional assessments to evaluate the laboratory abnormality as per the Investigator's standard practice). In addition, subjects (whether on study treatment, having dosing temporarily withheld, or permanently discontinued) must have the abnormal laboratory result rechecked at the central laboratory as follows:

- For all analytes, with the exception of lymphocytes, results will be rechecked at least every 2 weeks 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.
- For lymphocytes, results will be rechecked at least every 4 weeks until the lymphocyte count is ≥LLN or for 24 weeks after the last dose (whichever is sooner). Depending on the severity and clinical significance of the abnormality, the Investigator may need to perform the retests more frequently.

11.2.2. Resumption of Study Treatment Dosing

Resumption of BG00012 treatment is to be considered on a case-by-case basis and must be discussed with the Medical Monitor.

Subjects with lymphocyte <LLN

Subjects who temporarily withhold study treatment due to decreases in lymphocyte count (at the discretion of the Investigator) may resume study treatment when lymphocyte counts recover (defined as a lymphocyte count ≥LLN on 2 consecutive occasions at least 4 weeks apart).

Resumption of study treatment after an interruption

Subjects who are allowed to resume BG00012 dosing after an interruption of ≥2 weeks will restart dosing at a reduced dosage for 1 week. Subjects will take one 120-mg capsule BID for 1 week. After 1 week at the reduced dose, subjects will resume taking two 120-mg capsules BID.

11.2.3. 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 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, then 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 3) on a third occasion must discontinue dosing for the remainder of the study.

11.2.4. 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, then 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 AM void). If the spot protein/creatinine ratio is >0.2 mg/mg, then the subject should be fully investigated for possible causes and referred for evaluation by a nephrologist if appropriate in the opinion of the Investigator.

11.2.5. Treatment Schedule for Subjects With Abnormal Lymphocyte Count

11.2.5.1. 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 Criteria 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 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.

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 2]. If the lymphocyte count does not recover, the treating neurologist should contact the Medical Monitor.

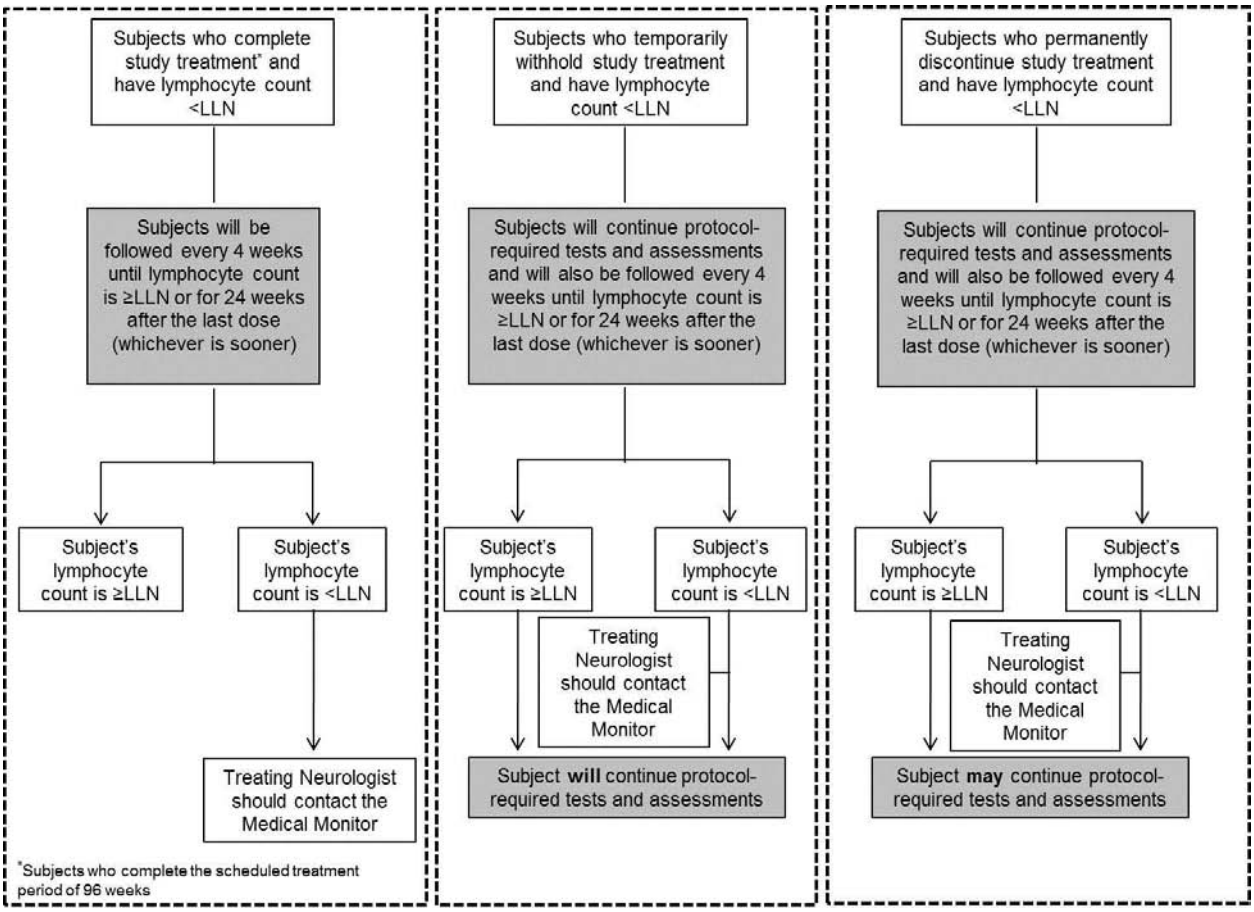
11.2.5.2. Schedule for Subjects Who Complete, Temporarily Withhold, or Permanently Discontinue Study Treatment for Any Reason and Have a Lymphocyte Count <LLN

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 10.1) 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 Table 4]. If the lymphocyte count does not recover after 24 weeks, the treating neurologist should contact the Medical Monitor.

See Figure 2 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 2: Schedule for Subjects who Complete, Temporarily Withhold, or Permanently Discontinue Study Treatment for Any Reason and Have a Lymphocyte Count <LLN



LLN = lower limit of normal.

11.2.6. Dosage Reductions

Dosage reduction will be allowed only for subjects **who are unable to tolerate BG00012 treatment due to flushing and/or GI disturbances** (dosage reductions will not be allowed for abnormal laboratory values; for management of abnormal laboratory values, see Sections 11.2.1, 11.2.2, and 11.2.3). Subjects who do not tolerate BG00012 treatment will reduce their dosage by taking one 120-mg capsule BID for up to 4 weeks. Within 4 weeks at the reduced dosage, subjects will resume taking the full dose of 240 mg (two 120-mg capsules) BID. If the subject is still unable to tolerate BG00012 treatment at the 240-mg BID dose, the subject may continue in the study taking the 120-mg BID dose.

11.3. 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.

11.4. Compliance

Compliance with treatment dosing is to be monitored and recorded by site staff. Compliance for BG00012 will be monitored by capsule count and captured in the eCRF.

11.5. Concomitant Therapy and Procedures

11.5.1. Concomitant Therapy

A concomitant therapy is any drug or substance administered between the Baseline Visit and the Safety Follow-Up Visit.

11.5.1.1. Allowed Concomitant Therapy

Symptomatic therapy, such as treatment for spasticity, depression, or fatigue, is not restricted but should be consistent for the duration of the study.

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

11.5.1.2. Disallowed Concomitant Therapy

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

- Any alternative drug treatments directed toward the treatment of MS, such as immunomodulatory treatments (including but not limited to, interferon-beta, glatiramer acetate, natalizumab, fingolimod, teriflunomide, alemtuzumab, mitoxantrone, mycophenolate mofetil, laquinimod, cyclophosphamide, methotrexate, azathioprine, cyclosporine, etc.) and 4-aminopyridine or related products with the

exception of acute management of protocol-defined relapse (as described in Section 11.5.2).

- 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 11.5.2. Steroids that are administered by nonsystemic routes (e.g., topical, inhaled) are allowed.
- Total lymphoid irradiation, cladribine, T-cell or T-cell receptor vaccination, any therapeutic monoclonal antibody, intravenous (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 10.2.

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

11.5.2. 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 Final Study Visit.

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

11.5.3. Treatment of Relapses on Scheduled or Unscheduled Visits

The only protocol-approved treatment for relapse in this study is either 3 or 5 days with IVMP, up to 1000 mg/day. IVMP 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.

11.6. Continuation of Treatment

There is no provision for additional courses of BG00012 provided by Biogen beyond the treatment period defined in this protocol.

If and when BG00012 is commercially available at the time the study treatment period is completed, subjects will be allowed to take commercial BG00012 during the Safety Follow-Up Period if deemed appropriate by product labeling and at the discretion of their treating physician.

12. STUDY TREATMENT MANAGEMENT

Study site staff should follow the DHA for specific instructions on the handling, preparation, administration, and disposal of the study treatment. The DHA supersedes all other references (e.g., protocol).

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

12.1. 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.

12.1.1. BG00012 Preparation

BG00012 will be provided as capsules. Drug wallets will be prepared to ensure that the appropriate treatment is provided to each subject. Drug wallets will be supplied from Interactive Voice/Web Response System 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 study treatment, do not use the study treatment. The drug wallet in question should be quarantined at the study site and the problem immediately reported to Biogen.

12.1.2. BG00012 Storage

Study treatment must be stored in a secure location.

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. For the most up-to-date storage requirements, follow the instructions provided in the DHA.

12.1.3. BG00012 Handling and Disposal

The Investigator must return all used and unused drug wallets of BG00012 as instructed by Biogen unless approved for onsite destruction.

If any BG00012 supplies are to be destroyed at the study site, the institution or appropriate site personnel must obtain prior approval from Biogen by providing, in writing, the destruction policy or details of the method of destruction. After such destruction, Biogen must be notified, in writing, of the details of the study treatment destroyed (e.g., lot or kit numbers, quantities), the date of destruction, and proof of destruction.

12.1.4. BG00012 Accountability

Accountability for study treatment is the responsibility of the Investigator. 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 accidentally or deliberately destroyed or lost.

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, lost, or returned to Biogen. A written explanation must be provided for any discrepancies.

13. EFFICACY ASSESSMENTS

See Section 4 for the timing of all assessments.

13.1. Clinical Efficacy Assessments

The following clinical assessments will be performed to evaluate the efficacy of BG00012:

- Relapse assessment
- EDSS

13.2. MRI Efficacy Assessments

The following MRI efficacy assessments will be performed to evaluate the efficacy of BG00012:

- The total number of new or newly enlarging T2 hyperintense lesions from baseline as well as from the scan of the previous visit on brain MRI scans

14. SAFETY ASSESSMENTS

Refer to Section 4 for the timing of all safety assessments.

14.1. Clinical Safety Assessments

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

- Physical examinations, including body weight and height
- Vital sign measurements, including body temperature, pulse rate, and systolic and diastolic blood pressure
- 12-Lead electrocardiograms
- Concomitant therapy and procedure recording
- AE and SAE recording

14.2. Laboratory Safety Assessments

The following laboratory assessments will be performed to evaluate the safety profile of BG00012:

- Hematology: complete blood count with differential and platelet count
- Blood chemistry: sodium, potassium, chloride, bicarbonate, calcium, magnesium, phosphate, BUN, creatinine, uric acid, glucose, albumin, ALT, AST, gamma-glutamyl transferase, total bilirubin, and alkaline phosphatase
- Urinalysis: dipstick for blood, protein, and glucose (microscopic examination, if abnormal)
- Vitamin D and PTH levels

15. SAFETY DEFINITIONS, RECORDING, REPORTING, AND RESPONSIBILITIES

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 or his/her legally authorized representative and/or main caregiver must be given the names and telephone numbers of study site staff for reporting AEs and medical emergencies.

15.1. Definitions

15.1.1. 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.

Determination of whether an abnormal laboratory value meets the definition of an AE will be made by the Investigator. Although abnormal laboratory values are typically not considered AEs, the following considerations may result in an abnormal laboratory value being considered an AE:

- A laboratory test result that meets the criteria for an SAE
- A laboratory test result that requires the subject to receive specific corrective therapy
- A laboratory abnormality that the Investigator considers to be clinically significant

15.1.2. 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
- 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.)

15.1.3. 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.

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 in Section 15.1.2 is met.

15.2. Safety Classifications

15.2.1. Investigator Assessment of Events

All events must be assessed to determine the following:

- If the event meets the criteria for an SAE as defined in Section 15.1.2 .
- The relationship of the event to study treatment as defined in Section 15.2.2.
- The severity of the event as defined in Section 15.2.3.

15.2.2. 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 reasonable 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, 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 reasonable 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.

15.2.3. 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 symptoms 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 symptoms 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 symptoms may be given and/or subject hospitalized.

15.2.4. Expectedness of Events

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

15.3. Monitoring and Recording Events

15.3.1. Adverse Events

Any AE experienced by the subject between the time of first dose of study treatment in the extension study 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.

15.3.2. Serious Adverse Events

Any SAE experienced by the subject between the time of the signing of the ICF 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 Biogen Safety and Benefit-Risk

Management (SABR) or designee within 24 hours as described in Section 15.3.3. Follow-up information regarding an SAE also must be reported with 24 hours.

Subjects will be followed for all SAEs until the Safety Follow-Up Visit. Thereafter, the event should be reported to Biogen SABR or designee only if the Investigator considers the SAE to be related to study treatment.

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

15.3.3. 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 SAE that occurs between the time that the subject has signed the ICF 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. Thereafter, the event should be reported only if the Investigator considers it related to study treatment. 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 the 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 an SAE, please fax (please refer to the Study Reference Guide) or email [redacted].

15.3.3.1. Deaths

Death is an outcome of an event. The event that resulted in death should be recorded on the appropriate eCRF. All causes of death must be reported as SAEs within 24 hours of the site becoming aware of the event. The Investigator should make every effort to obtain and send death certificates and autopsy reports to Biogen SABR or designee. The term death should be reported as an SAE only if the cause of death is not known and cannot be determined.

15.3.4. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are SAEs that are unexpected and judged by the Investigator or Biogen 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.

15.4. Procedures for Handling Special Situations

15.4.1. Pregnancy

Subjects should not become pregnant during the study and for 30 days after their last dose of study treatment. If a female subject becomes pregnant, study treatment must be discontinued *immediately*.

The Investigator must report a pregnancy by faxing or emailing the appropriate form within 24 hours of the study site staff becoming aware of the pregnancy to Biogen SABR or designee (fax: please refer to the Study Reference Guide; email: [redacted]. The Investigator or study site staff must report the outcome of the pregnancy to Biogen SABR or designee.

Congenital abnormalities and birth defects in the offspring of male or female subjects should be reported as an SAE if conception occurred during the study treatment period.

15.4.2. Overdose

An overdose is any dose of study treatment administered to a subject or taken by a subject that exceeds the dose assigned to the subject according to the protocol. Overdoses are not considered AEs and should not be recorded as an AE on the eCRF; however, all overdoses must be recorded on an Overdose form and faxed to Biogen SABR or designee within 24 hours of the site becoming aware of the overdose. An overdose must be reported to Biogen or designee even if the overdose does not result in an AE. If an overdose results in an AE, the AE must be recorded. If an overdose results in an SAE, both the SAE and Overdose forms must be completed and faxed to Biogen SABR or designee. All study treatment-related dosing information must be recorded on the dosing eCRF.

15.4.3. Medical Emergency

In a medical emergency requiring immediate attention, study site staff will perform appropriate medical interventions, according to current standards of care. The Investigator (or designee) should contact the study's Medical Director. Refer to the Study Reference Guide's Official Study Contact List for complete contact information.

15.4.3.1. Unblinding for Medical Emergency

Not Applicable

15.5. Contraception Requirements

Sexually active subjects of reproductive potential must practice effective contraception during the study and for at least 30 days after their last dose of study treatment. Investigators should advise subjects of the potential risks associated with pregnancy while taking BG00012 and on the appropriate use of contraceptives (as defined below).

For the purposes of the study, highly effective contraception is defined as use of 1 or more of the following:

For females:

- Established use of oral, injected, or implanted hormonal methods of contraception.
- Placement of an intrauterine device or intrauterine system.
- Barrier methods of contraception with use of a spermicide: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream suppository. The use of barrier contraceptives should always be supplemented with the use of a spermicide (where approved/applicable).
- Female surgical sterilization (e.g., bilateral tubal ligation).

For males:

- Effective male contraception includes the use of condoms with spermicide.

True abstinence, when this is consistent with the preferred and usual lifestyle of the subject, can be considered an acceptable method of contraception based on the evaluation of the Investigator who should also take into consideration the duration of the clinical trial. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not considered acceptable methods of contraception.

Pregnancy reporting is described in Section 15.4.1.

15.6. Safety Responsibilities

15.6.1. The Investigator

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 to study treatment, and severity of each event.
- Determine the onset and resolution dates of each event.
- Monitor and record all pregnancies and follow up on the outcomes.
- Complete an SAE form for each SAE 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.
- Report SAEs to local ethics committees, as required by local law.
- Ensure all AE and SAE reports are supported by documentation in the subjects' medical records.

- Pursue AE follow-up information, if possible, until the event has resolved or become stable.

15.6.2. Biogen

Biogen's responsibilities include the following:

- Before study site activation and subject enrollment, the Clinical Monitor 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 ethics committees, and Investigators of SAEs, as required by local law, within required time frames.

16. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

The objectives of the study and the endpoints to be analyzed are listed in Section 6.

16.1. Efficacy

16.1.1. Analysis Population

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

16.1.2. Methods of Analysis

16.1.2.1. Analysis of the Primary Endpoint

The primary analysis will be summaries of the incidence of treatment-emergent AEs, SAEs, and discontinuations from study treatment due to AEs.

16.1.2.2. Analysis of the Secondary Endpoints

The number of new or newly enlarging T2 hyperintense lesions on brain MRI scans will be summarized over time using descriptive statistics.

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

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

16.2. Pharmacokinetics

Not applicable.

16.3. Pharmacodynamics

Not applicable.

16.4. Biomarker Analyses/Pharmacogenomics

Not applicable.

16.5. Safety

16.5.1. Analysis Population

The safety population is defined as all subjects who received at least 1 dose of BG00012 in this study.

16.5.1.1. Adverse Events

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

The primary analysis will be summaries of the incidence of treatment-emergent AEs, SAEs, and discontinuations from study treatment due to AEs.

16.5.1.2. Clinical Laboratory Results

Clinical laboratory evaluations including hematology, blood chemistry, and urinalysis will be summarized using the incidence of shifts outside the normal range. In addition, summary statistics for quantitative laboratory values and changes from baseline will be presented. Lymphocyte count data will be summarized by timepoints on study treatment. Additionally, lymphocyte count over time post-treatment and the time to recovery will be descriptively summarized for subjects who develop decreases in lymphocyte count (<LLN).

16.5.1.3. Vital Signs

The analysis of vital signs will focus on clinically relevant abnormalities. The incidence of subjects experiencing these abnormalities will be summarized.

16.6. Antigenicity/Immunogenicity Data

Not applicable.

16.7. Interim Analyses

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

16.8. Sample Size Considerations

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

17. ETHICAL REQUIREMENTS

Biogen, [redacted], 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.

The Investigator may delegate responsibilities for study-related tasks where appropriate to individuals sufficiently qualified by education, training, and experience, in accordance with applicable ICH and GCP guidelines. The Investigator should maintain a list of the appropriately qualified persons to whom significant study-related duties have been delegated.

17.1. Declaration of Helsinki

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

17.2. Ethics Committee

The Investigator must obtain ethics committee approval of the protocol, ICF, and other required study documents prior to starting the study. Biogen 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 ethics committee. 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 ethics committee and Biogen.

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

Biogen must receive a letter documenting ethics committee 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 ethics committee 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 ethics committee and Biogen.

17.3. 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 or subject's legally authorized representative (e.g., parent or legal guardian), as applicable, in accordance with local practice and regulations.

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 (or the

subject's legally authorized representative). The subject must be given sufficient time to consider whether to participate in the study.

In addition, subjects who have the capacity should provide their assent to participate in the study. The level of information provided to subjects should match their level of understanding as determined by the Investigator and in accordance with applicable regulations and guidelines.

A copy of the signed and dated ICF and assent if applicable must be given to the subject or the subject's legally authorized representative. The signed and dated ICF will be retained with the study records. Local regulations must be complied with in respect to the final disposition of the original (wet signature) and copies of the signed and dated ICFs.

Confirmation of informed consent and assent if applicable must also be documented in the subject's medical record.

17.4. 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., Protected Health Information 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, ethics committees, 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.

17.5. Compensation for Injury

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

17.6. Conflict of Interest

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

17.7. Registration of Study and Disclosure of Study Results

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

18. ADMINISTRATIVE PROCEDURES

18.1. Study Site Initiation

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

18.2. Quality Assurance

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

18.3. Monitoring of the Study

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

The Clinical Monitor will visit the Investigator at regular intervals during 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.

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.

18.4. 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.

18.5. Publications

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

19. FURTHER REQUIREMENTS AND GENERAL INFORMATION

19.1. External Contract Organizations

Biogen will be responsible for all administrative aspects of this study including but not limited to study initiation, monitoring, management of AEs, and data management.

19.1.1. Contract Research Organization

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

19.1.2. Electronic Data Capture

Subject information will be captured and managed by study sites on eCRFs by a Web-based electronic data capture tool OR remote data capture tool developed and supported by iMedidata RAVE and configured by [redacted].

19.1.3. Central Laboratories for Laboratory Assessments

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

19.1.4. Central Facility for Other Assessments

Central and specialty facilities have been selected by Biogen to read and interpret all MRI scans for this study.

19.2. Study Committees

19.2.1. Advisory Committee

An advisory committee will be formed to provide scientific and medical direction for the study and to oversee the administrative progress of the study. The advisory committee will conduct regular reviews to monitor subject accrual and to monitor compliance with the protocol at individual study sites. The advisory committee will determine whether the study should be stopped or amended for reasons other than safety.

Members of the advisory committee will include the Medical Director, Clinical Operations Lead, and Project Statistician from Biogen, and participating Investigators. Biogen will designate one of the participating Investigators to be the chairperson of the advisory committee.

19.2.2. Independent Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) 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 IDMC organization and procedures will be outlined in the IDMC Charter.

19.3. Changes to Final Study Protocol

Protocol modifications that affect subject safety, the scope of the investigation, or the scientific quality of the study must be approved by the ethics committee 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 ICF may require corresponding modifications (see Section 17).

19.4. Ethics Committee Notification of Study Completion or Termination

Where required, the regulatory authorities and ethics committees must be notified of completion or termination of this study, and sent a copy of the study synopsis in accordance with necessary timelines.

19.5. 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 offsite facility or transfer of ownership if the Investigator leaves the site.

19.6. Study Report Signatory

Biogen will designate 1 or more 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.

20. REFERENCES

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21. SIGNED AGREEMENT OF THE STUDY PROTOCOL

I have read the foregoing protocol, "A Multicenter Extension Study to Determine the Long-Term Safety and Efficacy of BG00012 in Pediatric Subjects With Relapsing-Remitting Multiple Sclerosis," 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.

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Investigator's Signature Date

_____

Investigator's Name (Print)

_____

Study Site (Print)